Partial Reduction | Hot Paper

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Catalytic 1,4-Selective Hydrosilylation of Pyridines and Benzannulated Congeners**

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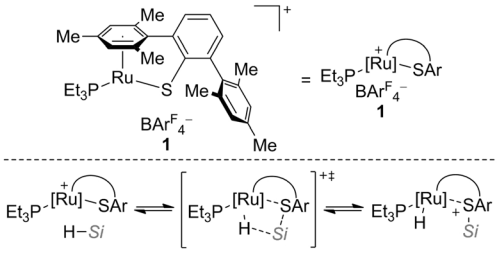
The NAD(P)H/NAD(P)$^+$ redox cycle with its 1,4-dihydropyridine/pyridinium ion interconversion is one of the fundamental transformations in biological systems.[1] Outside living organisms, the forward reaction, that is, reduction through oxidation of the 1,4-dihydropyridine, is straightforward, and the use of 1,4-dihydropyridines[2] as reducing agents in organocatalysis is a prime example of that.[3] The back reaction poses, however, a remarkable challenge, and there is, to date, no general method available for the partial reduction of pyridines.[4,5] The notion that breaking the aromaticity of pyridines by a Birch-type reduction to provide an entry to synthetically useful building blocks was realized close to a century ago.[6] Birch and Karakhanov later investigated these reductions with solvated electrons more systematically with limited success,[7] and it was only recently that Donohoe and co-workers demonstrated the potential of this method for a few selected systems.[8] Another obvious approach is the partial hydrogenation of pyridines with dihydrogen under transition-metal catalysis,[9] but the problem of overreduction of the more reactive enamine intermediate remains unsolved. Recently, the Hill and Suginome groups independently introduced a noteworthy alternative strategy that allows for partial reduction of pyridines, either by magnesium(II)-[10] or rhodium(I)-catalyzed[11] hydroboration.[12] Prior to these seminal contributions, homogeneous hydrosilylation of pyridines[13] had been probed by Harrod and co-workers with a titanocene(III) catalyst but the chemoselectivity was moderate.[14] Aside from this isolated report, the unsolved challenge had lain dormant for another decade until Nikonov and co-workers disclosed a pyridine hydrosilylation using cationic ruthenium(II) complexes [Cp(*i*Pr$_3$P)Ru(MeCN)$_2$]$^+$ X$^-$ [X = PF$_6$ or B(C$_6$F$_5$)$_4$; Cp = Cyclopentadienyl].[15] The scope of this catalysis was, in the end, relatively narrow, but a few pyridines reacted 1,4-selectively at room temperature, and that certainly was a major step forward. Despite these recent significant advances in pyridine hydroboration[10,11] and hydrosilylation,[14,15] the latter methods are still far from being general.

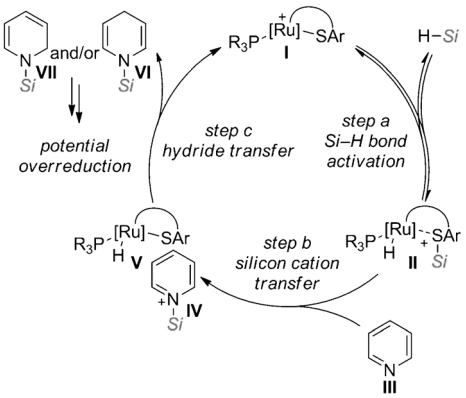
Our laboratory together with the group led by Ohki and Tatsumi demonstrated that the tethered cationic ruthenium(II) complex **1**[16] (Scheme 1, top) cooperatively activates Si–H bonds.[17] The polar Ru–S bond in **1** mediates the heterolytic splitting of Si–H bonds to give a ruthenium(II)



Scheme 1. The tethered cationic ruthenium(II) complex **1** with a polar Ru–S bond and its application to Si–H bond activation by σ-bond metathesis (*Si* = triorganosilyl; Ar^F = 3,5-bis(trifluoromethyl)phenyl).

hydride and a sulfur-stabilized silicon cation by σ-bond metathesis (Scheme 1, bottom). The catalytically generated silicon electrophile in combination with the ruthenium(II) hydride opened the door to several remarkable dehydrogenative coupling reactions[17a–c] and is also able to catalyze the hydrodefluorination of CF$_3$ groups by a unique mechanism.[17d]

We, therefore, entertained the idea that intermediate **II**, formed from **I** and a triorganosilane in the Si–H bond-activation step (step a in Scheme 2), could transfer the silicon cation onto the nitrogen atom of **III** (step b in Scheme 2). The pyridinium cation **IV** would then be susceptible to nucleophilic attack of the hydride released from **V** (step c in



Scheme 2. Tentative catalytic cycle of the pyridine hydrosilylation (counteranion BAr$^F{}_4^-$ omitted for clarity).

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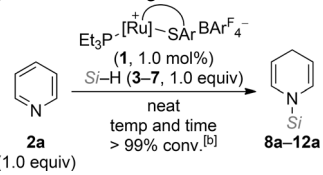
Scheme 2), affording **VI** (1,4-hydride transfer) and/or **VII** (1,2-hydride transfer). The mechanisms of nucleophilic attack at pyridinium and, likewise, quinolinium ions are still a matter of debate.[18] As to the proposed hydride as nucleophile, Norton and co-workers produced sound evidence that the 1,4-reduction pathway of a ruthenium(II)-catalyzed hydrogenation of an acyl pyridinium ion obeys a two-step radical mechanism while 1,2-reduction occurs by a one-step ionic mechanism.[9a] Also, Nikonov's work included EPR measurements that indicate the existence of a ruthenium-centered paramagnetic intermediate.[15] We report here the application of catalyst **1** to the regioselective hydrosilylation of pyridines and its benzannulated congeners without any overreduction. The new methodology tolerates challenging substitution patterns and is shown to likely follow a different reaction mechanism.

We began testing various triorganosilanes in the reduction of the parent compound, pyridine (**2a**; Table 1). For the Si–H bond activation to occur at catalyst **1**, these triorganosilanes

Table 1: Screening of suitable triorganosilanes as reducing agents.[a]



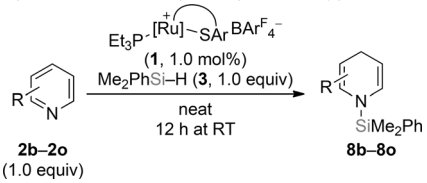
Entry	Silane *Si*–H	*T* [°C]	*t* [h]	Prod.	Yield [%][c]
1	Me_2PhSiH (**3**)	RT	7	**8a**	94[d]
2	$MePh_2SiH$ (**4**)	45	14	**9a**	96
3	$EtMe_2SiH$ (**5**)	RT	7	**10a**	84
4	Et_3SiH (**6**)	60	14	**11a**	–[e]
5	Ph_3SiH (**7**)	60	14	**12a**	–[e]

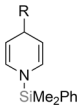
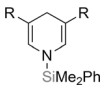
[a] All reactions were performed according to the General Procedure 1 (see the Supporting Information for details). [b] Conversion was monitored by ^1H NMR spectroscopy. [c] Yield of isolated product after the catalyst had been removed by filtration through a short plug of deactivated silica gel. [d] 91% yield with formation of catalyst **1** in situ according to the General Procedure 2 (see the Supporting Information for details). [e] No reaction.

must fit into the pocket that the bulky thiolate ligand and the ruthenium fragment create around the Ru–S bond. From our previous work, we already knew that the steric situation is well-balanced with Me_2PhSiH (**3**), $MePh_2SiH$ (**4**), and $EtMe_2SiH$ (**5**) but not with Et_3SiH (**6**) and Ph_3SiH (**7**).[17] We were then delighted to see that triorganosilanes **3**–**5** reacted with equimolar amounts of **2a** in the presence of just 1.0 mol% of preformed ruthenium(II) complex **1**, affording 1,4-dihydropyridines **8a**–**10a** as the sole regioisomers without overreduction (Table 1, entries 1–3). The reactions using silanes **3** and **5** proceeded smoothly at room temperature without the need of a solvent, and catalyst loadings as low as 0.1 mol% still promoted the hydrosilylation of **2a** in 86% yield, yet at a prolonged reaction time of 30 h. Notably, in situ formation of the coordinatively unsaturated catalyst **1** from the corresponding air-stable chloride complex by treatment with $NaBAr^F_4$ is not detrimental to catalytic turnover; in this way it is not necessary to handle the oxygen-sensitive 16-electron complex **1** in a glove-box (Table 1, entry 1, footnote [d]). Somewhat unexpectedly, $MePh_2SiH$ (**4**) was not as reactive as in previous studies (Table 1, entry 2).[17] The bulkier triorganosilanes **6** and **7** showed no conversion even at elevated temperatures (Table 1, entries 4 and 5) but, again, that is due to lack of reactivity in the Si–H bond-activation step.

The facile 1,4-hydrosilylation of pyridine compares well with Nikonov's finding[15] but we found our protocol to be broadly applicable to 3-substituted pyridines **2b**–**2f** decorated with either electron-donating or -withdrawing groups (Table 2, entries 1–5). Even halides were tolerated (Table 2,

Table 2: Catalytic 1,4-selective hydrosilylation of pyridines.[a,b]



Entry	Substrate		Product		Yield [%][c,d]
1		**2b** (R = Me)		**8b**	84
2		**2c** (R = Ph)		**8c**	98
3		**2d** (R = Br)		**8d**	96
4		**2e** (R = Cl)		**8e**	76
5		**2f** (R = F)		**8f**	76
6		**2g** (R = Me)		**8g**	80
7		**2h** (R = CF_3)		**8h**	88
8		**2i** (R = Et)		**8i**	89[e]
9		**2j** (R = *i*Pr)		**8j**	75[f]
10		**2k** (R = Ph)		**8k**	13[f]
11		**2l** (R = Cl)		**8l**	–[g]
12		**2m** (R = Me)		**8m**	80[h]
13		**2n** (R = Cl)		**8n**	98
14		**2o** (R = F)		**8o**	84

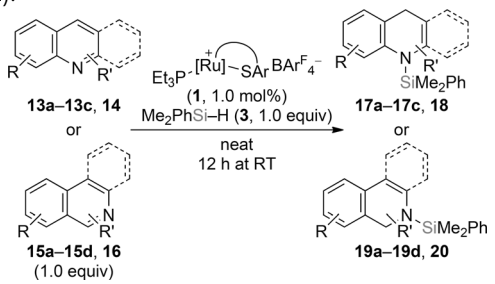
[a]–[c] See Table 1. [d] Formation of trace amounts of $(Me_2PhSi)_2O$ as a result of incomplete conversion due to hydrolysis of the remaining (activated) silane. [e] Conversion, 15% $(Me_2PhSi)_2O$ as contamination. [f] Conversion. [g] Formation of 1,4-dihydropyridine **8a** (R = H) along with $(Me_2PhSi)_2O$ was observed. [h] 80% conversion after 12 h at 45 °C.

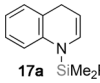
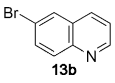
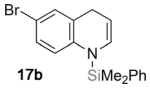
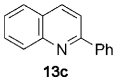
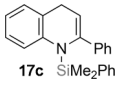
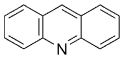
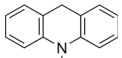
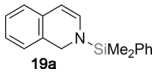
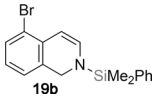
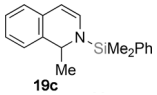
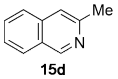
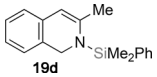
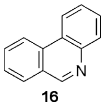
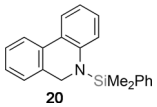
entries 3–5), and no debromination was observed (cf. Ref. [15]). We note here that Lewis basic functional groups, e.g., carboxyl and cyano groups, were not compatible with catalyst **1** and the silicon electrophile. Remarkably, substitution *para* to the nitrogen atom neither thwarted the hydrosilylation nor steered the regioselectivity from 1,4- to 1,2-reduction. The 4-substituted pyridines **2g** and **2h** reacted smoothly; **2i** and **2j** were too sterically demanding but were still selectively transformed into the 4-substituted 1,4-dihydropyridines (Table 2, entries 6–9). Phenyl substitution at C4 as in **2k** nearly fully disrupted the hydrosilylation (Table 2, entry 10).

In an independent experiment using deuterated silane [^{2}H]-**3** and pyridine **2g**, deuterium incorporation was found exclusively in the 4-position (see the Supporting Information for details). Dehalogenation was seen for the substrate with a chloro substituent at C4 (Table 2, entry 11). Pyridines **2m**–**2o** with 3,5-substitution also reacted cleanly (Table 2, entries 12–14). Only pyridines with *ortho* substitution would not participate in the catalysis. We attribute this to sterics hampering the transfer of the silicon cation from the sulfur-stabilized silylium ion to the pyridine nitrogen atom (cf. step b in Scheme 2).

Nevertheless, we subjected quinolines/acridine as well as isoquinolines/phenanthridine to our method (Table 3). To our surprise, quinolines **13a** and **13b** with and without a bromine atom at C6 and even 2-phenyl-substituted quinoline **13c** were selectively reduced in 1,4-fashion (Table 3, entries 1–3). These results, in terms of both regio- and chemoselectivity, were highly unexpected in the light of the literature precedence.[19,20] Acridine (**14**) reacted equally well (Table 3, entry 4). With isoquinolines **15a**–**15d**, 1,4-reduction would require breaking the aromaticity of the annulated benzene, and these heteroarenes including phenanthridine (**16**) yielded the 1,2-reduced heterocycles instead (Table 3, entries 5–9). Reactions of the more hindered 1- and 3-methyl-substituted **15c** and **15d** did not go to completion but, again, these are particularly challenging substrates. Partial reduction of isoquinolines is difficult, and overreduction is usually observed.[19]

Table 3: Catalytic 1,4-selective hydrosilylation of quinolines/acridine (top) and 1,2-selective hydrosilylation of isoquinolines/phenanthridine (bottom).[a,b,d]



Entry	Substrate	Product	Yield [%][c]
1	 **13a**	 **17a**	97
2	 **13b**	 **17b**	94
3	 **13c**	 **17c**	92
4	 **14**	 **18**	97[e]
5	 **15a**	 **19a**	97
6	 **15b**	 **19b**	91
7	 **15c**	 **19c**	71[f]
8	 **15d**	 **19d**	75[g]
9	 **16**	 **20**	98

[a]–[d] See Table 2. [e] Reaction was performed at 45 °C. [f] Conversion. [g] Conversion, 27% $(Me_2PhSi)_2O$ as contamination.

The finding that 4-alkyl-substituted pyridines underwent hydrosilylation with exclusive 1,4-selectivity suggested the opportunity to distinguish between a two-step radical[9a,15] and a one-step ionic 1,4-hydride transfer by "radical clocks"[21] installed at C4. We chose the potential ring opening of the cyclopropylmethyl radical (as in **2p**) and the potential spirocyclization of the hex-5-enyl radical (as in **2q**) as mechanistic probes (Figure 1). Both **2p** and **2q** reacted slowly under the standard conditions (cf. Table 2) yet were transformed cleanly into the corresponding 1,4-dihydropyridines **8p** and **8q** (not shown). We found no spectroscopic evidence for either the ring opening or the spirocyclization (see the Supporting Information for details). These results are, however, not totally conclusive as the hypothetical radical intermediate is tertiary and resonance-stabilized, and rate constants are not available for such systems but expected to be rather low. The fact that the cyclopropyl group remains intact, admittedly at low conversion, nevertheless indicates to us that an ionic mechanism is operative.

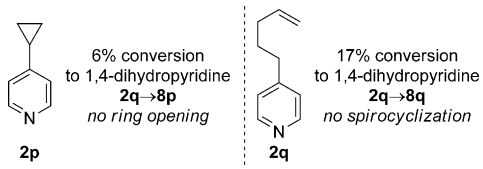


Figure 1. Potential "radical clocks" to probe the 1,4-hydride transfer: one-step ionic mechanism versus two-step radical mechanism.

The present method provides a viable tool for the chemo- and regioselective hydrosilylation of various pyridines and related nitrogen-containing heterocycles. Using equimolar amounts of substrate and silane at low catalyst loading, the reactions are exceptionally clean (aside from $(Me_2PhSi)_2O$ contamination at incomplete silane consumption in a few cases) and do not require complicated purification of partially saturated heterocycles susceptible to oxidation. The pronounced 1,4-selectivity in the hydrosilylation of pyridines and quinolines is likely achieved in an ionic one-step hydride transfer onto the pyridinium/quinolinium ion intermediate, and that distinguishes the present work from previous reports of a radical mechanism.

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