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# KOt-Bu-Catalyzed Dehydrogenative C–H Silylation of Heteroaromatics: A Combined Experimental and Computational Mechanistic Study

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KEYWORDS: silvlation, heteroaromatics, cross-dehydrogenative coupling, transition-metal free, radical chain process, mechanistic investigation, computational chemistry.

**ABSTRACT:** We recently reported a new method for the direct dehydrogenative C–H silylation of heteroaromatics utilizing Earthabundant potassium *tert*-butoxide. Herein we report a systematic experimental and computational mechanistic investigation of this transformation. Our experimental results are consistent with a radical chain mechanism. A trialkylsilyl radical may be initially generated by homolytic cleavage of a weakened Si–H bond of a hypercoordinated silicon species as detected by IR, or by traces of oxygen which can generate a reactive peroxide by reaction with (KOt-Bu)<sub>4</sub> as indicated by density functional theory (DFT) calculations. Radical clock and kinetic isotope experiments support a mechanism in which the C–Si bond is formed through silyl radical addition to the heterocycle followed by subsequent  $\beta$ -hydrogen scission. DFT calculations reveal a reasonable energy profile for a radical mechanism and support the experimentally observed regioselectivity. The silylation reaction is shown to be reversible, with an equilibrium favoring products due to the generation of H<sub>2</sub> gas. In situ NMR experiments with deuterated substrates show that H<sub>2</sub> is formed by a cross-dehydrogenative mechanism. The stereochemical course at the silicon center was investigated utilizing a <sup>2</sup>Hlabeled silolane probe; complete scrambling at the silicon center was observed, consistent with a number of possible radical intermediates or hypercoordinate silicates.

**Introduction** Heteroarenes are important components of natural products and bioactive molecules, and considerable research has focused on their functionalization and derivatization.<sup>1</sup> Direct functionalization of unactivated C–H bonds in heteroarenes is a powerful method to access heteroarylsilanes and heteroarylboranes.<sup>2</sup> These intermediates provide routes to build complexity in molecules by well-established cross-coupling techniques.<sup>3</sup> Heteroarylsilanes are stable and find widespread use in polymer synthesis, medical imaging applications, and drug discovery.<sup>4</sup> Given the diversity and abundance of both heteroarenes and silanes is a powerful tool for the selective construction of C–Si bonds.<sup>5,6</sup> In comparison with traditional methods (i.e., metalation/nucleophile trapping), direct cross-dehydrogenative C–H silylation constitutes an

appealing alternative without requiring prefunctionalization of the heteroarene, cryogenic conditions, or pyrophoric reagents.<sup>7</sup> Significant advances in this field include the development of Ir/Rh catalysts that efficiently enable C–H silylation of heteroarenes in the presence of super-stoichiometric sacrificial hydrogen acceptors (Scheme 1a) and more recent examples of catalytic Friedel-Crafts silylation of arenes.<sup>6,8,9</sup> Given the state of the art in C–H silylation, we sought a practical, sustainable, and scalable silylation method achieving efficient silylation of a broad scope of substrates. We have demonstrated that potassium *tert*-butoxide (KO*t*-Bu) alone can catalyze the direct cross-dehydrogenative coupling of heteroarenes with hydrosilanes (Scheme 1b).<sup>10</sup> This method features mild reaction conditions, an operationally simple procedure, good functional group tolerance, and environmentally friendly reagents. However, the mechanism by which this reaction occurs is not obvious and has driven a broad collaborative study toward gaining insight into the reaction, described in both this and the accompanying paper.<sup>11</sup> Herein we report a collection of evidence consistent with a radical mechanism, indicated by both experimental and computational mechanistic investigations. The companion publication describes an ionic and neutral mechanism for this reaction.

# Scheme 1. Synthesis of Heteroarylsilanes by Catalytic Direct C–H Silylations

(a) Previous Transition-Metal-Catalyzed C–H Silylation Work



(b) KOt-Bu-Catalyzed Cross-Dehydrogenative C-H Silylation Method



**Computational details.** Calculations were carried out with Gaussian 09.<sup>12</sup> Geometry optimizations and energy calculations were performed with the B3LYP and UB3LYP (for radical species) method.<sup>13</sup> The 6-31G (d) basis set was used for all atoms.<sup>14</sup> Frequency analysis verified the stationary points are minima or saddle points. Single point energies were calculated at the M062X (UM062X)/6-311+G(d,p) level.<sup>15</sup> Solvent effect (solvent = THF) was calculated by using CPCM solvation model.<sup>16</sup> The radical species were calculated with the

#### Results and Discussion:

Effect of Catalyst Identity. We have previously reported that the combination of a bulky basic anion and a potassium cation is crucial for the C-H silvlation of 1-methylindole.<sup>10</sup> A detailed study of the catalytic competency of a variety of alkali, alkaline earth, and other metal derived bases has been conducted. As shown in Table 1, alkoxides and hydroxides of alkali metals with larger radius cations (i.e. radius  $\geq K^+$ ), such as K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup> could provide the silulation product in moderate to good yields (Table 1, entries 1-4, 6, 9 and 10). Among all the catalysts examined, KOt-Bu was proven to be the ideal catalyst, affording the highest overall yield. However, no product was detected when KOAc or KH was employed as the catalyst (entries 5 and 7). Perhaps surprisingly, potassium on graphite (KC<sub>8</sub>) afforded the desired product in good yield (entry 8). Alkali metal bases with small cations (e.g. LiOt-Bu and NaOt-Bu) demonstrated a complete lack of reactivity and no product was observed even after extended reaction time (entries 11 and 12). Alkoxides of alkali earth metals or aluminum were also investigated as catalysts and failed to afford any product (entries 13-16).

#### Table 1. Evaluation of Base Metal Catalyst<sup>4</sup>

Me 1	catalyst (20 mol%) Et <sub>3</sub> SiH (3 equiv) THF, 45 °C		)-SiEt <sub>3</sub> + ( Ne	SiEt <sub>3</sub> N Me
entry	catalyst	time (h)	conv (%) <sup>b</sup>	2:3 <sup>b</sup>
1	KOt-Bu	10	88	11:1
2	KOEt	10	55	9:1
3	KOMe	20	35	9:1
4	KOTMS	20	53	12:1
5	KOAc	60	0	-
6	KOH <sup>c,e</sup>	20	52	11:1
7	КН	36	0	-
8	KC <sub>8</sub> <sup>d</sup>	10	73	8:1
9	CsOH·H <sub>2</sub> O <sup>e</sup>	10	64	8:1
10	RbOH∙xH <sub>2</sub> O <sup>e</sup>	10	38	10:1
11	LiOt-Bu	36	0	-
12	NaOt-Bu	36	0	-
13	Mg(Ot-Bu) <sub>2</sub>	36	0	-
14	Ca(O <i>i</i> -Pr) <sub>2</sub>	36	0	-
15	Ba(O <i>t</i> -Bu) <sub>2</sub>	36	0	-
16	Al(Ot-Bu) <sub>3</sub>	36	0	-

<sup>*a*</sup>Reaction conditions: **1** (0.5 mmol), Et<sub>3</sub>SiH (1.5 mmol), and catalyst (0.1 mmol, 20 mol%) in THF (0.5 mL) at 45 °C. <sup>*b*</sup>Determined by GC analyses. <sup>*c*</sup>Dried KOH, see Supporting Information for details. <sup>*d*</sup> Potassium graphite. <sup>*e*</sup>The hydroxides may be converted to silanolates, and subsequently silicates, which serve as the active catalysts under the reaction conditions. <sup>17</sup>



**Figure 1.** A representative time course of the silylation of 1, monitored by in situ <sup>1</sup>H NMR. Reaction conditions: 1 (0.25 mmol),  $Et_3SiH$  (0.75 mmol), and KOt-Bu (0.05 mmol, 20 mol%) in THF-D<sub>8</sub> (0.25 mL) at 45 °C in a sealed NMR tube.

The kinetic behavior of the silylation reaction with KO*t*-Bu catalyst was studied using in situ <sup>1</sup>H NMR spectroscopy. As depicted in Figure 1, the silylation reaction was found to take place in three stages: an induction period (Figure 1, 0-3500 s), an active period with rapid formation of product (3500-4500 s).<sup>18</sup> and a final period with significantly reduced reaction rate (>4500 s). Our investigations were then expanded to include each active catalyst presented in Table 1 (Figure 2). The length of the induction period was found to depend on the nature of both metal and counter ion. For anions, the induction period increased in the order of KC<sub>8</sub> (shortest) < KOEt <

KOt-Bu < KOH (longest). An increase in induction period was observed with decreasing radius of cations, with CsOH (shortest) < RbOH < KOH (longest).<sup>19</sup> It is worth noting that the induction periods vary based on catalyst loading, solvents, and reaction temperature. Additives and moisture could also have a significant impact on the induction period, generally prolonging the duration of such period (see Supporting Information) Nevertheless, the induction period showed good reproducibility for identical reactions setup at different times. Although the induction period with KOt-Bu is not the shortest of all catalysts tested (Figure 2), this catalyst provides the highest post-initiation turnover frequency and product yield. Further discussion related to the cause of this induction period is explored in later spectroscopic and computational experiments.



**Figure 2**. A comparison of the kinetic profiles of multiple base catalysts. Data was acquired via GC analysis of aliquots of crude reaction mixture.

Regioselectivity and Reversibility. Although the major product of KOt-Bu-catalyzed silvlation is the incorporation of a triethylsilyl group at the C2-position of 1-methylindole (2), C3-silylation product 3 is also formed. Increase in reaction time and temperature tends to shift the major product from C2to C3-silvlation. As illustrated in Table 2, the reaction in THF at 45 °C affords an 11:1 ratio of C2-:C3-products (2:3) after 10 h, but after 15 days under the same conditions only C3product 3 is observed (i.e. 1:>20 C2-:C3-, entries 1 and 2). Similarly, when the reaction is conducted at 100 °C, C3silvlation predominates with a 1:9 ratio of products 2:3 (entry 3). These results are consistent with C2-silylation as the kinetic product, while C3-silvlation is the thermodynamic product. Finally, solvent selection was found to have a dramatic impact on the C2- and C3-selectivity. In the absence of solvent, the C2-product is exclusively observed at 45 °C and even at 100 °C C2-silylation is still the major pathway (entries 4 and 5).

 
 Table 2. Regioselectivity as a Function of Reaction Conditions<sup>a</sup>



<sup>*a*</sup>Reaction conditions: **1** (0.5 mmol), Et<sub>3</sub>SiH (1.5 mmol), and KO*t*-Bu (0.1 mmol, 20 mol%) in THF (0.5 mL, if indicated). <sup>*b*</sup>Determined by GC analyses. <sup>*c*</sup>After 15 days.

Several experiments were conducted to probe the reversibility of the silvlation reaction (Scheme 2). Treatment of C2silvlated compound 2 with KOt-Bu in THF does not result in conversion to the C3-silvlated 3 (Scheme 2a), showing that catalyst alone is insufficient for reversibility. However, treatment of 2 with both Et<sub>3</sub>SiH and KOt-Bu in THF led to the conversion of C2-silylated product 2 to C3-silylated product 3, along with approximately 5% of desilylated product 1 (Scheme 2b). Moreover, a crossover experiment involving compound 2, stoichiometric EtMe<sub>2</sub>SiH, and catalytic KOt-Bu provided a mixture of starting material 2, cross-silvlation product 4, and desilvlation product 1 (Scheme 2c). These results indicate that the conversion of C2- to C3-silvlation product likely does not occur through intramolecular silvl migration. In fact, the observation of cross-silvlation and desilylation can be better explained by a reversible silvlation reaction under these conditions.

#### Scheme 2. Reversibility of the Silylation



**Cross-dehydrogenative Formation of H**<sub>2</sub>. The process of H<sub>2</sub> formation was probed by in situ NMR using deuterium labeled substrates.<sup>20</sup> As shown in Scheme 3a, a trace amount of H<sub>2</sub> was detected during the induction period. This is followed by rapid H<sub>2</sub> evolution along with generation of the silylation product **2**. Similarly, H<sub>2</sub> is initially slowly generated in the case of the 2-deuterated indole [**D**]-**1**, Et<sub>3</sub>SiH, and KO*t*-Bu under identical conditions, followed by the cross-dehydrogenative formation of HD (1:1:1 triplet, J = 43 Hz) after the induction period (Scheme 3b). Further experimenta-

tion with indole **1** and Et<sub>3</sub>SiD was also conducted under the same conditions. Small amounts of HD were detected at the beginning of the NMR study and further HD gas formation was observed with the formation of product (Scheme 3c). These data demonstrate that H<sub>2</sub> is generated from the cross-dehydrogenative pathway; moreover, a very small percentage of H<sub>2</sub> may be produced from the consumption of trace amounts of water or the radical initiation process.<sup>21</sup> Furthermore, large-scale reactions were performed and gas evolution was monitored via eudiometry (Figure 3). The results from two identical runs produced H<sub>2</sub> in 69–71% yields, consistent with yields of silylation product **2** based on <sup>1</sup>H NMR and the plot of H<sub>2</sub> vs time correlates well to a plot of silylation product **2** vs time (Figure 3 vs Figure 1).

Scheme 3. Hydrogen Gas Formation through Dehydrogenative Coupling





**Figure 3**. Hydrogen gas evolution. <sup>*a*</sup>Reaction conditions: **1** (5 mmol), Et<sub>3</sub>SiH (15 mmol), and KOt-Bu (1 mmol, 20 mol%) in THF (5 mL) (conducted in duplicate). <sup>*b*</sup>Conversion, determined by <sup>1</sup>H NMR. <sup>*c*</sup>Yield based on collected H<sub>2</sub> volume.

To probe the nature of the induction period, we performed a series of experiments using TEMPO as a radical inhibitor. As shown in Figure 4, although the addition of 3 mol% of TEMPO at the beginning of the reaction essentially doubles the delay in product formation (i.e. TEMPO inhibition plus induction) in contrast to the reaction without TEMPO (Figure 4, Plot a), the conversions are comparable after 8 h (Plot b). Similar trends were observed when TEMPO was added after the initiation period (i.e., at 3.33 h with 54 % conversion, Plot c and d); the product formation ceased for a period and then continued. A larger TEMPO addition, 6 mol% compared to 3 mol%, prolongs the resultant induction period accordingly. Interestingly, the addition of TEMPO to the initiated reaction mixture leads to immediate bleaching (from dark purple to light yellow), with the dark purple color returning over the period of hours. Careful analysis of the reaction with stoichiometric TEMPO by GC-MS displayed a signal with m/z that matches the expected mass of the TEMPO-SiEt<sub>3</sub> adduct formed from the capture of the triethylsilyl radical by TEMPO.<sup>22</sup> These experiments suggest that by coupling with the silvl radical, TEMPO terminates the radical chain process and the reaction restarts only after the substoichiometric amount of TEMPO has been fully consumed.<sup>23</sup> Further studies found that the mixture of KOt-Bu and Et<sub>3</sub>SiH in THF at 45 °C is EPR active.

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**Figure 4**. Reaction profiles with TEMPO addition. <sup>*a*</sup>Reaction conditions: **1** (0.5 mmol), Et<sub>3</sub>SiH (1.5 mmol), and KOt-Bu (0.1 mmol, 20 mol%) in THF (0.5 mL) at 45 °C. <sup>*b*</sup>With 3 mol% of TEMPO added during the reaction at t = 3.33 h. <sup>*d*</sup>With 6 mol% of TEMPO added during the reaction at t = 3.33 h, product formation resumes at 11 h. Conversion was determined by monitoring aliquots via GC.

Based on these results, we postulate that a silvl radical species is involved in this catalytic C-H silvlation reaction. Our efforts were focused on the understanding of radical initiation under the standard reaction conditions. Although there are a considerable number of examples of silyl radical reactions known in the literature, the means of generating silvl radicals are rather limited.<sup>24</sup> In our case, the silvlation reaction results in comparable yields when kept in the dark as exposed to ambient light, which rules out the possibility of visible lightinduced radical formation. Recently, Itami, Lei and others reported that KOt-Bu could mediate the cross-coupling of aryl bromide and benzene without the use of transition-metal catalvsis.<sup>25</sup> Subsequent mechanistic studies revealed that in the presence of 1,10-phenanthroline a radical species was generated.<sup>26</sup> This process is accelerated dramatically with catalytic amounts of organic electron transfer reagents, such as Nmethylpyrrolidone, N-methlyglycine, and glycine, as demonstrated by Murphy.<sup>27</sup> However, in our silvlation reaction the addition of any of these compounds resulted in a significant decrease in reactivity (Table 3, entries 1-4).

#### Table 3. Effect of Additives<sup>a</sup>

1	N Me Me KOt-Bu (20 mol%) Et <sub>3</sub> SiH (3 equiv) THF, 45 °C Me additive (5 mol%)	2	Ne SiEt <sub>3</sub> +	SiEt <sub>3</sub>
entry	additive	time (h)	conversion (%) <sup>b</sup>	2:3 <sup>b</sup>
1	1,10-phenanthroline	8 24	52 79	>20:1 >20:1
2	N-methylpyrrolidone	8 24	0 50	>20:1
3	N-methylglycine	8 24	7 67	>20:1 19:1
4	glycine	8 24	10 54	>20:1 >20:1
5	none	8	93	>20:1

<sup>*a*</sup>Reaction conditions: **1** (0.5 mmol), Et<sub>3</sub>SiH (1.5 mmol), KO*t*-Bu (0.1 mmol, 20 mol%), and additive (5 mol%) in THF (0.5 mL) at 45 °C. <sup>*b*</sup>Determined by GC analyses.

A reported method for the generation of silane based radicals is the abstraction of a hydrogen atom from hydrosilanes using organic radicals (e.g. n-Bu<sub>3</sub>Sn•, t-BuO•).<sup>28</sup> To test whether this mechanism is involved in our reaction, we have undertaken a series of experiments with tert-butoxy radicals generated in situ. No product was obtained with 20 mol% of di-tertbutyl peroxide (DTBP) at 135 °C (Table 4, entry 2). Utilizing stoichiometric DTBP at 135 °C led to only small amounts of desired product along with very complicated mixtures as indicated by the GC-MS traces (entry 3). Attempts to carry out the silvlation reaction under milder conditions with 10 mol% of di-tert-butyl hyponitrite (TBHN) or a mixture of TBHN and NaOt-Bu failed to furnish product (entries 5 and 6). Addition of KOt-Bu with either DTBP or TBHN furnished the desired silvlation product, albeit with decreased yields (entries 4 and 7). Moreover, under our standard reaction conditions (i.e. entry 1), the desired product was always accompanied by t-BuOSiEt<sub>3</sub> (5). The reactions with DTBP or TBHN did not produce t-BuOSiEt<sub>3</sub>, which suggests that t-BuOSiEt<sub>3</sub> may not be formed through the reaction of *t*-BuO• with silane or silyl radical, but through a differing pathway (vide infra). Although the involvement of a t-butoxy radical cannot be excluded based on these experiments, there is little evidence to support the initiation of a triethylsilyl radical via hydrogen atom abstraction from Et<sub>3</sub>SiH by *t*-butoxy radical.

#### Table 4. Effect of *t*-Butoxy Radical Precursors<sup>a</sup>

ĺ	Ì	Conditions Et <sub>3</sub> SiH (3 equ N THF Me	s uiv)	N Me	−SiEt <sub>3</sub>		SiEt <sub>3</sub> + <i>t</i> -BuOSil	Et;
	1			2		3	<sup>Me</sup> 5	
	entry	conditions	mol%	temp (°C)	time (h)	conv (%) <sup>b</sup>	detection of 5	ь
	1	KO <i>t</i> -Bu	20	45	24	80	yes	
	2	DTBP	20	135	14	1	no	
	3	DTBP	100	135	14	10	no	
	4	DTBP + KOt-Bu	20, 20	45	14	42	yes	
	5	TBHN	10	45	10 24	0 0	no no	
	6	TBHN + NaOt-Bu	10, 20	45	10 24	0 0	no no	
	7	TBHN + KOt-Bu	10, 20	45	10 24	0 54	no yes	

<sup>*a*</sup>Reaction conditions: **1** (0.5 mmol), Et<sub>3</sub>SiH (1.5 mmol), KOt-Bu (0.1 mmol, 20 mol%, if used), and radical initiator in THF (0.5 mL) at 45 °C. <sup>*b*</sup>Determined by GC analyses.

Investigation of Coordinated Silane Species by FTIR Studies. It has been well documented that the addition of strong silicophilic Lewis bases (e.g. fluoride, alkoxide) can increase the reactivity of hydrosilanes in the hydrosilylation of C=O bonds.<sup>29</sup> It is believed that strongly reducing hypercoordinate silicate complexes are formed by coordination of nucleophilic anions during such processes, which typically weakens the Si– H bond and increases the hydridic character of this bond.<sup>30,31</sup> Studies by Corriu et al. revealed that the direct reaction of (RO)<sub>3</sub>SiH with the corresponding KOR (R = alkyl or aryl) in THF at room temperature affords the anionic, five-coordinate hydridosilicate [HSi(OR)<sub>4</sub>]K in good yield.<sup>32</sup> Such species are found to be very effective in the reduction of carbonyl compounds, can act as an electron donor towards the dehalogenation of organic halides, or can donate one electron to a metal complex.<sup>32</sup> Although the formation of similar pentacoordinate species from trialkylsilanes and potassium alkoxide is unknown, we envisioned that such a complex is a possible intermediate in our reaction and may play a crucial role in radical initiation.

Unfortunately, attempts to isolate and structurally characterize such species by NMR were unsuccessful.<sup>33</sup> However, by monitoring the silylation reaction using ReactIR, we found evidence for the existence of a new, possibly pentacoordinate silicate species. As shown in Figure 5, the in situ IR spectrum, a new peak is visible at 2056 cm<sup>-1</sup> adjacent to the Si–H stretching band in Et<sub>3</sub>SiH (2100 cm<sup>-1</sup>). This lower frequency peak would be consistent with an elongated, weakened Si–H axial bond in a five-coordinate silicate, as expected in such pentacoordinate complexes.<sup>34</sup> A similar shift was reported previously by Mitzel et al. for the *trans* Si–H stretching in *N*,*N*-dimethylaminopropylsilane [H<sub>3</sub>Si(CH<sub>2</sub>)<sub>3</sub>NMe<sub>2</sub>] from 2151 to 2107 cm<sup>-1</sup>.<sup>35</sup> In this case, the authors rationalize the observed redshift occurs by an N–Si interaction to form a hypercoordinate complex as confirmed by X-ray analysis.

A correlation between the newly formed IR peak (Figure 5) and the onset of product formation (i.e. the induction period ending) was observed. Once the new IR peak reached a steady state, the consumption of indole 1 and formation of silylation product 2 occurs immediately. Furthermore, the new IR peak was visible throughout the reaction. This is consistent with the observation that premixing  $Et_3SiH$  and KOt-Bu in THF for 2 h at 45 °C followed by the addition of indole 1 eliminates the induction period, suggesting that the formation of pentacoordinate silicate is responsible for the observed induction period.



**Figure 5**. ReactIR plot of KO*t*-Bu and Et<sub>3</sub>SiH in THF. New peak adjacent to Si–H signal of Et<sub>3</sub>SiH clearly visible.

Further studies were undertaken with mixtures of Et<sub>3</sub>SiH and metal alkoxides listed in Table 1 utilizing ATR-FTIR in a nitrogen filled glove box after removal of the volatiles (i.e. THF, Et<sub>3</sub>SiH). As shown in Figure 6, any alkoxide base which was a competent silvlation catalyst developed a lower energy Si-H feature (from 2016–2051 cm<sup>-1</sup>, see Supporting Information for details) potentially corresponding to the Si-H bond of a pentacoordinate species. In sharp contrast, no such species were detected with unreactive catalysts [i.e., LiOt-Bu, NaOt-Bu (Figure 6F), alkali earth metals, or aluminum alkoxides] demonstrating that this new pentacoordinate complex is likely crucial for the radical initiation. For the pentacoordinate silicates formed from KOt-Bu and KOEt, the decrease in the frequencies of Si-H absorption correlates to a shortening of induction period, which is consistent with a longer bond requiring less energy for the homolytic cleavage (Figure 6c and 6d).

Finally, although there is a large variation in the induction periods with KOH, RbOH and CsOH, no differentiating Si–H frequencies of the pentacoordinate silicates derived from those bases are observed. We propose that this indicates the hydroxides are converted to the silanolates, and subsequently silicates, which serve as the active catalysts.<sup>36</sup> It is possible that the weak cation-anion interaction of late alkali metal bases could accelerate the formation of pentacoordinate silicates and thus account for the differing rate of radical initiation.<sup>37</sup>



**Figure 6**. FTIR spectra of Si–H stretching region of select metal alkoxides with hydrosilane. Spectra were acquired under an atmosphere of  $N_2$  and are normalized and stacked for clarity, see Supporting Information for full spectra. (A) Neat Et<sub>3</sub>SiH. (B) Neat KOt-Bu. (C), (D), (E), and (F) Prepared as indicated with MOR = KOt-Bu, KOEt, CsOH, and NaOt-Bu, respectively.

We also performed computational studies to understand the nature of the coordinated species. Figure 7 shows the calculated energetics of complex formation and the predicted Si–H stretching frequencies. Formation of the pentacoordinate silicate with the hydrogen atom in the axial position requires 6.4 kcal/mol, and with hydrogen in the equatorial position requires 7.2 kcal/mol. In both cases the pentacoordinate species are stable minima, however the entropy penalty of 12 kcal/mol for a 1M standard state causes the corresponding free energies to be unfavorable. The predicted IR shifts from trimethylsilane to these two silicate isomers are 604 cm<sup>-1</sup> and 223 cm<sup>-1</sup>, respectively. Both of these IR shifts are larger than the experi-

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mentally observed IR shift of 73 cm<sup>-1</sup>. The formation of tetrameric KO-*t*Bu associated silane complex is 3.2 kcal/mol endergonic, and the IR shift from silane to the corresponding (KO*t*-Bu)<sub>4</sub> associated silane complex is only 24 cm<sup>-1</sup>. The M062x functional and various basis sets were tested to probe the energetics of formation of these coordinated silicon species, and provided similar results (see Figure S1 in Supporting Information).



**Figure 7.** Calculated energetics of formation of pentacoordinate silicates or tetrameric KO*t*-Bu associated silane complex and the calculated IR stretching frequency of the Si–H bond. The Si–H bond length is shown in Angstrom.

**Radical Initiation.** The bond dissociation energy for the Si–H bond of Et<sub>3</sub>SiH is 90.1 kcal/mol,<sup>38</sup> and the corresponding Si–H bond of silicate **6** would be weakened due to a change in electronics in the pentacoordinate structure.<sup>34</sup> Thus a possible pathway for the radical initiation from silicate **6** would be the homolytic scission of Si–H to form a hydrogen radical (likely associated with other substances, e.g., solvent, substrate or base) and a coordination anion-radical complex **7** (consistent with the resultant *t*-BuOSiEt<sub>3</sub> detected by GC after workup of the reaction), as shown in Figure 8a. This hydrogen radical could then abstract a hydrogen atom from Et<sub>3</sub>SiH to generate hydrogen gas as detected by in situ <sup>1</sup>H NMR and a triethylsilyl radical, which we believe is the active species.<sup>39</sup>

Unfortunately, our attempts to calculate such a radical initiation mechanism resulted in large activation energies (Figure 8b). While we still believe a Si–H bond homolysis of a pentacoordinate silicate may be relevant given our aforementioned observations, we turned to DFT calculations to explore alternative initiation mechanisms with more reasonable activation energies.



**Figure 8.** Possible radical initiation: (a) Homolytic Si–H bond fission of hypercoordinate silane **6** (b) DFT calculated energetics of the generation of silyl radical through homolytic Si–H bond fission of hypercoordinate silicate.<sup>40</sup> Gibbs free energies including THF solvation are shown in kcal/mol.

Catalyst Speciation and Alternate Initiation Pathway.

The extent of KOt-Bu aggregation in this reaction may be key to determining its catalytic behavior. The X-ray structure of anhydrous KOt-Bu crystallized from THF–*n*-pentane reveals a tetrameric [KOt-Bu]<sub>4</sub>, with a cubane-like structure.<sup>41</sup> This tetrameric structure is very stable, and persists in the solid and gas phase. Even in solution, mild Lewis basic solvents such as THF and diethyl ether do not break up the tetramer and the calculated energy of dissociation shows that these processes are very unfavorable (Figure 9). Indeed, even the dissociation of tetramer (KOt-Bu)<sub>4</sub> to trimer (KOt-Bu)<sub>3</sub> associated with K<sup>+</sup> plus *t*-BuO<sup>-</sup> anion requires 25.9 kcal/mol. Therefore, the tetramer [KOt-Bu]<sub>4</sub> is used as reference point in further calculations unless otherwise noted.



**Figure 9.** Dissociation of potassium *tert*-butoxide to tetramer, trimer, dimer, and monomer in THF. Gibbs free energies are shown in kcal/mol. Bond distances are shown in Angstrom.

Our computational results show that the radical initiation pathway through homolytic Si–H bond fission of hypercoordinate silane is relatively high energy (Figure 8). To address this unrealistic barrier, we have explored many different pathways of generation of the silyl radical (see Figure S2 in SI), the most reasonable of which is shown in Figure 10.



**Figure 10.** Free energy profile for generation of silyl radical involving traces of oxygen. Gibbs free energies, including THF solvation, are shown in kcal/mol.

We postulate that trace molecular oxygen might serve as a temporary electron acceptor to drive the formation of *tert*-butoxide radical.<sup>42</sup> Upon reaction of dioxygen with tetramer [KOt-Bu]<sub>4</sub>, *tert*-butoxyl radical and potassium peroxide radical **C-3** are generated. This process requires 23.4 kcal/mol, while the same process with tetramer [NaOt-Bu]<sub>4</sub> requires 30.7 kcal/mol, shown in dashed line in Figure 10. This is con-

sistent with the failure of NaOt-Bu as a catalyst for the silylation reaction. This effect can be understood since the smaller sodium ion size would lead to a larger distortion from the tetramer structure C-2 to sodium peroxide radical C-4, as compared to KOt-Bu. Only one Na-O bond is formed in this transformation, as compared to two K-O bonds formed when KOt-Bu is used. Once the *tert*-butoxyl radical is formed, it can react with hydrosilane Me<sub>3</sub>SiH to generate the silvl radical through transition state TS-1 (36.0 kcal/mol, Figure 10). This whole silvl radical generation process is endergonic by 8.6 kcal/mol, but only a trace amount of radicals are needed to initiate the proposed chain mechanism. This high-energy barrier for initiation would be consistent with the observed induction period. An alternative radical initiation mechanism is presented in the accompanying ionic and neutral mechanism paper (S10 of accompanying paper).<sup>11</sup> This mechanism closely resembles that in Figure 10, but produces a hydroxyl radical instead of a t-butoxyl radical and has a lower overall energy barrier of 24.7 kcal/mol.

**Radical Clock Experiments and Kinetic Isotopic Effects** (KIE). To better understand how the triethylsilyl radical reacts with indole, cyclopropane containing substrates were employed as radical probes in an attempt to trap radical intermediates. Several indole substrates bearing cyclopropyl or cyclopropylmethyl groups were synthesized and subjected to the silvlation reaction conditions. With 3-cyclopropyl-substituted indole 8, a mixture of ring-opened products were observed, including both silvl radical C2-adducts 9 and 10, and hydrogen radical C2-adduct 11 (Scheme 4). The low yields of these trapped products may be explained by the termination of radical chain process by ring-opening and subsequent radical recombinations (see Supporting Information for detail). In substrates comparison, with 4-cvclopropyl-, 3cyclopropylmethyl-, and 1-cyclopropylmethyl-substitution delivered the desired silvlation products 12, 13, and 14 respectively in moderate yields without the detection of ring-opening reactions. These experiments support our hypothesized pathway which involves a C3-centered radical intermediate 15 (Scheme 6).

Scheme 4. Silylation Using Cyclopropyl-Containing Substrates



We envisioned that a  $\beta$  C–H fission from a C3-centered radical species (15, Scheme 6) resulting in the formation of hydrogen gas is most likely the rate determining step of the proposed radical chain process. To gather more information about this hypothesis, C2-deuterium labeled indole ([D]-1) was used to study the kinetic isotopic effects (KIE) during the C2-silylation. First, two separate, parallel reactions of triethylsilane with indoles 1 and [D]-1 were performed to deter-

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mine the KIE value (Scheme 5a). As monitored by in situ <sup>1</sup>H NMR, a significant KIE was observed using the initial rates method for each reaction at the onset of product formation  $(k_{\rm H}/k_{\rm D} = 9.3-11.8$ , see Supporting Information for details). The intermolecular competition reaction of [D]-1 and 1-CD<sub>3</sub>indole [CD<sub>3</sub>]-1 in the same pot also showed a clear isotopic effect ( $k_{\rm H}/k_{\rm D} = 2.5-2.8$ , see Supporting Information for details) calculated from the product ratio of  $[CD_3]$ -2 and 2. These results provide evidence that the C-H bond breaking of indole is involved in the rate-determining step. We also investigated the reaction using Et<sub>3</sub>SiH and Et<sub>3</sub>SiD, finding that the reactions with deuterated silane demonstrated a significantly longer induction period and a decreased reaction rate was observed (see Supporting Information for detail). We rationalized these differences since the homolytic cleavage of a Si-D bond in a pentacoordinate species would require higher energy, prolonging the induction period. Furthermore the slower abstraction of deuterium compared to hydrogen limits the overall reaction rate in the radical chain mechanism.43

Scheme 5. Isotope Effect of Deuterium-Labeled Substrates (a) Parallel reactions:



**Proposed Cycle.** The addition of silvl radicals to double bonds has been shown to readily occur, driven by the formation of a stronger  $\sigma$ -bond at the expense of a weaker  $\pi$ bond.<sup>44</sup> Therefore, we propose that Et<sub>3</sub>Si• adds to indole at the C2 position to generate a stabilized benzylic radical 15 (Scheme 6a), as evidenced by radical clock experiments shown in Scheme 4. Fragmentation of the weaker C2-H bond  $\alpha$  to the radical center by a  $\beta$ -H scission restores aromaticity in the indole system and generates H<sub>2</sub>, providing an entropic driving force for the overall reaction.<sup>45,46</sup> The resultant silicate radical anion 7 can then react with an equivalent of triethylsilane thereby regenerating the Et<sub>3</sub>Si•, continuing the chain process. Alternatively, tetrameric (KOt-Bu)<sub>4</sub> could act as a hydrogen atom transfer catalyst, by abstracting a hydrogen atom from benzylic radical 15, producing the silylated product 2 as well as the base-hydrogen radical adduct 16 (Scheme 6c). This radical adduct then reacts with another equivalent of hydrosilane to produce H<sub>2</sub> and regenerates the silvl radical, thus completing the catalytic cycle.

The significant KIE displayed by [D]-1 suggests that the β-H scission is the rate-determining step after radical initiation.
 The nucleophilic β-silyl radical 15 is slow to abstract a hydrogen atom from Et<sub>3</sub>Si–H due to the similar polarities of the two

radicals (i.e. **15** vs Et<sub>3</sub>Si•) and a hydrosilylation product was never observed.<sup>47</sup> The reversibility of the silylation reaction can be explained by the addition of H• to silylation product **2**, providing radical **15**, followed by C–Si bond scission to from an equivalent of Et<sub>3</sub>Si• instead of H• resulting in the formation of starting material (Scheme 6b, reverse).

Scheme 6. Proposed Chain Process: Radical Pathway Mediated by Pentacoordinate Silicon (a) or Tetrameric KOt-Bu (c)



**Reaction with Deuterium-Labeled Silolane as a Stereochemical Probe.** To gain further evidence for the proposed reaction mechanism, we envisioned using a method to study the stereochemical course at silicon during the C–H silylation. Since the synthesis of silicon-stereogenic silanes (chiral silane) and determination of stereochemical outcomes in Si–C bondforming reactions (i.e., determination of the absolute configuration of the silylated product) is challenging, we decided to utilize a recently reported method by the Oestreich group.<sup>48</sup> In this method, a mixture of isomers of deuterium-labeled silolanes **17** are used as a stereochemical probe (Figure 11).<sup>49</sup> The *syn* and *anti* designations are the relative orientation of deuterium to the *n*-hexyl group.

<sup>2</sup>H NMR allows for tracking the relative ratio of *syn*-17 and *anti*-17 and therefore determine configurational changes at the silicon atom based on changes in the *syn:anti* ratio, thus removing the need to know the exact distribution of deuterium in this complex mixture of isomers.



**Figure 11**. Oestreich's deuterium-labeled silolane. <sup>*a*</sup>Syn:anti ratio determined by <sup>2</sup>H NMR <sup>*b*</sup>Deuteration at the  $\beta$ -position is omitted for clarity.

Oestreich's deuterium labeled silolane was prepared according to the reported procedure, resulting in a mixture of isomers with the *syn*-**17** /*anti*-**17** ratio of 74:26. Interestingly, KOt-Bucatalyzed silylation of **18** under our previously reported conditions proceeds with complete scrambling of the configuration at the silicon atom as indicated by the 1:1 ratio of products *syn*-**19** and *anti*-**19** (Figure 12).



**Figure 12.** Following the stereochemistry of C–H silylation: scrambling of the configuration at the silicon atom.

This observed scrambling is in contrast to Falck's protocol using an iridium(I) catalyst, where complete retention of the stereochemistry at the silicon atom is observed due to a traditional oxidative addition/reductive elimination pathway.<sup>49,50</sup> Previous studies by Sommer, Oestreich, and others have shown that a nucleophilic substitution at the silicon center can occur with either retention or inversion of stereochemistry, depending on the nature of the nucleophile and the leaving group on silicon.<sup>51</sup> Yet these reactions are highly stereospecific and do not result in scrambling of the deuterium-labeled silolane.<sup>49</sup>

We theorized that the observed scrambling may occur without participation of the heteroarene. A control experiment treating a mixture of **17** with KO*t*-Bu alone in THF resulted in complete scrambling of the deuterium labeled silolane (Figure 13).



Figure 13. Base-catalyzed scrambling of the configuration at silicon.

While consistent with a number of our proposed intermediates, we cannot distinguish if stereochemical scrambling occurs at the stage of pentacoordinate silicate anion **6**, radical anion **7** or a tricoordinate silyl radical (cf. Figure 8). Pentacoordinate silicon intermediates may undergo pseudorotational processes resulting in loss of stereochemical information at the silicon atom.<sup>52</sup> Although silyl radicals are pyramidal and can be configurationally stable under certain conditions,<sup>53</sup> racemization of a chiral silyl radical could take place due to the fast inversion of the pyramidal radical.<sup>54</sup> Nevertheless, all three of these intermediates are on pathway in our proposed mechanism (Scheme 6).

Furthermore, a handful of examples of direct nucleophile trapping by a hydrosilane are known in the literature, including KOt-Bu-catalyzed protection of alcohols.<sup>55</sup> In such case, an inversion at the silicon center was observed with chiral silanes, which is not in line with our observed scrambling.

**Computational Study of the C–H Silylation Mechanism and Regioselectivity.** We have performed a computational study that explores the mechanism and origin of regioselectivity of this C–H silylation reaction. We propose that the reaction can proceed by either of the two radical chain mechanisms, shown in Scheme 6. The free energies of both C2- and C3silylation of 1-methylindole are shown in Figure 14 and 15, for the cycles in Scheme 6a and 6c, respectively.

Starting with the trimethylsilyl radical, the radical addition is facile and reversible, generating intermediate C-5. The pentacoordinate silicate anion can then abstract the ipso hydrogen atom to generate  $H_2$  gas, silylation product, and silicate radical anion. The silicate radical anion then dissociates to form silyl radical and *tert*-butoxide anion. Hydrogen atom abstraction is the rate-determining step, with a calculated barrier of 21.0 kcal/mol for C2-silylation.



**Figure 14.** Free energy profile for C–H silylation of 1methylindole at C2 and C3 positions. Hydrogen atom is abstracted by pentacoordinate silicate anion. Gibbs free energies including THF solvation are shown in kcal/mol.

Since the radical addition to 1-methylindole is fast and reversible, the subsequent hydrogen abstraction determines the regioselectivity. The hydrogen abstraction at C2 position, via **TS-4**, is lower than the competing hydrogen abstraction at C3 position, via **TS-5**, by 6.7 kcal/mol.

Alternatively, the mechanism in which (KOt-Bu)<sub>4</sub> acts as a hydrogen atom transfer catalyst is shown in Figure 15. The hydrogen atom abstraction at the C2 position, via **TS-8**, requires 19.1 kcal/mol. This pathway is lower energy than **TS-4**, which requires 16.9 kcal/mol relative to *t*-BuO<sup>-</sup> or 42.8 kcal/mol relative to tetrameric (KOt-Bu)<sub>4</sub>. Therefore, computational models predict the hydrogen atom abstraction by tetrameric (KOt-Bu)<sub>4</sub> is favorable compared to direct hydrogen evolution by pentacoordinate silicate anion.

**TS-8** or **TS-4** are lower in energy than the competing hydrogen abstraction at the C3 position via **TS-9** or **TS-5** respectively, indicating the C2 silvation product is the kinetic product. This result is consistent with the experimentally observed C2

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silvlation regioselectivity at room temperature (cf. Table 2). At higher temperatures or longer reaction times, C3 silvlation becomes the major product. The calculations indicate that the C3 silvlation product is 2.3 kcal/mol lower energy than the C2 silvlation product. This is consistent with the experimental observation that C3 silvlation is the thermodynamic product.



**Figure 15.** Free energy profile for C–H silylation of 1 at C2 and C3 positions. Hydrogen atom is abstracted by tetrameric (KO*t*-Bu)<sub>4</sub>. Gibbs free energies, including THF solvation, are shown in kcal/mol.

We also studied the reactivities of various 5-membered heterocycles (1-methlypyrrole, furan and thiophene). The relative rates from competition experiments are: thiophene > furan > 1-methylpyrrole.<sup>10</sup> Our computational results show that 1methylpyrrole has the highest reaction barrier for C-H silylation at the C2 position in the 5-membered aromatic heterocycles (Scheme 16). While electrophilic aromatic substitution reactions favor C3 regioselectivity, silyl radical additions favor C2 regioselectivity. This is due to the nucleophilic character of silyl radicals. The silyl radical is strongly bent out of the plane and highly prefers a pyramidal structure. The singly occupied molecular orbital (SOMO) of silyl radical has a high percentage of 3s character,<sup>44</sup> and is more nucleophilic than electrophilic.



**Figure 16.** Calculated silyl radical addition barriers at C2 and C3 positions  $(\Delta \Delta G_1^{\ddagger} \text{ and } \Delta \Delta G_2^{\ddagger})$ , hydrogen abstraction barriers by

pentacoordinate silicate anion at C2 and C3 positions ( $\Delta\Delta G_3^{\ddagger}$  and  $\Delta\Delta G_4^{\ddagger}$ ), and hydrogen abstraction barriers by tetrameric (KOt-Bu)<sub>4</sub> at C2 and C3 positions ( $\Delta\Delta G_5^{\ddagger}$  and  $\Delta\Delta G_6^{\ddagger}$ ) for C–H silylation of substrates 1-methylindole, 1-methylpyrrole, furan and thiophene at C2 and C3 positions. Gibbs free energies including THF solvation are shown in kcal/mol.

As seen in Figure 16, the product determining step for each of the 5-membered aromatic heterocycles is lower for the C2pathway (blue,  $\Delta\Delta G_3^{\dagger}$  or  $\Delta\Delta G_5^{\dagger}$ ) as compared to C3-silylation (red,  $\Delta\Delta G_4^{\dagger}$  or  $\Delta\Delta G_6^{\dagger}$ ) which matches with the observed experimental regioselectivity (i.e. C2 > C3).<sup>10</sup> Comparing the higheBst energy step for each of the 5-membered heterocycles, highlights the expected inverse relationship of energy barrier to relative reaction rate (i.e. thiophene has the lowest energy barrier and demonstrates the highest rate in the competition reaction).

**Conclusions**. We have reported a systematic mechanistic investigation of the KOt-Bu-catalyzed silvlation of indoles. Specifically, a wide array of experimental tools, including NMR and ReactIR in situ studies, radical trap and radical clock experiments, and stereochemical analysis, etc., were applied to elucidate the pathway for the silvlation reaction. These experimental results were further complemented by computational analysis of the reaction. The results of these experiments are consistent with a radical chain mechanism, wherein the triethylsilyl radical is generated by the thermal cleavage of Si-H bond of the coordinated silicon species or by traces of oxygen which facilitate radical formation. The radical clock and KIE experiments support a cycle in which C-Si bond formation through silvl radical addition and subsequent  $\beta$ -H scission regenerates the silvl radical and continues the chain process. Furthermore, the opening of only the cyclopropane near the C3-position of indole provides direct evidence for an indole radical intermediate. The overall reaction is reversible, with an equilibrium shifted toward product by the cross-dehydrogenative H<sub>2</sub> evolution as an entropic driving force. The use of deuterium-labeled silolane as a stereochemical probe supports a number of on-pathway intermediates in our postulated radical mechanism. Further studies will explore the relevance of such novel silvl radical mechanisms to other types of silvlation or hydrosilvlation reactions.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Full experimental procedures, FTIR spectra, characterization data and Cartesian coordinates of computational structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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