Brønsted Acid-Promoted Formation of Stabilized Silylium Ions for Catalytic Friedel–Crafts C–H Silylation

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Supporting Information

ABSTRACT: A counterintuitive approach to electrophilic aromatic substitution with silicon electrophiles is disclosed. A strong Brønsted acid that would usually promote the reverse reaction, i.e., protodesilylation, was found to initiate the C–H silylation of electron-rich (hetero)arenes with hydrosilanes. Protonation of the hydrosilane followed by liberation of dihydrogen is key to success, fulfilling two purposes: to generate the stabilized silylium ion and to remove the proton released from the Wheland intermediate.

Electrophilic aromatic substitution (S$_2$Ar) is a valuable method for the C–H functionalization of arenes. By exploiting the electrophilicity of Me$_3$SiOTf, Frick and Simchen accomplished a highly regioselective C–H silylation of indoles and pyrroles three decades ago (Scheme 1A). To overcome competing protodesilylation, i.e., the reverse reaction, excess base had to be added to absorb the released protons. According to a straightforward procedure reported by Corey et al., such Alkyl$_3$SiH are accessible from the reaction between Alkyl$_3$SiH and TIOH (Scheme 1B). It is notable that the hydride and proton are removed from the reaction in the form of dihydrogen. Inspired by Corey’s work, we imagined that Brønsted acids with weakly coordinating counteranions [X$^{-}$] would usually promote the aromatic substitution with silicon electrophiles is disclosed. A counterintuitive approach to electrophilic aromatic substitution with silicon electrophiles is disclosed. A strong Brønsted acid that would usually promote the reverse reaction, i.e., protodesilylation, was found to initiate the C–H silylation of electron-rich (hetero)arenes with hydrosilanes. Protonation of the hydrosilane followed by liberation of dihydrogen is key to success, fulfilling two purposes: to generate the stabilized silylium ion and to remove the proton released from the Wheland intermediate.

**Scheme 1. Merger of Electrophilic C–H Silylation and Brønsted Acid-Promoted Formation of Silicon Cations**

A) Proton removal using excess amines (Simchen, 1984)

B) Protolysis of hydrosilanes for trialkylsilyl triflate synthesis (Corey, 1981)

C) Proton-catalyzed C–H silylation of electron-rich (het)arenes (this work)

Finally, the thus-generated silicon electrophiles could then participate in situ in the Friedel–Crafts C–H silylation of electron-rich (hetero)arenes (Scheme 1C). Owing to the proton removal as dihydrogen, we expected this catalytic system to suppress protodesilylation.

To test our hypothesis, we investigated the stoichiometric formation of the silicon electrophile using Bronsted acid. Due to facile cleavage of the phenyl group (= protodesilylation) rather than loss of the hydride, the reaction of Me$_3$PhSiH (1a) with TIOH leads to HMe$_3$SiOTf but not to Me$_3$PhSiOTf (eq 1). We thus envisioned using a substantially weaker but still strong acid to avoid dephenylation. Accordingly, Brookhart’s acid [H-(OEt$_2$)$_2$]$^+$$\cdot$[BArF$_2$]$^{-}$ was employed to generate the corresponding ether-stabilized silicon cation. D–H gas immediately evolved from the reaction after treatment of deuteron-labeled Me$_3$PhSiD (1a-d$_2$) with 2 [eq 2], indicating smooth proton transfer with gas evolution and coordination of Et$_2$O as driving forces. The formation of D–H was verified by a triplet at δ 4.44 ppm with a diagnostic coupling constant of $J$ = 42.6 Hz in the $^1$H NMR spectrum. No cleavage of the phenyl group was observed. Instead, we obtained a biphasic system that usually indicates clathrate formation of the solvent and the newly generated silicon cation. Identification of that cation by $^{29}$Si NMR spectroscopy was however hampered by dynamic exchange between reversibly bound Et$_2$O and the benzene solvent, apparent from significant line broadening in the $^1$H NMR spectrum. By replacing C$_6$D$_6$ with 1,2-Cl$_2$C$_6$D$_4$ as solvent, we were then able to detect [Me$_3$PhSi(OEt$_2$)]$^+$$\cdot$[BArF$_2$]$^{-}$ (3a) by $^1$H/$^{29}$Si HMQC measurements and clearly establish the formation of the desired silyloxonium ion (eq 3 and Figure 1).

The $^{29}$Si NMR spectrum showed a characteristic signal at δ 53.2 ppm. In turn, the combination of TIOH and Et$_2$O in 1:2 ratio did not evolve any gas on addition to Me$_2$PhSiH but led to slow dephenylation.

Our group recently introduced catalytic electrophilic C–H silylations of electron-rich arenes such as indoles and anilines based on cooperative Si–H bond activation and Lewis-acid catalysis, respectively. With the present work, we now aim at the development of a complementary process promoted by Bronsted acid (Table 1). Good yield and excellent regioselectivity were obtained using 1.0 mol % of Brookhart’s acid 2 in the reaction between 1-methylindole (4a) and hydroxilane 1a (4a $\rightarrow$ 5aa, entry 1). No reaction was seen in the absence of [H(OEt$_2$)$_2$]$^+$$\cdot$[BArF$_2$]$^{-}$ (2), and Na$^+$$\cdot$[BArF$_2$]$^{-}$ alone did not promote this transformation (entries 2 and 3). A gradual increase of the catalyst loading from 1.0 to 4.0 mol % led to diminished yields (entries 4 and 5). This unusual trend is
understood as the result of protodesilylation prevalent at higher proton concentrations. It also emphasizes that proton release and removal, i.e., dihydrogen release, must be well balanced to overcome this intrinsic problem. To our delight, the addition of norbornene (nbe) as a proton scavenger dramatically improved the yield to near-quantitative (entries 6−8). We note here that 1-methylindoline (6a) always formed as the byproduct, which is why these reactions were performed with the hydrosilane as the limiting reagent. Importantly, the silylated indole 5aa (major) and the indoline 6a (minor) did not form in equimolar ratio (for an explanation, see Scheme 4).

Next, we examined the hydrosilane scope (Table 2). With Me₂PhSiH (1a) the isolated yield was essentially quantitative, and the reaction proceeded smoothly with MePh₂SiH (1b) even at room temperature (entries 1 and 2). Probably due to steric hindrance, low conversion was observed for Ph₃SiH (1c) and, likewise, for Et₃SiH (1d) (entries 3 and 4). The protocol was not compatible with (EtO)₂MeSiH (1e) as a result of silylated oxonium ion formation (entry 5). Dihydrosilanes 1f−1h also served as efficient coupling partners (entries 6−8). Monosubstitution was observed exclusively with Ph₂SiH₂ (1f) at room temperature (entry 6), but using a 3-fold excess of the indole, MePhSiH₂ (1g) underwent 2-fold C−H silylation to afford or the bis(indol-3-yl)-substituted silane 7ag (entry 7). Selective monosubstitution was achieved with Et₂SiH₂ (1h) when using the indole as the limiting reagent (entry 8). Again, bis(indol-3-yl)-substituted silane 7ai formed from trihydrosilane PhSiH₃ (1i) (entry 9); the molecular structure of 7ai was confirmed by X-ray diffraction (see the Supporting Information for details).

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Given the potential for further derivatization, Ph₃SiH₂ (1f) was used to study the scope of the regioselective C−H silylation of heteroarenes (Scheme 2). The isolated yield for 1-methylindole was 96% (4a−5af), and slightly higher

Table 1. Optimization of the C3 Silylation of Indole

<table>
<thead>
<tr>
<th>entry</th>
<th>2 (mol %)</th>
<th>nbe (equiv)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>—</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>—</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>4.0</td>
<td>—</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>0.50</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>1.0</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>1.0</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 2. Screening of Hydrosilanes in the Indole Silylation

<table>
<thead>
<tr>
<th>entry</th>
<th>hydrosilane</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂PhSiH (1a)</td>
<td>80</td>
<td>96 (5aa)</td>
</tr>
<tr>
<td>2</td>
<td>MePh₂SiH (1b)</td>
<td>rt</td>
<td>93 (5ab)</td>
</tr>
<tr>
<td>3</td>
<td>Ph₂SiH (1c)</td>
<td>80</td>
<td>8’ (5ac)</td>
</tr>
<tr>
<td>4</td>
<td>Et₂SiH (1d)</td>
<td>80</td>
<td>7’ (5ad)</td>
</tr>
<tr>
<td>5</td>
<td>(EtO)₂MeSiH (1e)</td>
<td>80</td>
<td>0’ (5ae)</td>
</tr>
<tr>
<td>6</td>
<td>Ph₂SiH₂ (1f)</td>
<td>rt</td>
<td>96 (5af)</td>
</tr>
<tr>
<td>7</td>
<td>MePhSiH₂ (1g)</td>
<td>rt</td>
<td>73’ (7ag)</td>
</tr>
<tr>
<td>8</td>
<td>Et₂SiH₂ (1h)</td>
<td>rt</td>
<td>61’ (5ah)</td>
</tr>
<tr>
<td>9</td>
<td>PhSiH₃ (1i)</td>
<td>rt</td>
<td>74’ (7ai)</td>
</tr>
</tbody>
</table>

All reactions were performed on a 0.20 mmol scale (based on the hydrosilane) using double the amount of the indole (0.40 mmol, 2.0 equiv) as well as the indicated amount of catalyst 2 and norbornene in toluene (0.10 mL) at the indicated temperature for 18 h. Isolated yield after flash chromatography on silica gel. Determined by ‘H NMR spectroscopy using CH₂Br₂ as internal standard. *The [H(OEt₂)₃]⁺[BArF₄]⁻ (2) was used instead of [H(OEt₂)₂]⁺[BArF₄]⁻ (2).
temperature was required to obtain 93% yield for 1,2-dimethylindole (4b → 5b). Conversely, 1,3-dimethylindole did not react (4c not to 5cf), furnishing proof of an SnAr mechanism with the more nucleophilic indole C3 position blocked by a methyl group. 1,5-Dimethylindole underwent the C3-selective SnAr at room temperature in high yield (4d → 5df) as did the 5-halogenated 1-methylindoles (4e→4g → 5ef→5gf); no dehalogenation was detected. These reactions were highly regioselective (C3:C2 > 95:5) as was the C3-dehalogenation of this protocol, a gram-scale synthesis of a C3-silylated indole (Scheme 3).7d,e As aniline reduction was not achievable (Scheme 2), we returned to using the more conventional substrate-to-reagent ratio; a 2-fold excess of the hydrosilane was required to reach high yields. The addition of electron-rich arenes in the Brønsted acid-promoted silylation was not able to facilitate the C3-selective SEAr at room temperature in high yield (4k→5kf). Along with <10% of the corresponding C3-silylated indoline. EDG = electron-donating group.

On the basis of the literature precedence2,18,20 and our own observations, we propose the following dominating catalytic cycle4 for the Brønsted acid-promoted SnAr with an in situ-generated silicon electrophile (Scheme 4). Brookhart’s acid 2 is sufficiently strong to protonate the hydrosilane to form a pentacoordinate siliconium ion (1 → 10),3,16 That transient intermediate will release dihydrogen18 to afford the donor-stabilized silylium ion \([\text{R}_3\text{Si}(\text{donor})]^+\) \([\text{BARF}^-]^{-} (10 \rightarrow 3)\). Et2O introduced with \([\text{H(OEt)}_2]^+\) \([\text{BARF}^-]^{-} (2)\) is likely to act as the stabilizing donor (cf eq 3 and Figure 1) but the toluene solvent12 will assume this role18b if ether cleavage occurs in the course of the reaction. The cationic silicon electrophile 3 is then attacked by the nucleophilic indole (4a → 11a). The resulting Wheland complex is a strong Brønsted acid with the weakly coordinating \([\text{BARF}^-]^{-}\) counteranion, and direct protonation of another hydrosilane molecule closes the catalytic cycle (1 → 10) concomitant with formation of the C3-silylated indole (11a → 5a).20,21

Formation of the indole byproduct 6a is rationalized by competing silyl-iodin-ion catalysis. Proton transfer from intermediate 11a to the indole substrate 4a used in excess not only
liberates the C3-silylated indole 5a but also arrives at another Wheland complex 12a. This step was NMR spectroscopically corroborated by the reaction of 4a with an independently prepared sample of 11a. Iminium ion 12a then accepts a hydride from hydrosilane 1 to yield indoline 6a as well as donor-stabilized sililylium ion 3; quantitative deuterium incorporation at C2 of 6a was seen when using Me2PhSiD (1a-d). This reduction pathway will not occur with the aniline substrates (not shown).

To recoup, we disclosed here a counterintuitive C-H silation of electron-rich (hetero)arenes passing through an S EAr mechanism. The transformation is initiated by Brønsted acid-mediated generation of a highly electrophilic silicon cation from hydrosilanes. Protonation of the hydrosilane leads to loss of dihydrogen and release of the stabilized sililylium ions. The Wheland intermediate then largely maintains the catalytic cycle as the proton source. No protodesilylation is observed when the amount of acid is well balanced. This protocol is a practical and straightforward way for the installation of silicon groups on arenes, thereby complementing existing transition-metal and Lewis-acid catalysis.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04878.

Experimental procedures and data (PDF)

Crystallographic data (CIF)

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**

(1) Frick, U.; Simchen, G. Synthesis 1984, 929.
(14) We were aware of the fact that [H(OEt)_3]−[BAR]^−−(2) is not stable in CH_2Cl_2 forming BAR^- and BA^- (ref 10). The electron-deficient borane BAR^- could act as the Lewis acid catalyst (cf. refs 7d and 7e). While we verified the instability of 2 in toluene, we also found that 2 shows enhanced stability in the presence of the hydrosilane and is perfectly stable in the presence of the indole. The [BAR^-]−counterion is recovered after the reaction.
(16) The fate of nbe is likely its cationic polymerization, as we detected neither norbornane nor its silylated congener by GLC–MS analysis.
(20) Heinekey et al. also noted in their work catalytic hydrosilation consumption by the benzene-stabilized silicon cation in benzene solvent (cf. ref 18b).