Silyl Anions in Organic Synthesis

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"Normal" thoughts about silicon in organic synthesis

All of these utilize electrophilic character on the silicon
What about silyl anions? What can they do for YOU?

Silyl anions can be roughly categorized as synthetically useful and not-yet-synthetically useful

**Synthetically useful silyl anions:**
- \( \text{Me}_3\text{SiLi} \) HMPA complex
- \( \text{Ph}_3\text{SiLi} \)
- \( \text{Ph}_2\text{MeSiLi} \)

![Diagram of Me_3SiLi HMPA complex](image1)

![Diagram of Ph_3SiLi](image2)

![Diagram of Ph_2MeSiLi](image3)

**Other silyl anions:**
- \( \text{RMe}_2\text{Si} \)CuCNLi
- \( \text{RMe}_2\text{Si} \)CuCNLi

| R = Ph, \( \alpha \)-anisyl, furyl, Me |

Compounds like these are interesting in terms of their physical properties, but have not found much use yet in organic synthesis due to difficulties in preparation.
Generation of early silyl anions

\[
\text{Ph-Si-H}_2\text{N}_{\text{Me}} \xrightarrow{\text{Li}} \text{Ph-Si-Li} \quad \text{Ph}_3\text{Si-SnMe}_3 \xrightarrow{\text{Na}} \text{Ph-Si-Na} + \text{Me}_3\text{SnNa}
\]


\[
\text{Et-Si-Ge-Ph}_{\text{Et}} \xrightarrow{\text{Li}} \text{Et-Si-Li} + \text{Li-Ge-Ph}_{\text{Et}}\text{NH}_2
\]


\[
\text{Ph-Si-Ph}_{\text{Me}} \xrightarrow{\text{Na/K, Ether}} \text{Ph-Si-Ph}_{\text{Me}}\Theta + \text{Ph-Si-K}_{\Theta}
\]


\[
\text{Ph-Si-Si-Ph}_{\text{Ph}} \xrightarrow{\text{Na/K, Ether}} 2 \text{Ph-Si-K}_{\Theta}
\]

**Improvements on early silyl anions by Gilman**

Na/K is not an ideal reagent in any reaction, if it can be avoided, and lithium in THF also cleaves disilanes

\[
\begin{align*}
\text{Ph}_2\text{Si} & \text{Si-Ph}_2 \xrightarrow{\text{Li, THF}} 2 \text{Ph}_2\text{Si-Li} \\
\text{Me}_2\text{Si} & \text{Si-Me}_2 \xrightarrow{\text{Li, THF}} 2 \text{Me}_2\text{Si-Li} \\
\text{Me}_2\text{Si} & \text{Si-Ph}_2 \xrightarrow{\text{Li, THF}} 2 \text{Me}_2\text{Si-Li}
\end{align*}
\]

Proof of silyllithium formation used by Gilman and coworkers

\[
\begin{align*}
\text{Ph}_2\text{Si-Li} & + \text{Me}_2\text{Si-Cl} \xrightarrow{} \text{Ph}_2\text{Si-Si-Ph}_2
\end{align*}
\]

What about TMSLi?

Hexamethyldisilane will not cleave in the presence of an alkali metal, so other procedures must be employed.

\[
\text{Me}_3\text{SiBr} + \text{Na/Hg} \rightarrow \text{Li} \rightarrow 2 \text{MeSi-Li} + \text{Hg}
\]

Drawback: Need to use mercury


\[
\text{Me-Si-Si-Me} \rightarrow \text{MeLi} \rightarrow 2 \text{Me-Si-Li} + \text{Me-Si-Me}
\]

Drawback: Need to use HMPA

Still, W. C., *JOC*, **1976**, *41*, 3063
Great, so I can make and fragment disilanes. Is this really useful?

Yes! These TMSLi can be added to organic compounds much like organocuprate reagents

Still, W. C., *JOC*, 1976, 41, 3063
**Utility of aryl groups on silicon for synthesis**

**Brook rearrangement**

Aryl groups on silicon speed up this process greatly
Useful for umpolung processes

Aryl groups can be removed from silicon under acidic conditions
Phenyldimethylsilyl group can be thought of as a masked hydroxyl group

**Tamao-Fleming oxidation**

\[
\text{SiMe}_2X + \text{KF, HOOH or MCPBA if } X = \text{F} \rightarrow \text{R}_1\text{R}_2\text{OH}
\]

\(X = \text{F, Cl, Br, OR}\)

100% retention
**NMR studies of silyl anion structure**

*How is charge delocalized in phenylated silyl anions?*

For corresponding carbanions, there is a substantial resonance stabilization as can be seen in $^{13}$C NMR.

For the silyl anions, this charge delocalization is reduced by a factor of **four to ten.**

Instead, one sees π-polarization of the phenyl rings, which results in a stabilization of the negative charge on silicon. Resonance stabilization would put partial negative charge on the *ortho* carbon and partial positive charge on the *meta* carbon on the phenyl rings. The opposite is observed by $^{13}$C NMR.

**Silyl cuprates as improved silyl anions (Fleming's reagent)**

\[ \text{PhMe}_2\text{Si-Cl} \overset{\text{Li}}{\underset{\text{THF}}{\rightarrow}} \text{PhMe}_2\text{Si-Li} \overset{0.5 \text{ eq. CuX}}{\underset{X=\text{I, CN}}{\rightarrow}} (\text{PhMe}_2\text{Si})_2\text{CuXLi}_2 \]

This reagent is much more reactive for conjugate additions than the silylolithium

\[ (\text{PhMe}_2\text{Si})_2\text{CuLi}_2 \text{ THF, } -23^\circ\text{C, 4 hr} \rightarrow \text{68\%} \]

**In addition, it is much more tolerant of various functionalities**

Phenyldimethylsilyl groups as $\alpha,\beta$-unsaturation of ketone protecting groups

*Application to the syntheses of carvone and jasmone*

Limitations of the Tamao-Fleming Oxidation

Desilylation of the phenyl group can be problematic

The T-F oxidation requires a heteroatom on the silicon to proceed. The easiest way to do this is either to protonate or brominate the phenyl group off the silicon.

Standard conditions (and their problems):

1. AlCl₃, HCl (g). This is very incompatible with acid-sensitive functionality and inconvenient.

2. HF gas. Also incompatible with acid-sensitive functionality, and using HF gas is very dangerous!

3. HBF₄ diethyl ether complex. Also incompatible with acid-sensitive functionality.

Proposed (but unsuccessful) improvements in silyl anions

Include electron-donating functional groups on the phenyl ring?

Methyl phenyl ethers are reduced to phenoxides under these conditions, but the reasons why lithium will not reduce these disilanes is unclear. What about other electron donating groups?

Improvements by Corey

Other anions made by this procedure:

These anions are unstable at temperatures above -30 °C, but the cuprates are stable at 0 °C, meaning they can be used in synthesis effectively.

Reactions with Corey's improved silanes

![Chemical reactions diagram]

Lee, T. W., Corey, E. J. *Org. Lett.* **2001**, *3*, 3337
Tamao-Fleming oxidation using Corey's silanes

1.2 eq NBS
THF, 23 °C
2.5h

2.5 eq TFA
THF, 23 °C
3.5h

KF, KHCO₃,
H₂O₂, THF-MeOH
23 °C, 18h, 72% overall

KF, KHCO₃,
H₂O₂, THF-MeOH
23 °C, 12h, 80% overall

Application of Corey's silanes to total synthesis

R = E,E-farnesyl

1. 3 N LiOH
2. TFA, CH₂Cl₂; KF, KHCO₃
3. cat. CSA, THF

Conclusions

- Silyl anions can be effectively used in the synthesis of complex natural products, as seen by the work of Fleming and Corey.

- The utility of the phenyldimethylsilyl group as a masked hydroxyl group has only begun to be explored with the advent of better silyl groups.

- Silyl anions can be synthesized easily in the lab, but the need for HMPA in the synthesis of more interesting anions limits the use of this methodology on the industrial scale.