

## Aziridine Lithiation Using Lewis Acid Activation

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Introduction of lithium  $\alpha$  to nitrogen is an important strategy in the synthesis of  $\alpha$ -substituted amines.<sup>1</sup> Attempts to use this approach for the functionalization of aziridines are also reported, but successful applications are rare.<sup>2–4</sup> An early report by Quast *et al.* describes the lithiation of 1-*tert*-butyl-2-methyleneaziridine and anion trapping by electrophiles at temperatures below  $-50$  °C to avoid decomposition.<sup>2</sup> Lithiation of *N*-*tert*-butoxycarbonylaziridine is also reported, but in this case the anion decomposes more rapidly,<sup>3c</sup> and trapping with  $\text{Me}_3\text{SiCl}$  requires an *in situ* technique. We now report a method for efficient and direct lithiation of simple aziridines. The procedure is based on Kessar's precedent for nitrogen activation by complexation with a Lewis acid,<sup>5,6</sup> and on the expectation that aziridine ring C–H bonds would be more acidic than hydrogens at exocyclic carbon due to increased *s* character in the former. The new examples reveal an unusual directing effect where the stereochemistry of the C–Li bond is influenced by the B–N configuration in the Lewis acid–Lewis base complex.

Commercially available *N*-(2-hydroxyethyl)aziridine **1** was protected as the TBS ether **2** and was then treated with  $\text{BH}_3$ –THF solution.<sup>6b,c</sup> The resulting borane complex **3** was easily isolated using standard chromatographic methods (82% overall), and the structure was clear from literature analogy and the presence of strong IR absorptions at  $2274\text{ cm}^{-1}$  (B–H).<sup>7</sup> Treatment of **3** with *s*-BuLi in THF at  $-78$  °C followed by quenching with electrophiles proceeded smoothly to give the trapping products **6a–d** (each as one dominant isomer). Careful <sup>1</sup>H NMR analysis of **6b** ( $\text{CH}_3\text{I}$  as the electrophile) revealed traces of a minor isomer **7**. These findings suggest that the dominant lithiated intermediate is diastereomer **4** (lithium syn

to boron) and not **5**. To prove the stereochemistry of **6b**, the TBS group was removed ( $\text{Bu}_4\text{NF/THF}$ ), the resulting alcohol **8** was converted to the *p*-nitrobenzoate **9**, and the structure was established by X-ray crystallography.

Complexation of 1,2-dimethylaziridine **10**<sup>8</sup> was investigated to evaluate B–N configurational stability. Treatment with  $\text{BH}_3$ /THF at  $-78$  °C gave a 10:1 ratio of diastereomers **11** and **12** (66% isolated; stereochemistry assigned assuming complexation of the favored *trans*-1,2-dimethyl invertomer).<sup>9</sup> In a second series of experiments, the borane complex **14** (from 2-methylaziridine **13** +  $\text{BH}_3$ ) was converted into the anion **15** using NaH,<sup>10</sup> and N-methylation with  $\text{CH}_3\text{I}$  afforded isomers **11** and **12** in an inverted ratio, **11:12** = 1:10 (55% isolated). No interconversion of diastereomers was detected at room temperature.

Next, we sought to establish whether the C–Li configuration of 2-lithioaziridine complexes such as **4** is subject to equilibration (thermodynamic control), or whether it reflects a kinetic preference for lithiation *syn* to the  $\text{BH}_3$  group. This required access to both diastereomers of the C-lithiated aziridine, following an approach based partly on the same logic used to probe nitrogen configuration. The stannylated complex **6d** was deprotected ( $\text{Bu}_4\text{NF}$ ) and converted into the iodide **17** (71% overall) via the *p*-nitrobenzenesulfonate **16** and Finkelstein displacement ( $\text{NaI/acetone}$ ). Reductive cleavage of **17** using *tert*-butyllithium (2.2 equiv,  $-78$  °C) afforded the N-deprotected aziridine complex **18** (92%), and N-methylation ( $\text{NaH/CH}_3\text{I}$ ) gave a 77:23 mixture of diastereomers **19** and **20**. Alternatively, lithiation of N-methylaziridine borane (**21**)<sup>11</sup> with *sec*-butyllithium followed by  $\text{Bu}_3\text{SnCl}$  afforded a 98:2 ratio of **19:20** (88%; stereochemistry assigned by analogy with **6d**). Treatment of the 77:23 mixture of **19** and **20** with *n*-butyllithium at  $-78$  °C resulted in complete conversion to **22** + **23**.<sup>12</sup> Subsequent quenching with  $\text{Bu}_3\text{SnCl}$  gave **19** and **20** in a ratio of 82:18, 90%, together with **21** (10%).<sup>13</sup> The product ratio in the latter experiment does not resemble the 98:2 ratio of diastereomers **19** and **20** obtained via lithiation of **21** and indicates that the intermediate 2-lithioaziridines **22** and **23** are configurationally stable. The evidence supports kinetically controlled lithiation of **21** *syn* to the  $\text{BH}_3$  group, followed by  $\text{Bu}_3\text{SnCl}$  trapping with retention of configuration. According to our interpretation, tin–lithium exchange also occurs with retention, as generally assumed in the literature.<sup>1b–h,j</sup>

Steric effects probably contribute to predominant lithiation *syn* to the  $\text{BH}_3$  subunit in **3**. The N–B bond is longer (ca. 1.61 pm) than the corresponding exocyclic N–C bond (ca. 1.48 pm), judging from the X-ray structure of **9**. This would mean that the  $\text{BH}_3$  unit in **3** is more tolerant of 1,2-eclipsing interactions with  $\text{LiC}_4\text{H}_9$  than is the exocyclic N-methylene substituent. However, nonsteric factors also appear to play a role. Thus, treatment of **6b** with *sec*-butyllithium followed by  $\text{D}_2\text{O}$  resulted in the formation **24** ( $\text{R} = \text{CH}_3$ ) as the dominant diastereomer,<sup>14a</sup> even though the effect of  $\text{C}_2$ – $\text{CH}_3$  should work against lithiation *syn* to  $\text{BH}_3$ . On the other hand, a similar lithiation;  $\text{D}_2\text{O}$  quenching sequence starting from **6c** produced

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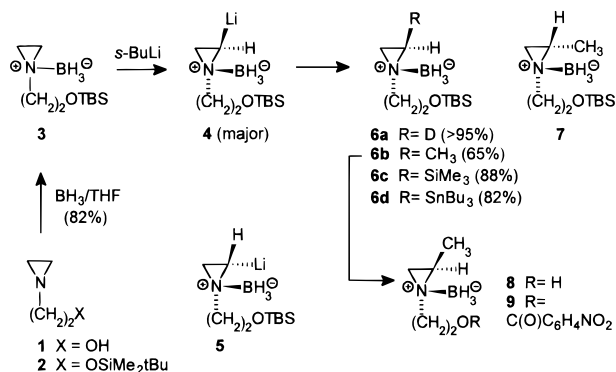
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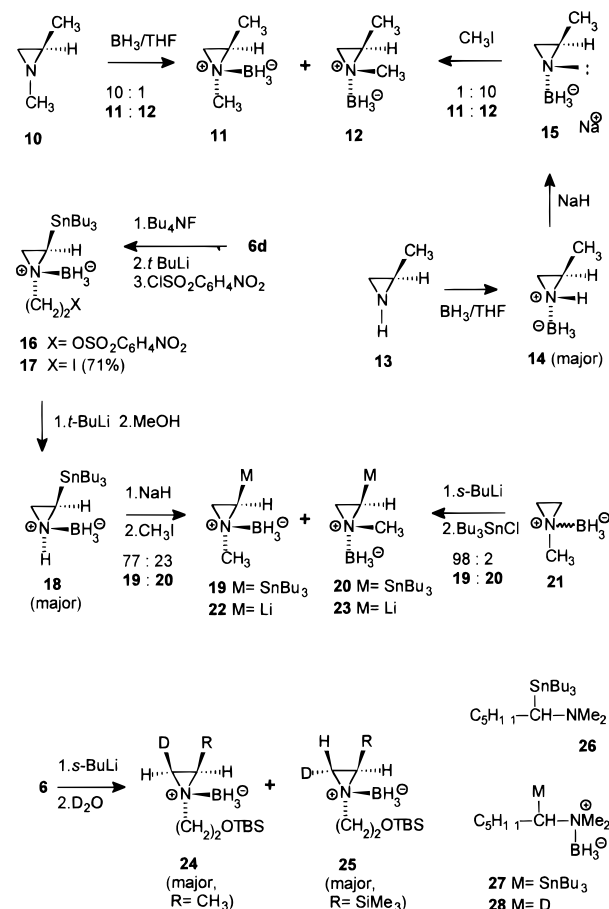
(12) Complete Sn–Li exchange was established by conversion to **21** by  $\text{H}_2\text{O}$  quenching.

(13) The small change in product ratio compared to the starting ratio of **19:20** is consistent with a small kinetic advantage for conversion of **23** into **21** by adventitious protons.

## Scheme 1



## Scheme 2



**25.**<sup>14b</sup> Evidently, the *syn*-directing effect of N–BH<sub>3</sub> is dominant over the steric effect of an aziridine C<sub>2</sub>–CH<sub>3</sub> group but not of a C<sub>2</sub>–Si(CH<sub>3</sub>)<sub>3</sub> substituent.

We suggest that an electrostatic effect is responsible for the nonsteric component of *syn*-direction in the lithiation step.

Ground state attractive interactions between Li(+) and hydri-doborate H–B bonds are well-known from solution or solid state studies,<sup>15a</sup> and a similar transition state effect may operate between the electron-rich H–B bonds of **3** and lithium as the positive end of a Li–C dipole in LiC<sub>4</sub>H<sub>9</sub>. This proximity effect<sup>15b</sup> would be expected to contribute to *syn*-lithiation as observed experimentally for **2**, **21**, and **6b**. However, the bulky C<sub>2</sub>–SiMe<sub>3</sub> substituent in **6c** is sufficient to overcome the *syn*-effect, and lithiation produces **25** (R = SiMe<sub>3</sub>) as the major isomer.

The reactions of **19** and **20** with butyllithium are the first examples of tin–lithium exchange in amine–borane complexes. In view of the good yields and convenience, we have briefly studied the corresponding process with **27**. Tin–lithium exchange was not observed with the parent  $\alpha$ -stannylamine **26** at –78 °C in the absence of Lewis acid activation.<sup>16</sup> However, the borane complex **27** reacted with 3 equiv of *n*-butyllithium at –42 °C, and D<sub>2</sub>O quench gave **28** (>98% conversion; > 90% D<sub>1</sub>). A similar experiment at –78 °C was 63% complete after 3 h.

In summary, direct access to lithiated aziridine borane complexes is demonstrated. Increased *s*-character in the aziridine ring C–H bonds promotes facile lithiation at C<sub>2</sub> and trapping with conventional electrophiles is feasible. The hybridization effect is probably also responsible for the faster tin–lithium exchange in **19** and **20** compared to **27**. The borane activation method should be of practical value for the synthesis of substituted aziridines because aziridine boranes are easily made and are efficiently cleaved by refluxing ethanol (>95% yield from **6b–d**).

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**Supporting Information Available:** Representative procedures and characterization of new compounds and X-ray data tables for **9** (13 pages). See any current masthead page for ordering and Internet access instructions.

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(14) (a) Selectivity, 90–95% by NMR integration, based on disappearance of that C<sub>3</sub>–H signal which has the smaller vicinal coupling constant (6.3 Hz) to C<sub>2</sub>–H. (b) The C<sub>3</sub>–H signal which has the larger vicinal coupling constant (9.3 Hz) to C<sub>2</sub>–H is exchanged selectively. (c) *Syn/anti* assay by *J* values: Booth, H. In *Progress In Nuclear Magnetic Resonance Spectroscopy*; Emsley, J. W., Feeney, J., Sutcliffe, L. H., Eds.; Pergamon Press: Oxford, 1969; Vol. 5, p 186.

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