Enantioselective Reactions

Synthesis and Stereoselective Lithiation of Enantiopure 2-(1-Aminoalkyl)aziridine–Borane Complexes**

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Ammonium salts are an important class of organic compounds with useful synthetic applications.[1] A limited number of syntheses of enantiopure ammonium salts, in which the nitrogen atom is tetrasubstituted by four different groups, have been reported.[2] In addition, formation of amine–borane complexes is a useful strategy to efficiently carry out regioselective metalations, and other functionalizations, of amines when direct metalation is not possible.[3] Amine–borane complexes have also been used to perform reductive amination of aldehydes[4] and ketones,[4a,5] to reduce ketones and imines,[6] and in hydroboration of alkenes.[5]

We have previously described the synthesis of enantiopure 2-(1-aminoalkyl)aziridines **1** (Scheme 1).[7] Subsequently, we reported their ring opening by several nucleophiles[8] with total regio- and stereoselectivity. Now, we

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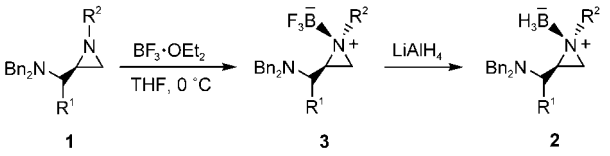
describe the first method for the selective formation of the aziridine–borane complex **2** by treatment of (2*S*,1′*S*)-2-(1′-aminoalkyl)aziridines **1** with $BF_3{\cdot}Et_2O$ and subsequent reduction with $LiAlH_4$. Direct reaction of **1** with borane afforded the same (1*R*,2*S*,1′*S*)-2-(1′-dibenzylaminoalkyl)aziridine(N^1–B) boranes **2**. In both syntheses, only one diastereoisomer of complexes **2** was obtained in an enantiopure form. Subsequent lithiation, deuteration, or silylation and decomplexation of the obtained aziridinioborane complexes **2** afforded 3-deuterated or 3-silylated aminoaziridines **7b** or **8b** (Scheme 4) with total regio- and very high diastereoselectivity.

Treatment of a solution of aminoaziridines **1** in THF with one equivalent of $BF_3{\cdot}Et_2O$ at 0 °C for 5 minutes, followed by the addition of two equivalents of $LiAlH_4$, at the same temperature, for 30 minutes afforded, after hydrolysis, enantiopure (1*R*,2*S*,1′*S*)-2-(1′-dibenzylaminoalkyl)aziridine(N^1–B) boranes **2** as the sole product in high yield (Scheme 1 and Table 1). To the best of our knowledge, this method of obtaining amine–borane complexes is novel.



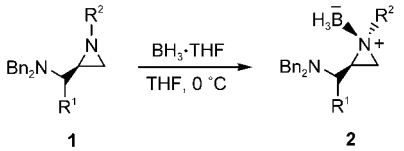
Scheme 1. Synthesis of aziridine–borane complexes **2** with $BF_3{\cdot}OEt_2$ and $LiAlH_4$. Bn = benzyl.

Table 1: Synthesis of aminoalkylaziridine–borane complexes **2**.

Entry	2	Method[a]	R^1	R^2	Yield [%][b]
1	**2a**	B	Me	propyl	79
2	**2b**	A	Me	allyl	76
3	**2b**	B	Me	allyl	80
4	**2c**	A	*i*Bu	allyl	75
5	**2d**	A	*i*Bu	Bn	81
6	**2d**	B	*i*Bu	Bn	77
7	**2e**	B	Bn	cyclohexyl	77
8	**2f**	A	Bn	Bn	83
9	**2f**	B	Bn	Bn	82

[a] Method A: $BF_3{\cdot}OEt_2$ and $LiAlH_4$. Method B: $BH_3{\cdot}THF$. [b] Yield of isolated product after column chromatography based on the starting aminoaziridine **1**.

When the complexation of aminoaziridines **1** was performed with a commercial $BH_3{\cdot}THF$ solution, the same borane complexes **2** were also isolated in high yield (Scheme 2 and Table 1).[3a] A similar yield and purity of complexes **2** (Table 1) was obtained with both methodologies and, consequently, the cheaper $BF_3{\cdot}Et_2O/LiAlH_4$ methodology is a valuable alternative to the use of $BH_3{\cdot}THF$ solution.

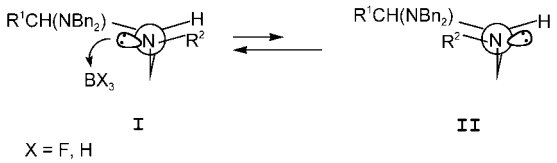


Scheme 2. Synthesis of aziridine–borane complexes **2** with $BH_3{\cdot}THF$.

Complexes **2** are surprisingly stable; they can be purified by column chromatography and stored for several weeks at room temperature. It is noteworthy that only one diastereoisomer of **2** was obtained, in an enantiopure form, with no apparent presence of any other diastereoisomers by NMR analysis of the crude reaction mixture (^1H NMR: 300 MHz, ^{13}C NMR: 75 MHz). It is clear that the level of diastereoisomeric purity of the borane–aziridine complexes **2** (> 97 %) was not affected by the size of R^1 and R^2 in the starting aminoaziridine (see Table 1). In contrast, previous work involving the reaction of tertiary amines with borane gave a mixture of diastereoisomers.[3d,9]

The orientations of the benzyl and the borane groups in **2d** were determined by a NOESY analysis. Positive NOESY interactions were observed between the methylene hydrogen atoms of the benzyl group and C2-H as well as with the C3-H, which is *cis* with respect to the aziridinium ring, thus confirming the *trans* relationship between the benzyl group and the 1-dibenzylaminoalkyl group. This configurational assignment of **2d**, as depicted in Schemes 1 and 2, was subsequently confirmed by single-crystal X-ray diffraction analysis.[10] The configuration of the other complexes **2** was assigned by analogy.

The described transformation and the observed stereochemistry of products **2** may be explained by assuming that coordination of either the Lewis acid ($BF_3{\cdot}Et_2O$) or BH_3 to the aziridine nitrogen atom is favored over coordination to the dibenzylamine nitrogen atom as a result of steric hindrance. The isolation of complexes **2** as a single diastereoisomer can be explained by taking into account the difference in stability between the two diastereoisomers **I** and **II** (Scheme 3): **I** predominates over **II** as a consequence of the steric hindrance involved, thus the reaction of **I** with $BF_3{\cdot}Et_2O$ or BH_3 is favored.[11]

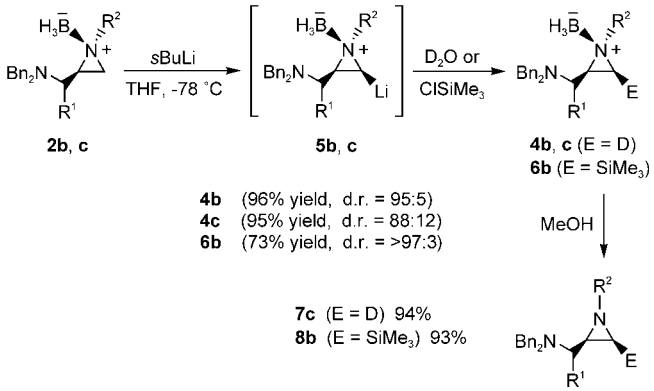


Scheme 3. Configurational equilibrium.

Aziridines are important building-blocks in organic synthesis,[12] and taking into account the usefulness of isotopically labeled compounds to establish the mechanism of organic reactions or the biosynthesis of many natural products,[13] the development of an effective general method for the stereoselective deuteration of aziridine would be of significant value. In addition, to the best of our knowledge only two papers describing the enantioselective lithiation of aziridines have been published previously.[3a,14] For this reason, preliminary attempts to deuterate complexes **2** were performed. Thus, lithiation experiments of complexes **2b,c** were carried out with *sec*-BuLi (45 min in THF at −78 °C), followed by deuterolysis with D_2O,[3a] to afford the corresponding 3-

deuterioaziridine-borane complexes **4b,c** with total regioselectivity (^{1}H and ^{13}C NMR analysis), and with complete incorporation of deuterium (> 95 %, ^{1}H NMR). The lithiated aziridine **5b** was subsequently treated with $ClSiMe_3$.

The diastereoselectivity of both the deuteration and silylation reactions was either very high or total. Thus, 3-deuterioaziridine or 3-(trimethylsilyl)aziridine-borane complexes **4b**,**c** or **6b** were isolated with high diastereoselectivity from **2b**,**c** (d.r. = 95:5, 88:12, and > 97:3 % respectively),[15] as determined from the ^{1}H NMR spectrum of the crude reaction products. Assuming retention of configuration from the C-Li intermediate through the C-D or C-$SiMe_3$ bond-forming step to obtain **4** or **6**, initial lithiation occurs *syn* to the boron atom, giving the enantiopure *trans* aziridinium **5** (Scheme 4). This



Scheme 4. Synthesis of deuterated or silylated aminoaziridines **7c** or **8b**.

assignment is based on the coupling constants between C2-H and C3-H of **4b**,**c** and **6b** (8.5, 8.2 and 9.6 Hz, respectively), in agreement with a *cis* relative configuration. This *syn*-directing effect of N-BH_3 has been reported for the lithiation of other aziridine-borane complexes.[3a]

The 3-deuterioaziridine and 3-(trimethylsilyl)aziridine-borane complexes **4c** and **6b**, respectively, were easily decomplexed by treatment with methanol, to give the corresponding enantiopure (2*S*,3*S*,1′*S*)-3-deuterio-2-(1′-dibenzylaminoalkyl)aziridine (**7c**) or (2*S*,3*S*,1′*S*)-2-(1′-dibenzylaminoalkyl)-3-(trimethylsilyl)aziridine (**8b**) in high yield (94 and 93 %, respectively). Thus, the successive treatment of aminoaziridines with BH_3 or $BF_3{\cdot}Et_2O/LiAlH_4$, *sec*-BuLi, D_2O, or $ClSiMe_3$, followed by decomplexation, is an easy and effective method for enantioselective deuteration or silylation of aziridine.

In conclusion, the above studies show that the enantiopure 2-(1-aminoalkyl)aziridine–borane complexes **2** can easily be obtained by two alternative methodologies: either reaction with $BF_3{\cdot}Et_2O$ followed by reduction with $LiAlH_4$ or by direct reaction with a solution of BH_3 in THF. In addition, regio- and stereoselective C3 deuteration or silylation of 2-(1-aminoalkyl)aziridine **1** can be effected by deprotonation/deuteration or silylation/decomplexation of the corresponding borane complex **2**. Application of this methodology to functionalize 2-(1-aminoalkyl)aziridines with other different electrophiles is currently under investigation.

Experimental Section

2: $BF_3{\cdot}OEt_2$ (0.025 mL, 0.2 mmol) and $LiAlH_4$ (0.4 mL, 0.4 mmol, 1 M in THF) were added successively at 0 °C to a stirred solution of the corresponding aminoaziridine **1** (0.2 mmol) in THF (2 mL). After stirring the reaction at this temperature for 30 min, it was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). Standard workup afforded the crude complexes **2**, which were purified by flash column chromatography on silica gel (hexane/EtOAc, 10:1). Yields are given in Table 1.

4 or **6**: A solution of *sec*-BuLi (0.54 mL, 1.4 M in cyclohexane) was added at −78 °C to a stirred solution of **2b** or **2c** (0.15 mmol) in THF (1 mL). After stirring the reaction mixture for 45 min at this temperature, it was quenched with D_2O (0.015 mL, 0.75 mmol) or with $ClSiMe_3$ (0.10 mL, 0.75 mmol). Standard workup afforded the crude complexes **4** or **6**. Treatment of **4c** or **6b** (0.10 mmol) with MeOH (1 mL) at room temperature for 24 h gave compound **7c** (94 %) or **8b** (93 %), respectively.

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[15] The observed difference in diastereoselectivity in the deuteration of **2b** and **2c** (d.r. = 95:5 and 88:12) is probably a consequence of higher steric hindrance for the metalation of the hydrogen C_3-H *cis* with respect to the BH_3 group in **2c** than in **2b**.

