Amino Alcohols

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Stereocontrolled Synthesis of β-Amino Alcohols from Lithiated Aziridines and Boronic Esters**

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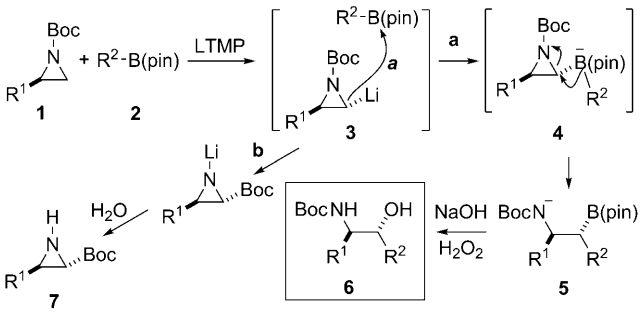
From natural products to ligands for asymmetric catalysis, the β-amino alcohol motif is ubiquitous.[1] The importance of this motif to such a broad spectrum of chemistry has prompted the development of a range of methodologies for its synthesis which include Sharpless aminohydroxylation[2] as well as the addition of nucleophiles to aminocarbonyls,[3] imines,[4] epoxides, and aziridines.[5] We considered a conceptually different route to prepare this class of compound: namely, the lithiation/borylation[6] of aziridines[7] (Scheme 1, pathway a).



Scheme 1. Lithiation/borylation of terminal aziridines. LTMP = lithium 2,2,6,6-tetramethylpiperidide, pin = pinacolato.

This route was attractive because: 1) it combines readily available aziridines **1** and boronic esters **2**, and creates a C–C bond, 2) high stereoselectivity for the overall process could be expected since lithiation of *N*-Boc[8] (*tert*-butoxycarbonyl) and *N*-Bus[9] (*tert*-butylsulfonyl) aziridines[10] had been shown to occur *trans* to the aziridine substituent, and the subsequent steps (**3** → **4** → **5** → **6**) were expected to be stereospecific, 3) there existed the potential to create quaternary stereogenic centers through lithiation at the internal position.[11]

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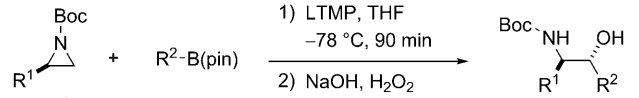
Although most studies have focused on lithiation and trapping of *N*-sulfonyl aziridines,[9,12] we were attracted to the *N*-Boc aziridines because: 1) they could be easily prepared in enantiomerically enriched form (either from the corresponding amino acid[13] or by Jacobsen's kinetic resolution of terminal epoxides[14] using Boc-NH_2[15]), and 2) the *N*-Boc amino alcohol products provide more useful functionality for further manipulation downstream. However previous studies had shown that lithiated aziridines bearing an *N*-Boc group undergo a rapid intramolecular [1,2] anionic rearrangement to give aziridinyl esters **7**, a useful reaction in its own right (Scheme 1, pathway b).[8] This rearrangement pathway made it virtually impossible to trap the C-lithiated aziridine with any external electrophile, including MeOD. However, if the electrophile was already present during the deprotonation step, it would be theoretically possible to trap the lithiated aziridine prior to the migration of the Boc group.[16] As we believed that most boronic esters/boranes would also be compatible with the hindered base (LTMP) required for deprotonation, this provided the possibility of using *N*-Boc aziridines in the lithiation–borylation reaction, without migration of the Boc group. This analysis gave us the motivation to embark on the following study.

To maximize the rate of the bimolecular trapping (and therefore minimize the migration rate of the Boc group), the reactions were conducted at the maximum concentration that was practical. Thus, slow addition of a THF solution of LTMP to a solution of *N*-Boc aziridine **1a** and ethyl boronic ester **2a** (1.5 equiv) at −78 °C followed by warming to 0 °C and oxidative workup gave a mixture of amino alcohol **6** and the aziridine **7**, in 40 % and 20 % yield, respectively (Scheme 1). This result showed that the rates of trapping and of rearrangement of the lithiated aziridine were similar, even at high concentration. However, on increasing the stoichiometry of the boronic ester to 3 equivalents none of the aziridine derivative where the Boc group has migrated was detected. These optimized reaction conditions were found to be general for a broad range of alkyl (Table 1, entries 1–5), vinyl (Table 1, entries 6 and 7), and aryl boronic esters (Table 1, entries 8 and, 9). The process was further extended to other alkyl and unsaturated aziridines thus demonstrating its scope (Table 1, entries 10–12).

In all cases β-amino alcohols **6** were obtained in high yield and as single diastereoisomers. The relative configuration of **6k** was proven by X-ray analysis,[17] and that of **6j** was confirmed by correlation with the literature.[18] The configuration of the product is consistent with the mechanism shown in Scheme 1, which involves lithiation *trans* to the aziridine substituent, reaction with the boronic ester with retention of configuration, migration of the boron substituent

Table 1: β-amino alcohol synthesis.[a]

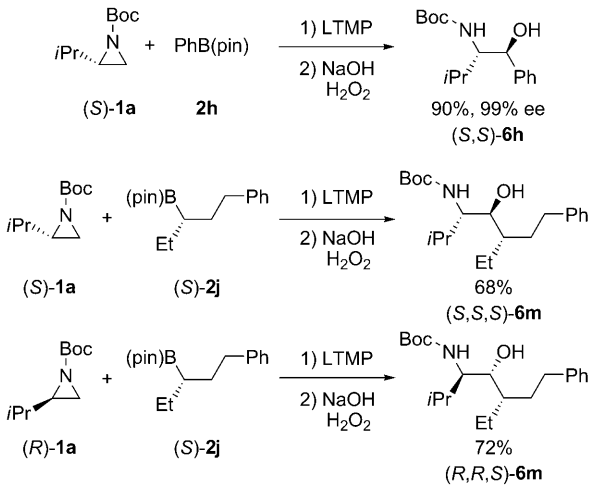


Entry	R^1 (aziridine **1**)	R^2 (boronic ester **2**)	Yield [%][b]
1	*i*Pr (**1a**)	Et (**2a**)	76 (**6a**)
2	*i*Pr (**1a**)	*i*Pr (**2b**)	75 (**6b**)
3	*i*Pr (**1a**)	*c*Pr (**2c**)	79 (**6c**)
4	*i*Pr (**1a**)	Cy (**2d**)	81 (**6d**)
5	*i*Pr (**1a**)	$PhCH_2CH_2$ (**2e**)	73 (**6e**)
6	*i*Pr (**1a**)	vinyl (**2f**)	93 (**6f**)
7	*i*Pr (**1a**)	*n*BuCH=CH (**2g**)	83 (**6g**)
8	*i*Pr (**1a**)	Ph (**2h**)	76 (**6h**)
9	*i*Pr (**1a**)	*p*MeOPh (**2i**)	70 (**6i**)
10	Me (**1b**)	Ph (**2h**)	63 (**6j**)
11	*n*Bu (**1c**)	Ph (**2h**)	86 (**6k**)
12	CH_2=$CH(CH_2)_2$ (**1d**)	Ph (**2h**)	75 (**6l**)

[a] All reactions were performed on a 0.5 mmol scale using boronic ester **2** (3 equiv), LTMP (0.6 M; 3 equiv) in THF (1 mL) at −78 °C for 90 minutes, then warming to 0 °C and subsequent oxidation. [b] Yield of isolated product. Cy = cyclohexyl.

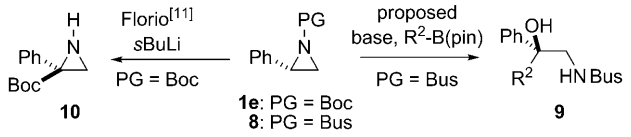
anti to the C–N bond, and finally retention of configuration in the oxidation step. The very high diastereoselectivity observed, even with the smallest of substituents (R^1 = Me; Table 1, entry 10) is indicative of a very high degree of selectivity in the lithiation step *trans* to the aziridine substituents and complete selectivity in trapping **3** with the boronic ester.

The process was easily extended to the enantioenriched series. Thus, treatment of (*S*)-**1a** with phenyl boronic ester **2h** gave **6h** in 99% *ee* (Scheme 2). Furthermore, the reaction of (*S*)-**1a** and (*R*)-**1a** with the enantioenriched boronic ester (*S*)-**2j**[6a] gave the amino alcohols (*S*,*S*,*S*)-**6m** and (*R*,*R*,*S*)-**6m** with complete diastereo- and enantioselectivity in 68% and 72% yield, respectively. This outcome shows that there are no matched/mismatched issues here, which can often complicate reaction outcomes.



Scheme 2. Synthesis of enantiopure β-amino alcohols.

Finally, phenylaziridines were investigated as an extension of the methodology. Lithiation of aziridine **1e** is known to occur adjacent to the phenyl group and so this has the potential to generate quaternary stereogenic centers (Scheme 3).[11] However, lithiation with LTMP and trapping

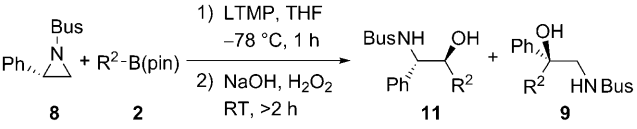


Scheme 3. Proposed lithiation and trapping of aryl-substituted aziridines.

of the *N*-Boc aziridine **1e** with boronic ester **2h** only gave the product **10** where the Boc group has migrated.[19] Presumably, the phenyl group has the effect of slowing down the trapping of the carbanion with the boronic ester as a result of increased steric demands and increased electronic stabilization of the carbanion. To inhibit this migration we decided to replace the *N*-Boc group with the less labile *N*-Bus group. Although substantial studies have been performed on lithiated *N*-Bus aziridines bearing alkyl substituents, particularly in relation to their carbenoid character,[8b,9c] there were no reports on lithiation and trapping of *N*-Bus aziridines bearing aryl substituents. We therefore studied the deprotonation/borylation of these more robust aziridine derivatives.

Treatment of *N*-Bus aziridine **8** with LTMP in the presence of different aryl and vinyl boronic esters gave the corresponding alcohols **11** in good yield and with complete diastereoselectivity (Table 2, entries 1–3). No racemization of the labile benzylic center was detected. Surprisingly, the use of alkyl boronic esters (Table 2, entries 4–7) led to an approximate 3.5:1 mixture of the secondary/tertiary alcohols (**11**/**9**), again with complete control over enantio- and diastereoselectivity. We had expected lithiation to occur

Table 2: Synthesis of β-amino alcohols from phenylaziridine **8**.[a]

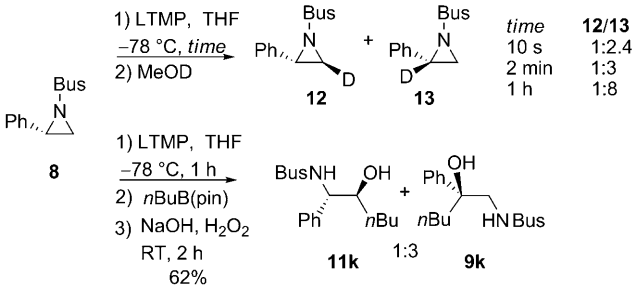


Entry	R^2 (boronic ester **2**)	Yield [%][b] of **11**	Yield [%][b] of **9**	e.r. **11**[c]	e.r. **9**[c]
1	vinyl (**2f**)	73 (**11f**)	<5	>99:1	–
2	Ph (**2h**)	83 (**11h**)	<5	>99:1	–
3	*p*MeO-Ph (**2i**)	87 (**11i**)	<5	>99:1	–
4	allyl (**2j**)	60 (**11j**)	23 (**9j**)	>99:1	>99:1
5	Et (**2a**)	63 (**11a**)	15 (**9a**)	>99:1	>99:1
6	*n*Bu (**2k**)	70 (**11k**)	20 (**9k**)	>99:1	>99:1
7	Cy (**2d**)	61 (**11d**)	20 (**9d**)	>99:1	>99:1

[a] All reactions were performed using boronic ester **2** (1.2 equiv), LTMP (0.5 M; 1.2 equiv) in THF at −78 °C for 1 hour, then at room temperature for a further 1 hour and subsequent oxidation. [b] Yield of isolated product (see the Supporting Information). [c] The enantiomeric ratio (e.r.) was determined by HPLC on a chiral stationary phase using a Chiralcel OD-H or AD column.

predominantly at the benzylic position as observed by Florio et al.,[11] who used *s*BuLi as the base and so expected to obtain predominantly the tertiary alcohol **9** (Scheme 3). Evidently, when the more hindered base LTMP is employed, steric factors outweigh electronic factors and lithiation occurs at the less acidic terminal position. However, it was surprising that the site of lithiation (which determines the product ratio) was dependent on the nature of the boronic ester employed: aryl and vinyl boronic esters resulted in lithiation at the terminal position, whereas alkyl boronic esters gave an approximate 3.5:1 ratio of terminal/benzylic lithiation.

Mechanistic studies have been undertaken to shed light on the factors affecting the regioselectivity of lithiation with LTMP. To determine whether the lithiated aziridine species could isomerize, aziridine **8** was treated with LTMP for 10 seconds, 2 minutes, and 1 hour before addition of MeOD. These experiments gave a 1:2.4 (27% deuterium incorporation), 1:3 (41% deuterium incorporation), and 1:8 (92% deuterium incorporation) ratio of products **12**/**13**, respectively (Scheme 4). The reactions were clean and there were no

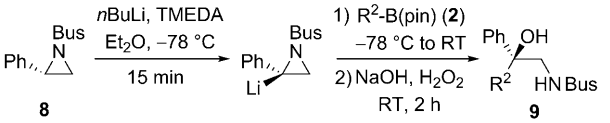


Scheme 4. Mechanistic studies to probe the site of lithiation and potential for equilibration.

products from dimerization of the lithiated aziridine species. Furthermore, lithiation with LTMP for 1 hour and subsequent addition of boronic ester **2k** gave a 1:3 ratio of adducts **11k**/**9k**, whereas trapping with the same boronic ester in situ gave a 3.5:1 ratio (Table 2, entry 6). Taken together, these results show that, in the absence of a boronic ester, LTMP favors benzylic lithiation and that the terminal lithiated aziridine equilibrates to the thermodynamically more stable benzylic lithiated aziridine over time. Possibly, the base forms a complex with the reactive boronic esters (aryl, vinyl) and therefore the more hindered complex leads to lithiation at the terminal position. In the presence of aliphatic boronic esters, the base LTMP may lead to a "looser complex" which gives an approximate 3.5:1 mixture of lithiated aziridine species (Table 2). That the regiochemical outcome of the lithiation process is dependent on the nature of the boronic ester is further illustrated by the fact that LTMP deprotonation of aziridine **8** in the presence of the less hindered ethyl neopentyl boronic ester gave an approximate 1:1 mixture of **11**/**9** whereas the ethyl pinacol boronic ester (**2a**) gave an approximate 4:1 mixture (Table 2, entry 5).[20]

Switching to a less hindered base (*n*BuLi, TMEDA) resulted in a completely regioselective deprotonation at the benzylic position and subsequent addition of alkyl boronic esters furnished the tertiary alcohols in high yield and with complete stereocontrol (Table 3). These hindered amino alcohols are especially difficult to make by other routes, including Sharpless aminohydroxylation, but are nevertheless an extremely important class of bioactive compounds.[21] However, aryl boronic esters were much less well behaved and gave mixtures of products which included alkenes.[22]

Table 3: Synthesis of amino alcohols bearing quaternary stereogenic centers.[a]



Entry	R^2 (boronic ester **2**)	Yield [%][b]	e.r.[c]
1	Cy (**2l**)[d]	84 (**9d**)	>99:1
2	allyl (**2j**)	87 (**9j**)	>99:1
3	*n*Bu (**2k**)	80 (**9k**)	>99:1

[a] All reactions were performed using boronic ester **2** (1.2 equiv), *n*BuLi (1.2 equiv) in Et_2O at −78 °C. [b] Yield of isolated product. [c] The enantiomeric ratio (e.r.) was determined by HPLC on a chiral stationary phase using a Chiralcel AD column. [d] The neopentyl boronic ester was used instead of the pinacol boronic ester.[23] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

In conclusion, we have presented a conceptually new route to β-amino alcohols, a common motif found across a wide spectrum of molecules in chemistry. This associative route employs terminal *N*-Boc aziridines which are lithiated and trapped with boronic esters to give *syn*-β-amino alcohols with complete diastereoselectivity. The process is easily rendered asymmetric and can be used to create carbon chains with multiple stereogenic centers with control over relative and absolute stereochemistry. The process can be further extended to the generation of 1,2-amino alcohols bearing quaternary stereogenic centers, thus providing a useful route to this especially challenging motif.

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[17] CCDC 706954 (**6k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. *Crystal data*: $C_{17}H_{27}NO_3$, $M=293.40$, monoclinic, $a=11.6558(3)$, $b=5.5918(2)$, $c=25.3966(7)$ Å, $\beta=91.628(2)°$, $V=1654.60(9)$ Å^3, $T=120(2)$ K, space group $P2_1/n$, $Z=4$, $\mu=0.080$ mm^{-1}, $R_{int}=0.0714$ (for 21087 measured reflections), $R_1=0.0583$ [for 2811 unique reflections with $>2\sigma(I)$], $wR_2=0.1479$ (for all 3797 unique reflections).
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[19] Florio et al. observed similar results using *s*BuLi in THF at −98 °C and lithiation/rearrangement occurred in less than 5 minutes, see Ref. [11].
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[23] For the more hindered cyclohexyl boronic ester we found that the neopentyl ester **2l** gave clean homologation whereas the pinacol ester **2d** led to a mixture of starting material (40%) and product (35%).

