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Stereocontrolled addition of boron enolates to *trans* α,β-aziridine aldehydes. A new route to *anti*-1,2-amino alcohols

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Abstract—A study of the addition of boron enolates of methyl ketones to *trans* α,β-aziridine aldehydes is reported. The reaction proceeds with excellent *anti* stereoselectivity furnishing functionalized products, capable of other controlled transformations, some of which are described.

Functionalized chiral aziridines can be considered attractive compounds due to their reactivity, mainly as a result of their ring strain.[1] Indeed, chemo-, regio- and stereocontrolled openings of aziridines with a variety of nucleophiles have been widely reported;[2] in particular, metal halides have been extensively used to ring-open aziridines, often functionalized with hydroxyl and carboxyl groups.[3] Moreover, it is known that the aziridine ring of α,β-aziridine aldehydes, which are easily obtainable in optically active form from the corresponding *trans* allylic alcohols, strongly influences the stereochemistry of nucleophilic additions to the carbonyl group. In fact, the reaction between these substrates and organometallic reagents generally results in the formation of *syn* aziridino alcohols in quite good yields and with good to excellent diastereomeric ratios.[4] For example, using Grignard reagents and *N*-Boc-activated aziridines only the *syn* stereoisomer was obtained, which can be explained by invoking a 'cyclic chelate model' for the T.S.[5]

Prompted by these results, we decided to explore the stereochemistry of the aldol addition of ketone enolates to *trans* α,β-aziridine aldehydes, the configurational stability of which overcomes the difficulty of using configurationally unstable α-amino aldehydes.

The stereoselective addition of enolates to α,β-aziridine-2-carbaldehydes, which, to the best of our knowledge, has never been exploited, could provide structures, which are suitably functionalized for selective elaboration to aminopolyhydroxylated structures (e.g., regioselective aziridine ring opening or diastereoselective carbonyl reductions[6]). Our preliminary studies were restricted, for convenience, to racemic compounds and we chose, as the standard test reaction, the addition of the enolate of pinacolone to *trans*-1-*tert*-butoxycarbonyl-3-propylaziridine-2-carbaldehyde. At first, lithium diisopropylamide was used to generate the enolate, however, a 1:1 mixture of diastereomeric aldols resulted.

In light of this unsatisfactory result, it was decided to adopt the methodology used in a recent similar study aimed at the stereocontrolled aldol addition to *trans* α,β-epoxy aldehydes,[7] namely the use of boron enolates, which had led to an excellent diastereoselection.

The reaction conditions were optimized by studying the addition of the dibutylboron enolate (formed by adding Bu_2BOTf and DPEA to pinacolone at 0 °C for 30 min) to *trans*-1-*tert*-butoxycarbonyl-3-propylaziridine-2-carbaldehyde **1**, at −78 °C, using CH_2Cl_2 as solvent (Et_2O and THF gave some side products) (Scheme 1).

When the reaction mixture was allowed to warm slowly from −78 °C to room temperature, only one diastereoisomer was detected.

Stereochemical assignments for the aziridino alcohols obtained were based on their spectral properties. It is

Keywords: α,β-Aziridine aldehydes; Boron enolates; Aldol condensation; 1,2-Amino alcohols.
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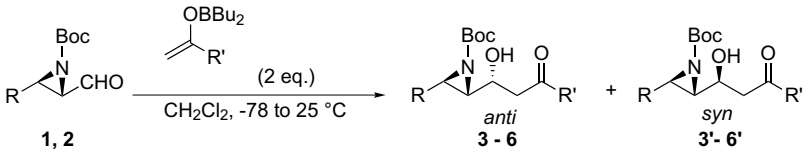


Scheme 1.

known that in their NMR spectra the methine hydrogens of the C*H*OH groups of *anti* isomers are always shifted to lower field than those of the corresponding *syn* isomers.[4a] Consistent with this general trend, the resonance of the C*H*OH of **3** (δ 3.95) is shifted by 0.35 ppm downfield relative to the corresponding resonance of the C*H*OH of **3′** (δ 3.61).[6] Consequently, we attributed the *anti* configuration to **3** and the *syn* configuration to **3′**.

The diastereoselectivity observed in favour of the *anti* isomers can be explained invoking the Felkin–Ahn model for the T.S. We can assume that the incoming nucleophile attacks the carbonyl in an *anti*-periplanar manner with respect to the aziridine ring, which can be considered the largest group attached to the stereogenic centre at C-2, thus leading to the *anti* isomer (see Fig. 1).[9]

This methodology was then tested on *trans*-1-*tert*-butoxycarbonyl-3-cyclohexylaziridine-2-carbaldehyde **2**, where a sterically demanding substituent is present at the C-3 position. Besides pinacolone, 3-methyl-2-butanone, a ketone having two different enolizable sites, was also used. As shown in Table 1, the results were satisfactory and demonstrated the general application of the methodology.

The aziridino alcohols obtained by this aldol addition can be used for further transformations. Since $MgBr_2$ has been extensively employed in regio- and stereocontrolled ring openings of α,β-aziridino alcohols,[10] it was deemed appropriate to explore the possibility of using this metal halide to open the aziridine rings of the aldol products.

The reaction was performed at room temperature on compounds **4** and **6** and afforded the expected bromo derivatives as single regio- and stereoisomers, independent of the substituent at C-3 (Scheme 2).[11] The regiochemistry of the ring opening was established by means of NMR spectroscopy, employing a spin–spin decoupling technique.[12] Furthermore, the high reactivity of the bromides **7** and **8** can be utilized for further elaboration: for example, radical reduction allowed the preparation of 4-keto-1,2-amino alcohols with various substituents.[13] Thus compounds **7** and **8** were reduced with tris(trimethylsilyl)silane[14] to give the corresponding *anti*-4-keto-1,2-amino alcohols **9** and **10** in good yields.[15] Moreover, this procedure is selective for the *anti* 1,2-amino alcohols, rather than the more accessible *syn* compounds.[16]

In conclusion, the aldol condensation of boron enolates with *trans* α,β-aziridine aldehydes proceeds with excellent stereoselectivity in favour of the *anti* diastereoisomer, consistent with the Felkin–Ahn model. Moreover, these functionalized compounds can be elaborated, through regio- and stereocontrolled transformations, to 1,2-amino alcohols, a structural feature characteristic of many natural products and drugs,[17] often utilized in the synthesis of biologically active molecules such as protease inhibitors,[18] glycosphingolipids[19] or polyhydroxylated nitrogen heterocycles.[20]

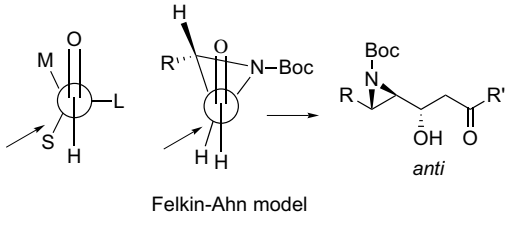
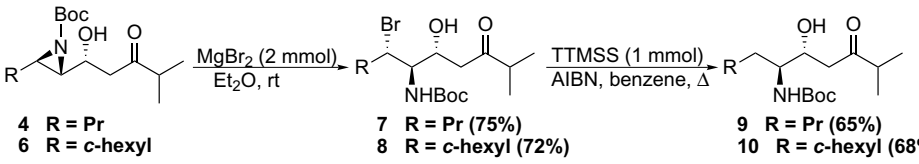


Figure 1.

Table 1. Addition of boron enolates to α,β-aziridine aldehydes[8]

α,β-Aziridine aldehyde	R	R′	Product	Yield (%)	*anti*/*syn*[a]
1	*n*-Pr	*t*-Bu	**3**	62	>95:5
		i-Pr	**4**	63	>95:5
2	*c*-Hexyl	*t*-Bu	**5**	64	>95:5
		i-Pr	**6**	67	>95:5

[a] The diastereomeric ratio was determined on crude mixtures, employing the integrations of the C*H*OH.



Scheme 2.

Acknowledgements

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References and notes

1. Reviews: (a) Davis, F. A.; McCoull, W. *Synthesis* **2000**, 1347–1365; (b) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519–1561; (c) Zwanenburg, B. *Pure Appl. Chem.* **1999**, *71*, 423–430; (d) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
2. (a) Lee, K. D.; Suh, J. M.; Park, J. H.; Ha, H. J.; Cha, H. G.; Park, G. S.; Chang, J. W.; Lee, W. K.; Dong, Y.; Yun, H. *Tetrahedron* **2001**, *57*, 8267–8276; (b) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903–907; (c) Tanner, D.; Gautun, O. R. *Tetrahedron* **1995**, *51*, 8279–8287; (d) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415–2417.
3. Righi, G.; Bonini, C. Functionalized Epoxides and Aziridines: Reactivity with Metal Halides and Synthetic Applications. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry, 2000; p 139–165.
4. (a) Hwang, G.-I.; Chung, J.-H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183–6188; (b) Andres, J. M.; de Elena, N.; Pedrosa, R.; Prez-Encabo, A. *Tetrahedron* **1999**, *55*, 14137–14144.
5. Righi, G.; Pietrantonio, S.; Bonini, C. *Tetrahedron* **2001**, *57*, 10039–10046.
6. (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939–5942; (b) Chen, K.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926.
7. Righi, G.; Spirito, F.; Bonini, C. *Tetrahedron Lett.* **2002**, *43*, 4737–4740.
8. General procedure for the aldol condensation: Di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 2.6 mmol) was added dropwise to a stirred solution of the ketone (2 mmol) in 4 mL of CH_2Cl_2 at 0 °C. After 10 min, diisopropylethylamine (4 mmol in 1 mL of CH_2Cl_2) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. To the above enolate solution was added a solution of aziridine aldehyde (1 mmol) in 2 mL of CH_2Cl_2. After a few minutes the reaction was allowed to warm to room temperature and was then quenched with a mixture of MeOH (6 mL), aqueous phosphate buffer (4 mL, pH = 7) and H_2O_2 (4 mL of a 30% solution). The aqueous layer was extracted with two portions of AcOEt and the combined organic extracts dried (Na_2SO_4) and concentrated. Generally TLC monitoring revealed about 20% of unreacted aldehyde also after a longer reaction time. The residue was purified on silica gel (petroleum ether/EtOAC 9:1).
   NMR data for representative compounds. Compound **3**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.98 (q, *J* 6.1 Hz, 1H), 3.41 (br s, 1H), 2.92 (dd, *J* 17.6, 7.3 Hz, 1H), 2.74 (dd, *J* 17.6, 5.1 Hz, 1H), 2.53–2.44 (m, 1H), 2.3 (dd, *J* 5.9, 3.7 Hz, 1H), 1.8–1.5 (m, 4H), 1.47 (s, 9H), 1.15 (s, 9H), 0.9 (t, *J* 6.9 Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 216.7, 161.3, 81.5, 67.5, 47.1, 41.4, 41.3, 32.9, 28.3, 27.9, 26.1, 20.2, 13.7. Compound **3′**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.62 (m, 1H), 3.19 (br d, *J* 3.6 Hz, 1H), 2.88 (dd, *J* 17.6, 2.2 Hz, 1H), 2.79 (t, *J* 10.2 Hz, 1H), 2.53–2.44 (m, 1H), 2.26 (dd, *J* 5.9, 3.7 Hz, 1 H), 1.8–1.5 (m, 4H), 1.47 (s, 9H), 1.15 (s, 9H), 0.9 (t, *J* 6.9 Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 215.4, 160.5, 81.1, 67.6, 45.6, 41.8, 40.9, 32.6, 28.3, 28.0, 26.2, 20.4, 13.7. Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.01–3.92 (m, 1H), 3.38 (br d, *J* 3.7 Hz, 1H), 2.86 (dd, *J* 17.0, 7.2 Hz, 1H), 2.69 (dd, *J* 17.0, 5.3 Hz, 1H), 2.62 (q, *J* 6.9 Hz, 1H), 2.5–2.42 (m, 1H), 2.29 (dd, *J* 6, 3.3 Hz, 1H), 1.46 (s, 9H), 1.60–1.20 (m, 4H), 1.1 (d, *J* 6.9 Hz, 6H), 0.9 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 213.1, 161.4, 81.6, 67.5, 47.1, 44.8, 41.5, 41.3, 32.8, 27.9, 20.2, 18.3, 17.8, 13.7. Compound **5**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (ddd, *J* 12.4, 6.6, 2.9 Hz, 1H), 3.78 (br d, *J* 2.9 Hz, 1H), 2.95 (dd, *J* 17.6, 7.3 Hz, 1H), 2.67 (dd, *J* 17.6, 5.9 Hz, 1H), 2.37–2.25 (m, 2H), 1.98–1.84 (m, 1H), 1.80–1.00 (m, 10H), 1.46 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 212.4, 161.7, 81.6, 68.5, 46.5, 46.2, 44.2, 41.3, 39.5, 30.5, 30.0, 28.3, 27.9, 26.2, 26.0, 25.6. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (q, *J* 7.3 Hz, 1H), 3.76 (br s, 1H), 2.88 (dd, *J* 16.8, 6.6 Hz, 1H), 2.70–2.54 (m, 2H), 2.33 (dd, *J* 7.3, 2.9 Hz, 1H), 2.27–2.21 (m, 1H), 1.98–1.85 (m, 1H), 1.81–1.6 (m, 4H), 1.72–0.84 (m, 6H), 1.46 (s, 9H), 1.1 (d, *J* 7.3 Hz, 6H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 212.5, 161.8, 81.8, 68.8, 46.5, 46.4, 44.8, 41.5, 39.5, 30.5, 29.9, 27.8, 26.0, 25.6, 25.4, 18.0, 17.9.
9. Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 49.
10. Righi, G.; Franchini, T.; Bonini, C. *Tetrahedron Lett.* **1998**, *39*, 2385–2388.
11. General procedure for the opening of the aldol with $MgBr_2$: To a solution of the aldol (1 mmol) in dry Et_2O (10 mL) was added $MgBr_2{\cdot}Et_2O$ (516.5 mg, 2 mmol). The solution was stirred at room temperature for 6 h (TLC monitoring), then filtered trough a Celite pad and the solvent evaporated in vacuo. The residue was chromatographed on silica gel (petroleum ether/EtOAc).
    NMR data for representative compounds. Compound **7**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.12 (br d, *J* 9.3 Hz, 1H), 4.31 (ddd, *J* 8, 5.6, 1.1 Hz, 1H), 4.14–4.03 (m, 1H), 3.64 (ddd, *J* 9, 8.2, 0.8 Hz, 1H), 2.81–2.53 (m, 3H), 1.91–1.55 (m, 3H), 1.45 (s, 9H), 1.32–1.15 (2H, m), 1.15 (d, *J* 6.9 Hz, 6H), 0.88 (3H, t, *J* 7.1 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 216.1, 155.4, 79.7, 68.4, 58.7, 57.6, 43.5, 41.5, 37.2, 28.3, 20.8, 17.9, 17.7, 13.4. Compound **8**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.96 (br d, *J* 10.3 Hz, 1H), 4.76 (dd, *J* 8.7, 3.2 Hz, 1H), 4.15–4.05 (m, 1H), 3.87–3.73 (dt, *J* 10.3, 0.7 Hz, 1H), 3.5 (br s, 1H), 2.6–2.54 (m, 3H), 1.90–0.83 (m, 11H), 1.46 (s, 9H), 1.12 (d, *J* 1.1 Hz, 3H), 1.09 (d, *J* 1.1 Hz, 3H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 216.2, 155.3, 79.8, 67.2, 63.3, 55.7, 43.7, 41.5, 39.6, 32.3, 28.3, 27.4, 26.4, 26.2, 25.9, 17.9.
12. 'Spin–spin decoupling' data for compound **8**:

δ_{irr}	C*H*OH 4.78 δ (ddd, *J* 8.7; 3.2; 0.6)	C*H*Br 4.12 δ (dd, *J* 10.4; 1.6)	C*H*NH 3.83 δ (ddd, *J* 10.4; 10.3; 0.6)
2.64 (CH_2CO)	d, *J* 0.6		
4.96 (N*H*)			dd, *J* 10.4; 0.6
1.8 (CH_2CHCH_2)		d, *J* 10.4	

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13. The direct reductive opening of the aziridine ring by catalytic hydrogenation resulted in different products.
14. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–204.
15. General procedure for the radical reduction of the bromo derivatives: To a solution of the bromo derivative (1 mmol) in benzene (10 mL) tris(trimethylsilyl)silane (0.31 mL, 1 mmol) and a catalytic amount of AIBN were added. The solution was refluxed for ∼5 h (TLC monitoring), then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 9:1).

NMR data for representative compounds. Compound **9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.58 (br d, J 8.0 Hz, 1H), 3.82–3.66 (m, 1H), 3.61–3.44 (m, 1H), 2.78–2.48 (m, 3H), 2.28 (quintet, J 6.9 Hz, 1H), 1.62–0.98 (m, 6H), 1.42 (s, 9H), 1.18 (d, J 6.9 Hz, 6H), 0.88 (t, J 6.6 Hz, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 216.3, 155.1, 79.1, 70.6, 56.4, 43.9, 41.5, 31.6, 27.9, 22.8, 22.4, 18.0, 13.9. Compound **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.68 (br d, J 10.2 Hz, 1H), 4.04–3.94 (m, 1H), 3.66–3.52 (m, 1H), 3.38 (br s, 1H), 2.78–2.52 (m, 2H), 2.32 (quintet, J 6.9 Hz, 1H), 2.12–0.88 (m, 13H), 1.44 (s, 9H), 1.08 (d, 6H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 216.2, 156.0, 79.6, 69.4, 51.4, 43.9, 41.5, 34.2, 29.6, 28.3, 27.2, 26.5, 17.9.

16. (a) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; p 243; (b) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326–332, and Refs. 5,6.
17. Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1771–1792, and references cited therein.
18. Kempf, D.; Sham, H. *Curr. Pharm. Des.* **1996**, *2*, 225–261.
19. Peterson, M. A.; Polt, R. *J. Org. Chem.* **1993**, *58*, 4309–4314, and references cited therein.
20. (a) Hummer, W.; Dubois, E.; Gracza, T.; Jager, V. *Synthesis* **1997**, 634–642; (b) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179–3180, and references cited therein.