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Terminal Aziridines by α-Deprotonation/ Electrophile Trapping of N-Protected Aziridine

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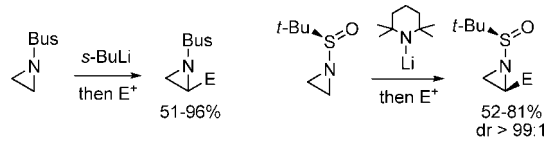
ABSTRACT

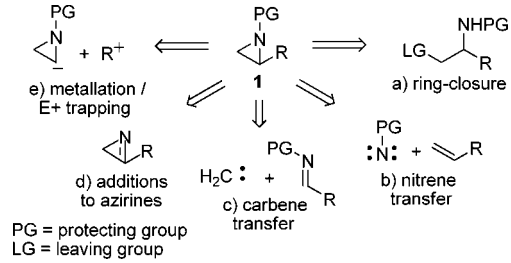


***N-tert*-Butylsulfonyl and *N-tert*-butylsulfinyl aziridine undergo α-lithiation/electrophile trapping providing a new entry to terminal aziridines. With *N-tert*-butylsulfinyl aziridine complete asymmetric induction is observed α to nitrogen.**

Aziridines are an important class of heterocycle currently receiving increased research interest.[1] Terminal aziridines are particularly useful owing to the ease, generality, and predictable regioselectivity of their ring-opening reactions with nucleophiles.[2] Currently, there are four conceptually different synthetic routes to produce N-protected terminal aziridines **1** (Scheme 1):[1b,3] (a) ring-closure of 2-substituted amines;[4] (b) (formal) nitrene transfer to alkenes; (c) (formal) carbene transfer to imines; and (d) additions to azirines.

Another potentially powerful strategy to terminal aziridines **1** involves α-metalation/electrophile trapping of N-protected aziridine (strategy e, Scheme 1). One isolated example of this latter process was described in 1994 by Beak and co-workers, which involved silylation of *N*-Boc aziridine using *s*-BuLi;[5] however, this method was "successful only if the electrophile, Me_3SiCl, was present during the lithiation" – a major limitation.

Scheme 1. Synthetic Strategies to Terminal Aziridines **1**



Following our investigations into the direct α-deprotonation/electrophile trapping of nonstabilized *N*-Bus (Bus = *tert*-butylsulfonyl)-protected terminal aziridines,[6] we considered whether further N-protected variants of aziridine itself could

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(1) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (b) Padwa, A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds; Elsevier: Oxford, 2008; Vol. 1, pp 1−104.

(2) (a) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599–619. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743. (d) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Eur. J. Org. Chem.* **2007**, 1717–1724.

(3) (a) Sweeney, J. B. In ref 1a, pp 117−144. (b) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.

(4) For a recent example, see: Hodgson, D. M.; Kloesges, J.; Evans, B. *Org. Lett.* **2008**, *10*, 2781–2783.

(5) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276–277.

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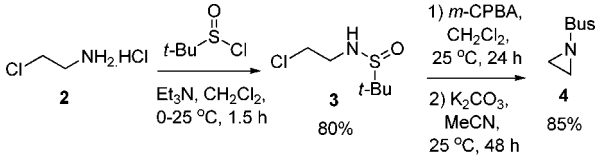
be lithiated and electrophile trapped.[7] In the present paper, we communicate our promising preliminary results on this theme.

Initially, lithiation of *N*-Ts, *N*-Tris, and *N*-Boc aziridine were investigated but, not unexpectedly, these unhindered (C-unsubstituted) systems underwent mainly dimerization, ring-opening, or in the *N*-Boc aziridine case, N-to-C migration.[8] Using *N*-Bus aziridine **4** (readily accessed on a multigram scale by *tert*-butylsulfinylation of 2-chloroethylamine hydrochloride **2**, followed by oxidation of the resulting chlorosulfinamide **3** and ring-closure, Scheme 2) in combination with *s*-BuLi/TMEDA[9] at low temperature did, however, produce the first direct external electrophile trapping (deuteration) of a simple N-protected, C-unsubstituted aziridine,[7] giving deuterated aziridine **5a** (90% yield, >95% D, Table 1).

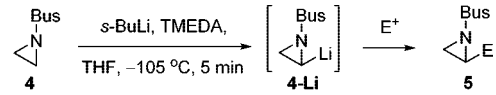
Scheme 2. Synthesis of *N*-Bus Aziridine **4**

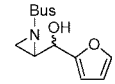
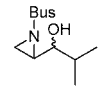
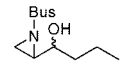
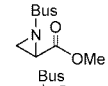


To examine the scope of this process, a range of other electrophiles were then reacted with lithiated *N*-Bus aziridine **4-Li** (Table 1). Me_3SiCl, Bu_3SnCl, and $PhSO_2F$ gave the corresponding C-heteroatom-substituted aziridines[10] **5b**−**d** in 81%, 86%, and 51% yields, respectively (Table 1, entries 2−4). The structure of aziridinylsulfone **5d** was confirmed with single-crystal X-ray diffraction data.[11] Pleasingly, both nonenolizable and enolizable aldehydes and ketones proved viable electrophiles to generate a range of aziridinyl alcohols **5e**−**j** (56−96% yield). Aziridinyl ester and ketone structural motifs **5k**,**l** could also be accessed using methyl cyanoformate and benzoyl cyanide as electrophiles (entries 11 and 12).[12]

Reactions illustrating the use of the *N*-Bus terminal aziridines **5** in subsequent ring-opening chemistry giving sulfonamides **6a**−**d** are shown in Scheme 3. Using Grignard and heteroatomic nucleophiles, ring-opening of aziridinyl alcohol **5j** occurred selectively at the less-hindered ring carbon, whereas with aziridinyl ketone **5l**, ring-opening took place at the more substituted ring carbon (likely due to transition-state stabilization by the adjacent C═O group).[13]

Table 1. Terminal Aziridines **5** by α-Lithiation of *N*-Bus Aziridine **4**



entry	electrophile	aziridine		yield (%)
1	CD_3OD		**5a**	90 (>95% D)
2	Me_3SiCl		**5b**	81
3	Bu_3SnCl		**5c**	86
4	$PhSO_2F$		**5d**	51
5	PhCHO		**5e**	89 (56:44 dr)
6	furfural		**5f**	96 (60:40 dr)
7	*t*-BuCHO		**5g**	62 (70:30 dr)
8	*i*-PrCHO		**5h**	61 (53:47 dr)
9	*n*-PrCHO		**5i**	56 (50:50 dr)
10	Et_2CO		**5j**	65
11	$MeCO_2CN$		**5k**	52
12	PhCOCN		**5l**	65

For the asymmetric synthesis of terminal aziridines by the above strategy, we first considered modifying the chemistry by attempting enantioselective deprotonation.[7] Enantioselective chiral ligand-induced lithiation/electrophile trapping of saturated N-protected heterocycles is currently well-established only for *N*-Boc pyrrolidine.[14] In our hands,[14c] addition of *N*-Boc aziridine to premixed *s*-BuLi and (−)-sparteine in ethereal solvents at low temperature, followed by an electrophile, consistently resulted only in isolation of

(6) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153–1156.

(7) For (enantioselective) deprotonation-electrophile trapping of *N*-alkyl aziridine borane (where the *N*-alkyl group can be removed by a four-step procedure), see: (a) Vedejs, E.; Bhanu Prasad, A. S.; Kendall, J. T.; Russel, J. S. *Tetrahedron* **2003**, *59*, 9849–9856.

(8) (a) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 935–938. (b) Hodgson, D. M.; Humphreys, P. G.; Xu, Z.; Ward, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2245–2248. (c) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009–10021.

(9) Dimerization of α-lithiated epoxides is known to be inhibited by TMEDA, see: (a) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615–618.

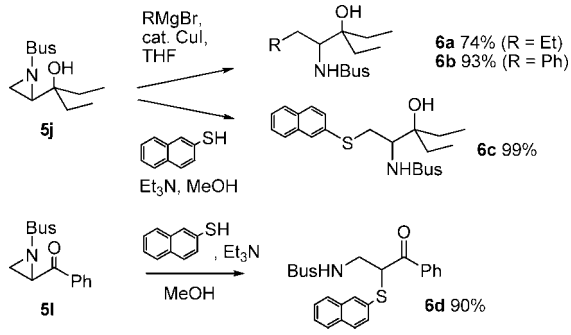
(10) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135.

(11) See the Supporting Information for details.

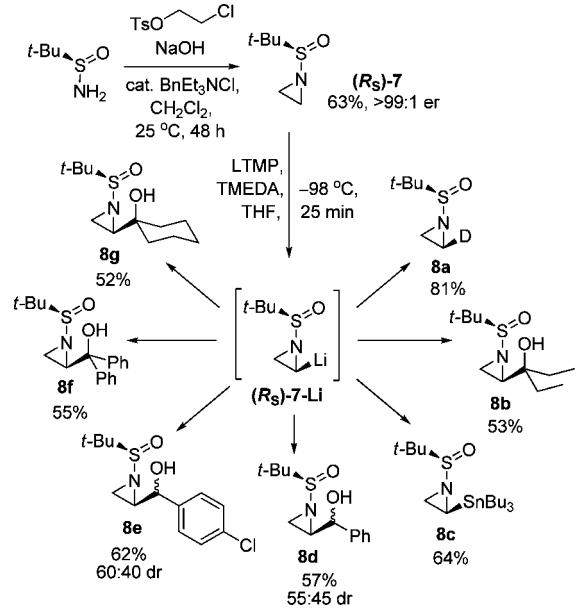
(12) Attempted trapping with other electrophiles, such as allyl bromide, BnBr, BuOTf, and MeI, has so far been unsuccessful.

(13) For examples of nucleophilic ring opening of aziridinyl ketones occurring at the internal carbon, see: Kim, Y.; Ha, H.-J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, H. J.; Kim, M. S.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407–4409.

Scheme 3. Ring-Opening of *N*-Bus Terminal Aziridines **5**



Scheme 4. Studies with *N-tert*-Butylsulfinyl Aziridine (R_S)-**7**[23]



3,5-dimethylheptan-4-one, arising from reaction of *s*-BuLi at the Boc group. Adding a mixture of *N*-Bus aziridine **4** and Me_3SiCl (1.2 equiv) dropwise via cooled cannula to a premixed solution of *s*-BuLi/(−)-sparteine (1.2 equiv) in THF at −105 °C did form aziridinylsilane **5b** in 38% yield, but with a negligible er.[11] We therefore considered using a chiral N-protecting group that might activate and bias the ring to (highly) diastereoselective deprotonation.[15] Aware of the high levels of diastereocontrol often observed during the addition of nucleophiles to *N-tert*-butylsulfinyl imines,[4,16] we felt that the *tert*-butylsulfinyl group might fulfill such a role.

First, a direct synthesis of *N-tert*-butylsulfinyl aziridine **7** in either enantiomeric form and in one step from commercial starting materials was developed (Scheme 4).[17] Deprotonation of **(**R_S)-**7** using *s*-BuLi/TMEDA in THF at −98 °C and trapping with CD_3OD gave the anticipated 2-deuteroaziridine **8a**; however, yields proved to be variable under these conditions (potentially due to attack at the sulfinyl group by the organolithium).[18] Moving to the less nucleophilic base LTMP (lithium 2,2,6,6-tetramethylpiperidide) in combination with TMEDA[19] improved the yields, and after a 25 min lithiation time at −98 °C the desired 2-deuteroaziridine **8a** was generated in 81% yield with >90% D-incorporation. Using the symmetrical ketone pentan-3-one as the electrophile gave aziridinyl alcohol **8b** in 53% yield and, significantly, only a single diastereomer was observed in the crude ^1H and ^{13}C NMR spectra. Analysis of single-crystal X-ray diffraction data for aziridinyl alcohol **8b** allowed the determination of the absolute configuration (R_S,*R*), as shown in Scheme 4.[11,20] Confirmation of the highly diastereoselective nature of the lithiation/electrophile trapping was obtained by *m*-CPBA-mediated oxidation of crude aziridinyl alcohol **8b** to the *N*-Bus aziridinyl alcohol **5j** (>99:1 er, by chiral HPLC analysis of the 2-thionaphthalene ring-opened derivative **6c**).[11]

Several other electrophiles were successfully trapped out using (R_S)-**7**-Li giving adducts **8c**−**g** with similarly complete control at the newly generated aziridine stereocenter (Scheme

(14) (a) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. In *Organolithiums in Enantioselective Synthesis, Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin, 2003; Vol. *5*, pp 139−176. (b) Gawley, R. E.; O'Connor, S.; Klein, R. In *Science of Synthesis*; Snieckus, V., Majewski, M., Eds.; Thieme: Stuttgart, 2006; Vol. 8a, pp 677−757. (c) For a patent claiming enantioselective lithiation/trapping of 3−8-ring saturated *N*-Boc azacycles, see: Deng, X.; Mani, N. (Johnson & Johnson) U.S. Pat. Appl 20060069250, 2006. For recent enantioselective lithiation/trapping of *N*-Boc piperidines, see: (d) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113–2119.

(15) Montagne, C.; Prévost, N.; Shiers, J. J.; Prié, G.; Rahman, S.; Hayes, J. F.; Shipman, M. *Tetrahedron* **2006**, *62*, 8447–8457.

(16) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905.

(17) For a related synthesis of *N*-(diethoxyphosphoryl)aziridine, see: Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis* **1996**, 333–335. The less nucleophilic tert-butylsulfonylamide did not allow a synthesis of **4** by this route.

(18) (a) Davis, F. A.; Liu, H.; Liang, C. -H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929–8935. (b) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251–3260. (c) Arroyo, Y.; Meana, Á.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Tetrahedron* **2006**, *62*, 8525–8532.

(19) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448–454.

(20) X-ray diffraction data was determined by refinement of the Flack enantiopole parameter, see: Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143–1148.

(21) The aziridinyl methanol motif found in **8b**,**d**−**g** is currently of interest in organocatalysts, see: (a) Bonini, B. F.; Capitò, E.; Comes-Franchini, M.; Fochi, M.; Riccia, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **2006**, *17*, 3135–3143. (b) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879–2882.

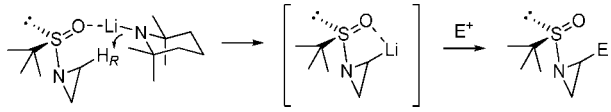
(22) Terminal aziridinyl ketone functionality is present in antimalarial agents, see: (a) Schulz, F.; Gelhaus, C.; Degel, B.; Vicik, R.; Heppner, S.; Breuning, A.; Leippe, M.; Gut, J.; Rosenthal, P. J.; Schirmeister, T. *ChemMedChem* **2007**, *2*, 1214–1224.

(23) Representative procedure for lithiation/electrophile trapping of sulfinyl anion **(**R_S)-**7**-Li: *n*-BuLi (0.56 mL, 1.6 M in hexanes, 0.90 mmol) was added dropwise to a stirring solution of 2,2,6,6-tetramethylpiperidine (0.15 mL, 0.90 mmol) in THF (7 mL) at −78 °C. The solution was then warmed to 25 °C for 20 min and then cooled to −98 °C. TMEDA (0.13 mL, 0.90 mmol) was added, followed by a solution of *N-tert*-butylsulfinyl aziridine (R_S)-**7** (44 mg, 0.30 mmol) in THF (1 mL). After 25 min, pentan-3-one (95 μL, 0.90 mmol) was added. After 1 h, MeOH (1 mL) was added. The solution was warmed to 25 °C over 15 min and saturated aq NH_4Cl (15 mL) and Et_2O (20 mL) added. The organic phase was separated and the aqueous phase re-extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petroleum ether/Et_2O, 70:30) to give (R_S,*R*)-aziridinyl pentan-3-ol **8b** as a white solid (37 mg, 53%).

4).[12,21] While low asymmetric induction was seen at the carbinol carbon in the aziridinyl alcohols **8d**,**e** arising from addition of (R_S)-**7**-Li to prochiral aldehydes, Swern oxidation of **8d** could be used to subsequently generate the corresponding diasteromerically pure sulfinyl ketone[11] in 78% yield.[22]

A tentative explanation of the diastereoselectivity observed in lithiation/electrophile trapping with *N*-*tert*-butylsulfinyl aziridine (R_S)-**7** is indicated in Scheme 5. LTMP may coordinate to the sulfinyl oxygen of (R_S)-**7** and form a prelithiation complex in which a *pro*-*R* hydrogen on the aziridine is closer than a *pro*-*S* hydrogen to the lithium amide, thereby minimizing nonbonded interactions between the *tert*-butyl group and the sterically demanding base. Following deprotonation, the lithiated aziridine undergoes electrophile trapping with retention of configuration.

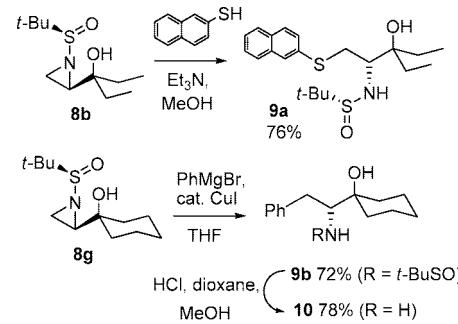
Scheme 5. Possible Origin of Diastereoselectivity in the Lithiation/Electrophile Trapping of *N*-*tert*-Butylsulfinyl Aziridine (R_S)-**7**



Reaction of aziridinyl alcohols **8b**,**g** with 2-thionaphthalene and PhMgBr gave secondary sulfinamides **9a**,**b**, respectively, illustrating regioselective ring-opening and also demonstrating that preoxidation to the more electron-withdrawing *N*-Bus group is not required for such chemistry (Scheme 6). Sulfinyl deprotection of the Grignard-derived adduct **9b** using HCl in dioxane generates 1,2-amino alcohol **10** in which the potentially acid-sensitive tertiary alcohol functionality is preserved.

In summary, this work demonstrates a new access to terminal aziridines by ring-lithiation of *N*-sulfonyl and *N*-sulfinyl protected aziridine, and the products have been shown to undergo a range of synthetically useful ring-opening reactions with nucleophiles. The α-lithiation/electrophile trapping of *N*-*tert*-butylsulfinyl aziridine **7** to provide terminal aziridines **8** is notable not only for overcoming the ring-opening and sulfenic acid elimination pathways previously observed in related systems,[18a] but also for the controlled stereocenter generation adjacent to nitrogen by electrophile incorporation. The latter suggests further opportunities for sulfinamide group utilization in asymmetric synthesis beyond its current importance in sulfinyl imines for stereocontrolled nucleophile incorporation α to nitrogen.[16,24]

Scheme 6. Ring-Opening of *N*-*tert*-Butylsulfinyl Terminal Aziridines **8**



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Supporting Information Available: Preparation and characterization data for aziridines **4**, **5**, **7**, and **8** and amines **6**, **9**, and **10**, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801224G

(24) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z. -H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93–104.