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Synthesis of Optically Active Arylaziridines by Regio- and Stereospecific Lithiation of *N*-Bus-Phenylaziridine

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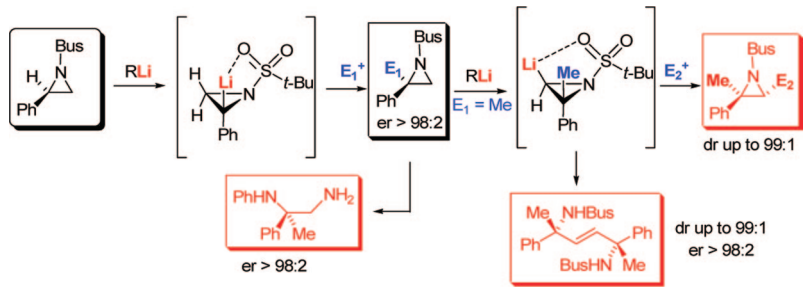
ABSTRACT



α,α-Disubstituted aziridines can be produced in good yields by selective lithiation of *N*-*tert*-butylsulfonyl-2-phenylaziridine (*n*-BuLi/TMEDA, Et_2O) at the benzylic position and subsequent trapping with a range of electrophiles. Repetition of the lithiation/electrophilic trapping sequence provides a stereocontrolled route to trisubstituted aziridines. Using (*R*)-*N*-*tert*-butylsulfonyl-2-phenylaziridine, the α,α-disubstituted aziridines can be produced as single enantiomers (er >98:2), indicating that the intermediate organolithium is configurationally stable. Efficient aziridine ring-opening reactions leading to 1,2-diamines and 1,4-diamines are also reported.

Aziridines are important compounds because of their widespread use in organic synthesis and their presence in many natural products and biologically active molecules.[1] In recent years, a variety of methods have been developed for the synthesis of functionalized aziridines. Of these, aziridinyl anion methodology (AAM), based on the metalation/electrophile trapping of simple, readily available aziridines, has become one of the most useful strategies to this class of compounds.[2] Normally, the presence of an electron-withdrawing group (EWG) on the nitrogen or the carbon atoms of the heterocyclic ring is crucial for successful metalation.[3]

Recently, investigation of lithiation/electrophile trapping of simple 2-arylaziridines[4] established that *N*-alkyl phenylaziridines undergo predominantly *ortho*-lithiation[5] upon treatment with organolithiums, an outcome that is in stark

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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. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.

(2) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1–22. For a special issue on oxiranyl and aziridinyl anions (Florio, S., Ed.), see: (c) Florio, S. *Tetrahedron* **2003**, *59*, 9693.

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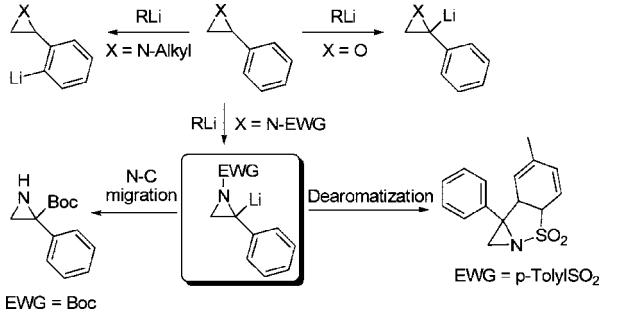
contrast to phenyloxirane,[6] which gives exclusively α-lithiation (Scheme 1).

Scheme 1. Reactivity of Lithiated Arylaziridines

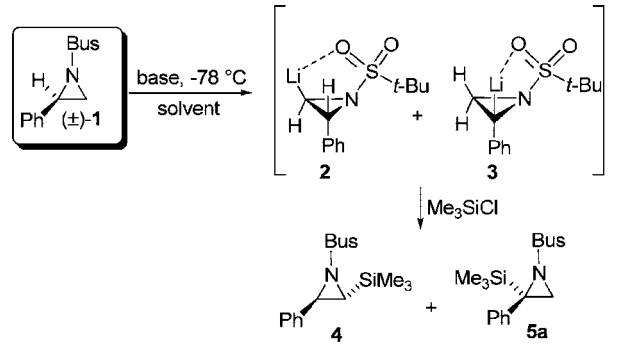


Aware of the considerable utility of α-lithiated aziridines, we sought conditions for the lithiation at the benzylic position of 2-arylaziridines. We envisaged that the presence of an EWG on the aziridine ring nitrogen might help direct lithiation to this site. Initial studies revealed that although *N*-Boc-2-phenylaziridine undergoes the required α-lithiation, fast N → C Boc migration leads to quenching of the initial organolithium (Scheme 1).[5] *N*-Tolylsulfonyl-2-phenylaziridine also undergoes α-lithiation, but this is rapidly followed by a 1,4-like addition of the carbanion to the phenyl ring of the *N*-substituent resulting in dearomatization (Scheme 1).[7] In a bid to counteract this, we turned our attention to the *N*-*tert*-butylsulfonyl-2-phenylaziridine, driven by the awareness that the *tert*-butylsulfonyl (Bus) group is strongly electron-withdrawing, stable to a wide range of reaction conditions, and easily removable under mild acidic conditions.[8] Recently, lithiation/electrophile trapping of unsubstituted and 2-alkylsubstituted *N*-Bus-aziridines has been reported,[3b,9] but no efficient methods for the α-lithiation of *N*-Bus-substituted monoarylaziridines have been disclosed. In this paper, we report conditions for the regioselective α-lithiation of *N*-Bus-2-phenylaziridine **1** and demonstrate its use in the preparation of a range of functionalized arylaziridines.

N-Bus-2-phenylaziridine **1**, prepared as reported,[10] was initially subjected to deprotonation conditions reported for similar aziridines (LTMP, 3 equiv, THF).[3b] Unfortunately, under such conditions a competition between α- and *β*-lithiation was observed as demonstrated by the trapping of organolithiums **2**and **3** with trimethylsilyl chloride (TMSCl) to give **4** and **5a** in a 50:50 ratio (Scheme 2).[11] The *trans* configuration of **4** was unambiguously established by single crystal X-ray diffraction (see Supporting Information).[12] The poor selectivity observed in this reaction can be rationalized in terms of a complex induced proximity effect[13] whereby the Bus group, positioned *anti*- to the Ph ring, directs lithiation to both ring hydrogens that are located *syn* to it.

Other base/solvent combinations were explored to try and improve the regioselectivity. Using LDA (3 equiv) in THF, some preference for the required α-lithiated product was observed (**4**/**5a**; 12:88). Similar results were achieved using *n*-BuLi/TMEDA in THF (**4**/**5a**; 15:85). Finally, using *n*-BuLi/TMEDA in Et_2O facilitated almost exclusively lithiation at the α-position. Capture of the corresponding lithiated intermediate **3** with TMSCl gave aziridine **5a** (86% yield; **5a**/**4** > 99:1) as the sole product (Scheme 2).

Scheme 2. Regioselective Lithiation of *N*-Bus-2-Phenylaziridine



Having developed conditions for the regioselective deprotonation of **1**, the scope of this chemistry was explored by trapping lithiated intermediate **3** with a variety of electrophiles. Thus, deuteration, methylation, tributylstannylation, benzylation, and hydroxyalkylation provided **5b**−**f**, respectively, in moderate to good yields (Table 1). Trapping with aldehydes gave hydroxyalkyl derivatives **5 g**−**i** in good yields

(3) (a) Luisi, R.; Capriati, V.; Di Cunto, P.; Florio, S.; Mansueto, R. *Org. Lett.* **2007**, *9*, 3295–3298. (b) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153–1156. (c) Alezra, V.; Bonin, M.; Mivouin, L.; Policar, C.; Husson, H. P. *Eur. J. Org. Chem.* **2001**, 2589–2594. (d) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779–9791. (e) Montagne, C.; Prevost, N.; Shiers, J. J.; Prie, G.; Rahman, S.; Hayes, J. F.; Shipman, M. *Tetrahedron* **2006**, *62*, 8447–8457. (f) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941–6942. (g) Bisseret, P.; Bouis-Peter, C.; Jacques, O.; Henriot, S.; Eustache, J. *Org. Lett.* **1999**, *1*, 1181–1182. (h) Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839–9847.

(4) Examples of lithiation/substitution of polysubstituted arylaziridines have been reported: (a) Luisi, R.; Capriati, V.; Florio, S.; Ranaldo, R. *Tetrahedron Lett.* **2003**, *44*, 2677–2681. (b) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251–3260.

(5) (a) Luisi, R.; Capriati, V.; Florio, S.; Musio, B. *Org. Lett.* **2005**, *7*, 3749–3752. (b) Hodgson, D. M.; Humphreys, P. G.; Xu, Z.; Ward, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2245–2248.

(6) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448.

(7) (a) Breternitz, H.-J.; Schaumann, E. *Tetrahedron Lett.* **1991**, *32*, 1299–1302. (b) Aggarwal, V.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335–2344.

(8) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604–8608.

(9) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453–3456.

(10) (a) Sharpless, K. B.; Gontcharov, A. V.; Liu, H. U.S. Patent US6008376, 1999. (b) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783–786.

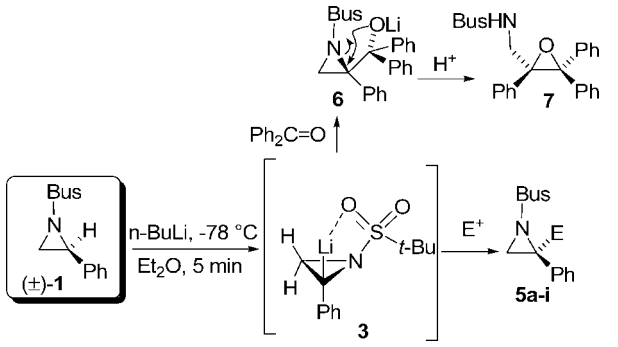
(11) The use of trimethylsilyl chloride allowed easy separation of the regioisomeric products **4** and **5a**.

(12) CCDC 706652 contains the supplementary crystallographic data for compound **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) For a review, see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

and moderate diastereoselectivity.[14,15] Aminomethyl triphenyloxirane **7**, which is most likely the result of an aza-Payne rearrangement[16] of the intermediate aziridine **6**, was obtained when lithiation of **1** was followed by trapping with benzophenone.

Table 1. Lithiation/Electrophile Trapping of Aziridine **1**



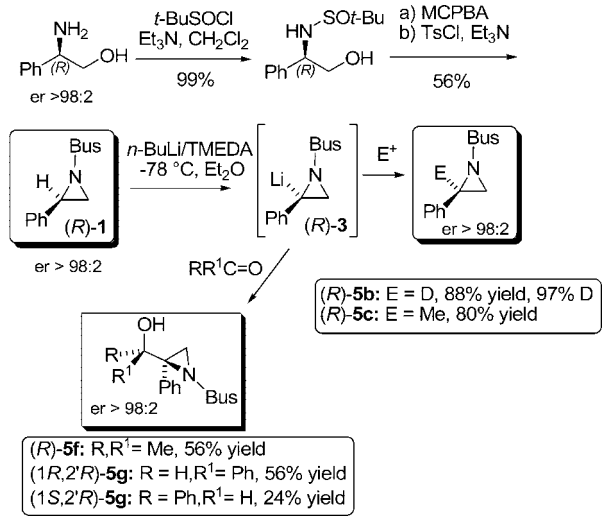
aziridine **5**	electrophile (E^+)	yield (%)[a]	dr[b]
5a	TMSCl	86	
5b	D_2O	88[c]	
5c	MeI	80	
5d	Bu_3SnCl	90	
5e	$PhCH_2Br$	36	
5f	$(Me)_2CO$	56	
5g	PhCHO	80[d]	70:30
5h	*i*-PrCHO	55[d]	80:20
5i	*t*-BuCHO	60[d]	80:20

[a] Isolated yields. [b] Diastereomeric ratio with respect to the newly created alcohol-bearing stereogenic center, ascertained by ^{1}H NMR analysis of the crude product. [c] 97% deuterium incorporation. [d] Combined yield of the separated diastereoisomers.

With a view to developing an approach to stereodefined α,α-disubstituted aziridines using the same lithiation/electrophile trapping sequence, the preparation of enantiomerically enriched *N*-Bus-2-phenylaziridine (*R*)-**1** was undertaken. This compound was prepared from (−)-phenylglycinol by a high-yielding sequence that involved *N*-sulfinylation, oxidation, *O*-tosylation, and cyclization (Scheme 3).

Lithiation with *n*-BuLi/TMEDA in Et_2O at −78 °C resulted in the generation of (*R*)-**3**, which proved to be configurationally stable as demonstrated by comparison of optical rotation values and HPLC analysis of deuterated compound (*R*)-**5b** (er >98:2) with the chiral aziridine (*R*)-**1**. In a similar way, (*R*)-**3** reacted with MeI, Me_2CO, and

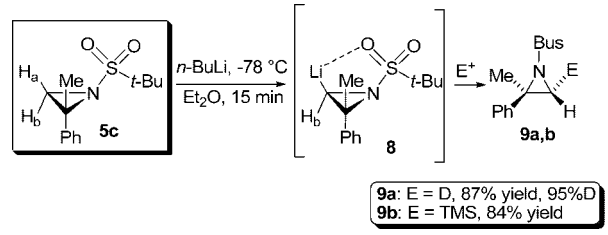
Scheme 3. Synthesis of Optically Active Arylaziridines



PhCHO to give the corresponding products (*R*)-**5c**, (*R*)-**5f**, and diastereoisomers (1*R*,2′*R*)-**5g** and (1*S*,2′*R*)-**5g** (Scheme 3).[17,18]

To develop a stereoselective route to optically active trisubstituted arylaziridines and to further assess the role of the *N*-Bus group in the lithiation reaction, a second functionalization of **5c** was investigated. Lithiation/deuteration and lithiation/silylation sequences resulted in the formation of *N*-Bus phenylaziridine **9a,b** as single diastereomers (dr >99:1) (Scheme 4). This second lithiation involves stereoselective deprotonation of H_a *cis* to the aziridine methyl group (Scheme 4), as deduced by analysis of 1D-selective NOESY experiments conducted on aziridine **5c**.[19] Equally highly regioselective was the silylation reaction leading to aziridine **9b**, whose stereochemistry was also ascertained by low temperature 1D-selective NOESY experiments conducted on a slowly equilibrating mixture of two nitrogen invertomers.

Scheme 4. Double Functionalization of Aziridine **5c**



To further demonstrate the utility of the α,α-disubstituted aziridines, optically active aziridine (*R*)-**5c** was subjected to two further transformations. When it was reacted with aniline

(14) The structure and relative configuration of the major diastereomer of the trapping reaction with benzaldehyde was confirmed by X-ray analysis (see Supporting Information).

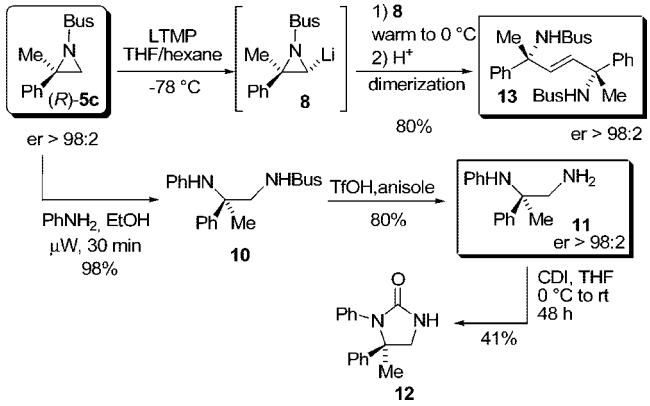
(15) CCDC 706653 contains the supplementary crystallographic data for compound **5g**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) (a) Nakai, K.; Ibuka, T.; Otaka, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **1995**, *36*, 6247–6250. (b) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145–154.

(17) The enantiomeric ratios were determined by comparison with a racemic sample by using chiral HPLC analysis or by ^{1}H NMR analysis in the presence of a chiral solvating agent (see Supporting Information).

under microwave irradiation, sulfonamide **10** (er >99:1) was obtained as a result of a highly regioselective benzylic ring opening.[20] Sulfonamide **10** was further subjected to Bus-deblocking with TfOH/anisole to furnish diamine **11**. In order to confirm the regioselectivity of the ring-opening reaction, diamine **11** was transformed into the imidazolidinone **12** upon cyclization with *N*,*N*′-carbonyldiimidazole (CDI) (Scheme 5).[21] NOE measurements conducted on **12** established that aziridine opening of **5c** had occurred at the benzylic carbon without loss of stereochemical integrity (see Supporting Information). Alternatively, by exploiting the known carbenoidic character of lithiated aziridines, chiral diamino alkene **13**[22] bearing two quaternary centers was obtained by lithiation of (*R*)-**5c** with LTMP, which underwent ring-opening and dimerization upon warming to 0 °C.[23]

Scheme 5. Synthesis of 1,2- and 1,4-Diamines



In conclusion, an efficient method for a regioselective benzylic lithiation/functionalization of 2-phenylaziridines has been established allowing access to di- and trisubstituted aziridines with defined stereochemistry. The use of an *N*-Bus group is critical for success. Moreover, it has been shown that enantioenriched α-lithiated *N*-Bus-2-phenylaziridine is configurationally stable so that reaction with electrophiles occurs with complete retention of configuration, giving access to chiral α,α-disubstituted aziridines. The synthetic utility of these aziridines has been demonstrated by the transformation of (*R*)-**5c** into 1,2- and 1,4-diamines[24] by ring opening and eliminative dimerization reactions, respectively. Work is ongoing on the development of new synthetic strategies based on AAM and on clarifying the role of the Bus group on the regiochemical outcome of the reactions reported herein.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" by the University of Bari. We thank EPSRC (EP/C007999/1) for the provision of mass spectrometers at the University of Warwick, and the EPSRC X-ray Crystallographic Service for recording the crystallographic data.

Supporting Information Available: Experimental procedures and compound characterization data for aziridine **5a**−**1**, **9a,b**, **10**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The absolute configuration of (*R*)-**5c** and (*R*)-**5f** was assigned assuming that reaction proceeds with retention of configuration [cf. (*R*)-**5b**]. For the two diastereoisomers (1*R*,2′*R*)-**5g** and (1*S*,2′*R*)-**5g**, the absolute configuration of the major isomer was deduced by comparison with the spectral data of the corresponding racemic compounds (**5g**) for which X-ray analysis was available (see text).

(19) The ^{1}H NMR spectrum of deuterated aziridine **9a** (%D >95%) lacks the signal corresponding to H_a. Strong reciprocal NOEs were seen within **5c** between H_a and the aziridine Me group, confirming their *syn* relationship (see Supporting Information).

(20) Low levels of regioselectivity were observed in the ring-opening reactions using aliphatic amines.

(21) Wright, W. B., Jr *J. Heterocycl. Chem.* **1965**, 41–43.

(22) The (*E*)-configuration was ascertained by measurement of the $^3J_{H-H}$ coupling constant on the ^{13}C satellite signals in the ^{1}H NMR spectrum; see Supporting Information.

(23) This reaction is the result of the carbenoidic behavior of α-heterosubstituted carbanion; see: (a) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756. (b) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 935–938.

(24) For the usefulness of diamino compounds, see: (a) Hems, W. P.; Groarke, M.; Zanotti-Gerosa, A.; Grasa, G. A. *Acc. Chem. Res.* **2007**, *40*, 1340–1347. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627. (c) Lake, F.; Moberg, C. *Eur. J. Org. Chem.* **2002**, *317*, 9–3188.