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Intramolecular Cyclopropanation of Unsaturated Terminal Aziridines

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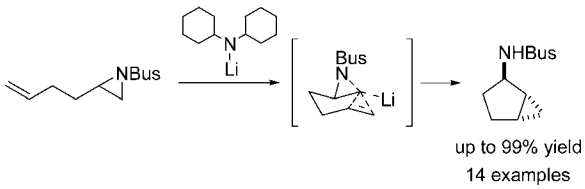
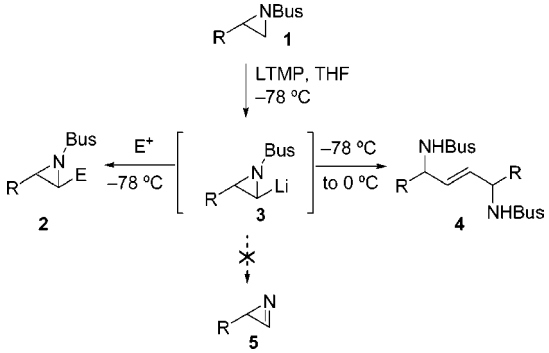
ABSTRACT



Regio- and stereoselective deprotonation of bishomoallylic terminal *N*-Bus (Bus = *tert*-butylsulfonyl)-protected aziridines generate aziridinyl anions that undergo diastereoselective intramolecular cyclopropanation giving *trans*-2-aminobicyclo[3.1.0]hexanes in good to excellent yields.

Aziridine chemistry is currently seeing increasing research interest.[1] The widespread availability of terminal aziridines (typically accessed from terminal alkenes[2] or imines[3]) and recent reports on the synthesis of enantiomerically pure terminal aziridines from epoxides[4] suggest that new methods to utilize such aziridines would be of considerable value.[5] With this in mind we recently reported the diastereoselective lithium 2,2,6,6-tetramethylpiperidide (LTMP)-induced deprotonation-electrophile trapping of terminal *N*-Bus (*tert*-butylsulfonyl)[6]-protected aziridines **1** to give *trans*-disubstituted aziridines **2** (Scheme 1).[7] We also recently demonstrated the

Scheme 1. Reactivity of α-Lithiated Aziridine **3**[a]



[a] See refs 7 and 8.

LTMP-induced dimerization of enantiopure terminal *N*-Bus-protected aziridines to give enantiopure 2-ene-1,4-diamines **4**.[8] This latter work was the first report demonstrating carbenoid reactivity of α-lithiated terminal aziridines **3**,[9] something that was perhaps surprising given the potential for elimination leading to 2*H*-azirines **5** (Scheme 1).[10,11]

We recently revisited and advanced the LTMP-induced intramolecular cyclopropanation of unsaturated terminal

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(1) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258.
(2) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845.
(3) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587−1589.
(4) (a) Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952−3954. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973−3975. Also, for reviews on enantioselective aziridination, see: (c) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 607−618. (d) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919.
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(6) Sun, P.; Weinreb, S. M.; Shang, M. J. *J. Org. Chem.* **1997**, *62*, 8604−8608.
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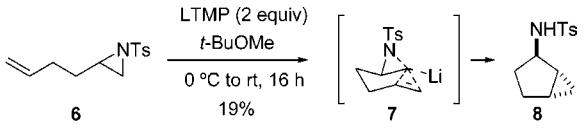
epoxides[12] to give *trans*-bicyclo[3.1.0]hexan-2-ols in excellent yields and diastereoselectivity.[13] In the present communication, we report adaptation of this methodology with unsaturated terminal aziridines to achieve access to 2-aminobicyclo[3.1.0]hexanes. The latter structural motif is found in analgesics,[14] antiviral agents,[15] and antiobesity therapeutics.[16]

Preliminary evaluation of our LTMP-mediated intramolecular cyclopropanation protocol[13] with terminal unsaturated aziridines used *N*-tosyl aziridine **6**,[2,17] which on addition of LTMP over 1 h gave bicyclic amine **8** as a single *trans*-diastereomer,[18] albeit in only 19% yield (Scheme 2). The

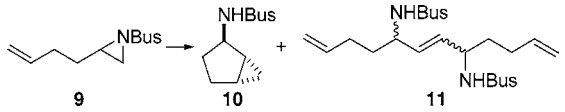
Scheme 2. Synthesis of Bicyclic Amine **8**



yield of bicyclic amine **8** could be increased to 37% by using a slightly less hindered lithium amide in the reaction, lithium dicyclohexylamide ($LiNCy_2$, conditions otherwise as Scheme 2).[19]

On the basis that complications arising from competitive *ortho*-lithiation of the tosyl group could be contributing to the low yields of **8**,[20] other *N*-protecting groups not (or less) susceptible to this process were screened. The *t*-Bu,[21] Boc,[22] trisyl,[23] mesitylsulfonyl, *p*-methoxybenzenesulfonyl, and Bus[6−8] *N*-protected variants of aziridine **6** were examined under the cyclopropanation conditions using LTMP and also $LiNCy_2$. However, use of all of these protecting groups led to <15% yields of the corresponding bicyclic amines, apart from Bus, which after 16 h resulted in a 23% yield of amine **10**[24] when LTMP was used and a 38% yield with $LiNCy_2$ (Table 1, entries 1 and 2).[25] 2-Ene-1,4-diamine **11**[8] (as a mixture of diastereomers) was also isolated in these reactions in 44% and 35% yields, respectively. It is noteworthy that significant levels of cyclopropanation occur with *N*-Bus aziridine **9**, given the propensity of this and related *N*-Bus aziridines to efficently dimerize under closely related conditions (Scheme 1).[8] Variation in the experimental conditions with *N*-Bus aziridine **9** was then studied further, with the aim of favoring cyclopropanation relative to dimerization (Table 1).

Table 1. Optimization of the Synthesis of Bicyclic Amine **10**[a]



						yield (%)	
entry	base	equiv	solvent	conc (M)	temp	**10**	**11**
			base added to aziridine **9** over 1 h				
1	LTMP	2	*t*-BuOMe	0.07	0 °C to rt	23	44
2	$LiNCy_2$	2	*t*-BuOMe	0.07	0 °C to rt	38	35
			aziridine **9** added to base over 1 h				
3	LTMP	2	*t*-BuOMe	0.07	0 °C to rt	41	23
4	$LiNCy_2$	2	*t*-BuOMe	0.07	0 °C to rt	54	6
5	$LiNCy_2$	2	*t*-BuOMe	0.07	0 °C	65	6
6	$LiNCy_2$	2	*t*-BuOMe	0.03	0 °C	68	<5
7	$LiNCy_2$	2	*t*-BuOMe	0.03	−10 °C	67	7
8	$LiNCy_2$	2	*t*-BuOMe	0.03	−40 °C	67	16
9	$LiNCy_2$	3	*t*-BuOMe	0.03	0 °C	73	<5
10	LTMP	3	*t*-BuOMe	0.03	0 °C	69	10
11	LDA	3	*t*-BuOMe	0.03	0 °C	63	9
12	$LiNCy_2$	3	THF	0.03	0 °C	29	36
13	$LiNCy_2$	3	Hexane	0.03	0 °C	71	<5
14	$LiNCy_2$	3	Et_2O	0.03	0 °C	68	<5
15[b]	$LiNCy_2$	3	*t*-BuOMe	0.03	0 °C	72	<5
16[c]	$LiNCy_2$	3	*t*-BuOMe	0.03	0 °C	75	<5

[a] 16 h reaction duration, unless otherwise indicated. [b] 1 h reaction duration. [c] 2 h reaction duration.

Reversing the addition order, so that aziridine **9** was added dropwise to the base, led to increased yields of bicyclic amine

(9) For recent reviews on aziridinyl and oxiranyl anions, see: (a) Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry. Florio, S., Ed.; *Tetrahedron* **2003**, *59*, 9683−9864. (b) Hodgson, D. M.; Bray, C. D. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; pp 145−184. (c) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1−22.

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(11) Carbene reactivity has been observed for ring-fused aziridines, where 2*H*-azirine formation is less likely; see: Müller, P.; Riegert, D.; Bernardinelli, G. *Helv. Chim. Acta* **2004**, *87*, 227−239. See also: Hodgson, D. M.; Štefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234−2235.

(12) (a) Originally observed as minor reaction pathway; see: Crandall, J. K.; Lin, L.-H. *J. Am. Chem. Soc.* **1967**, *89*, 4526−4527. (b) Apparu, M.; Barelle, M. *Tetrahedron* **1978**, *34*, 1691−1697.

(13) (a) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664−8665. (b) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *Synthesis* **2005**, 2264−2266.

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(15) (a) Rodriquez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi, Jr., J. J. *J. Med. Chem.* **1994**, *37*, 3389−3399. (b) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3379−3747. (c) Tchilibon, S.; Joshi, B. V.; Kim, S.-K.; Duong, H. T.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2005**, *48*, 1745−1758. (d) Lee, J. A.; Moon, H. R.; Kim, H. O.; Kim, K. R.; Lee, K. M.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jacobsen, K. A.; Jeong, L. S. *J. Org. Chem.* **2005**, *70*, 5006−5013.

(16) McBriar, M. D.; Guzik, H.; Xu, R.; Paruchova, J.; Li, S.; P. A.; Clader, J. W.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neill, K.; Spar, B.; Weig, B. *J. Med. Chem.* **2005**, *48*, 2274−2277.

(17) Lapinsky, D. J.; Bergmeier, S. C. *Tetrahedron* **2002**, *58*, 7109−7117.

(18) Determined by NOE analysis and by comparison with the analogous epoxide cyclopropanation product; see ref 13a.

(19) Use of LDA under these conditions gave 30% yield of amine **8**.

(20) Huang, J.; O'Brien, P. *Tetrahedron Lett.* **2005**, *46*, 3253−3256.

(21) (a) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941−6942. (b) Vedejs, E.; Prasad, A. S. B.; Kendall, J. T.; Russel, J. S. *Tetrahedron* **2003**, *59*, 9849−9857.

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

(23) Huang, J.; O'Brien, P. *Chem. Commun.* **2005**, 5696−5698.

(24) Isolated as a single diastereomer. Structure supported by X-ray crystallographic analysis: CCDC 292434 available at http://www.ccdc.cam.ac.uk.

(25) With $LiNCy_2$, quenching directly after addition of the aziridine **9** (1 h) indicated incomplete reaction; **9** (52%), amine **10** (10%), and dimer **11** (22%) were obtained.

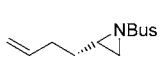
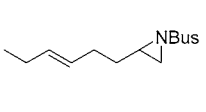
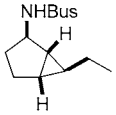
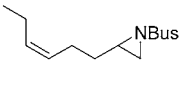
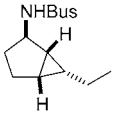
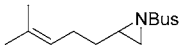
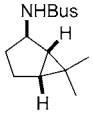
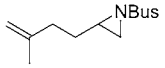
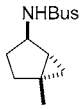
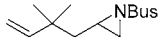
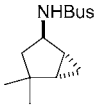
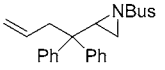
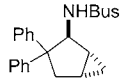
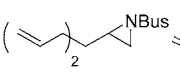
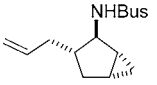
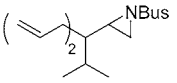
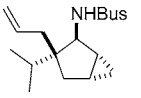
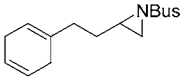
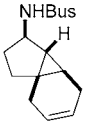
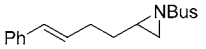
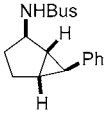
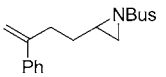
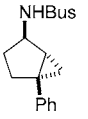
10 (Table 1, entries 3 and 4) and reduced dimer **11**, the latter reduction being particularly noticeable when using $LiNCy_2$ (entries 2 and 4). Maintaining the reaction temperature at 0 °C further increased the yield of bicyclic amine **10** (entry 5). Halving the reaction concentration led to only a further modest increase in yield, but no dimer was now isolated (entry 6). Decreasing the reaction temperature to −10 or −40 °C maintained the yields of bicyclic amine **10**, but the amount of dimer **11** rose (entries 7 and 8). Increasing the quantity of $LiNCy_2$ to 3 equiv allowed a 73% yield of desired bicyclic amine **10** to be obtained, with only trace amounts of 2-ene-1,4,-diamine **11** detectable by ^{1}H NMR analysis of the crude reaction mixture (entry 9).[26] Re-examination of LTMP and LDA under these latter conditions resulted in only slightly lower yields of amine **10**; however, dimer formation was more noticeable (entries 10 and 11). With $LiNCy_2$ the process was relatively insensitive to switching solvent from *t*-BuOMe to ether or hexane (entries 13 and 14), but dimer formation increased significantly when using THF[8] (entry 12).

Finally, quenching the reaction in *t*-BuOMe directly after addition of the aziridine **9** (1 h) and also 1 h after addition indicated essentially complete reaction (entries 15 and 16); this is in stark contrast to when $LiNCy_2$ was added to the aziridine.[25] Deprotonation (and cyclopropanation) of the aziridine **9** is therefore rapid when it is added to the base over 1 h at 0 °C. Perhaps dimerization is minimized under these latter conditions because deprotonation of more than one aziridine is unlikely to occur from a single lithium amide aggregate.[27] In contrast, when the base is added to the aziridine, this may create a localized high concentration of lithiated aziridine (due to the aggregated nature of the lithium amide), which allows dimerization to become competitive with intramolecular cyclopropanation.

The optimized conditions (Table 1, entry 16) were subsequently applied to a variety of other unsaturated terminal aziridines to assess the scope of the method (Table 2).

No erosion of ee was observed for cyclopropanation of an enantiopure terminal aziridine (Table 2, entry 1).[29] The process tolerates di- and trisubstituted alkenes (entries 2−5), and the stereochemistry of the bicyclic amines **13b**,**c** demonstrates that cyclopropanation occurs stereospecifically (entries 2 and 3).[18] The lower yield with *cis*-alkene **12c** was associated with noticeably increased dimer signals in the ^{1}H NMR spectrum of the crude product; this suggests cyclopropanation was slowed, which could be due to the ethyl substituent residing axial in the proposed chairlike transition state (cf. Scheme 2). Substitution on the link between the aziridine and alkene functionality led to very efficient cyclopropanation (entries 6−9). Similarly to observations made with intramolecular cyclopropanation of epoxides,[13] no competitive aromatic C−H insertion was observed (entry 7). Efficient selection between diastereotopic allyl groups

Table 2. Bicyclic Amines from Unsaturated Terminal Aziridines[a]

entry	aziridine **12**	amine **13**	time	yield (%)
1			2 h	**13a** 74
2			3 h	**13b** 85
3			4 h	**13c** 46
4			2 h	**13d** 56
5			2 h	**13e** 81
6			1.5 h	**13f** 99
7			2 h	**13g** 85
8			2 h	**13h** 98
9			2 h	**13i** 98
10			3 h	**13j** 80
11			2 h	**13k** 47
12			3 h	**13l** 90

[a] See ref 28.

(26) Use of *N*-Ts aziridine **6** under these conditions gave a 47% yield of amine **8**.

(27) (a) Aubrecht, K. B.; Collum, D. B. *J. Org. Chem.* **1996**, *61*, 8674−8676. (b) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567−5572.

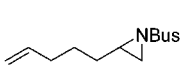
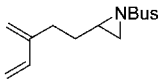
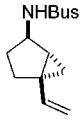
(28) **General Procedure.** *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol) was added dropwise to a stirred solution of dicyclohexylamine (0.30 mL, 1.5 mmol) in *t*-BuOMe (5 mL) at −78 °C under argon. Following warming to room temperature over 30 min, the reaction was cooled to 0 °C, a solution of aziridine (0.5 mmol) in *t*-BuOMe (10 mL) at 0 °C was added via cannula over 1 h, and the reaction left to stir at 0 °C. On completion of the reaction (TLC monitoring), saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL) were added. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O) gave the bicyclic amine.

(29) Determined by chiral GC analysis.

occurred (entries 8 and 9) and synthesis of a tricyclic system could also be achieved (entry 10). Aziridinyl-substituted styrenes also underwent cyclopropanation (entries 11 and 12). Access to 2-amino-5-aryl substituted bicyclo[3.1.0]hexanes such as in entry 12 is of interest in the context of antiobesity therapeutics.[16]

We also investigated the cyclopropanation of trishomoallylic aziridines (Table 3). Trishomoallylic aziridine **14a** underwent cyclopropanation in low yield (Table 3, entry 1), although the bicyclic amine was isolated as a single diastereomer that was assigned *trans* stereochemistry by comparison with the analogous trishomoallylic epoxide cyclopropanation product.[13] Significant quantities of 2-ene-1,4-diamine were observed in the ^{1}H NMR of the crude reaction mixture, so the low yield of amine **15a** probably reflects a slower cyclopropanation rate compared to the corresponding homoallylic aziridine **9**.

Table 3. Cyclopropanation with Trishomoallylic Aziridines

entry	aziridine **14**	amine **15**	time[a]	yield (%)	
1			4 h	**15a**	34
2			3 h	**15b**	85

Intrigued as to whether this result could be turned to our advantage, an aziridine containing both bis- and trishomoallyl functionality was synthesized and subjected to the reaction conditions (entry 2). Pleasingly, an 85% yield of a 2-amino bicyclo[3.1.0]hexane **15b** containing a potentially useful vinyl cyclopropane moiety[30] was obtained.

In conclusion, we have demonstrated a new facet of aziridine chemistry, the ability of aziridines, following lithiation, to undergo cyclopropanation. The scope of this process has been examined, and a variety of synthetically useful bicyclic amines[14−16] have been synthesized as single diastereomers in good to excellent yields. These amines retain a useful nitrogen protecting group[6] to enable further synthetic transformations. Work is ongoing in the area of aziridine cyclopropanation and the synthetic utility of the resulting bicyclic amines.

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Supporting Information Available: Characterization data for aziridines **12** and **14** and amines **8**, **10**, **13**, and **15**, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060101N

(30) (a) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247−335. (b) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1992; Vol. 5, pp 899−970. (c) Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* **2003**, 1454−1462. (d) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277−2279.