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Dimerization and Isomerization Reactions of α-Lithiated Terminal Aziridines

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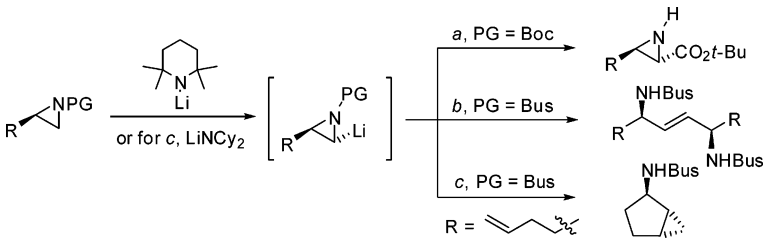
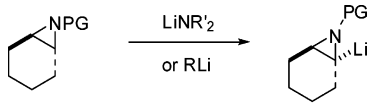


The scope of dimerization and isomerization reactions of α-lithiated terminal aziridines is detailed. Regio- and stereoselective deprotonation of simple terminal aziridines with lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium dicyclohexylamide ($LiNCy_2$) generates *trans*-α-lithiated terminal aziridines. These latter species can then undergo dimerization or isomerization reactions depending on the nature of the *N*-protecting group. α-Lithiated terminal aziridines bearing *N*-alkoxycarbonyl (Boc) protection undergo *N*- to *C*-[1,2] migration to give N−H *trans*-aziridinylesters. In contrast, aziridines bearing *N*-organosulfonyl [*tert*-butylsulfonyl (Bus)] protection undergo rapid dimerization to give 2-ene-1,4-diamines or, if a pendant alkene is present, diastereoselective cyclopropanation to give 2-aminobicyclo[3.1.0]hexanes. All of these reactions were used as key steps in the preparation of synthetically and biologically important targets.

Introduction

Aziridines are useful synthetic intermediates[1] that are seeing increasing research interest, both in their synthesis and elaboration.[2,3] Treatment of a suitably *N*-protected aziridine **1** (PG = protecting group) with a hindered lithium amide, or an organolithium/diamine combination typically results in lithiation of the aziridine ring to give an α-lithiated aziridine **2**, in a similar fashion to their more thoroughly studied epoxide cousins (Scheme 1).[4]

SCHEME 1. Aziridine α-Lithiation



1 **2**

In the absence of an anion-stabilizing group lithium carbenoid **2** is rather unstable, which is attributable to the potential for

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(4) For recent reviews of lithiated epoxide and aziridine chemistry, see: (a) Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry. Florio, S., Ed. *Tetrahedron* **2003**, *59*, 9683−9864. (b) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; Wiley and Sons: New York, 2004; pp 1165−1242. (c) Hodgson, D. M.; Bray, C. D. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 145−184. (d) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1−22. (e) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure. Appl. Chem.* **2007**, *79*, 269−280.

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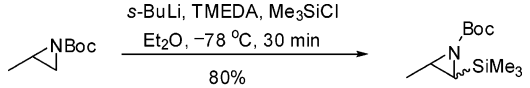
α-elimination driven by relief of aziridine ring-strain;[5] as such, most studies to date have focused on aziridines bearing anion-stabilizing substitution at the site of metallation. The nature of the substituent alters the reactivity profile of the lithium carbenoid species markedly: α-lithiated aziridines bearing an anion-stabilizing group undergo electrophile trapping reactions,[4] whereas those derived from disubstituted alkenes have been shown to react by carbenoid pathways such as C−H insertion,[6] reductive elimination,[7] and conversion into alkynyl amino alcohols.[7b,8] α-Lithiated aziridines without substitution at the site of lithiation (i.e., those derived from terminal aziridines) have received little attention to date. Although there are examples of α-lithiated aziridines generated by tin−lithium exchange[9] and by activation of the aziridine ring by complexation with a Lewis acid,[10] prior to our studies in this area,[11] only a single account existed of the direct hydrogen−lithium exchange reaction to generate an α-lithiated terminal aziridine: the *N*-Boc aziridine of propene **3** together with TMEDA and an excess of Me_3SiCl was treated with *s*-BuLi at −78 °C to give a trans/cis[12] mixture of aziridinylsilanes **4** (Scheme 2).[13]

SCHEME 2. In Situ Lithiation−Silylation[13]



3 **4**

In this paper we report in detail our studies which significantly expand the area of α-lithiated terminal aziridine chemistry. The isomerization of α-lithiated *N*-Boc aziridines to N−H *trans*-aziridinylesters,[14] the dimerization of α-lithiated *N*-Bus aziridines to 2-ene-1,4-diamines,[15] and the intramolecular cyclopropanation of α-lithiated unsaturated *N*-Bus aziridines to *trans*-2-aminobicyclo[3.1.0]hexanes[16] is described.

Results and Discussion

Seeking to extend the chemistry of Beak and co-workers (Scheme 2), we considered whether our previously developed protocol for the diastereoselective in situ lithiation/silylation of terminal epoxides using a mixture of the sterically demanding lithium 2,2,6,6-tetramethylpiperide (LTMP) and Me_3SiCl[17] could be applied to a regio- and diastereoselective synthesis of *trans*-α,*β*-aziridinylsilanes.

The synthesis of terminal *N*-Boc aziridine **5** was accomplished by radical mediated amino-bromination of 1-hexene,[18] followed by aziridine ring-closure on treatment with NaH (Scheme 3). With aziridine **5** in hand, in situ lithiation/silylation was found to be possible at −78 °C, giving α,*β*-aziridinylsilane **6** as a single trans-diastereomer, in 69% yield. In trying to extend this chemistry further, we investigated the use of external electrophiles. However, reaction of terminal *N*-Boc aziridine **5** with LTMP at −78 °C for 90 s, followed by the addition of CD_3OD as an external electrophile, did not lead to any of the expected trans-deuterated *N*-Boc aziridine; instead, a 31% yield of N−H aziridinylester **7** was isolated as a single diastereomer along with 50% recovered starting material with 0% D incorporation. The stereochemistry of ester **7** was initially assigned trans due to previously observed trans-selective lithiation/silylation by the sterically demanding LTMP with terminal epoxides and *N*-Bus aziridines,[19] and this assignment was later supported by crystallographic analysis of a related aziridinylester prepared by similar chemistry (vide infra).

It appeared that a *N*- to *C*-[1,2] lithiation-induced shift had occurred resulting in synthetically valuable aziridinylester functionality,[20] along with concomitant *N*-deprotection. Although lithiation-induced *N*- to *C*-1,2-shifts are known,[9,21] to the best of our knowledge only a single isolated example of this type of *N*-Boc aziridine 1,2-migration has been previously noted.[21e] In this latter work, the *N*-Boc aziridine of styrene was treated with *s*-BuLi in THF at −98 °C to give a phenyl-stabilized α-lithiated aziridine that underwent migration to give 2-phenyl-2-Boc aziridine (90%). As this migration is only mentioned as an undesired byproduct, albeit in excellent yield, we considered that the [1,2] shift of an α-lithiated terminal *N*-Boc aziridine was of sufficient synthetic novelty and potential to investigate further. Since terminal *N*-Boc aziridines are simple to access in an enantiopure manner in two steps from a racemic terminal epoxide,[2d] the migration reaction could potentially allow straightforward access to important enantiopure N−H aziridinylesters.[20]

The first necessity was to improve the yield of the [1,2] shift reaction. As only a mixture of aziridinylester **7** and starting material **5** had been returned from leaving the reaction for 90 s, then initially the reaction time was investigated (Table 1).

Simply by increasing the reaction duration prior to quenching led to an excellent 90% yield of aziridinylester **7** after 90 min (entries 1−4). The reactions were remarkably clean with no

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SCHEME 3. Terminal *N*-Boc Aziridine Synthesis and Lithiation−Electrophile Trapping

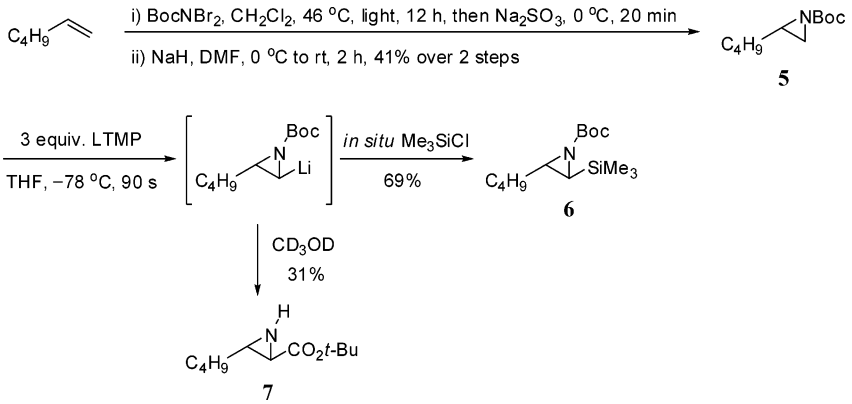
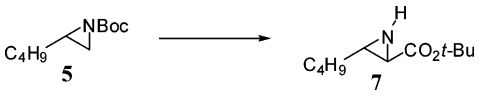


TABLE 1. Optimization of Lithiation-Induced Migration



entry	base (equiv)	solvent	temp (°C)	time	recvd **5** (%)	yield of **7** (%)
1	LTMP (3)	THF	−78	90 s	50[a]	31
2	LTMP (3)	THF	−78	5 min	42[a]	37
3	LTMP (3)	THF	−78	60 min	2[a]	88
4	LTMP (3)	THF	−78	90 min	0	90
5	LTMP (3)	Et_2O	−78	90 min	98[a]	0
6	LTMP (3)	pentane	−78	90 min	10	24
7	LTMP (3)	*t*-BuOMe	−78	90 min	12	34
8	LDA (3)	THF	−78	90 min	98	0
9	$LiNCy_2$ (3)	THF	−78	90 min	98	0
10	LTMP (0.1)	THF	−78	12 h	*b*	trace
11	LTMP (0.5)	THF	−78	12 h	86	5
12	LTMP (1.1)	THF	−78	90 min	49	50
13	LTMP (2)	THF	−78	90 min	26	64
14	LTMP (3)	THF	−78 to 0	90 min	0	74
15	LTMP (3)	THF	−78 to rt	90 min	0	0
16	LTMP (3)	THF	0	90 min	0	60
17	*s*-BuLi (1.2)	THF	−98	5 min	0	56

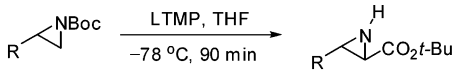
[a] 0% D incorporation observed following quenching reaction with CD_3OD. [b] Not determined.

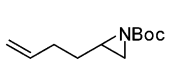
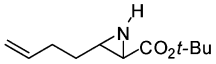
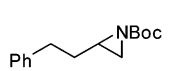
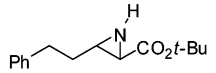
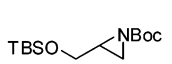
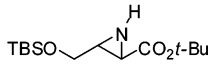
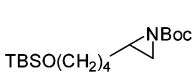
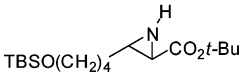
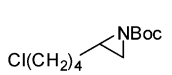
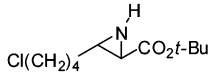
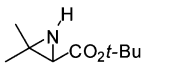
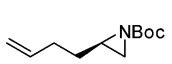
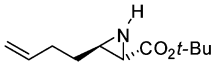
evidence of any 2-ene-1,4-diamine (as a result of carbene dimerization, vide infra) observed by careful analysis of the crude reaction mixture by TLC and ^1H NMR spectroscopy.

Changing the solvent to diethyl ether resulted in shutting down the migration reaction completely (entry 5): quenching the reaction in Et_2O after 90 min with CD_3OD resulted in 0% D incorporation into aziridine **5**, implying that no lithiation was occurring at −78 °C (entry 5). Changing the solvent to pentane or *t*-BuOMe did result in small amounts of the desired aziridinylester **7**, but considerable amounts of unidentified byproducts were also returned from these reactions (entries 6 and 7). Using the less basic lithium amides LDA or $LiNCy_2$[22] resulted in no migration occurring (entries 8 and 9). As treatment of the *N*-Boc aziridine would generate an aziridine lithium amide (following [1,2] shift), it was considered whether catalytic LTMP could be used in the reaction, with the aziridine lithium amide regenerating LTMP from TMP. However, substoichiometric amounts of LTMP only resulted in poor conversions, indicating that the reaction is not catalytic in LTMP (entries 10 and 11). Using 1.1 or 2 equiv of LTMP also resulted in poor conversion to the product, with starting aziridine **5** recovered (entries 12 and 13). Allowing the temperature of the reaction to rise from −78 °C to 0 °C gave a 74% yield of the desired aziridinylester **7**, although increasing the temperature to ambient temperature resulted in decomposition (entries 14 and 15). Running the reaction at 0 °C throughout is also possible, though a decreased yield (60%) was observed (entry 16). Finally, direct application of the conditions of Florio and co-workers[21e] gave a reduced 56% yield of aziridinylester **7**, along with several unidentified byproducts (entry 17).

With conditions that gave access to *trans*-aziridinylester **7** in 90% yield (entry 4), the scope of the reaction was next investigated with a variety of terminal *N*-Boc aziridines (Table 2).

TABLE 2. Scope of Lithiation-Induced Migration Reaction



entry	aziridine **8**	aziridinylester **9**	yield (%)
1			**9a** 86
2			**9b** 79
3			**9c** 90
4			**9d** 87
5			**9e** 84
6			**9f** 67[a]
7			(*S,R*)-**9a** 84
8		–	**9g** 0

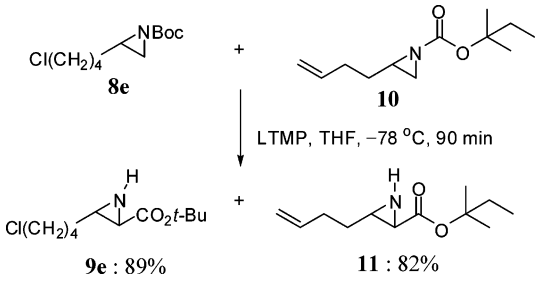
[a] Reaction warmed from −78 °C to 0 °C for 90 min.

Tethered olefin and aromatic functionality were tolerated with potentially competitive allylic deprotonation,[23] cyclopropana-

tion,[16] or benzylic deprotonation all avoided under the reaction conditions (Table 2, entries 1 and 2). X-ray crystallographic analysis of aziridinylester **9b** supported the assigned trans-stereochemistry.[24] TBS protected alcohols were tolerated (entries 3 and 4),[25] along with a potentially eliminable/displaceable primary chloride (entry 5). Using 2,2-disubstituted aziridine **8f**[2a] only returned starting material at −78 °C; however, on warming to 0 °C a 67% yield of the desired aziridinylester was isolated (entry 6). No degradation of ee was observed under the reaction conditions (entry 7),[24] though the reaction was not extendable to 2,3-disubtituted aziridines: attempted reaction of aziridine **8g**[26] returned starting material at −78 °C (entry 8), presumably due to unfavorable steric interactions. Warming the reaction from −78 °C to 0 °C gave a mixture of starting material and decomposition products and, consistent with results observed with aziridine **5** (Table 1, entry 15), only decomposition was observed upon warming to room temperature.

Due to the rapidity of carbenoid dimerization of α-lithiated *N*-Bus terminal aziridines (vide infra), we sought to ascertain whether the *N*- to *C*-migration reaction was inter- or intramolecular in nature. A crossover experiment was designed[21c] whereby different *N*-protecting groups would allow these two processes to be distinguished (Scheme 4). Reaction of a 1:1 mixture of *N*-Boc aziridine **8e** and *N*-*tert*-amylcarboxy aziridine **10** under the optimized migration conditions only gave a mixture of aziridinylesters **9e** and **11**.[27] No evidence of crossover of either of the protecting groups was observed following careful analysis of the crude reaction mixture and purified products, indicating the migration reaction is intramolecular.

SCHEME 4. Crossover Experiment



As part of the optimization investigation of the lithiation-induced [1,2]-shift reaction, the length of time the reaction needed to progress to completion at −78 °C was studied (Table 1, entries 1−4). Following quenching these reactions after 90 s, 5 min, 60 min, and 90 min with CD_3OD and careful analysis of the ^1H NMR spectra, no D incorporation was observed in the starting material in any of the reactions. These results suggest that once lithiation has occurred, the migration is rapid. The length of reaction time required for consumption of the starting material (90 min) indicates that slow lithiation by LTMP is the rate-limiting step. Cleavage−recombination mechanisms have been proposed for lithiation-induced *N*- to *C*-[1,2] shifts, though these typically require warmer (>−78 °C) temperatures and migration is the rate-limiting step.[21a] In the current reaction, the [1,2] shift is complete within 90 min at −78 °C and lithiation by LTMP appears to be the rate-limiting step. While a solvent-caged (homolytic) cleavage−recombination mechanism cannot be ruled out at this time, these results suggest that the reaction could alternatively proceed via intramolecular attack of the α-lithiated aziridine at the carbamoyl carbonyl.[28] As simple α-lithiated *N*-Boc heterocycles (5−8 membered rings) do not display this rapid propensity of protecting group migration,[13,29] then in the present case, migration may be assisted by a comparatively reduced *N* lone pair/σ^* C═O overlap due to the significant increase in aziridine ring strain that such an overlap would introduce.[30] An indication of this reduced overlap can be seen in the NMR spectra of terminal *N*-Boc aziridines where rotameric signals typical of *N*-Boc amines are not observed.[24] The increase of carbonyl stretching frequency in the IR spectrum from ∼1690 cm^{-1} for typical secondary *N*-Boc amines to ∼1720 cm^{-1} for *N*-Boc aziridines also indicates a decreased level of amide character in the latter case.

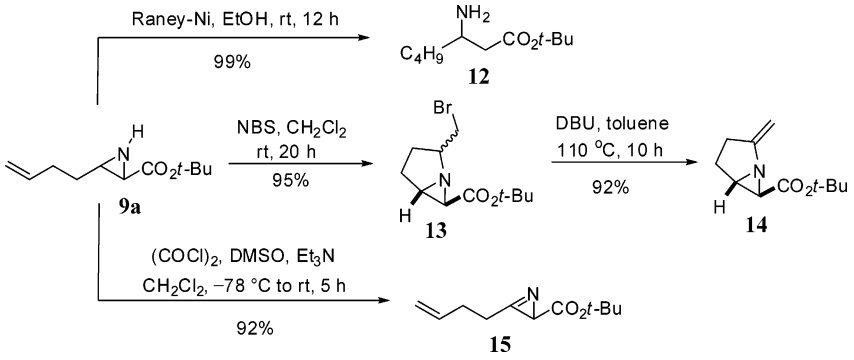
tert-Butyl protected N−H aziridinylesters accessed by this methodology can undergo a variety of synthetically useful subsequent transformations, such as those shown in Scheme 5.

Completely regioselective hydrogenolysis[31] of aziridinylester **9a** gave potentially useful[32] protected *β*-amino acid **12**. No recourse to chromatography was necessary, with pure product isolated following simple filtration and aqueous workup. Oxidative cycloamination of the tethered olefin of **9a** with *N*-bromosuccinimide following the procedure of Yudin and co-workers[30] gave azabicycle **13** as a separable 3.4:1 mixture of diastereomers. Attempted elimination with KOH in methanolic THF resulted in decomposition;[30] however, use of DBU in toluene gave enamine **14** in an excellent overall yield. Such bicyclic enamines are known to undergo regioselective ring-opening to give substituted pyrrolidines.[30] With a view to achieving a synthesis of the azirine containing natural product azirinomycin (vide infra),[33] regioselective Swern oxidation of aziridinylester **9a** was carried out according to the procedure of Zwanenburg and co-workers.[34] Synthetically useful[35] azirine **15** was isolated as a single regioisomer in 92% yield, setting the stage for a short asymmetric synthesis of the *tert*-butyl ester of the unstable natural product antibiotic azirinomycin (**16**)[33] (Scheme 6).

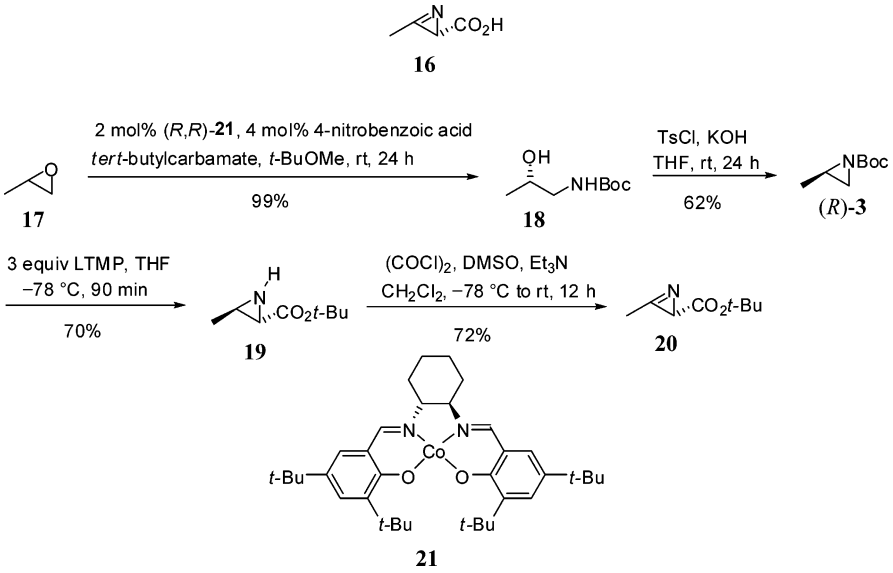
Treatment of racemic propylene oxide (**17**) with 0.45 equiv of *tert*-butyl carbamate under the aminolytic kinetic resolution

(22) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442−3443.
(23) Mordini, A.; Peruzzi, D.; Russo, F.; Valacchi, M.; Reginato, G.; Brandi, A. *Tetrahedron* **2005**, *61*, 3349−3360.
(24) See the Supporting Information for details.
(25) TBS protected alcohol **9c** has the potential to serve as a useful intermediate in the synthesis of the aziridine-containing antibiotic (2*S*,3*S*)-dicarboxyaziridine, isolated from a *Streptomyces* strain in 1975, see: Naganawa, H.; Usui, N.; Takita, T.; Hamada, M.; Umezwa, H. *J. Antiobiot.* **1975**, *28*, 828−829.
(26) Mordini, A.; Russo, F.; Valacchi, M.; Zani, L.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron* **2002**, *58*, 7153−7163.
(27) Reaction of aziridine **10** alone gave aziridinylester **11** in 86% yield.
(28) (a) Eisch, J. J.; Kovacs, C. A. *J. Organomet. Chem.* **1971**, *30*, C97−C100. (b) Eisch, J. J.; Dua, S. K.; Kovacs, C. A. *J. Org. Chem.* **1987**, *52*, 4437−4444.
(29) Gawley, R. E.; O'Connor, S.; Klein, R. In *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*; Snieckus, V., Ed.; Thieme: Stuttgart, Germany, 2005; Vol. 8a, pp 677−758.
(30) Chen, G.; Sasaki, M.; Li, X.; Yudin, A. K. *J. Org. Chem.* **2006**, *71*, 6067−6073.
(31) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135−7143.
(32) *Enantioselective Synthesis of β-Amino Acids*; 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: New York, 2005.
(33) (a) Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. K.; Hernandez, S.; Mata, J. M. *J. Antibiot.* **1971**, *24*, 42−47. (b) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48−50.
(34) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665−4668.
(35) (a) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Eur. J. Org. Chem.* **2001**, 2401−2414. (b) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Org. Prep. Proced. Int.* **2002**, *34*, 219−269.

SCHEME 5. Aziridinylester Transformations



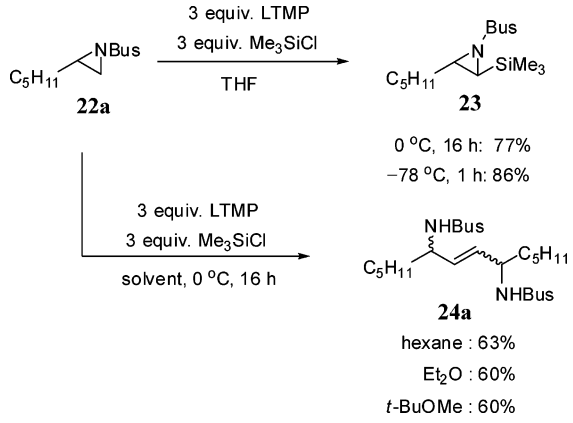
SCHEME 6. Synthesis of (*S*)-Azirinomycin Ester



conditions developed by Bartoli and co-workers[2d] gave amino alcohol **18** in quantitative yield (based on *tert*-butyl carbamate) and >99% ee.[24] Alcohol tosylation, followed by KOH-mediated aziridine ring-closure gave volatile aziridine (*R*)-**3** in a single flask transformation.[2a] Treatment with LTMP under the optimized migration conditions gave the aziridinylester as a 19:1 trans/cis mixture that was purified to give *trans*-aziridinylester **19** in 70% yield. Presumably the formation of traces of the cis-diastereomer is due to the reduced steric demand of the aziridine methyl substituent. Finally, Swern oxidation with the previously successful conditions (cf. Scheme 5) gave the *tert*-butyl ester of natural (*S*)-azirinomycin **20** as a single regioisomer in only 4 steps from racemic propylene oxide.

Dimerization. While the above rapid *N*- to *C*-migration in α-lithiated terminal *N*-Boc aziridines prevented electrophile trapping at carbon (apart from Me_3SiCl in situ, Scheme 3), we have previously found this can be overcome by using *N*-Bus[36] (*tert*-butylsulfonyl) protection. In the latter chemistry, provided the electrophile is added relatively quickly (90 s after addition to a solution of LTMP) then access to a wide variety of trans α,*β*-substituted *N*-Bus aziridines was found to be possible.[19] During our initial studies on the lithiation of terminal *N*-Bus aziridines using in situ silylation, we investigated our previously developed conditions[17] for the in situ silylation of terminal epoxides (3 equiv of LTMP, 3 equiv of Me_3SiCl, THF, 0 °C, 16 h) with terminal *N*-Bus aziridine **22a** (Scheme 7).

SCHEME 7. Silylation or Dimerization of Terminal *N*-Bus Aziridine 22a

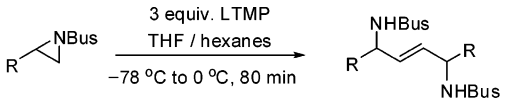


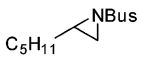
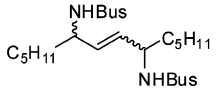
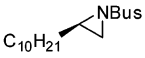
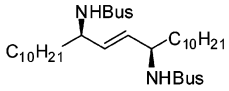
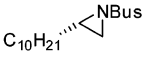
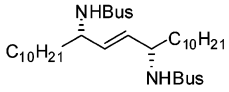
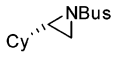
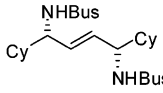
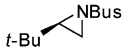
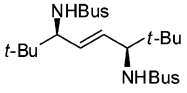
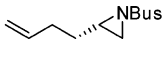
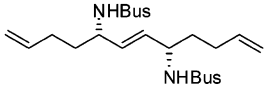
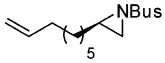
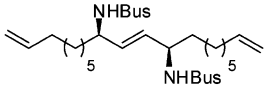
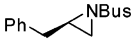
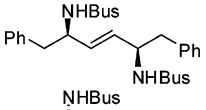
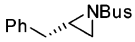
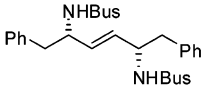
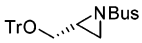
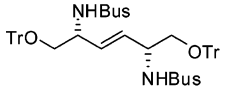
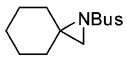
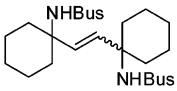
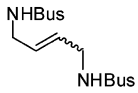
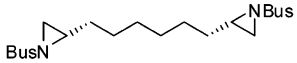
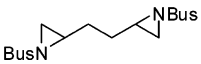
α,*β*-Aziridinylsilane **23** was isolated as a single trans-diastereomer, and no evidence of *N*- to *C*-sulfonyl migration, insertion by LTMP to give an enamine/aldehyde,[37] or 2*H*-azirine[38]/amino aldehyde formation (from hydrolysis of the azirine) was observed, following careful analysis of the crude

(36) (a) Sun, P.; Weinreb, S. M.; Shang, M. J. *J. Org. Chem.* **1997**, *62*, 8604−8608. (b) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783−786.

(37) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871.

TABLE 3. Dimerization of Terminal *N*-Bus Aziridines



entry	aziridine **22**	2-ene-1,4-diamine **24**	yield (%)	
1			**24a**	90[a]
2			(*R*,*R*)-**24b**	97
3			(*S*,*S*)-**24b**	95
4			(*S*,*S*)-**24c**	97
5			(*S*,*S*)-**24d**	81
6			(*S*,*S*)-**24e**	88
7			(*R*,*R*)-**24f**	94
8			(*R*,*R*)-**24g**	94
9			(*S*,*S*)-**24g**	91
10			(*R*,*R*)-**24h**	70
11			**24i**	86[b]
12			**24j**	41[c]
13		–	**24k**	0
14		–	**24l**	0

[a] Mixture of three diastereomers isolated. [b] Inseparable mixture of olefin isomers in 93:7 ratio. [c] Reaction quenched after 10 min at −78 °C to give an inseparable mixture of olefin isomers in a 57:43 ratio.

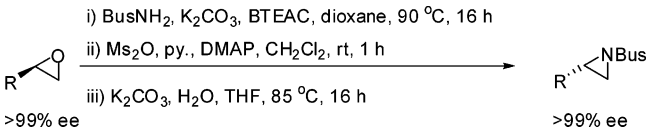
reaction mixture. Although this silylation was later optimized to 86% by running the reaction at −78 °C for 1 h,[19] during these optimization studies, switching the solvent to hexane, Et_2O, or *t*-BuOMe did not lead to formation of the expected α,β-

aziridinylsilane **23**; instead a 60−63% yield of a mixture of three distinct diastereomers of 2-ene-1,4-diamine **24a** was isolated (Scheme 7). The formation of diamine **24a** was not totally unexpected as analogous terminal epoxides undergo rapid carbenoid eliminative dimerization at −5 °C to give 2-ene-1,4-diols upon treatment with LTMP.[39] Although the dimerization reaction of an *N*-alkyl lithiated methylene aziridine (to give a cyclopentene) had been demonstrated previously,[40] the current observation represented the first example of the carbenoid nature of α-lithiated terminal aziridines, something that was of interest given the potential for 2*H*-azirine formation via elimination of the Bus group.[38]

2-Ene-1,4-diamines and their saturated derivatives are of significant interest, as they have been used as chiral ligands in catalysis and could serve as potential precursors for biologically active HIV protease inhibitors.[41−43] The current reaction parameters were investigated, and it was found that the presence of the potentially Lewis acidic chlorotrimethylsilane was not necessary for the dimerization reaction to proceed. The yield of diamine **24a** could be increased to 90% by increasing the concentration (from 0.1 to 0.4 M in aziridine **22a**), using a solvent mixture of THF/hexanes (2:3) and warming the reaction from −78 °C to 0 °C over 80 min (Table 3, entry 1).

As there are only two possible alkene geometries that could arise from the dimerization of enantiopure terminal aziridines, we anticipated that the reaction would have more potential for the synthesis of symmetrical enantiopure 2-ene-1,4-diamines from enantiopure terminal aziridines. Although there are some excellent aminolytic kinetic resolution routes to access enantiopure *N*-Boc, *N*-Ns, and *N*-SES terminal aziridines,[2c,d] we envisaged a simple, robust three-step epoxide ring-opening/aziridine ring-closure sequence to allow access to enantiopure terminal *N*-Bus aziridines (Scheme 8).

SCHEME 8. Synthesis of Enantiopure *N*-Bus Aziridines



Regioselective ring-opening of an enantiopure terminal epoxide (accessed by Jacobsen's hydrolytic kinetic resolution)[44] with *tert*-butylsulfonamide gave the corresponding *N*-Bus 1-amino-2-ol.[45] Alcohol mesylation, followed by base-induced ring-closure gave the enantiopure terminal *N*-Bus aziridine in typically good yields over the three steps.[2c] With a straightforward route to access a variety of enantiopure terminal *N*-Bus aziridines, the scope of the reaction was investigated (Table 3).

Crucially, treatment of enantiopure (*R*)-**22b** with the optimized dimerization conditions gave a 97% yield of diamine (*R*,*R*)-**24b** as a single *E*-alkene isomer (as determined by ^{1}H NMR analysis), with none of the *Z*-alkene detectable in either the crude or purified products (Table 1, entry 2). This is in contrast to the epoxide dimerization reaction process, which typically gives *E*/*Z* alkene mixtures of the 2-ene-1,4-diol products.[39] Importantly for asymmetric synthesis, both enantiomers of **22b** could be readily obtained and underwent the dimerization reaction in excellent yields to allow access to either enantiomer of diamine **24b** (entries 2 and 3). The *E*-alkene stereochemistry was proven unambiguously by X-ray crystallographic analysis of diamine (*S*,*S*)-**24c** (entry 4).[24] Steric bulk in the γ-position had little effect on the reaction, with *tert*-butyl and cyclohexyl groups tolerated (entries 4 and 5). Tethered olefin functionality gave no evidence of allylic deprotonation[23] and/or cyclopropanation (vide infra) (entries 6 and 7). Benzylic deprotonation was avoided (entries 8 and 9); this is significant since the enantiopure diamine products **24g** are of interest in the context of HIV protease inhibitor synthesis (vide infra).[42] Interestingly, subjection of the analogous epoxide, 2,3-epoxypropylbenzene, to the dimerization conditions gave cinnamyl alcohol as the major product with no evidence of the 2-ene-1,4-diol observed. This suggests that an (*N*-Bus) terminal aziridine is more activated to α-(ring)-deprotonation than a terminal epoxide. A trityl-protected alcohol was tolerated, as was an achiral 2,2-disubstitued aziridine and an unsubstituted aziridine (entries 10−12). With the two latter examples, a mixture of heterochiral and homochiral dimerization of the α-lithiated aziridines is possible, which could be the origin of the *E*/*Z* alkene mixture of diamine products. Attempted intramolecular dimerization was unsuccessful, even under dilute conditions, with mixtures of intermolecular dimerization and starting material recovered (entries 13 and 14).

The highly selective formation of the *E*-alkene isomer from enantiopure substrates is consistent with an initial diastereoselective trans-lithiation,[19] followed by nucleophilic attack of one α-lithiated aziridine onto another acting as an electrophile; the latter could occur via a 1,2-metallate shift process (Scheme 9).[46] Subsequent syn elimination driven by the steric demand of the aziridine substituents and the *N*-Bus groups leads to the observed *E*-alkenes. The improved *E*/*Z* selectivity compared to the analogous epoxide dimerization reactions is attributed to the extra steric demand brought about by the presence of the Bus

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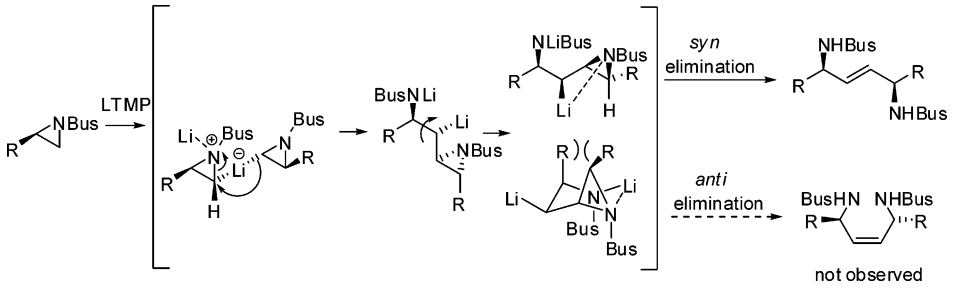
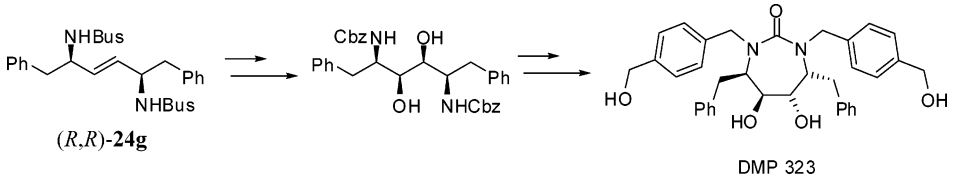
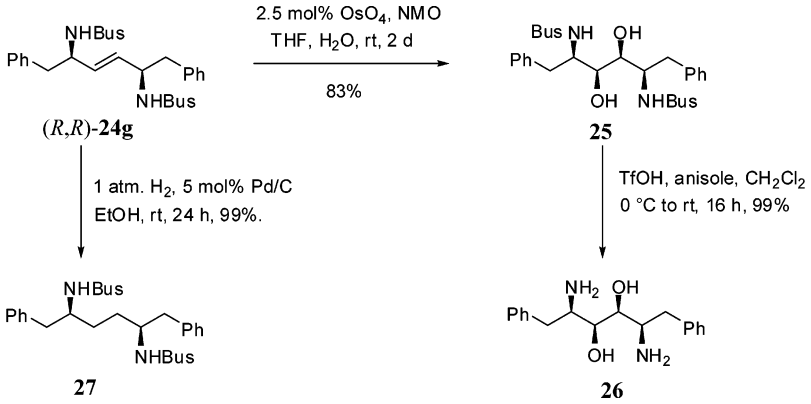
SCHEME 9. Potential Dimerization−Elimination Pathways



SCHEME 10. DMP 323 and Its Potential Formation from a 1,4-Diamine-2,3-diol



SCHEME 11. Applications of Enediamine (*R,R*)-24g to the Synthesis of HIV Protease Inhibitors and Chiral Ligands

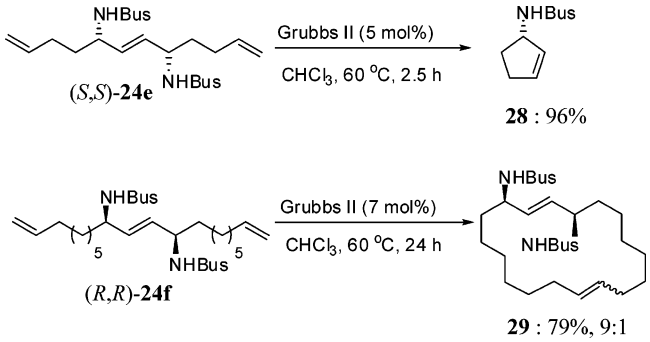


groups. At this time, the origin of reaction pathway dependence on protecting group (1,2 *N*- to *C*- for Boc, dimerization for Bus) is unclear, although it should be mentioned that α-lithiated *N*-phosphonate aziridines also undergo the 1,2 rearrangement pathway to give *trans*-α,*β*-aziridinylphosphonates.[14]

1,4-Diamine derivatives, particularly cyclic ureas such as the DuPont Merck compound DMP 323 have received considerable interest due to their use as peptidomimetic HIV protease inhibitors (Scheme 10).[42] As mentioned above, a common motif of these biologically active molecules is a 1,4-diamine-2,3-diol unit with *R,S,S,R* configuration with 1,4-benzyl groups which could conceivably be derived from enantiopure diamine (*R,R*)-**24g**.[42b]

To demonstrate the utility of the dimerization methodology, enantiopure diamine (*R,R*)-**24g** was dihydroxylated by using catalytic OsO_4 with stoichiometric NMO to give 1,4-amine-2,3-diol **25** in a 7:1 diastereomeric crude mixture that was purified to give an 83% yield of (*R,S,S,R*)-**25** (Scheme 11). X-ray crystallographic analysis also proved the assigned stereochemistry.[24] The dihydroxylation diastereoselectivity is in contrast to the 2:3 *syn*:*anti* selectivity previously observed with the analogous *N*-Boc 2-ene-1,4-diamine.[47] Global Bus deprotection was achieved upon treatment with triflic acid in the presence of anisole[36a] to give the fully deprotected amine **26**,

SCHEME 12. Metathesis Reactions of Trienediamines



in excellent yield. This is not only the core asymmetric unit of a number of highly active HIV protease inhibitors,[42,48] but it also has found use as a ligand or ligand precursor in a number of enantioselective transformations.[49] Derivatization of *ent*-**26**, which could be accessed similarly from (*S,S*)-**24g** (Table 3, entry 9), has also previously been used to produce arrays of HIV protease inhibitors for biological evaluation, yielding a number of very active compounds.[50] Hydrogenation of diamine (*R,R*)-**24g** under mild conditions was achieved over palladium on carbon with a balloon of hydrogen to give saturated diamine **27** in 99% yield. This latter reaction illustrates the utility of the

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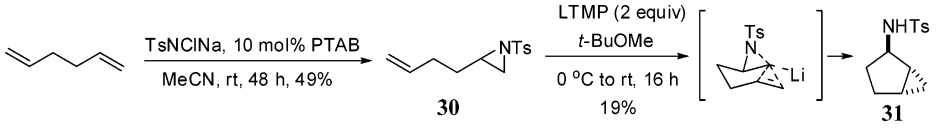
SCHEME 13. α-Lithiated Aziridine Intramolecular Cyclopropanation



dimerization methodology to access enantiopure C_2 symmetric 1,4-diamines which have found use as chiral ligands in asymmetric transformations.[41]

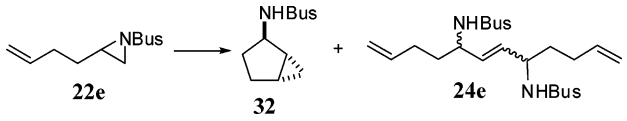
As a further use of the diamine products, the metathesis reactivity of 2-ene-1,4-diamines (*S*,*S*)-**24e** and (*R*,*R*)-**24f** bearing further unsaturation was investigated. Interestingly, treatment of (*S*,*S*)-**24e** with 5 mol % of Grubbs second generation catalyst gave cyclopentene **28**, whereas reaction of (*R*,*R*)-**24f** under similar conditions gave 18-membered macrocycle **29** as a 9:1 mixture of olefin geometric isomers (Scheme 12).

Intramolecular Cyclopropanation. Following on from the success of the *N*-Bus group in α-lithiated aziridine carbenoid dimerization chemistry, we considered whether conditions could be developed for an alternative carbenoid process, namely intramolecular cyclopropanation to access 2-aminobicyclo[3.1.0]-hexanes. This latter structural motif is found in a variety of biologically and pharmaceutically interesting targets, such as analgesics,[51] potential anti-obesity therapeutics,[52] anti-viral agents,[53] and anti-diabetic agents.[54]

We began investigations using our previously developed conditions for the intramolecular cyclopropanation of unsaturated terminal epoxides to bicyclo[3.1.0]hexan-2-ols.[55] Reaction of *N*-tosyl aziridine **30**[2b,56] with 2 equiv of LTMP at 0 °C followed by warming to room temperature for 16 h gave bicyclic amine **31** as a single trans-diastereomer as judged by NOE analysis,[24] albeit in only 19% yield (Scheme 13). A screen of different lithium amides revealed that the yield could be increased to 37% by using the slightly less hindered lithium dicyclohexylamide.[24]

We suspected that competitive ortho-lithiation of the tosyl group was responsible for the reduced yield of bicyclic amine **31**.[8] As such, a screen was initiated with use of *t*-Bu, Boc, mesitylsulfonyl, *p*-methoxybenzenesulfonyl, trisyl, and Bus as alternative protecting groups either less likely, or unable to undergo ortho-lithiation.[24] All of the protecting groups investigated resulted in <15% yield of the bicyclic amine, apart from *N*-Bus, which gave a 23% and 38% yield of a single diastereomer of bicyclic amine **32** with LTMP or lithium dicyclohexylamide, respectively (Table 4, entries 1 and 2). The trans-stereochemistry of bicyclic amine **32** was supported by X-ray crystallographic analysis.[24] As might be expected, considering the rapidity of dimerization of aziridine **22e** (cf. Table 3), racemic 2-ene-1,4-diamine **24e** was also isolated in 44% and 35% yield, respectively, as a mixture of three diastereomers. It is noteworthy that cyclopropanation can occur at all at 0 °C, given the propensity of α-lithiated *N*-Bus aziridines to undergo competitive dimerization.

TABLE 4. Optimization of the Synthesis of Bicyclic Amine 32



entry[a]	base	equiv	solvent	concn (M)	temp	yield (%) 32	yield (%) 24e
			base added to aziridine **22e** 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 **22e** 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.

As dimerization is an intermolecular process, it was considered that the reaction parameters might be able to be biased to

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(55) (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.; Nuzzo, I.; Freixas, G.; Kulikiewicz, K. K.; Cleator, E.; Paris, J.-M. *J. Am. Chem. Soc.* **2007**, *129*, 4456−4462.

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favor the intramolecular cyclopropanation reaction pathway (Table 4).

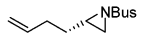
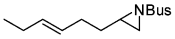
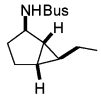
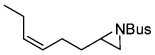
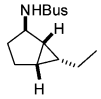
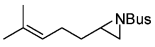
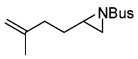
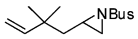
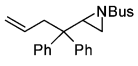
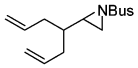
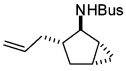
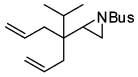
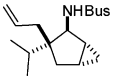
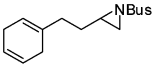
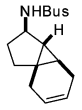
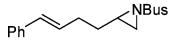
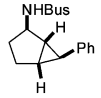
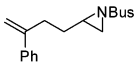
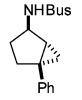
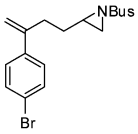
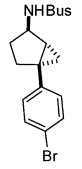
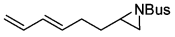
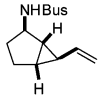
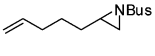
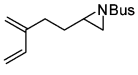
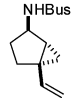
A drop in yield of diamine **24e** and an increase in yield of bicyclic amine **32** was seen by simply reversing the order of addition, so that the aziridine was added to base over 1 h (entries 3 and 4). This trend was particularly noticeable when using $LiNCy_2$ as the base (entry 4). Maintaining the reaction temperature at 0 °C led to an increase in yield of bicyclic amine **32** and levels of diamine **24e** were reduced to trace amounts by halving the reaction concentration (entries 5 and 6). Further lowering the temperature gave increased amounts of diamine **24e** (entries 7 and 8). Increasing the equivalents of $LiNCy_2$ to 3 allowed a 73% yield of bicyclic amine **32** to be obtained (entry 9). Reinvestigation of alternative lithium amides (LTMP and LDA) gave increased amounts of diamine **24e** (entries 11 and 12). A solvent screen revealed that the reaction proceeded smoothly in hexane or Et_2O, but diamine **24e** formation increased significantly in THF (entries 12−14). The latter result with THF was expected, as the optimal conditions for the dimerization reaction use THF as the solvent (Table 3). Finally, quenching the reaction directly after competition of addition and following stirring for 1 h demonstrated complete conversion to bicyclic amine **32** (entries 15 and 16). This is in direct contrast to carrying out the reaction by adding $LiNCy_2$ to aziridine **22e** and quenching following complete addition: aziridine **22e** was recovered in 52%, bicyclic amine **32** in 10%, and diamine **24e** in 22% yield.

These results demonstrate that aziridine deprotonation and intramolecular cyclopropanation is rapid when the aziridine is added to the base. The dependence on order of addition could be related to the aggregated nature of lithium amides:[57] under the latter conditions deprotonation of more than one aziridine is unlikely to occur from the same lithium amide aggregate. In contrast, when the base is added to the aziridine, this may create a localized high concentration of lithiated aziridine,[58] which allows dimerization to become competitive with intramolecular cyclopropanation. The greater success with $LiNCy_2$ may be related to a slightly reduced pK_a value relative to LTMP,[59] which allows for a more matched rate of deprotonation and cyclopropanation of aziridine **22e** thus preventing formation of a high α-lithiated aziridine concentration and so retarding the dimerization pathway.

To examine the scope of the intramolecular cyclopropanation reaction, a range of unsaturated terminal *N*-Bus aziridines **34a**−**p** were synthesized[24] and subjected to the optimized conditions (Table 5).

Cyclopropanation of an enantiopure terminal aziridine gave chiral bicyclic amine (+)-**34a** with no loss of enantiopurity (entry 1).[24] The reaction tolerated di- and trisubstituted alkenes (entries 2−5) with the olefin geometry maintained into the product (entries 2 and 3), indicating the stereospecificity of the process. The decreased yield of with *Z*-olefin **34c** was attributed to a reduced rate of cyclopropanation brought about by the ethyl group residing in a pseudoaxial position in the chairlike transition state (cf. Scheme 13). This was also supported by increased levels of dimer signals in the ^{1}H NMR of the crude

TABLE 5. Bicyclic Amines from Unsaturated Terminal Aziridines

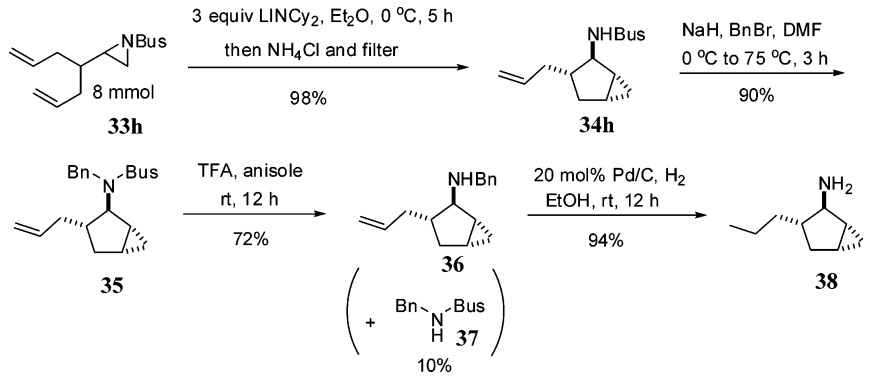
entry	aziridine **33**	bicyclic amine	time (h)	yield (%)	
1			2	**34a**	74
2			3	**34b**	85
3			4	**34c**	46
4			2	**34d**	56
5			2	**34e**	81
6			1.5	**34f**	99
7			2	**34g**	85
8			2	**34h**	98
9			2	**34i**	98
10			3	**34j**	80
11			2	**34k**	47
12			3	**34l**	90
13			3	**34m**	97
14			15	**34n**	38
15			4	**34o**	34
16			3	**34p**	85

(57) (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.

(58) For an example of the effect of localized high concentrations of organolithium reagents, see: Beak, P.; Musick, T. J.; Chen C. *J. Am. Chem. Soc.* **1988**, *110*, 3538−3545.

(59) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442−3443.

SCHEME 14. *N*-Bus Deprotection



reaction mixture. X-ray crystallographic analysis supported the trans stereochemistry of bicyclic amine **34d**.[24] Substitution on the tether was also tolerated (entries 6−9), with excellent selection between diastereotopic allyl groups obtained (entries 8 and 9). A tricyclic amine could be accessed as a single diastereomer and aziridinyl-substituted styrenes were tolerated under the reaction conditions (entries 10−14). Efficient access to 2-amino-5-aryl-substituted bicyclo[3.1.0]hexanes such as **34m** is of interest for the synthesis of the potential anti-obesity therapeutic *trans*-SCH-A (vide infra) and analogues.[52] Attempted cyclopropanation of an aziridine containing a conjugated diene was poor yielding, attributed to competing allylic deprotonation (entry 14).[55b] Trishomoallylic aziridine **34o** underwent cyclopropanation in low yield, which was attributed to a slower rate of cyclopropanation relative to dimerization, indicated by increased dimer signals in the ^{1}H NMR spectrum of the crude reaction mixture. Using the slower rate of cyclopropanation for a trishomoallylic aziridine to our advantage, an aziridine containing both bis- and trishomoallylic groups underwent selective cyclopropanation to give an 85% yield of 2-aminobicyclo[3.1.0]hexane **34p** containing a potentially useful vinylcyclopropane moiety.[60]

With access to a variety of *trans*-2-aminobicyclo[3.1.0]hexanes, our attention turned to deprotection of the *N*-Bus group. Given the ability of cyclopropanes to assist in stabilization of adjacent carbocation formation,[61] we were concerned that the strongly acidic conditions required for *N*-Bus removal[36a] could result in degradation via elimination of the sulfonamide. Weinreb and co-workers have shown that *N*-Bus protected primary amines undergo deprotection more slowly and require stronger acidic conditions than analogous *N*-Bus protected secondary amines.[36a] Initial attempts with bicyclic amine **34g** using conditions developed for the deprotection of *N*-Bus primary amines (triflic acid/anisole) resulted in decomposition. Switching to trifluoroacetic acid, typically used for the deprotection of *N*-Bus secondary amines, only returned starting material, even after extended reaction times of 48 h. As conditions suitable for the removal of *N*-Bus groups from protected secondary amines did not result in cyclopropane rupture, conversion of bicyclic amine **34h** to protected secondary amine **35** to allow deprotection under mild conditions was considered. Cyclopropanation of aziridine **33h** on an 8 mmol scale used slightly modified conditions that avoided chromatography and demonstrated the potential for (modest) scale-up (Scheme 14). Benzylation was achieved by using BnBr and NaH[62] which gave protected secondary amine **35** in 90% yield. Subjecting protected secondary amine **35** to an excess of trifluoroacetic acid and anisole at room temperature for 12 h gave the desired *N*-Bn bicyclic amine **36** in 72% yield, along with 10% of acidic decomposition product *N*-Bus amine **37**. Finally, hydrogenolysis using a balloon of hydrogen over palladium on carbon gave primary bicyclic amine **38**, in 94% yield.

To demonstrate the utility of this intramolecular α-lithiated aziridine cyclopropanation process, we focused on a synthesis of the epimer of the melanin-concentrating hormone receptor 1 (MCH-R1) antagonist *trans*-SCH-A (**39**), a highly promising potential anti-obesity therapeutic developed by Schering−Plough (Figure 1).[52]

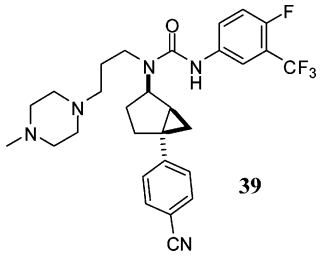


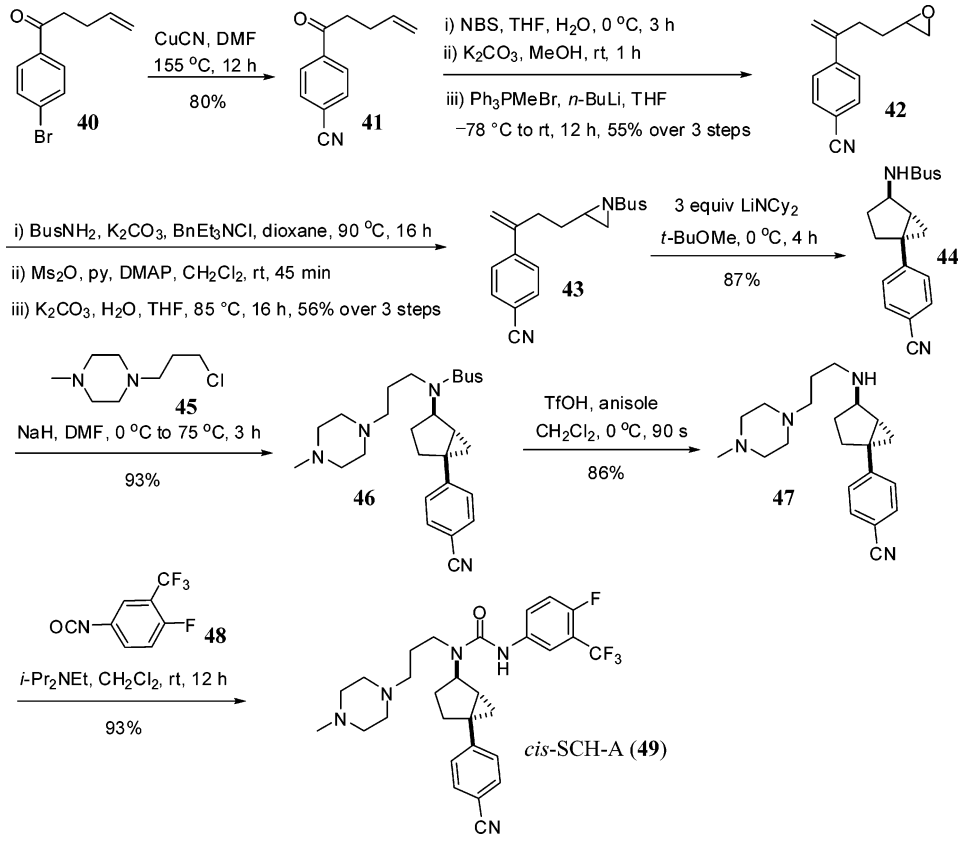
FIGURE 1. *trans*-SCH-A.

The synthesis commenced with Rosenmund−von Braun coupling between known alkenone **40**[63] (accessed by homoallylic Grignard addition to 4-bromobenzaldehyde, followed by Swern oxidation)[24] and CuCN (Scheme 15).[64] Epoxide formation via the bromohydrin, then Wittig olefination gave the desired bishomoallylic epoxide **42** in 55% yield over the three steps. Conversion to the bishomoallylic aziridine **43** was simply accomplished by the three-step protocol discussed previously (cf. Scheme 8). Crucially, given the potential for ortho-lithiation of the aromatic ring upon treatment with $LiNCy_2$,[65] cyclopropanation of aziridine **43** proceeded smoothly to give key bicyclic amine **44**, in 87% yield. Monoalkylation with the known piperazine **45**[66] gave protected secondary amine **46** in 93% yield. Deprotection with triflic acid and anisole at 0 °C for 90 s was found to be optimal[24] for *N*-Bus removal, with the desired amine **47** being isolated in 86% yield as a single trans-diastereomer as judged by NOE analysis.[24] Importantly, the potentially acid labile nitrile group was carried unscathed through the depro-

(60) (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, UK, 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.

(61) Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: Oxford, UK, 1996; pp 44−46.

SCHEME 15. Synthesis of *cis*-SCH-A



tection step. Finally, urea formation with the commercially available isocyanate **48** completed the synthesis of *cis*-SCH-A (**49**) in 93% yield (16% over 11 steps).

Biological assay of *cis*-SCH-A (**49**) in a melanin concentrating hormone receptor 1 binding assay demonstrated no inhibition of MCH-R1,[24] presumably indicating a crucial dependence on efficacy of the *anti* geometry between the amine and aromatic ring of *trans*-SCH-A (**39**).

In conclusion, we report the discovery and development of three new reactions of α-lithiated terminal aziridines and their application to synthetically and biologically important targets. In seeking to extend the scope of in situ lithiation/silylation reactions of terminal *N*-Boc aziridines, a novel mode of *N*- to *C*-Boc migration was observed. In general, good yields and excellent diastereoselectivities were obtained for the synthetically useful *trans*-α,*β*-aziridinylesters and their utility has been demonstrated with the synthesis of a protected *β*-amino acid, and an asymmetric synthesis of (*S*)-azirinomycin *tert*-butyl ester (**20**) in four steps from racemic propylene oxide. On switching aziridine protecting groups from alkoxycarbonyl to organosulfonyl, a change in α-lithiated terminal aziridine reactivity was observed. Access to a wide range of enantiopure 2-ene-1,4-diamines in good yields was achieved by the carbenoid dimerization of enantiopure terminal *N*-Bus aziridines. The utility of these diamines was demonstrated by the efficient and selective synthesis of diaminodiol (*R*,*S*,*S*,*R*)-**26**, the core unit of a number of potent HIV protease inhibitors. α-Lithiated terminal *N*-Bus aziridines bearing unsaturation were shown to undergo intramolecular carbenoid cyclopropanation to give single trans-diastereomers of synthetically useful 2-aminobicyclo[3.1.0]hexanes in good yields. The utility of this latter methodology was demonstrated in the diastereoselective synthesis of *cis*-SCH-A (**49**), the epimer of a highly effective potential anti-obesity therapeutic.

Experimental Section

General experimental details are described in the Supporting Information.

General Procedure: Optimized Conditions for α,*β*-Aziridinylester Formation via LTMP-Mediated Migration of Terminal *N*-Boc Aziridines, Described for *tert*-Butyl (2*R,3*S**)-3-Butylaziridine-2-carboxylate 7.** *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3.8 mL) at −78 °C under argon. Following warming to room temperature for 30 min, the resulting solution was re-cooled to −78 °C and a solution of aziridine **5** (100 mg, 0.50 mmol) in THF (1.5 mL) was added dropwise over 1 min. Following stirring for 90 min at −78 °C, sat. aq NH_4Cl (2 mL) was added and the flask was warmed to room temperature. The aqueous phase was washed with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O, 9:1) gave aziridinylester **7** as a colorless oil (90 mg, 90%). R_f 0.15 (petroleum ether/Et_2O 9:1); IR (neat) 3287 m (N−H), 2933 s, 861 s, 1721 s (C═O), 1459 m, 1429 m, 1393 s, 1229 s, 1164 s, and 1029 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16−2.11 (2H, m), 1.46−

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(63) Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736−1738.
(64) Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522−2524.
(65) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790−7791.
(66) Barrett, P. A.; Caldwell, A. G.; Walls, L. P. *J. Chem. Soc.* **1961**, 2404−2418.

1.33 (15H, m), 1.23−1.18 (1H, m), 0.89 (3H, t, $J = 7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 81.7 (C), 39.1 (CH), 36.1 (CH), 32.3 (CH_2), 29.2 (CH_2), 28.0 ($3 \times CH_3$), 22.3 (CH_2), 14.0 (CH_3); MS CI *m*/*z* (rel intensity) 200 ($M + H^+$, 5), 144 (100), 100 (10), 98 (15); HRMS *m*/*z* calcd for $C_{11}H_{22}NO_2$ 200.1651, found 200.1656.

General Procedure: Optimized Conditions for 2-Ene-1,4-Diamine Formation via LTMP-Mediated Dimerization of Enantiopure Terminal *N*-Bus Aziridines, Described for (12*E*,11*R*,-14*R*)-*N*,*N*′-Bis(*tert*-butylsulfonyl)tetracos-12-ene-11,14-diamine (*R*,*R*)-24b. *n*-BuLi (1.6 M in hexanes, 0.24 mL, 0.39 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (66 μL, 0.39 mmol) in THF (0.4 mL) at −78 °C. The mixture was warmed to 0 °C over 15 min, then re-cooled to −78 °C before dropwise addition of aziridine (*R*)-**22b** (38 mg, 0.13 mmol) in THF (0.8 mL). The mixture was stirred at −78 °C for 20 min, then at 0 °C for 1 h, before the addition of MeOH (0.8 mL), sat. aq NH_4Cl (8 mL), and Et_2O (16 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (16 mL). The combined organic phase was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O, 3:7) gave 2-ene-1,4-diamine (*R*,*R*)-**24b** as a colorless oil (37 mg, 97%). $[\alpha]^{25}_D$ −9.2 (*c* 2.0, $CHCl_3$); R_f 0.50 (petroleum ether/Et_2O 3:7); IR (neat) 3277 br s, 2957 s, 2925 s, 2855 s, 1633 w, 1480 s, 1457 s, 1433 s, 1366 m, 1306 s, 1263 m, 1126 s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59−5.55 (2H, m), 4.01−3.90 (4H, m), 1.65−1.49 (4H, m), 1.37 (18H, s), 1.33−1.24 (32H, m), 0.87 (6H, t, $J = 7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2 ($2 \times$ CH), 59.7 ($2 \times$ C), 56.4 ($2 \times$ CH), 37.2 ($2 \times CH_2$), 31.8 ($2 \times CH_2$), 29.5 ($2 \times CH_2$), 29.5 ($2 \times CH_2$), 29.5 ($2 \times CH_2$), 29.4 ($2 \times CH_2$), 29.2 ($2 \times CH_2$), 25.6 ($2 \times CH_2$), 24.2 ($6 \times CH_3$), 22.6 ($2 \times CH_2$), 14.0 ($2 \times CH_3$); MS CI *m*/*z* (rel intensity) 624 ($M + NH_4^+$, 15), 489 (15), 472 (30), 352 (80), 170 (100); HRMS *m*/*z* calcd for $C_{32}H_{70}N_3O_4S_2$ requires 624.4808, found 624.4839.

General Procedure: Optimized Conditions for *trans*-2-Aminobicyclo[3.1.0]hexane Formation via $LiNCy_2$-Mediated Cyclopropanation of Bis-Homoallylic Terminal *N*-Bus Aziridines, Described for *N*-[(1*R,2*R**,5*S**)-Bicyclo[3.1.0]hexan-2-yl]-2-methylpropane-2-sulfonamide 32**. *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 for 30 min, the reaction was cooled to 0 °C and a solution of aziridine **22e** (109 mg, 0.5 mmol) in *t*-BuOMe (10 mL) at 0 °C was added dropwise over 1 h via cannula and the reaction was left to stir at 0 °C. On completion of the reaction (2 h, tlc monitoring), sat. aq NH_4Cl (5 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous layer extracted with Et_2O (2×15 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O, 4:1) gave bicyclic amine **32** as a white solid (82 mg, 75%). Mp 101−102 °C; R_f 0.38 (petroleum ether/Et_2O 4:1); IR (film) 3273 s (N−H), 3036 m (cyclopropane), 2935 s, 1454 m, 1364 w (S═O), 1297 s, 1131 s (S═O), 1108 m, 1058 w, and 1025 m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (1H, d, $J = 9$ Hz), 3.88−3.84 (1H, m), 1.89−1.79 (1H, m), 1.73−1.63 (2H, m), 1.52−1.46 (1H, m), 1.44−1.41 (2H, m), 1.40 (9H, s), 0.48−0.42 (1H, m), 0.13−0.10 (1H, m); ^{13}C NMR-(100 MHz, $CDCl_3$) δ 59.6 (C), 57.6 (CH), 29.6 (CH_2), 24.4 (CH_2), 24.3 ($3 \times CH_3$), 23.1 (CH), 16.4 (CH), 7.0 (CH_2); MS CI *m*/*z* (rel intensity) 235 ($M + NH_4^+$, 45), 218 ($M + H^+$, 30), 98 (100), 81 (50); HRMS *m*/*z* calcd for $C_{10}H_{20}NO_2S$ 218.1215, found 218.1209.

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Supporting Information Available: Full experimental details of the syntheses and characterization of aziridine substrates, 2-ene-1,4-diamines, bicyclic amines, and aziridinylesters not described in the Experimental Section, X-ray data for aziridinylester **9b**, aziridine **22j**, diamines (*S*,*S*)-**24c** and **25**, and bicyclic amines **32** and **34d** in CIF format, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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