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Addition Reactions of Chloro- or Iodomethyllithium to Imines. Synthesis of Enantiopure Aziridines and β-Chloroamines

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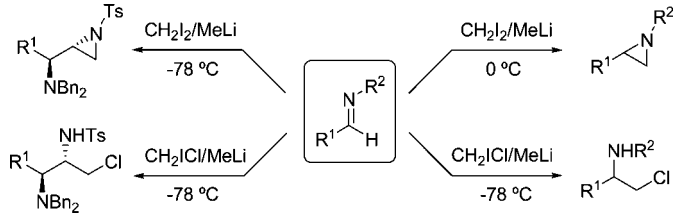

We report a novel, simple, and efficient synthesis of aziridines and 1-chloroalkan-2-amines by the reaction of imines derived from various aldehydes and *p*-toluenesulfonamide or benzenesulfonamide with iodo- or chloromethyllithium, respectively. Both halogenated anions were generated in situ by treatment of diiodo- or chloroiodomethane with methyllithium at −78 or 0 °C. The reaction of in situ generated iodo- or chloromethyllithium could also be performed from chiral 2-aminoaldimines to yield enantiopure aziridines or (2*S*,3*S*)-2,3-diamino-1-chloroalkanes with high stereoselectivity.

Introduction

Aziridines and their precursors β-haloamines are important building blocks in organic synthesis. The former heterocycles can undergo highly regioselective nucleophilic ring opening reactions[1] and can be employed as starting materials for the synthesis of important biomolecules such as amino acids, β-lactams, and alkaloids.[2]

Moreover, the aziridine ring is present in molecules that show biological activity. Naturally occurring compounds with the aziridine moiety exhibit antitumor and/or antibiotic activity, due to their ability to cross-link DNA,[3] or inhibit the bacterial enzyme diaminopimelic acid epimerase.[4] Other molecules related to mitosanes and mytomycins and bearing the aziridine ring have been synthesized and have been demonstrated to possess activity against a variety of cancers.[5]

As a result of this, a large number of methods for the preparation of aziridines have been reported in recent years.[6] The main synthetic routes toward aziridines have included the addition of nitrenes to alkenes,[7] α-metalation/electrophile trapping of N-protected aziridines,[8]addition reactions to azirines,[9]

(1) (a) Kasai, M.; Kono, M. *Synlett* **1992**, 778–790. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619. (c) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A; pp 1−60. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365. (e) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.

(2) (a) Kumar, K. S. A.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol. Chem.* **2008**, *6*, 703–711. (b) Kumar, K. S. A.; Chaudhari, V. D.; Puranik, V. G.; Dhavale, D. D. *Eur. J. Org. Chem.* **2007**, 4895–4901. (c) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357–2359. (d) Caldwell, J. J.; Craig, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2631–2634. (e) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995–3998. (f) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213–215. (g) Smith, A. B., III; Kim, D. *Org. Lett.* **2004**, *6*, 1493–1495.

(3) Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohnos, N. *J. Am. Chem. Soc.* **1962**, *34*, 3184–3185.

(4) Gerhart, F.; Higgins, W.; Tardif, C.; Ducep, J. *J. Med. Chem.* **1990**, *33*, 2157–2162.

(5) (a) Han, I; Kohn, H. *J. Org. Chem.* **1991**, *56*, 4648–4653. (b) Skibo, E. B.; Islam, I; Heileman, M. J.; Schultz, W. G. *J. Med. Chem.* **1994**, *37*, 78–92.

(6) (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135. (b) Iain, D. G.; Watson, L. Y.; Andrei, K. Y. *Acc. Chem. Res.* **2006**, *39*, 194–206.

(7) (a) Armstrong, A. Baxter, C. A. Lamont, S. G. Pape, A. R. Wincewicz, R. *Org. Lett.* **2007**, *9*, 351–353. (b) Li, Z. Ding, X. He, C. *J. Org. Chem.* **2006**, *71*, 5876–5880. (c) Catino, A. J. Nichols, J. M. Forslund, R. E. Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787–2790. (d) Ma, L. Jiao, P. Zhang, Q. Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3718–3734. (e) Mahoney, J. M. Smith, C. R. Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354–1355. (f) Chen, D. Timmons, C. Guo, L. Xu, X. Li, G. *Synthesis* **2004**, 2479–2484. (g) Siu, T. Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530–531. (h) Kantam, M. L. Kavita, B. Neeraja, V. Haritha, Y. Chaudhuri, M. K. Dehury, S. K. *Tetrahedron Lett.* **2003**, *44*, 9029–9032. (i) Ando, T. Minakata, S. Ryu, I. Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309–312. (j) Jeong, J. U. Tao, B. Sagasser, I. Henniges, H. Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844–6845. (k) Atkinson, R. S. Tughan, G. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 2803–2807(l) Reference 6b.

(8) (a) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453–3456. (b) Concellón, J. M.; Álvarez, J. R.; García-Granda, S.; Díaz, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4333–4336. (c) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276–277.

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and methods based on the use of epoxides,[10] β-amino alcohols,[11] or imines[12] as starting materials. This last class of compounds has been most widely employed as starting materials to obtain aziridines, and several protocols have been developed to transform imines into aziridines through methylene transfer by using sulfur ylides[13] or a mixture of dihalomethanes and diethylzinc[13f] or potassium.[14] Generally, the reported methods to obtain aziridines required long reaction times and took place in low yields.

β-Chloroamines have also been extensively used as starting compounds to prepare aziridines. As well as being precursors to aziridines, β-chloroamines are important building blocks in organic synthesis, which could complement those synthetic applications of aziridines. Generally, β-chloroamines have been prepared by nucleophilic addition of various nucleophiles (hydride, cyanide, Grignard reagents, etc.) to α-chloroimines.[15] An improvement of these reported syntheses could be the addition reaction of chloromethyllithium to imines, since the starting imines are simpler compounds and are more readily available than 2-chloroimines.

In this context, and to the best of our knowledge, only one example of an aziridine ring has been prepared through the reaction of in situ generated chloromethyllithium and a specific imine derived from 2-pyridinecarboxaldehyde. However, when the method was applied to other imines without the 2-pyridineimine moiety, such as those derived from benzaldehyde, no reaction took place. Thus, the authors assumed that the presence of the 2-pyridineimine moiety was a necessary requirement for the successful aziridination. In addition, both the removal of the N-substituent and the ring opening of this aziridine with various nucleophiles could not be performed.[16] As expected, preparation of enantiopure aziridines by reaction of chiral aldimines with halomethyllithium has not been reported to date, despite enantiopure compounds having greater value than the corresponding racemic compounds.

The use of halomethyllithium compounds in synthesis presents a drawback given their instability: These reagents spontaneously decompose through an α-elimination process even at −100 °C. In order to use these organometallic compounds as anionic reagents, halomethyllithium compounds must be generated in situ, in the presence of the corresponding electrophile to avoid decomposition prior to the reaction with the electrophile.[17] Generally, chloro-, bromo-, or iodomethyllithium are prepared in situ by treating a mixture of chloroiodo-, dibromo-, or diiodomethane and the corresponding electrophile with methyllithium at low temperature (−78 °C).[18] Indeed, the reaction of in situ generated halomethyllithium with aldehydes or ketones,[19] esters,[20] carboxylic acid chlorides,[21] boronic esters,[22] or N-protected 3-oxazolidin-5-ones[23] has been reported. However, the in situ generated halomethyllithium compounds did not react with less electrophilic reagents, such as imines, and suffer an α-elimination reaction. The lack of reactivity of imines could explain the absence of precedents concerning the reaction of halomethyllithium compounds with imines. Given this background, the development of a novel and efficient method to obtain aziridines or chloroamines, including the

(9) (a) Atkinson, R. S.; Coogan, M. P.; Lochrie, I. S. T. *Chem Commun.* **1996**, 789–790. (b) Roth, P.; Somfai, P.; Andersson, P. G. *Chem. Commun.* **2002**, 1752–1753. (c) Sjöholm-Timen, A.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958–9963. (d) Risberg, E.; Fischer, A.; Somfai, P. *Chem. Commun.* **2004**, 2088–2089. (e) Risberg, E.; Fischer, A.; Somfai, P. *Tetrahedron* **2005**, *61*, 8443–8450.

(10) (a) Bilke, J. L.; Dzuganova, M.; Fröhlich, R.; Würthwein, E.-U. *Org. Lett.* **2005**, *7*, 3267–3270. (b) Bouyacoub, A.; Volatron, F. *Eur. J. Org. Chem.* **2002**, 4143–4150. (c) Hudlicky, T.; Rinner, U.; González, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726–8743. (d) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145–154.

(11) To see recent reviews on the synthesis of aziridine: (a) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715. (b) Hou, X. L.; Wu, J.; Fan, R. H.; Ding, D. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181–193. (c) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194–206. (d) Schaumann, E.; Kirschning, A. *Synlett* **2007**, 177–190.

(12) (a) Hodgson, D. M.; Kloesges, J.; Evans, B. *Org. Lett.* **2008**, *10*, 2781–2783. (b) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 3211–3217. (c) Sweeney, J. B.; Cantrill, A. A.; Drew, M. G. B.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3694–3703. (d) Sweeney, J. B.; Cantrill, A. A.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3681–3693. (e) Concellón, J. M.; Bernad, P. L.; Riego, E.; García-Granda, S.; Forcén-Acebal, A. *J. Org. Chem.* **2001**, *66*, 2764–2768. (f) Kim, D. Y.; Suh, K. H.; Choi, J. S.; Mang, J. Y.; Chang, S. K. *Synth. Commun.* **2000**, *30*, 87–95. (g) Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *Chem. Commun.* **1996**, 2631–2632. (h) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511–1514.

(13) (a) García-Ruano, J. L.; Fernández, I.; del Prado-Catalina, M.; Alcudia-Cruz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407–3414. (b) Higashiyma, K.; Matsumura, M.; Shiogama, A.; Yamauchi, T.; Ohmiya, S. *Heterocycles* **2002**, *58*, 85–88. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, 1353–1354. (d) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Synlett* **2003**, 1985–1988. (e) Midura, W. H. *Tetrahedron Lett.* **2007**, *48*, 3907–3910. (f) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587–1589. (g) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Chem. Commun.* **2006**, 1833–1835.

(14) tom Dieck, H.; Haupt, E. *Chem. Ber.* **1983**, *116*, 1540–1546.

(15) (a) Singh, G. S. D'hooghe, M. De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135. (b) De Kimpe, N. Verhé, R. De Buyck, L. Schamp, N. *Synth. Commun.* **1975**, *5*, 269–274. (c) De Kimpe, N. Schamp, N. Verhé, R. *Synth. Commun.* **1975**, *5*, 403–408. (d) De Kimpe, N. Verhé, R. De Buyck, L. Schamp, N. *J. Org. Chem.* **1980**, *45*, 5319–5325. (e) De Kimpe, N. Sulmon, P. Verhé, R. De Buyck, L. Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320–4326. (f) De Kimpe, N. Moens, L. *Tetrahedron* **1990**, *46*, 2965–2974. (g) Denolf, B. Mangelinckx, S. Törnroos, K. W. De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129–3132(h) Reference 12b.

(16) Savoia, D.; Alvaro, G.; Di Fabio, R.; Gualandi, A.; Fiorelli, C. *J. Org. Chem.* **2006**, *71*, 9373–9381.

(17) For reviews on the synthesis and synthetic applications of functionalized halomethyllithium compounds: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181. (b) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67–96. (c) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435. (d) Yus, M.; Foubelo, F. *Targets Heterocycl. Syst.* **2002**, *6*, 136–171. (e) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926. (f) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139–3176.

(18) A synthesis of epoxides has been reported by reaction of iodomethyllithium with aldehydes and ketones at 0 °C: Concellón, J. M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* **2001**, *57*, 8983–8987.

(19) (a) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1665–1665. (b) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915–916. (c) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans.1* **1988**, 3339–3343. (d) Barluenga, J.; Llavona, L.; Bernad, P.; Concellón, J. M. *Tetrahedron Lett.* **1993**, *34*, 3173–3176. (e) Concellón, J. M.; Llavona, L.; Bernad, P. L., Jr. *Tetrahedron* **1995**, *51*, 5573–5584. (f) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696–6699. (g) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1999**, *64*, 2843–2846. (h) Einhorn, C.; Allavena, C.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1999**, 333–334. (i) Barluenga, J.; Baragaña, B.; Concellón, J. M.; Piñera-Nicolás, A.; Díaz, M. R.; García-Granda, S. *J. Org. Chem.* **1999**, *64*, 5048–5052. (j) Concellón, J. M.; Baragaña, B.; Riego, E. *Tetrahedron Lett.* **2000**, *41*, 4361–4362.

(20) (a) Barluenga, J. Llavona, L. Concellón, J. M. Yus, M. *J. Chem. Soc., Perkin Trans.* **1990**, *1*, 417. (b) Barluenga, J. Llavona, L. Concellón, J. M. Yus, M. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 297–300. (c) Barluenga, J. Pedregal, B. Concellón, J. M. *Tetrahedron Lett.* **1993**, *34*, 4563–4564. (d) Barluenga, J. Baragaña, B. Alonso, A. Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 969–970(e) Reference 19f.

(21) (a) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *Synthesis* **1987**, 584–586. (b) Barluenga, J.; Concellón, J. M.; Fernández-Simón, J. L.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 536–537. (c) Barluenga, J.; Concellón, J. M.; Fernández-Simón, J. L.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 77–80.

(22) (a) Matteson, D. S.; Sadhu, K. M. *Tetrahedron Lett.* **1986**, *27*, 795–798. (b) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819. (c) Brown, H. C.; Gupta, A. K.; Rangaishenvi, M. V.; Vara Prasad, J. V. N. *Heterocycles* **1989**, *28*, 283–294. (d) Brown, H. C.; Phadke, A. S.; Bhat, N. G. *Tetrahedron Lett.* **1993**, *34*, 7845–7848. (e) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957–8960. (f) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8961–8964.

(23) Onishi, T.; Hirose, N.; Takashi, N.; Masakazu, N.; Kunisuke, I. *Tetrahedron Lett.* **2001**, *42*, 5883–5885.

reaction with chiral imines to afford a range of enantiopure aziridines and chloroamines without racemization, would be desirable.

Recently, we reported our preliminary results concerning the synthesis of aziridines by reaction of imines derived from *p*-toluenesulfonamide with in situ generated iodomethyllithium. The synthesis of the enantiopure (2*R*,1′*S*)-2-(1′-dibenzylamino-2′-phenylethyl)aziridine with high stereoselectivity in good yield from the aziridination of the enantiopure *N*-tosylimine derived from phenylalaninal was also described.[24]

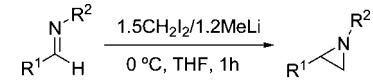
The main advantage of this reported method is that the experimental protocol is simple and rapid. Taking into account the synthetic interest of this procedure, in this paper we describe a generalization of the reported aziridination of racemic imines from *p*-toluene and benzenesulfonamide and the synthesis of enantiopure aziridines from the chiral α-aminoimines. In addition, a new method to obtain *β*-chloroamines by reaction of the imines derived from *p*-toluenesulfonamide and benzenesulfonamide, including the chiral version using enantiopure aminoimines, with chloromethyllithium instead of iodomethyllithium is also reported.

Results and Discussion

Synthesis of Aziridines 2 Starting from Imines Derived from Sulfonamides 1. Initial attempts to prepare aziridines were performed by starting from the imines derived from *p*-methoxyphenylamine and octanal or benzaldehyde, which were prepared according to a previously reported method.[25] The iodomethyllithium was generated in situ by treatment of diiodomethane with methyllithium in the presence of the corresponding imine at −78 °C. Unfortunately, no addition of iodomethyllithium to either imine took place under various reaction conditions. To overcome this problem, we tried to find the appropriate amine in order to enhance the electrophilicity of the carbonyl to facilitate the addition of iodomethyllithium. This objective was achieved using imines derived from *p*-toluenesulfonamide and octanal or benzaldehyde which were prepared according to literature procedures.[26] The reactions of imines **1a** and **1e** with iodomethyllithium at low temperature (−78 °C) afforded the corresponding aziridine in both cases **2a**and **2e**, respectively. After testing several reaction conditions, the best results were obtained by treatment of a solution of 1.5 equiv of diiodomethane and 1 equiv of imine **1** in THF with 1.2 equiv of MeLi at 0 °C for 30 min, and further stirring at the same temperature for 30 min (Table 1).

To study the generality of the aziridination reaction, additional imines derived from *p*-toluenesulfonamide and a range of aldehydes were prepared and allowed to react with iodomethyllithium. As can be observed in Table 1, the reaction seems to be general and aziridines derived from linear, branched, and cyclic aliphatic or aromatic aldehydes afforded the corresponding aziridines in good to high yields. The reaction could also be generalized by using other imines derived from benzenesulfonamide **1f**−**h** (prepared by the same method as that used for *p*-toluenesulfonamide),[26] and the corresponding aziridines **2f**−**h** were obtained, under the same reaction conditions ($LiCH_2I$, 0 °C), without showing any major differences in comparison to those reactions of $LiCH_2I$ with imines derived from *p*-toluenesulfonamide (Table 1).

TABLE 1. Synthesis of Aziridines 2

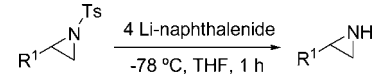


1 2

entry	2	R^1	R^2	yield (%)[a]
1	**2a**	*n*-C_7H_{15}	Ts	80
2	**2b**	*s*-Bu	Ts	71
3	**2c**	*c*-Hex	Ts	87
4	**2d**	$PhCH_2$	Ts	58
5	**2e**	Ph	Ts	88
6	**2f**	*c*-Hex	SO_2Ph	98
7	**2g**	*p*-ClC_6H_4	SO_2Ph	62
8	**2h**	*p*-$MeOC_6H_4$	SO_2Ph	75

[a] Isolated yield after column chromatography based on compound **1**.

TABLE 2. Deprotection of *N*-Tosyl Aziridines



2 3

entry	3	R^1	yield (%)[a]
1	**3a**	*n*-C_7H_{15}	62
2	**3c**	*c*-Hex	65
3	**3d**	$PhCH_2$	75

[a] Isolated yield after column chromatography based on the compound **2**.

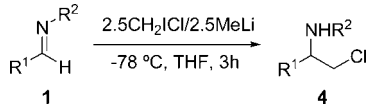
The N-substituent on aziridines derived from *p*-toluenesulfonamide **1a**,**c**,**d**, has been readily removed by using lithium-naphthalenide following a method previously reported,[27] in which the isolation and purification of the obtained aziridines were modified by us, since the previously described purification by column chromatography resulted in poor yields of deprotected aziridines **3**. To improve the yields of isolated compounds **3a**,**c**,**d** an acid−base treatment of the crude reaction products was performed yielding compounds **3a**,**c**,**d** as they are shown in Table 2.

The use of chloromethyllithium instead of iodomethyllithium to prepare aziridines was also tested under the same reaction conditions, furnishing the corresponding aziridines in yields 10% lower than those observed for the previous case. Therefore, taking into account that diiodomethane is cheaper than chloroiodomethane, the aziridination reaction of imines was carried out using iodomethyllithium instead of chloromethyllithium.

Synthesis of *β*-Chloroamines 4. The synthesis of *β*-chloroamines could be interesting, since the synthetic applications of aziridines and *β*-chloroamines could be complementary. Thus, we attempted the development of a method to transform imines **1** into *β*-chloroamines **4** instead of the aziridines **2**. So, to avoid the heterocyclization of *β*-chloroamines, the reaction was performed at lower temperature starting from the same imines derived from *p*-toluenesulfonamide **1a**−**e** and benzenesulfonamide **1f**−**g**. After we tested several reaction conditions, the best yields of *β*-chloroamines were obtained by treating a solution of 2.5 equiv of chloroiodomethane and the corresponding *N*-sulfonyl imine (1 equiv) in THF with 2.5 equiv of methyllithium at −78 °C and hydrolyzing at the same temperature. In

(24) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Org. Lett.* **2008**, *10*, 4457–4460.
(25) Reetz, M. T.; Lee, W. K. *Org. Lett.* **2001**, *3*, 3119–3120.
(26) Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
(27) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455–9461.

TABLE 3. Synthesis of β-Chloroamines 4



1 4

entry	4	R^1	R^2	yield (%)[a]
1	**4a**	*n*-C_7H_{15}	Ts	71
2	**4b**	*s*-Bu	Ts	81
3	**4c**	*c*-Hex	Ts	72
4	**4d**	$PhCH_2$	Ts	65
5	**4e**	Ph	Ts	69
6	**4f**	*c*-Hex	SO_2Ph	>98
7	**4g**	*p*-ClC_6H_4	SO_2Ph	78
8	**4h**	*p*-$MeOC_6H_4$	SO_2Ph	60

[a] Isolated yield after column chromatography based on compound **1**.

SCHEME 1. Proposed Mechanism for the Synthesis of Compounds 2 and 4

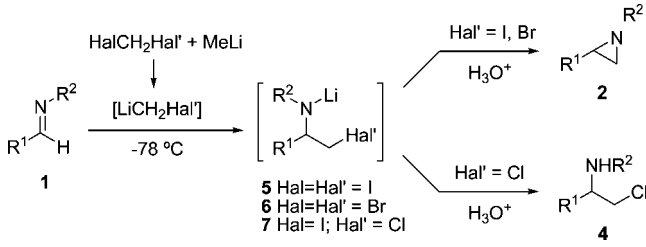


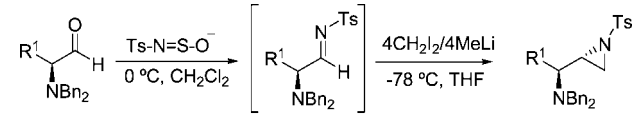
Table 3, the results obtained in the synthesis of compounds **4** are compiled, showing that yields of chloroamines **4** at −78 °C were similar to those obtained in the syntheses of aziridines **2** using iodomethyllithium at 0 °C.

The synthesis of β-bromoamines with bromomethyllithium (generated in situ from the reaction of dibromomethane with methyllithium) was also tested. However, when the reaction of bromomethyllithium and imines **1a** and **1c** was performed, under the same reaction conditions as those used in the synthesis of chloroamines **4**, the corresponding aziridines **2a** and **2c** were obtained instead of β-bromoamines. The use of other reaction conditions (lower temperature, amounts of solvent, reaction time, etc.) in order to obtain the β-bromoamines was tested. Unfortunately, the corresponding aziridines were always obtained, instead of the β-bromoamines, in yields similar to those obtained with iodomethyllithium compiled in Table 1.

The synthesis of aziridines **2** and β-chloroamines **4** can be explained by assuming an addition process of iodo-, bromo-, or chloromethyllithium to the imine group generating an iodated, bromated, or chlorinated lithium amide **5**, **6**, or **7**. The obtained lithium 2-iodoamide or 2-bromoamide undergoes a spontaneous heterocyclization to afford the corresponding aziridines **2** in both cases; in contrast, no heterocyclization took place from 2-chloroamides at −78 °C and the corresponding β-chloroamines **4** were finally isolated (Table 3). The isolation of β-chloroamines when chloromethyllithium was used at −78 °C could proceed via the proposed mechanism, in which the generation of halomethyllithium, rather than a carbene, was the suggested active intermediate to carry out the aziridination process (Scheme 1).

Synthesis of Enantiopure 2-(1-Dibenzylaminoalkyl)aziridines 11. Previously, we reported the synthesis of nonactivated enantiopure *syn*-aminoalkyl aziridines by reduction of α-amino ketimines derived from 1-aminoalkyl chloromethyl ketones.[12e] In addition, Reetz published the synthesis of enantiopure *anti*-aminoalkyl aziridines by reaction of chiral aminoaldimines derived from anisidine with sulfur ylides.[25]

SCHEME 2. Synthesis of Chiral 2-(1-Dibenzylaminoalkyl)-aziridines 11



9 10 11

TABLE 4. Synthesis of Enantiopure 2-(1-Dibenzylaminoalkyl)-aziridines 11

entry	11	R^1	dr	yield (%)[a]
1	**11a**	Me	7/1	54
2	**11b**	*i*-Bu	5/1	58
3	**11c**	$PhCH_2$	9/1	61

[a] Isolated yield after column chromatography based on the starting aminoaldehyde **9**.

Given the synthetic utility of optically active *syn*-aminoaziridines,[28] we performed the aziridination reaction described above, with enantiopure aldimines **10** derived from chiral *N*,*N*-dibenzyl 2-aminoaldehydes **9**, with the goal of synthesizing the *anti*-aminoaziridine (the diastereoisomer of that *syn*-diastereoisomer previously reported by us),[12e] and improving the stereoselectivity of the synthesis of *syn*-aminoaziridines reported by Reetz.[25] The required *N*-tosylimines **10** were prepared by the Weinreb procedure.[29] The obtained imines were unstable and could not be purified. Thus, the reaction with iodomethyllithium was carried out using crude aminoimines, rendering aminoaziridines **11** (Scheme 2). After testing several reaction conditions, the best result was obtained by treating a solution of crude aminoimines **10** in THF with 4.0 equiv of diiodomethane and 4.0 equiv of MeLi at −78 °C for 2 h (Scheme 2).[30]

After hydrolysis and the usual workup, crude aminoaziridines **11** were obtained in good yields (79% from the imine derived from phenylalaninal). Purification by conventional column chromatography, afforded the expected pure aminoaziridines **11** in low yields (42% from imine derived from phenylalaninal), which disagreed with the good purity observed in the crude reaction material (^1H and ^{13}C NMR). The yields of the pure aziridines **11** were increased by avoiding the hydrolysis step and directly purifying the crude material by column chromatography. Table 4 shows the overall yields of the two-step transformations of aminoaldehydes **9** into aminoaziridines **11**, which were determined after column chromatography purification of compounds **11** using a simpler isolation method in which the hydrolysis of the crude reactions was not carried out.

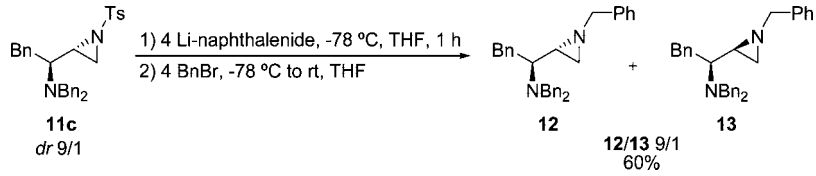
The good stereoselectivity of the addition reaction of iodomethyllithium (Table 4) was determined, on the crude reaction products, by 300 MHz ^1H NMR. It is noteworthy that the previously reported synthesis of (2*R*,1′*S*)-2-(1′-dibenzylamino-

(28) (a) Concellón, J. M. Riego, E. *J. Org. Chem.* **2003**, *68*, 6407–6410. (b) Concellón, J. M. Riego, E.Álvarez, J. R. *J. Org. Chem.* **2003**, *68*, 9242–9246. (c) Concellón, J. M. Riego, E. Rivero, I. A. Ochoa, A. *J. Org. Chem.* **2004**, *69*, 6244–6248. (d) Concellón, J. M. Riego, E. Suárez, J. R. García-Granda, S. Díaz, M. R. *Org. Lett.* **2004**, *6*, 4499–4501. (e) Concellón, J. M. Bernad, P. L. Suárez, J. R. *Chem. Eur. J.* **2005**, *11*, 4492–4501. (f) Concellón, J. M. Bernad, P. L. Suárez, J. R. García-Granda, S. Díaz, M. R. *J. Org. Chem.* **2005**, *70*, 9411–9416(g) Reference 8b.

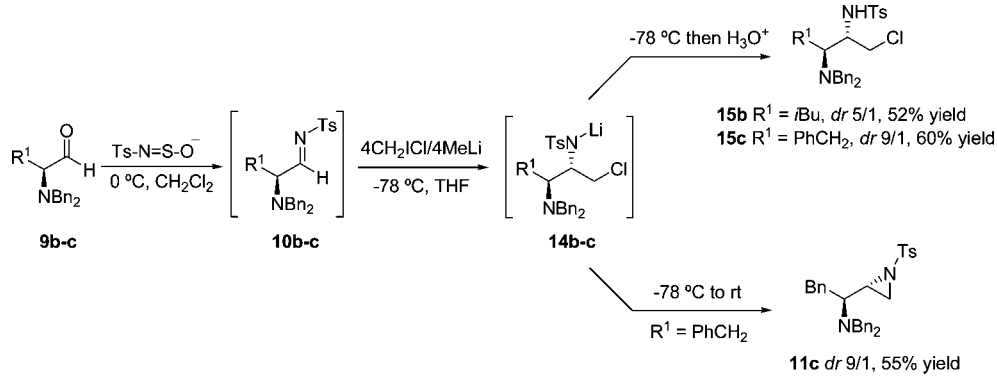
(29) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393–395.

(30) An excess of iodomethyllithium was necessary due to the presence of *N*-tosylamine in the mixture reaction, as a consequence of the *N*-sulfinyl-*p*-toluenesulfonamide required for the synthesis of aminoaldimines **10**, which is purchased with a purity of ∼70%.

SCHEME 3. Deprotection/Benzylation of Compound 11c



SCHEME 4. Synthesis of (2*S*,3*S*)-2,3-Diamino-1-chloroalkanes 15



2′-phenylethyl)-1-(4-methoxyphenyl)aziridine by reaction of the corresponding α-aminoaldimine with dimethylsulfonium methylide took place with lower stereoselectivity.[25]

In general terms, it is noteworthy that this reported method for the synthesis of aziridines **2** and **11** is experimentally simple, the reaction times are short and proceed with high stereoselectivity in the case of compounds **11**.

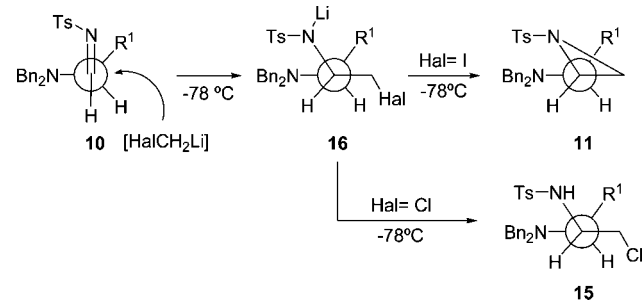
The structure and absolute configuration of the aziridine ring of aminoaziridines **11** was unambiguously established by transformation of the aminoaziridine **11c** into the corresponding *N*-benzyl aziridine through a deprotection/benzylation protocol (Scheme 3). ^{1}H and ^{13}C NMR of the minor product **13** was consistent with the *syn*-aminoaziridine previously reported by us starting from the corresponding chloromethyl ketimine derived from phenylalaninal.[20] Consequently, we deduced that the absolute configuration of the major stereoisomer **11c** was 2*R*. The assigned structure for compound **13** shown in Scheme 3 was corroborated by its spectroscopic data. The absolute configuration of the other aziridines **11** were assigned by analogy.

Synthesis of Enantiopure (2*S*,3*S*)-2,3-Diamino-1-chloroalkanes 15. The synthesis of chiral β-chloroamines derived from aminoimines **10** was also carried out by using a methodology similar to that developed for the synthesis of chloroamines **4**. Thus, when 4 equiv of methyllithium was added to a mixture of 4 equiv of chloroiodomethane and crude aminoimines **10** at −78 °C, the corresponding chloroamines **15** were obtained after hydrolysis in yields similar to those observed in the synthesis of aminoaziridines **11b** and **11c** (Table 4).

The stereoselectivity of the addition reaction of chloromethyllithium to imines **10** (Scheme 4) was also determined, on the crude reaction products, by 300 MHz ^{1}H NMR. The structure of diaminochloroalkanes **15** was established on the basis of spectroscopic data for compounds **15b**,**c** and by allowing the reaction mixture to reach room temperature, in the case of compound **15c**, to promote the heterocyclization. In this latter experiment, aminoaziridine **11c** was obtained instead of **15c** in a 55% yield (Scheme 4).

The absolute configuration of compounds **11** and **15** was according to an addition reaction of chloro- or iodomethyllithium

SCHEME 5. Proposed Addition Reaction of Chloro- and Iodomethyllithium to Aminoimines 10



to α-aminoimines **10** under nonchelation control. This fact could be explained by assuming that the energetically more favored transition state has the larger substituent (*N*,*N*-dibenzylamino group) anti to the attack of the halomethyllithium (Scheme 5). The same stereochemical course was established to explain the reduction of chloromethyl ketones[19f] or chloromethyl ketimines.[19i] In addition, the stereochemistry of aziridine **11** was also in agreement with the anti epoxides, previously described by treatment from α-aminoaldehydes with iodomethyllithium.[19f]

Finally, the enantiomeric purities of compounds **11** and **15** were evaluated by chiral HPLC. To carry out this analysis, a racemic mixture of **11c** was previously prepared from the imine obtained with racemic phenylalaninal (±)-**9b**. The chiral HPLC analysis of this racemic mixture allowed the discovery of the best conditions to separate both enantiomers. These conditions were used to analyze the aziridine **11c** obtained from the treatment of **10c** with iodomethyllithium at −78 °C or chloromethyllithium at −78 °C allowing the reaction mixture to reach room temperature. After obtaining **11c** through both pathways, HPLC analysis showed an enantiomeric purity >98% in both cases. This fact excluded a partial racemization from phenylalaninal **9c** during its transformation into **11c** or **15c**.[31]

In conclusion, an efficient, simple, and rapid aziridination process by reaction of imines derived from *p*-toluenesulfonamide

(31) The determination of the absence of racemization was carried out with the phenylalaninal, due to its high proclivity to racemize: Rittle, K. E.; Homnick, C. F.; Ponciello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016–3018.

with in situ generated iodomethyllithium at 0 °C is reported. The addition reaction of chloromethyllithium to imines derived from *p*-toluenesulfonamide at −78 °C afforded the corresponding chloroamines. The reaction with aldimines derived from various aminoaldehydes afforded the corresponding enantiopure (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine and (2*S*,3*S*)-2,3-diamino-1-chloroalkanes with very high diastereoselectivity.

Experimental Section

Compounds **2a**−**e**, **3a**,**c**,**d**, **11c**, **12**, and **13** displayed analytical data in accordance with the published values.[24]

Synthesis of Sulfonylimines 1. *N*-Sulfonylimines **1** were synthesized following the method reported in ref 26.

Cyclohexyl-*N*-phenylsufonylmethanimine (1f): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51 (d, J = 4.3 Hz, 1 H), 7.93 (d, J = 7.1 Hz, 2 H), 7.64−7.52 (m, 3 H), 2.46−2.43 (m, 1 H), 1.86−1.64 (m, 5 H), 1.35−1.25 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.6 (CH), 137.8 (C), 133.5 (CH), 129.0 (2×CH), 127.9 (2×CH), 43.6 (CH), 28.2 (2×CH_2), 25.5 (CH_2), 25.0 (2×CH_2); MS (70 eV) *m*/*z* (%) 251 [M^+] (20), 196 (34), 183 (51), 141 (39), 110 (74), 77 (100), 55 (47), 41 (39); HRMS (ESI)$^+$ calcd for $C_{13}H_{18}NO_2S$ [M + H]$^+$ 252.1058, found 252.1053; IR (neat) $\tilde{\nu}$ = 3343, 1565, 1266, 1012, 738 cm^{-1}; R_f = 0.37 (hexane:ethyl acetate 3:1).

(4-Chlorophenyl)-*N*-phenylsulfonylmethanimine (1g): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.02 (s, 1 H), 8.01 (d, J = 8.6 Hz, 2 H), 7.88 (d, J = 8.6 Hz, 2 H), 7.68−7.46 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.0 (CH), 141.5 (C), 137.9 (C), 133.6 (CH), 132.4 (2×CH), 130.7 (C), 129.6 (2×CH), 129.1 (2×CH), 128.0 (2×CH); MS (70 eV) *m*/*z* (%) 279 [M^+] (11), 141 (59), 77 (100); HRMS calcd for $C_{13}H_{10}ClNO_2S$ 279.0121, found 279.0097; IR (neat): $\tilde{\nu}$ = 3338, 1593, 1266, 1008, 738 cm^{-1}; R_f = 0.32 (hexane:ethyl acetate 3:1).

(4-Methoxyphenyl)-*N*-phenylsulfonylmethanimine (1h): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.96 (s, 1 H), 7.98 (d, J = 6.9 Hz, 2 H), 7.88 (d, J = 8.9 Hz, 2 H), 7.63−7.49 (m, 3 H), 6.96 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.6 (CH), 165.3 (C), 138.6 (C), 133.7 (2×CH), 133.2 (CH), 128.9 (2×CH), 127.7 (2×CH), 125.0 (C), 114.6 (2xCH), 55.6 (CH_3); MS (70 eV) *m*/*z* (%) 275 [M^+] (56), 134 (100), 77 (70), 155 (49), 133 (51), 91 (100), 65 (28); HRMS calcd for $C_{14}H_{13}NO_3S$ 275.0616, found 275.0618; IR (neat) $\tilde{\nu}$ = 3318, 1590, 1266, 1005, 738 cm^{-1}; R_f = 0.25 (hexane:ethyl acetate 3:1).

Synthesis of Sulfonylaziridines 2. To a mixture of the requisite *N*-sulfonylimine **1** (0.4 mmol) and CH_2I_2 (0.6 mmol, 1.5 equiv) in dry THF (2 mL) was added at 0 °C a solution of MeLi in ether (1.5 M, 0.48 mmol, 1.2 equiv). The solution was stirred at the same temperature for 30 min and then was left to stir at room temperature for an additional 30 min. The reaction mixture was then quenched with NH_4Cl (aq), and the organic layer was then extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield crude *N*-sulfonylaziridines **2** which were purified by flash chromatography on silica gel (hexane/EtOAc 10/1).

2-Cyclohexyl-1-phenylsulfonylaziridine (2f): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.64−7.48 (m, 3 H), 2.60 (d, J = 7.0 Hz, 1 H), 2.55−2.49 (m, 1 H), 2.09 (d, J = 4.5 Hz, 1 H), 1.70−1.40 (m, 5 H), 1.19−0. 80 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.9 (C), 133.3 (CH), 128.8 (2×CH), 127.8 (2×CH), 45.1 (CH), 39.1 (CH), 32.6 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 25.1 (CH_2); MS (70 eV) *m*/*z* (%) 265 [M^+] (<1), 124 (91), 95 (100), 77 (74), 67 (30), 51 (27), 42 (73); HRMS calcd for $C_{14}H_{19}NO_2S$ 265.1136, found 265.1110; IR (neat) $\tilde{\nu}$ = 3055, 1449, 1265, 1012, 738 cm^{-1}; R_f = 0.40 (hexane:ethyl acetate 3:1).

2-(4-Chlorophenyl)-1-phenylsulfonylaziridine (2g): pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.3 Hz, 2 H), 7.68−7.52 (m, 3 H), 7.27 (d, J = 8.5 Hz, 2 H), 7.15 (d, J = 8.3 Hz, 2 H), 3.77 (dd, J = 7.1, 4.5 Hz, 1 H), 3.01 (d, J = 7.1 Hz, 1 H), 2.37 (d, J = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.8 (C), 134.2 (C), 133.7 (CH), 133.4 (C), 129.1 (2×CH), 128.8 (2×CH), 127.8 (4×CH), 40.3 (CH), 36.1 (CH_2); MS (70 eV) *m*/*z* (%) 293 [M^+] (<1), 152 (100), 125 (92); HRMS calcd for $C_{14}H_{12}ClNO_2S$ 293.0277, found 293.0279; IR (neat) $\tilde{\nu}$ = 3056, 1327, 1266, 1000, 739 cm^{-1}; R_f = 0.27 (hexane:ethyl acetate 3:1).

2-(4-Methoxyphenyl)-1-phenylsulfonylaziridine (2h): orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.5 Hz, 2 H), 7.68−7.53 (m, 3 H), 7.27 (d, J = 8.6 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H), 3.89 (s, 3 H), 3.77 (dd, J = 7.2, 4.4 Hz, 1 H), 3.01 (d, J = 7.2 Hz, 1 H), 2.37 (d, J = 4.4 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.4 (C), 139.7 (C), 133.4 (CH), 128.9 (2×CH), 127.7 (2×CH), 127.6 (2×CH), 126.1 (C), 113.8 (2×CH), 55.0 (CH_3), 40.8 (CH), 35.6 (CH_2); MS (70 eV) *m*/*z* (%) 289 [M^+] (24), 267 (10), 231 (22), 148 (100), 121 (25); HRMS calcd for $C_{15}H_{15}NO_3S$ 289.0773, found 289.0778; IR (neat) $\tilde{\nu}$ = 3292, 1514, 1266, 1165, 999 cm^{-1}; R_f = 0.22 (hexane:ethyl acetate 3:1).

Synthesis of Aziridines 3. To a cooled (−78 °C) suspension of Li powder (1.44 mmol) and naphthalene (1.62 mmol) in dry THF (4 mL) previously stirred for 1 h at rt was added under N_2 atmosphere the corresponding *N*-sulfonylaziridine **2** (0.36 mmol). The mixture was then stirred for an additional hour at the same temperature and then was quenched with brine (10 mL). The corresponding pure aziridine was obtained in a good yield after an acid−base extraction.

Synthesis of Chloroamines 4. To a mixture of *N*-sulfonyl imine (0.4 mmol) and CH_2ICl (1 mmol, 2.5 equiv) in dry THF (2 mL) was added at −78 °C a solution of MeLi in ether (1.5 M, 1 mmol, 2.5 equiv). The solution was stirred at the same temperature for 3 h and then was quenched with NH_4Cl (aq) at the same temperature. The organic layer was extracted with diethyl ether (3 × 10 mL), and the combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield the *N*-sulfonylchloroamine which was purified by flash chromatography on silica gel (hexane/EtOAc 10/1) to afford pure products.

1-Chloro-*N*-tosylnonan-2-amine (4a): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 4.84 (d, J = 8.1 Hz, 1 H), 3.55−3.42 (m, 3 H), 2.43 (s, 3 H), 1.68−1.00 (m, 12 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 143.5 (C), 137.7 (C), 129.7 (2×CH), 126.9 (2×CH), 53.7 (CH), 48.1 (CH_2), 32.3 (CH_2), 31.6 (CH_2), 28.9 (2×CH_2), 25.2 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 14.0 (CH_3); MS (70 eV) *m*/*z* (%) 331 [M^+] (<1), 282 (100), 232 (24), 155 (68), 91 (89), 65 (19), 41 (17); HRMS calcd for $C_{16}H_{26}ClNO_2S$ 331.1373, found 331.1378; IR (neat) $\tilde{\nu}$ = 3370, 3055, 1265, 1012, 740 cm^{-1}; R_f = 0.45 (hexane:ethyl acetate 3:1).

1-Chloro-3-methyl-*N*-tosylpentan-2-amine (4b): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.3 Hz, 4 H), 7.30 (d, J = 8.3 Hz, 4 H), 5.01 (d, J = 8.6 Hz, 2 H), 3.58−3.52 (m, 2 H), 3.42−3.22 (m, 4 H), 2.43 (s, 6 H), 1.79−1.51 (m, 2 H), 1.28−1.19 (m, 2 H), 1.12−0.95 (m, 2 H), 0.80 (d, J = 6.9 Hz, 6 H), 0.74 (d, J = 7.4 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major stereoisomer) δ = 143.5 (C), 137.6 (C), 129.6 (2×CH), 127.0 (2×CH), 57.7 (CH), 45.4 (CH_2), 35.0 (CH), 25.5 (CH_2), 21.4 (CH_3), 13.8 (CH_3), 11.0 (CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) (minor stereoisomer) δ = 143.5 (C), 137.7 (C), 129.6 (2×CH), 126.9 (2×CH), 58.1 (CH), 45.9 (CH_2), 35.7 (CH), 24.3 (CH_2), 21.4 (CH_3), 14.9 (CH_3), 10.9 (CH_3); MS (70 eV) *m*/*z* (%) 240 [$M^+ - CH_2Cl$] (32), 232 (65), 155 (92), 91 (100), 65 (28), 41 (17); HRMS calcd for $C_{13}H_{20}ClNO_2S$ 289.0903, found 289.0943; IR (neat) $\tilde{\nu}$ = 3373, 1599, 1266, 1161, 989 cm^{-1}; R_f = 0.30 (hexane:ethyl acetate 3:1).

2-Chloro-1-cyclohexyl-*N*-tosylethanamine (4c): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.78 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H), 5.11 (d, J = 9.1, 1 H), 3.58 (dd, J = 11.4, 3.3 Hz, 1 H), 3.41 (dd, J = 11.4, 4.7 Hz, 1 H), 3.28−3.20 (m, 1 H), 2.43 (s, 3 H), 1.82−1.55 (m, 6 H), 1.35−0.69 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.4 (C), 137.8 (C), 129.5 (2×CH), 126.9

(2×CH), 58.5 (CH), 45.6 (CH_2), 38.3 (CH), 29.1 (CH_2), 28.3 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 21.4 (CH_3); MS (70 eV) *m/z* (%) 315 [M^+] (<1), 266 (64), 232 (79), 184 (18), 155 (97), 65 (28), 55 (25), 41 (28); HRMS calcd for $C_{14}H_{20}NO_2S$ [$M^+ - CH_2Cl$] 266.1214, found 266.1208; IR (neat) $\tilde{\nu}$ = 3282, 2930, 1265, 1161, 1010 cm^{-1}; R_f = 0.45 (hexane:ethyl acetate 3:1).

1-Chloro-3-phenyl-*N*-tosylpropan-2-amine (4d): pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.27−7.03 (m, 7 H), 4.90 (d, *J* = 8.2 Hz, 1 H), 3.75−3.65 (m, 1 H), 3.52−3.42 (m, 1 H), 2.89 (dd, *J* = 13.8, 7.7 Hz, 1 H), 2.77 (dd, *J* = 13.8, 6.7 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 143.4 (C), 137.1 (C), 136.0 (C), 129.6 (2×CH), 129.1 (2×CH), 128.7 (2×CH), 126.9 (CH), 126.8 (2×CH), 55.0 (CH), 45.8 (CH_2), 38.1 (CH_2), 21.4 (CH_3); MS (70 eV) *m/z* (%) 323 [M^+] (<1), 232 (70), 151 (76), 91 (100), 65 (35); HRMS calcd for $C_{15}H_{16}NO_2S$ [$M^+ - CH_2Cl$] 274.0902, found 274.0933; IR (neat) $\tilde{\nu}$ = 3288, 2947, 1598, 1334, 1011 cm^{-1}; R_f = 0.40 (hexane:ethyl acetate 3:1).

2-Chloro-1-phenyl-*N*-tosylethanamine (4e): white solid; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.28−7.16 (m, 7 H), 5.39 (d, *J* = 6.2 Hz, 1 H), 4.59 (q, *J* = 6.2 Hz, 1 H), 3.74 (d, *J* = 6.2 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.6 (C), 137.1 (C), 136.9 (C), 129.5 (2×CH), 128.6 (2×CH), 128.3 (CH), 127.1 (2×CH), 126.8 (2×CH), 58.3 (CH), 47.8 (CH_2), 21.4 (CH_3); MS (70 eV) *m/z* (%) 260 [$M^+ - CH_2Cl$] (100), 155 (43), 91 (86), 65 (21); HRMS calcd for $C_{14}H_{14}NO_2S$ [$M^+ - CH_2Cl$] 260.0745, found 260.0750; IR (neat) $\tilde{\nu}$ = 3338, 3055, 1632, 1007, 673 cm^{-1}; R_f = 0.30 (hexane:ethyl acetate 3:1).

2-Chloro-1-cyclohexyl-*N*-sulfonylphenylethanamine (4f): white solid; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.6 Hz, 2 H), 7.47−7.35 (m, 3 H), 5.16 (d, *J* = 8.6, 1 H), 3.44 (dd, *J* = 11.4, 3.4 Hz, 1 H), 3.28 (dd, *J* = 11.4, 4.5 Hz, 1 H), 3.19−3.08 (m, 1 H), 1.68−1.33 (m, 6 H), 1.12−0.54 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.7 (C), 132.6 (CH), 128.9 (2×CH), 126.8 (2×CH), 58.6 (CH), 45.6 (CH_2), 38.3 (CH), 29.0 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 25.5 (CH_2); MS (70 eV) *m/z* (%) 252 [$M^+ - CH_2Cl$] (79), 218 (90), 170 (25), 141 (69), 95 (16), 77 (100), 55 (29), 41 (29); HRMS calcd for $C_{13}H_{18}NO_2S$ [$M^+ - CH_2Cl$] 252.1058, found 252.1057; IR (neat) $\tilde{\nu}$ = 3371, 2930, 1266, 1164, 997 cm^{-1}; R_f = 0.42 (hexane:ethyl acetate 3:1).

2-Chloro-1-(4-chlorophenyl)-*N*-sulfonylphenylethanamine (4g): white solid; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.06 (d, *J* = 8.3 Hz, 2 H), 5.45 (d, *J* = 6.1 Hz, 1 H), 4.60 (q, *J* = 6.1 Hz, 1 H), 3.68 (d, *J* = 6.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.6 (C), 135.5 (C), 134.2 (C), 132.8 (CH), 128.9 (2×CH), 128.7 (2×CH), 128.2 (2×CH), 127.0 (2×CH), 57.7 (CH), 47.6 (CH_2); MS (70 eV) *m/z* (%) 330 [M^+] (8), 280 (97), 141 (100); HRMS calcd for $C_{13}H_{11}ClNO_2S$ [$M^+ - CH_2Cl$] 280.0199, found 280.0197; IR (neat) $\tilde{\nu}$ = 3252, 1448, 1266, 1014, 738 cm^{-1}; R_f = 0.62 (hexane:ethyl acetate 1:1).

2-Chloro-1-(4-methoxyphenyl)-*N*-sulfonylphenylethanamine (4h): pale yellow solid;^1H NMR (300 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 7.4 Hz, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.41 (t, *J* = 7.4 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 6.74 (d, *J* = 8.6 Hz, 2 H), 5.28 (d, *J* = 6.3, 1 H), 4.54 (q, *J* = 6.3 Hz, 1 H), 3.76 (s, 3 H), 3.70 (d, *J* = 6.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.5 (C), 139.9 (C), 132.6 (CH), 129.0 (C), 128.9 (2×CH), 128.0 (2×CH), 127.1 (2×CH), 114.0 (2×CH), 57.9 (CH), 55.2 (CH_3), 47.8 (CH_2); MS (70 eV) *m/z* (%) 325 [M^+] (2), 276 (100), 141 (20), 134 (39), 77 (65), 51 (16); HRMS calcd for $C_{15}H_{16}ClNO_3S$ 325.0539, found 325.0535; IR (neat) $\tilde{\nu}$ = 3338, 1514, 1266, 1006, 738 cm^{-1}; R_f = 0.47 (hexane:ethyl acetate 1:1).

Synthesis of Aminoaziridines 11. α-Aminoimines **10** were prepared using the method described by Weinreb (see ref 29). However, no isolation of **10** was carried out due to its instability. Therefore, after applying the Weinreb conditions, CH_2Cl_2 was removed and THF (5 mL) was added. The reaction mixture was cooled to −78 °C, and CH_2I_2 (1.6 mmol, 4 equiv) was added followed by a solution of MeLi in ether (1.5 M, 1.6 mmol, 4 equiv). The reaction mixture was stirred for 30 min and then warmed to room temperature and left to stir for an additional 30 min. The reaction mixture was then quenched with NH_4Cl (aq), and the organic layer was then extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield crude aminoaziridines **11** which were purified by flash chromatography on silica gel (hexane/EtOAc 10/1).

(2*S*,1′*R*)-1-Tosyl-2-[1′-(dibenzylamino)ethyl]aziridine (11a): yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 8.4 Hz, 2 H), 7.35−7.20 (m, 12 H), 3.82 (d, *J* = 13.8 Hz, 2 H), 3.62 (d, *J* = 13.8 Hz, 2 H), 2.85−2.75 (m, 2 H), 2.44 (s, 3 H), 2.39−2.32 (m, 1 H), 2.15 (d, *J* = 4.4 Hz, 1 H), 1.14 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.9 (C), 139.3 (2×C), 135.1 (C), 129.9 (2×CH), 129.7 (2×CH), 128.6 (4×CH), 128.3 (4×CH), 127.1 (2×CH), 59.8 (CH), 53.9 (2×CH_2), 39.9 (CH), 33.4 (CH_2), 21.6 (CH_3), 13.5 (CH_3); MS (70 eV) *m/z* (%) 420 [M^+] (<1), 405 (7), 329 (100), 224 (30), 196 (12), 91 (69); HRMS (ESI^+) calcd for $C_{25}H_{29}N_2O_2S$ [M + H]$^+$ 421.1949, found 421.1944; IR (neat) $\tilde{\nu}$ = 2957, 1495, 1455, 1326, 1161 cm^{-1}; $[\alpha]_{20}$ = −12.2 (*c* = 0.75, $CHCl_3$); R_f = 0.43 (hexane:ethyl acetate 5:1).

(2*R*,1′*S*)-1-Tosyl-2-[1′-(dibenzylamino)-3′-(methyl)butyl]aziridine (11b): pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 7.35−7.24 (m, 12 H), 3.80 (d, *J* = 13.7 Hz, 2 H), 3.56 (d, *J* = 13.7 Hz, 2 H), 2.85−2.76 (m, 2 H), 2.45 (s, 3 H), 2.39−2.32 (m, 1 H), 2.16 (d, *J* = 4.3 Hz, 1 H), 1.78−1.69 (m, 1 H), 1.57−1.41 (m, 1 H), 0.93−0.80 (m, 1 H), 0.72 (d, *J* = 6.5 Hz, 3 H), 0.45 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6 (C), 139.5 (2×C), 135.0 (C), 129.6 (2×CH), 129.0 (2×CH), 128.5 (4×CH), 128.2 (4×CH), 127.0 (2×CH), 61.0 (CH), 56.8 (CH), 56.0 (CH), 53.9 (2×CH_2), 53.0 (2×CH_2), 40.1 (CH), 38.5 (CH_2), 33.9 (CH_2), 33.2 (CH_2), 25.4 (CH), 23.9 (CH), 23.2 (CH_3), 22.0 (CH_3), 21.8 (CH_3), 21.5 (CH_3); MS (70 eV) *m/z* (%) 419 [$M^+ - i$Pr] (5), 371 (100), 331 (14), 266 (35), 196 (65); HRMS calcd for $C_{28}H_{34}N_2O_2S$ 462.2341, found 462.2311; IR (neat) $\tilde{\nu}$ = 2956, 1495, 1455, 1325, 1162 cm^{-1}; $[\alpha]_{20}$ = −13.4 (*c* = 0.82, $CHCl_3$); R_f = 0.40 (hexane:ethyl acetate 5:1).

Deprotection/Benzylation Protocol of 11c toward the Synthesis of Compounds 12 and 13. To a cooled (−78 °C) suspension of Li powder (1.44 mmol) and naphthalene (1.62 mmol) in dry THF (4 mL) previously stirred for 1 h at rt was added under a N_2 atmosphere 0.36 mmol of **11c**. The mixture was stirred for an additional hour at the same temperature, and then benzyl bromide (1.44 mmol) was added. The reaction was stirred overnight and quenched with $NaHCO_3$ subsequently. The organic layer was extracted with diethyl ether (3 × 10 mL), and the combined extracts were dried over Na_2SO_4 and concentrated under vacuum. The *N*-benzylaziridine crude was purified by flash chromatography on silica gel (hexane/EtOAc 20/1) to afford the pure products **12** and **13**.

Synthesis of Enantiopure Chloroamines 15. After applying the Weinreb conditions to aminoaldehydes **9b**,**c**, CH_2Cl_2 was removed and THF (5 mL) was added. The reaction mixture was cooled to −78 °C and CH_2ICl (1.6 mmol, 4 equiv) was added followed by a solution of MeLi in ether (1.5 M, 1.6 mmol, 4 equiv). The reaction mixture was stirred for 3 h at −78 °C and then quenched with NH_4Cl (aq), and the organic layer was then extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield crude chloroamines **15** which were purified by flash chromatography on silica gel (hexane/EtOAc 10/1).

(2*S*,3*S*)-1-Chloro-N^3,N^3-dibenzyl-5-methyl-N^2-tosylhexane-2,3-diamine (15b): orange oil; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 8.2 Hz, 2 H), 7.41−7.24 (m, 12 H), 4.86 (d, *J* = 9.3 Hz, 1 H), 3.87 (dd, *J* = 10.9, 3.0 Hz, 1 H), 3.66 (d, *J* = 13.9 Hz, 2 H), 3.48 (d, *J* = 13.9 Hz, 2 H), 3.44−3.35 (m, 1 H), 3.22 (dd, *J* = 10.9, 5.8 Hz, 1 H), 2.73 (q, *J* = 7.0 Hz, 1 H), 2.43 (s, 3 H), 1.78−1.40 (m, 3 H), 0.84 (d, *J* = 6.3 Hz, 3 H), 0.76 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.5 (C), 139.5 (2×C), 137.3 (C), 129.6 (2×CH), 128.9 (4×CH), 128.4 (4×CH), 127.2 (2×CH),

127.0 (2×CH), 57.0 (CH), 54.9 (2×CH_2), 54.7 (CH), 45.8 (CH_2), 34.8 (CH_2), 25.8 (CH), 23.0 (CH_3), 22.1 (CH_3), 21.4 (CH_3); MS (70 eV) *m*/*z* (%) 455 [M^+ − *i*Pr] (52), 330 (35), 316 (23), 230 (36), 210 (100), 169 (51), 118 (30); HRMS calcd for $C_{21}H_{27}N_2O_2S$ [M^+ − CH_2Ph, − HCl] 371.1793, found 371.1790; IR (neat) $\tilde{\nu}$ = 3060, 1601, 1495, 1456, 1162 cm^{-1}; $[\alpha]_{20}$ = −4.9 (*c* = 0.90, $CHCl_3$); R_f = 0.30 (hexane:ethyl acetate 5:1).

(2*S*,3*S*)-1-Chloro-N^3,N^3-dibenzyl-4-phenyl-N^2-tosylbutane-2,3-diamine (15c): orange oil; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42−7.15 (m, 19 H), 4.70 (d, *J* = 9.42 Hz, 1 H), 3.93−3.79 (m, 1H), 3.81 (d, *J* = 13.56 Hz, 2 H), 3.58−3.43 (m, 1 H), 3.50 (d, *J* = 13.65 Hz, 2 H), 3.19−3.04 (m, 4 H), 2.42 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.3 (C), 140.0 (C), 139.1 (2×C), 137.3 (C), 129.6 (2×CH), 129.2 (2×CH), 128.8 (5×CH), 128.5 (5×CH), 127.3 (2×CH), 126.8 (2×CH), 126.0 (CH), 61.2 (CH), 55.2 (CH), 55.1 (2xCH_2), 45.4 (CH_2), 31.9 (CH_2), 21.5 (CH_3); MS (70 eV) *m*/*z* (%) 533 [M^+] (100), 497 (71), 441 (12), 393 (20), 300 (26), 91 (27); HRMS calcd for $C_{24}H_{25}N_2O_2S$ [M^+ − CH_2Ph, − HCl] 405.1636, found 405.1633; IR (neat) $\tilde{\nu}$ = 3063, 1600, 1496, 1455, 1162 cm^{-1}; $[\alpha]_{20}$ = +9.1 (*c* = 0.82, $CHCl_3$); R_f = 0.25 (hexane: ethyl acetate 5:1).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all new compounds **2**, **4**, **11**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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