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Diastereomerically and Enantiomerically Pure 2,3-Disubstituted Pyrrolidines from 2,3-Aziridin-1-ols Using a Sulfoxonium Ylide: A One-Carbon Homologative Relay Ring Expansion

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Abstract: An ylide-based aza-Payne rearrangement of 2,3-aziridin-1-ols leads to an efficient process for the preparation of pyrrolidines. The aza-Payne rearrangement under basic reaction conditions favors the formation of epoxy amines. Subsequent nucleophilic attack of the epoxide by the ylide yields a bis-anion, which upon a 5-*exo-tet* ring-closure yields the desired pyrrolidine, thus completing the relay of the three-membered to the five-membered nitrogen-containing ring system. This process takes place with complete transfer of stereochemical fidelity and can be applied to sterically hindered aziridinols.

Introduction

Substituted pyrrolidines are important heterocycles by virtue of their frequent appearance in a large number of biologically active natural products and pharmaceuticals.[1] Enantiomerically pure pyrrolidines are also used as chiral auxiliaries for various organic transformations.[2] Conformationally restrained analogues of proline are also being utilized in the synthesis of unnatural oligomers as scaffolds for biological applications such as antimicrobial activity.[3] As such, much effort has been devoted to the synthesis of pyrrolidines in enantiomerically and diastereomerically pure form, including, but certainly not limited to, 3 + 2 cycloadditions of azomethine ylides with alkenes or nitrones with cyclopropanes,[4] oxidative decarboxylation−β-iodination of amino acids,[5] palladium-catalyzed carboamination reactions,[6] intramolecular cyclization of epoxy and halogenated sulfones under basic conditions,[7] acid-catalyzed cyclization of vinylsilanes,[8] intramolecular carbolithiation of homoallylic amines,[9] radical cyclizations,[10] Brønsted acid-catalyzed intramolecular hydroamination of alkenylamines,[11] manipulations of sugars from the chiral pool,[12] various other metal-catalyzed cyclizations,[13] and ring-closing metathesis.[14] Clearly, the importance of pyrrolidines can be directly inferred from the

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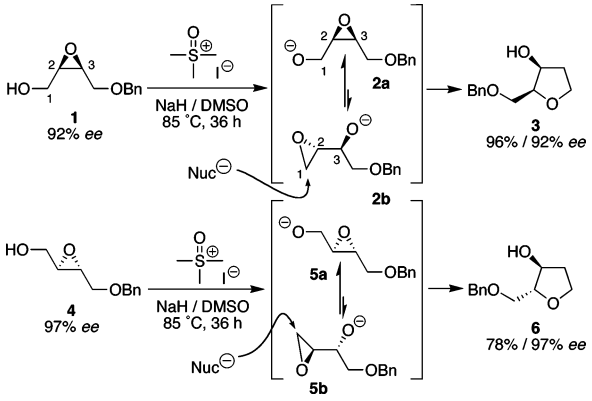
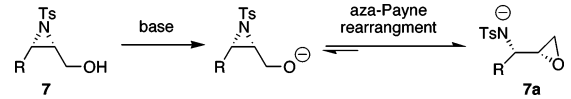
Scheme 1



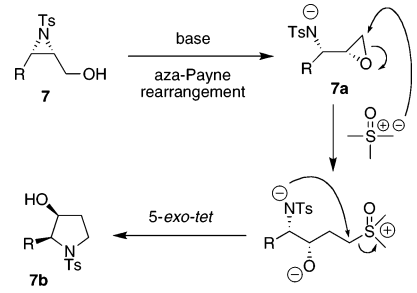
significant amount of effort that has led to the development of various methodologies for their synthesis. Our interest in the synthesis of pyrrolidines stems from our desire to develop methods that translate the stereochemistry embedded in simple and easy-to-obtain starting materials into more complex products with complete fidelity. As such, herein we report a general methodology for conversion of hydroxy aziridines into pyrrolidines via a one-carbon homologative relay ring expansion that is initiated by an aza-Payne rearrangement.

The Payne rearrangement is a base-mediated isomerization of epoxy alcohols and has been well-utilized in organic synthesis to reveal the latent electrophilicity at C-1 of a 2,3-epoxy-1-ol such as **1** (Scheme 1).[15] We have recently used this approach to control attack at C-1 with dimethylsulfoxonium methylide in the synthesis of a series of 2,3-substituted tetrahydrofurans (Scheme 1).[16a] These reactions can be high-yielding and deliver the THF ring in a regio- and stereocontrolled manner. The Payne rearrangement of *trans*-epoxides is not as facile as that of *cis*-epoxides (release of steric strain of *cis*-epoxides is the driving force), as can be seen by comparing the yields of THF products **3** and **6**, which originate from *cis*- and *trans*-epoxy diols **1** and **4**, respectively (Scheme 1). However, the presence of an electron-withdrawing atom at C-4 or C-5 of the epoxy alcohol is sufficient for successful THF formation with 2,3-disubstituted epoxy-1-ols. Certain substrates, mainly alkyl-disubstituted and trisubstituted 2,3-epoxy-1-ols, do not undergo sufficient Payne rearrangement to allow for successful nucleophilic attack on the less hindered 1,2-epoxy-3-ol (structures analogous to **2b** and **5b** in Scheme 1). Mixtures of products often result from competing nucleophilic attack at C-2 and C-3, as well as base-mediated elimination reactions.

Scheme 2



Scheme 3



In contrast to the Payne rearrangement, the aza-Payne rearrangement of activated 2,3-aziridin-1-ols (Scheme 2) has not received as much attention, despite its great potential for the synthesis of enantiomerically pure nitrogen-containing compounds.[17] Ibuka and co-workers have described the aza-Payne rearrangement of a series of *cis*- and *trans*-2,3-disubstituted aziridin-1-ols, as well as the reaction of the resulting epoxy amines with a few selected nucleophiles, including organocuprates and amines.[17−19] A particularly useful feature of the aza-Payne rearrangement is that, under aprotic conditions, the equilibrium for both *cis*- and *trans*-disubstituted 2,3-aziridin-1-ols lies exclusively toward the epoxy amine. This may result from the greater ability of the activated amine to stabilize the negative charge under the basic reaction conditions and/or the greater thermodynamic stability of the epoxy amine vs the aziridinol.[20] Thus, it was envisaged that an ylide-based aza-Payne rearrangement of 2,3-aziridin-1-ols could lead to an efficient process for the preparation of pyrrolidines (Scheme 3).[16b] The aza-Payne rearrangement is expected to favor epoxide **7a** over aziridine **7**, and subsequent nucleophilic attack to yield the bis-anion is anticipated. A 5-*exo-tet* ring-closure of the bis-anion would yield the desired pyrrolidine **7b**, thus completing the relay of the three-membered to the five-membered nitrogen-containing ring system.

Aza-Payne Rearrangment

To our knowledge, the facility of the aza-Payne rearrangement in more highly substituted compounds, such as 2,3,3- or 2,2,3-

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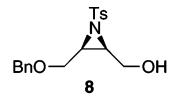
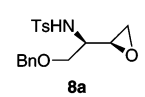
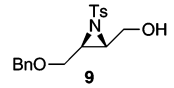
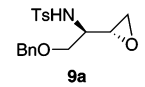
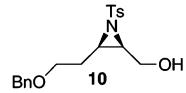
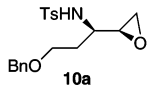
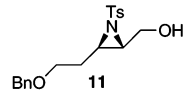
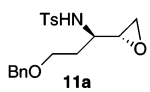
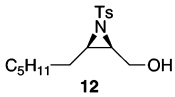
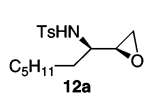
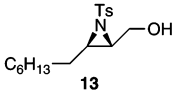
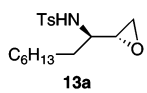
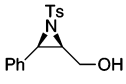
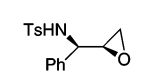
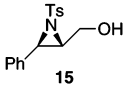
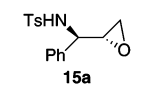
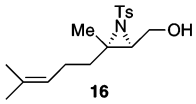
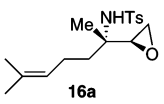
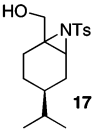
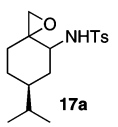
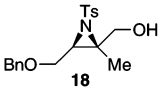
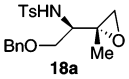
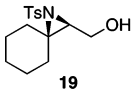
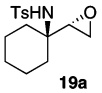
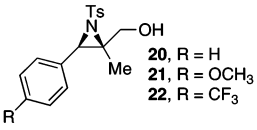
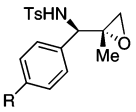
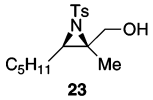
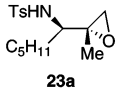
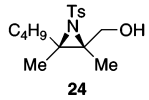
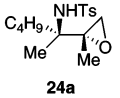
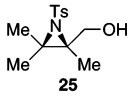
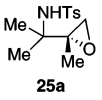
Table 1. Aza-Payne Rearrangement of 2,3-Aziridin-1-ols to Epoxy Amines[a]

entry	aziridinol	method	epoxy amine	yield
1	 **8**	A	 **8a**	90%
2	 **9**	A	 **9a**	89%
3	 **10**	A	 **10a**	86%
4	 **11**	A B	 **11a**	87% 86%
5	 **12**	A	 **12a**	84%
6	 **13**	A	 **13a**	86%
7	 **14**	A	 **14a**	85%
8	 **15**	A B	 **15a**	79% 83%
9	 **16**	A	 **16a**	89%
10	 **17**	A	 **17a**	78%
11	 **18**	A	 **18a**	94%
12	 **19**	A	 **19a**	93%
13 14 15	 **20**, R = H **21**, R = OCH_3 **22**, R = CF_3	A A A		**20a**, 81% **21a**, 93% **22a**, 66%
16	 **23**	A	 **23a**	70%
17	 **24**	C	 **24a**	67%
18	 **25**	C	 **25a**	74%

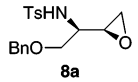
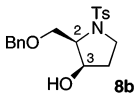
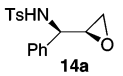
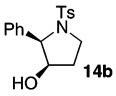
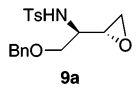
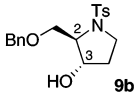
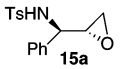
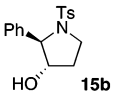
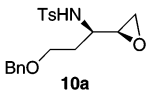
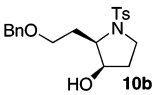
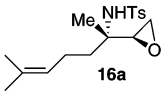
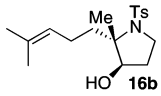
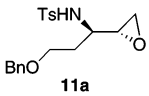
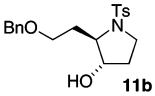
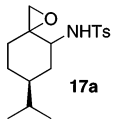
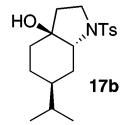
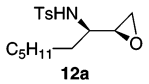
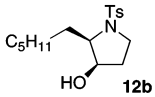
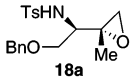
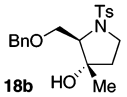
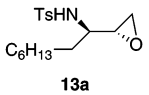
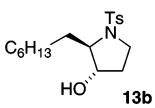
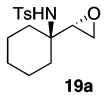
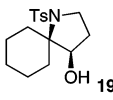
[a] Method A: a 0.1 M solution of the aziridinol was treated with 4.0 equiv of NaH in THF at room temperature. Method B: a 0.1 M solution of the aziridinol in DMSO was treated with 4−8 equiv of dimethylsulfoxonium methylide at room temperature. Method C: a 0.1 M solution of the aziridinol was treated with 4.0 equiv of NaH in 20:1 to 12:1 THF/HMPA at room temperature.

trisubstituted and tetrasubstituted aziridinols, has not been well-studied. In order to utilize aziridinols for the synthesis of pyrrolidines, a closer inspection of the aza-Payne rearrangement for a variety of substituted aziridines was necessary. The desired aziridinols could be accessed in several ways. Enantiomerically pure 2,3-disubstituted aziridin-1-ols such as **8** and **9** (Table 1) could be obtained via the asymmetric epoxides **1** and **4** using literature procedures.[21,22] Ring-opening of the corresponding epoxide with sodium azide was followed by a one-pot Staudinger reduction/cyclization and tosyl protection to give the desired aziridine. The Sharpless asymmetric aminohydroxylation could be used to synthesize disubstituted aziridinols.[23] The use of a VAPOL-catalyzed aziridination developed by the Wulff group could be implemented to access *cis*-aryl-substituted compounds.[24] Tetrasubstituted aziridinols could be accessed via stereoselective nucleophilic attack of an azirine, as described by Davis and co-workers.[25] The majority of the racemic substrates were synthesized via treatment of the corresponding allylic alcohols with Chloramine T and catalytic NBS.[26]

The aza-Payne rearrangement of tosylated aziridinols was accomplished in excellent yields using 4.0 equiv of NaH in THF or, in some cases, dimethylsulfoxonium methylide in dimethylsulfoxide (DMSO) (Table 1). Other bases and solvents that could be utilized for the aza-Payne rearrangement include NaH in toluene, DMSO or 12:1 THF/HMPA, as well as KH in either THF or toluene. The use of NaHMDS or KHMDS in THF, toluene, or DMSO was much less successful. In previous work directed toward the synthesis of tetrahydrofurans (Scheme 1), compounds containing an oxygen substituent at either C-4 or C-5 of the epoxy alcohol were excellent substrates for the Payne rearrangement/one-carbon homologative ring-opening/cycliza-

(21) Fujii, N.; Nakai, K.; Habashita, H.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2241−2250.
(22) (a) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981. (b) Andres, J. M.; de Elana, N.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **1999**, *55*, 14137. (c) Nayak, S. K.; Thijs, L.; Zwandenburg, B. *Synlett* **1998**, 1187. (d) Hwang, G. I.; Chung, J. H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183.
(23) (a) Kolb, H. C.; Sharpless, B. K. Asymmetric aminohydroxylation. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 309−326. (b) Schlingloff, G.; Sharpless, K. B. Asymmetric aminohydroxylation. In *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, UK, 2001; pp 104−114.
(24) (a) Patwardhan, A. P.; Lu, Z.; Pulgam, V. R.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 2201−2204. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518−4521. (c) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099−5100. (d) Patwardhan, A. P.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169−6172.
(25) (a) Davis, F. A; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894−6898. (b) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135−7143. (c) Davis, F. A.; Liu, H.; Liang, C.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929−8935. (d) Davis, F. A.; Liang, C.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796−3797.
(26) Thakur, V. V.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 989−992.

Table 2. Conversion of Epoxy Amines to 2,3-Substituted Pyrrolidines[a]

entry	epoxy amine	pyrrolidine	yield	entry	epoxy amine	pyrrolidine	yield
1	 **8a**	 **8b**	99%	7	 **14a**	 **14b**	88%
2	 **9a**	 **9b**	97%	8	 **15a**	 **15b**	71%
3	 **10a**	 **10b**	89%	9	 **16a**	 **16b**	86%
4	 **11a**	 **11b**	85%	10	 **17a**	 **17b**	76%
5	 **12a**	 **12b**	92%	11	 **18a**	 **18b**	88%
6	 **13a**	 **13b**	95%	12	 **19a**	 **19b**	52%

[a] Reactions were run in a 0.1 M solution of epoxy amine in DMSO using 4−8 equiv of dimethylsulfoxonium methylide at 80−85 °C for 24 h.

tion sequence to yield 2,3-disubstituted tetrahydrofurans. Likewise, these substrates (entries 1−4, Table 1) performed well in the aza-Payne rearrangement by treatment with NaH in THF, as described by Ibuka.[17] There were no notable disparities in the yields of epoxy amines utilizing either *cis*- or *trans*-disubstitituted aziridinols as substrates (Table 1, entries 1−8). Alkyl epoxides analogous to **12** and **13** (entries 5 and 6) were not good substrates for Payne rearrangement, but the corresponding 2,3-aziridin-1-ols **12** and **13** gave only epoxy amine products **12a** and **13a**, with no trace of the starting materials. It was also of note that the 2,3,3-trisubstituted aziridinol **16** (entry 9) derived from geraniol was converted successfully to the epoxy amine **16a** in excellent yield, despite the fact that the analogous geraniol epoxide was resistant to the Payne rearrangement and gave only 14% of the tetrahydrofuran product.[16a] A cyclic 2,3,3-trisubstituted substrate **19** (entry 12) was also successful in the aza-Payne rearrangement, the analogous epoxy alcohol substrate giving only 21% yield of the desired product in our previous work.[16a] Gratifyingly, 2,2,3-trisubstituted aziridinols such **17** and **18** (entries 10 and 11) underwent facile rearrangement, even though the electrophilic center was tertiary, to yield epoxy amines **17a** and **18a**, respectively. Relief of steric strain in the epoxide analogue of **17** on going from the fused ring system to the spiro ring system has been cited as the reason for the 1:2 mixture of 1,2-epoxy-3-ol and 2,3-epoxy-1-ol in the Payne rearrangement.[27] In contrast, aziridinol **17** leads to the production of only one isomer. A series of 2,2,3-trisubstituted aziridinols bearing an aryl group at C-3 were also examined. An electronic component to the facility of the aza-Payne rearrangement was noted, as the *p*-methoxyphenyl-containing **21** gave a 93% yield of the epoxy amine, while the trifluoromethylphenyl-containing substrate **22** gave only a 66% yield of **22a**. The 2,2,3-trialkylsubstituted aziridinol **23** gave the epoxy amine **23a**. Finally, the tetrasubstituted aziridinols **24** and **25** (entries 17 and 18) also underwent successful aza-Payne rearrangement to yield epoxy amines **24a** and **25a**. A small amount of HMPA was necessary to improve the yield of the transformation.[17] The ability to use tri- and tetrasubstituted aziridinols in the aza-Payne rearrangement allows transfer of the terminal oxygen to a sterically congested tertiary center, yielding a quaternary hydroxyl center upon opening of the unhindered epoxide with various nucleophiles. This can yield synthetically useful 1,2-amino alcohols of various substitution patterns that might not otherwise be easily accessible.

(27) Swindell, C. S.; Britcher, S. F. *J. Org. Chem.* **1986**, *51*, 793−797.

Pyrrolidines from Aza-Payne Rearranged Aziridinols

The data in Table 1 illustrate the efficiency of the aza-Payne rearrangement for a number of aziridinols. In all cases the epoxide is isolated in high yields; however, more importantly, the rearrangement was facile using dimethylsulfoxonium methylide as the base. This is critical for the implementation of the next series of transformations. As depicted in Scheme 3, it was envisaged that epoxide **7a**, obtained via the aza-Payne rearrangement of **7**, could undergo nucleophilic trapping with the sulfoxonium ylide to yield the bis-anion intermediate. Ring-closure with loss of DMSO would yield the desired pyrrolidine **7b**.

The epoxy amine products listed in Table 1 were treated with dimethylsulfoxonium methylide in DMSO at 85 °C to afford the 2,3-disubstituted pyrrolidine rings in good to excellent yields and with complete control of diastereoselectivity (Table 2). Epoxy amine **8a**, generated from the *cis*-aziridinol **8**, led to the corresponding *cis*-disubstituted pyrrolidine ring **8b**, while the

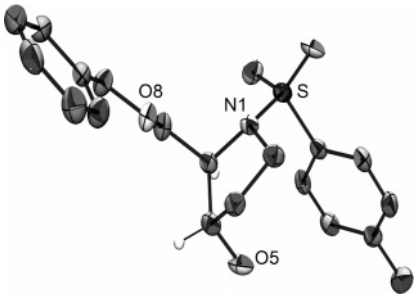


Figure 1. X-ray crystal structure of **9b**. Most of the hydrogen atoms are not shown for better clarity.

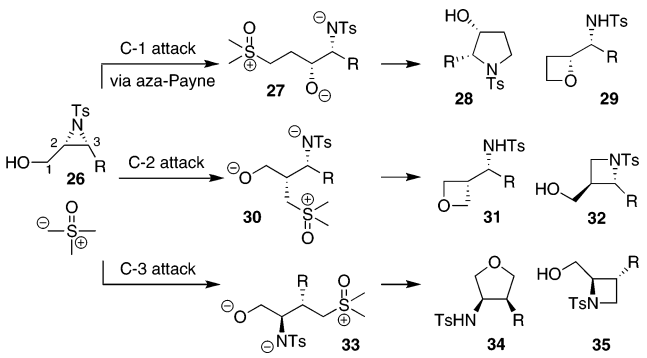
epoxy amine **9a**, obtained from the *trans*-aziridinol **9**, gave the *trans*-disubstituted pyrrolidine **9b**, both in excellent yields (Table 2, entries 1 and 2). The relative stereochemistries were verified by NOE experiments of the *cis*- and *trans*-pyrrolidines **8b** and **9b** that showed a greater enhancement of the H-2 proton when H-3 of the *cis* compound was irradiated as compared to the *trans* product. To further establish the relative stereochemistry of the substituents at C-2 and C-3, an X-ray crystal structure of compound **9b** was obtained that clearly indicated the *trans* orientation of the C-2 and C-3 substituents (Figure 1).

The remaining epoxy amines obtained from disubstituted aziridinol substrates (Table 2, entries 3−8) gave the corresponding pyrrolidines in high yields as single diastereoisomers. Epoxy amines derived from 2,3,3-trisubstituted aziridinols (Table 2, entries 9 and 12) also gave good yields of the pyrrolidines bearing a quaternary nitrogen center. This is again in contrast to the analogous reactions with similarly substituted epoxy alcohols as substrates, which gave the THF products in yields less than 30%. The steric hindrance of the nucleophilic nitrogen of **19a** in entry 12, along with the strain of the spiro ring system, presumably led to a lower yield of pyrrolidine **19b**. Entries 10 and 11 illustrate the conversion of epoxy amines **17a** and **18a**, derived from 2,2,3-trisubstituted aziridinols, to pyrrolidines that contain a chiral 3° hydroxyl group at C-3. The relative stereochemistry of the trisubstituted pyrrolidine **18b** was established via NOE enhancements observed between the benzyl-protected hydroxymethyl side chain at C-2 and the C-3 methyl group. This again verified the anticipated stereochemical outcome of the reaction based on the mechanism depicted in Scheme 3.

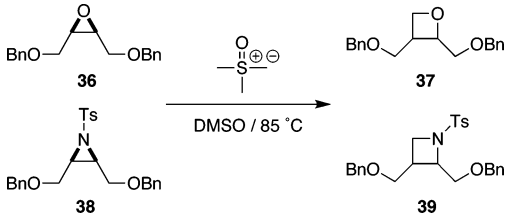
One-Pot Conversion of Aziridinols to Pyrrolidines

Having established high efficiency in the preparation of pyrrolidines from aziridinols in two steps, i.e., aza-Payne rearrangement of aziridinols followed by treatment of products isolated from the latter reaction with dimethylsulfoxonium methylide, we directed our attention toward a one-pot preparation of pyrrolidines. As such, the ylide itself would serve as the base to promote aza-Payne rearrangement (already shown to be effective, Table 1), leading to an epoxide that would undergo attack with the ylide (Scheme 3). Ring-closure to the pyrrolidine would deliver the desired product. An issue of particular concern was competing ring-opening of the aziridine at either C-2 or C-3 by the ylide prior to aza-Payne rearrangement, particularly since excess ylide is used to compensate for its degradation at the elevated reaction temperatures. Several products could then be obtained, depending on the relative

Scheme 4



Scheme 5



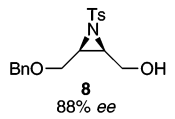
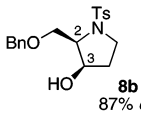
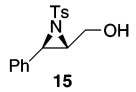
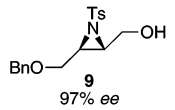
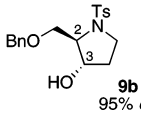
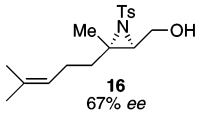
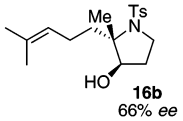
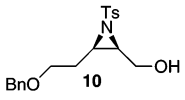
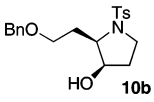
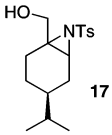
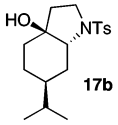
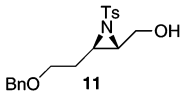
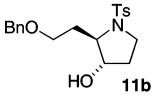
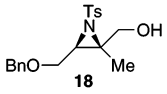
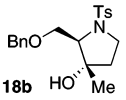
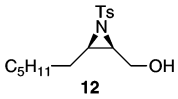
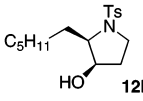
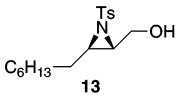
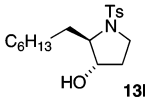
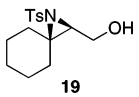
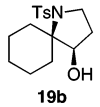
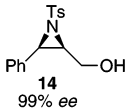
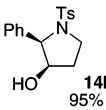
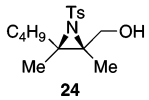
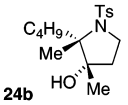
nucleophilicities of the oxygen and nitrogen anions to form oxetanes, azetidines, tetrahydrofurans, or pyrrolidines (Scheme 4).[28]

In order to determine the facility of epoxide vs aziridine ring-opening with dimethylsulfoxonium methylide, a competition experiment was performed (Scheme 5). A 1:1 mixture of **36** and **38** was treated with 1.0 equiv of dimethylsulfoxonium methylide in DMSO at room temperature for 1 h and then at 85 °C for 24 h. Epoxide **36** was recovered in 95% yield, while aziridine **38** was consumed completely. The azetidine **39** was obtained in 64% yield. Clearly, the higher reactivity of the aziridine as compared to that of the epoxide toward nucleophilic attack by the ylide could lead to the aforementioned mixture of undesired products (Scheme 4). However, two factors were crucial in our belief that a choreographed sequence of events (aza-Payne; nucleophilic attack of epoxide; ring-closure) could be achieved (Scheme 3). First, the aza-Payne rearrangement is an intramolecular process and may compete favorably with the intermolecular process of aziridine ring-opening with the ylide. Second, the epoxide that undergoes attack by the ylide is *less* hindered than the starting aziridine. Another important piece of information obtained from the experiment shown in Scheme 5 was that heating to 85 °C was necessary to cause ylide ring-opening of the aziridine. We reasoned that the aza-Payne rearrangement could be accomplished at a lower temperature and then the temperature could be raised to 85 °C to promote epoxide ring-opening and subsequent ring-closure to the pyrrolidine. In this manner, the undesired ring-opening of the aziridine should not compete with the desired epoxide ring-opening by the ylide.

In the first successful attempt at a one-pot reaction to form pyrrolidines, the ylide generated from trimethylsulfoxonium iodide and NaH was added to the aziridinol, stirred at room temperature for 30 min, and heated to 85 °C for 24 h. Conversion of aziridinols **8** and **9** to pyrrolidines **8b** and **9b** occurred with moderate yields of 67% and 61%, respectively. We suspected that the lower yields might be caused by

(28) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

Table 3. One-Pot Conversion of 2,3-Aziridin-1-ols to 2,3-Substituted Pyrrolidines

entry	aziridinol	pyrrolidine	yield	entry	aziridinol	pyrrolidine	yield
1	 **8** 88% *ee*	 **8b** 87% *ee*	82%	8	 **15**	 **15b**	68%
2	 **9** 97% *ee*	 **9b** 95% *ee*	78%	9	 **16** 67% *ee*	 **16b** 66% *ee*	70%
3	 **10**	 **10b**	77%	10	 **17**	 **17b**	76%
4	 **11**	 **11b**	71%	11	 **18**	 **18b**	79%
5	 **12**	 **12b**	79%				
6	 **13**	 **13b**	71%	12	 **19**	 **19b**	69%
7	 **14** 99% *ee*	 **14b** 95% *ee*	79%	13	 **24**	 **24b**	67%

[a] Reactions were run by stirring a 0.1 M solution of the aziridinol with excess dimethylsulfoxonium methylide in DMSO for 4 h, followed by heating at 80 °C for 24 h.

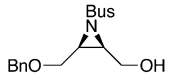
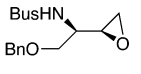
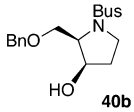
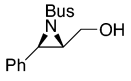
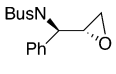
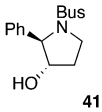
competitive ring-opening of the aziridine at the elevated reaction temperatures prior to complete aza-Payne rearrangement.

The effect of the ylide counterion on the efficacy of the aza-Payne/ring-opening/ring-closure reaction was briefly examined. Dimethylsulfoxonium methylide was generated using both NaH and KH as bases in DMSO. Varying amounts of the ylide were added to solutions of **8** in DMSO, and the reactions were stirred for 4 h at room temperature to ensure aza-Payne rearrangement was complete. After an additional 4 h, the reactions were analyzed by HPLC. The reactions utilizing potassium as the counterion were reanalyzed at 22 h. The results indicate that the sodium counterion is more effective for ring-closure to the desired pyrrolidine **8b**, with a 90% conversion to product after 8 h. The potassium cation was less effective, resulting in a 40% conversion to **8b** after 8 h. However, high conversions were obtained using KH by running the reaction overnight. As expected, increasing the amount of ylide from 2 to 10 equiv greatly increased the rate, although this effect leveled out after 8 equiv.

With these results in hand, we repeated the one-pot reaction with **8** using 8.0 equiv of ylide generated from NaH as the base in DMSO. The reaction was stirred at room temperature overnight, and pyrrolidine **8b** was obtained in 82% yield. However, the reaction was often not complete for *trans* and more hindered aziridinols, resulting in a mixture of pyrrolidine, epoxy amine, and *N*-methylated products. Prolonged heating of the more stubborn reactions proved to be a general solution, and thus heating of all reactions at 80−85 °C for 24 h was adopted as standard protocol. These reactions could also be performed in THF with a small amount of DMSO (5 equiv). Substrate **8** (Table 3) was treated with dimethylsulfoxonium methylide (generated by refluxing trimethylsulfoxonium iodide with NaH in THF for 4 h), stirred at room temperature for 4 h, and heated to 80 °C overnight in a sealed tube. In this manner, the pyrrolidine **8b** could be obtained in 82% yield.

The general reaction conditions discussed above were adopted for the one-pot conversion of 2,3-aziridin-1-ols to pyrrolidines (Table 3). The *cis*-substituted aziridinols tended to give slightly higher yields than the corresponding *trans* analogues. As previously described in the discussion of Table 2, substrates containing alkyl substituents (entries 5 and 6) or trisubstituted aziridines (entries 9−12) proceeded under the reaction conditions to give pyrrolidines in good yields, in contrast to our analogous work using 2,3-epoxy-1-ols to prepare THFs. Aryl aziridines **14** and **15** (entries 7 and 8) were also successfully converted to pyrrolidines **14b** and **15b**, respectively, without any indication of C-3 ring-opening by the ylide. The major byproduct in the *trans*-aziridine substituted with an aryl group at C-3 (entry 10) was *N*-methylated epoxy amine. Other *trans*-aziridinols were also prone to *N*-methylation if the temperature was lowered below 75 °C or any extra trimethylsulfoxonium iodide was present. The *ee*'s of selected aziridinols and pyrrolidines were determined by preparing the corresponding MPA esters to ensure that racemization had not occurred under

Table 4. Use of a Bus Protecting Group[a]

entry	aziridinol	epoxy amine (yield)	pyrrolidine	yield (one-pot)
1	 **40**	 **40a** (70%)	 **40b**	74%
2	 **41**	 **41a** (61%)	 **41b**	52%

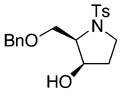
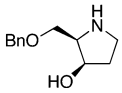
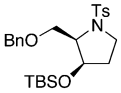
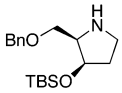
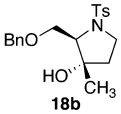
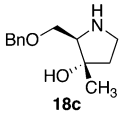
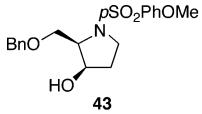
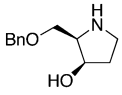
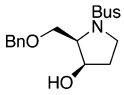
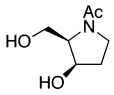
[a] Epoxy amines were prepared by treating a 0.1 M solution of the aziridinol in THF with 4.0 equiv of NaH and stirring at room temperature for 4−6 h. The pyrrolidines were prepared by treating a 0.1 M solution of the aziridinol in DMSO with 4-8 equiv of dimethylsolfoxonium methylide, stirring at room temperature for 4 h, and heating to 80 °C for 24 h.

the reaction conditions (entries 1, 2, 7, and 9).[21] Thus, a successful one-pot strategy for the synthesis of pyrrolidines from 2,3-aziridin-1-ols was developed by decoupling the roles of the ylide as a base and a nucleophile by judicious modulation of temperature.

Lengthy reaction times for some of the sterically demanding aziridinols prompted a quick screen of possible remedies. Microwave reactions have the potential to decrease reaction times dramatically while increasing the yield.[29] Aziridinols **8**, **13**, and **16** were subjected to microwave irradiation studies to ascertain the potential reduction in reaction time for the preparation of pyrrolidines. The ylide was prepared as usual, and the aziridinols were allowed to stir initially at room temperature for 4 h to ensure that aza-Payne rearrangement was complete. The reactions were then subjected to microwave irradiation (30 pulses, 15 s/pulse). Gratifyingly, the reaction times of **8** and **13** decreased substantially (24 h vs ∼8 min), and the yields of their corresponding products **8b** and **13b** increased to 91% (from 82%) and 79% (from 71%), respectively. Microwave-assisted reaction of aziridinol **16** produced a yield similar to that obtained under the typical conditions at a fraction of the time required with conventional heating. Further microwave studies are ongoing, and the results will be reported in due course.

Having established the viability of generating substituted pyrrolidines in a stereocontrolled fashion, it was important to ensure that the activating groups could be removed efficiently to give the free pyrrolidine. The use of an electron-withdrawing group on the aziridine nitrogen was necessary to activate the ring toward nucleophilic ring-opening, but tosyl (Ts) groups can be difficult to remove under acidic or basic conditions. We wanted to examine other activating groups that allow for easier deprotection of the pyrrolidine products. Typical nitrogen protecting groups such as acetyl, Boc, and benzyl did not facilitate aza-Payne rearrangement. The use of the *tert*-butylsulfonamide (Bus) group as an activating/protecting group for aziridines has been documented and provides a complementary alternate to the Ts group, as it can be easily removed under acidic conditions.[30] As depicted in Table 4, Bus analogues of aziridinols **8** and **15** (**40** and **41** in Table 4) were synthesized and subjected to treatment with NaH in THF to effect the aza-Payne rearrangement. The yield of the aza-Payne rearrangement was lower as compared to that obtained with the Ts-activated counterpart, perhaps due to the sterics of the bulky *tert*-butyl group or the decreased ability of the *tert*-butylsulfonyl group to stabilize the resulting negative charge on nitrogen following rearrangement. The lower yield of pyrrolidine in the one-pot reaction to give **40b** and **41b** reflects the lower yield of the *in situ* aza-Payne rearrangement compared to that of the Ts-protected analogues. We also attempted the use of a $-P(O)Ph_2$ protecting group that has been documented to activate aziridines toward nucleophilic ring-opening but can be removed under mild acidic conditions.[31] However, we could not obtain aza-Payne rearranged products, much less the pyrrolidines.

Table 5. Deprotection of Pyrrolidine Products

entry	substrate	product	yield
1	 **8b**	 **8c**	64%[a]
2	 **42**	 **42c**	56%[a]
3	 **18b**	 **18c**	65%[a]
4	 **43**	 **43c**	41% at 78% conversion[a]
5	 **40b**	 **40c**	88%[b]

[a] 6.0 equiv of Mg metal in MeOH, sonicate 30 min, room temperature overnight. [b] TfOH, *p*-anisole, CH_2Cl_2, −78 °C, then NaOH/EtOAc.

Removal of the Nitrogen Protecting Group

Finally, the pyrrolidine products were subjected to various deprotection conditions in order to ascertain the efficiency in removal of the nitrogen activating group (Table 5). The Ts-protected pyrrolidines could be deprotected with sodium naphthalide in glyme in moderate to good yields, but a substantial amount of debenzylated product was also formed for benzyl-protected substrates.[32] In contrast, the Ts group was easily removed under mild conditions using Mg metal in MeOH (Table 5) to provide the free amines.[33] TBS-protected alcohols under the tosyl deprotection conditions were stable, as can be seen in conversion of **42** to **42c**. The *p*-methoxy variant of the Ts protecting group (see structure **43** in Table 5) was also utilized; however, it was less efficient. The Bus group in **40b** was easily removed using conditions previously described by Weinreb

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(31) Sweeney, J. B.; Cantrill, A. A. *Tetrahedron* **2003**, *79*, 3677−3690.
(32) (a) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455. (b) Casadei, M. A.; Gessner, A.; Inesi, A.; Achille, J.; Werner, M.; Micheletti, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, *122*, 7−9.
(33) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006−10010.

(solution of triflic acid in MeOH with *p*-anisole as a cation scavenger) in good yields to provide the free amine.[34] The benzyl protecting group was also removed under these conditions, giving a highly polar product that was acetylated to facilitate isolation of **40c**. Thus, we can remove the nitrogen protecting group under either acidic or basic conditions, provided care is taken in the protection of hydroxyls in the molecule.

Conclusion

In conclusion, we have developed a new method for the synthesis of 2,3-disubstituted, 2,2,3- and 2,3,3-trisubstituted, and 2,2,3,3-tetrasubstituted pyrrolidine rings. The stereochemistry present in the asymmetric aziridinol is translated fully to the final product. Since it is simple to access these substrates in high enantiomeric excess via the Sharpless asymmetric epoxidation, Sharpless aminohydroxylation, or Wulff VAPOL-catalyzed aziridination, this can be a powerful methodology for gaining entry into 2,3-substituted pyrrolidines with stereodefined substituents. Future work includes efforts to further functionalize the pyrrolidine ring via the use of aziridinols substituted at C-1 and utilization of substituted ylides.

Experimental Section

General Procedures. Aza-Payne Rearrangement. The aziridinol **8** (1.0 g, 2.9 mmol, 1.0 equiv) dissolved in a small amount of THF was added to a suspension of NaH (0.46 g as a 60% dispersion in mineral oil, 4.0 equiv, 11.5 mmol) in dry THF (30 mL). The reaction was stirred at room temperature for 4 h and then cooled to 0 °C and quenched carefully with saturated ammonium chloride. The aqueous layer was extracted three times with portions of ethyl acetate, and the combined organics were washed with brine. The organics were dried over sodium sulfate and the volatiles removed via rotary evaporation. The residue was purified by column chromatography (hexanes/ethyl acetate gradient) to give the epoxy amine **8a** in 90% yield.

Synthesis of Pyrrolidines from Epoxy Amines. A suspension of NaH (58.2 mg as a 60% dispersion in mineral oil (washed twice with dry pentane), 1.45 mmol, 5.0 equiv) in DMSO (3 mL, 0.1 M in aziridinol) was treated with trimethylsulfoxonium iodide (0.32 g, 1.45 mmol, 5.0 equiv) and the reaction stirred at room temperature for 30 min to give a milky-white solution. The epoxy amine **8a** (0.1 g, 0.29 mmol, 1.0 equiv), dissolved in a small amount of DMSO, was added to the ylide, stirred at room temperature for 30 min, and heated to 80 °C for 24 h. The cooled reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted three times with portions of ethyl acetate. The combined organics were washed with brine and dried over sodium sulfate, and the volatiles evaporated. The residue was purified by column chromatography (hexanes/ethyl acetate gradient) to give the desired pyrrolidine **8b** in 99% yield as a thick oil that eventually crystallized to a low-melting solid.

Synthesis of Pyrrolidines from Aziridinols. DMSO was dried by stirring overnight over CaH_2 and distilled under high vacuum into a flame-dried flask containing activated molecular sieves. Trimethylsulfoxonium iodide was dried overnight at room temperature under high vacuum. Dimethylsulfoxonium methylide was prepared fresh for each reaction. Sodium hydride (0.32 g as a 60% dispersion in mineral oil, 8.0 mmol, 8.0 equiv, washed twice with pentane dried over sodium metal) was placed in a flame-dried flask, and dry DMSO (10 mL) was added via syringe. Trimethylsulfoxonium iodide (1.77 g, 8.0 mmol, 8.0 equiv) was added in small portions over 20−30 min. After addition of the trimethylsulfoxonium iodide was complete, the reaction was stirred for an additional 30 min until the bubbling of the milky-white suspension ceased. The aziridinol **8** (0.35 g, 1.0 mmol, 1.0 equiv), dissolved in a small amount of DMSO, was added dropwise, and the reaction was stirred at room temperature for 4 h to complete the aza-Payne rearrangement. The reaction was then covered with aluminum foil and heated to 80−85 °C for 24 h. The dark brown mixture was cooled and diluted with 2× volume of water and saturated ammonium chloride (1 mL). The reaction was extracted several times with ethyl acetate, and the combined organics were washed with brine and dried over sodium sulfate. After evaporation of the solvent, the residue was column chromatographed using a hexane/ethyl acetate gradient to give compound **8b** in 82% yield as a thick oil that eventually crystallized to a low-melting solid.

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Supporting Information Available: Experimental procedures and spectral data for compounds **8**−**43c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA065833P

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