JOC*Article*

Development of a [3+3] Cycloaddition Strategy toward Functionalized Piperidines

Simon J. Hedley,[†] Wesley J. Moran,[†] David A. Price,[‡] and Joseph P. A. Harrity*,[†]

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, United Kingdom, and Discovery Chemistry, Pfizer Central Research, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom

j.harrity@sheffield.ac.uk

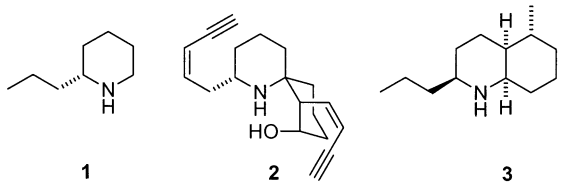
Received January 3, 2003

This paper describes a novel route to functionalized piperidines via a formal [3+3] cycloaddition reaction of activated aziridines and palladium−trimethylenemethane (Pd-TMM) complexes. The cycloaddition reaction generally proceeds enantiospecifically with ring opening at the least hindered site of the aziridine. Therefore, readily available enantiomerically pure 2-substituted aziridines can be utilized to prepare enantiomerically pure 2-substituted piperidines in good to excellent yield. The *N*-substituent on the aziridine proved to be crucial to the success of this reaction with only 4-toluenesulfonyl (Ts) and 4-methoxybenzenesulfonyl (PMBS) aziridines permitting smooth cycloaddition to take place. Additionally, spirocyclic aziridines have been found to participate in the [3+3] cycloaddition reaction, whereas 2,3-disubstituted aziridines can be applied to provide fused bicyclic piperidines, albeit in low yield.

Introduction

The piperidine ring system is one of the most common structural subunits in natural products and synthetic compounds of biological significance.[1] Indeed, it has been stated recently that a substructure search of the piperidine ring using the electronic version of the Drug Data Report (July 1988 through to December 1998) revealed over 12 000 discrete piperidine entities that have been mentioned in clinical or preclinical studies.[2] In the context of naturally occurring piperidines, a variety of structural features surround the heterocyclic core. Notable examples include (−)-coniine **1**, a *Conium maculatum* hemlock alkaloid;[3] (−)-histrionicotoxin **2**, isolated from the skin extracts of the "poison dart" frog *Dendrobates histrionicus*,[4] which has shown the ability to act as a noncompetitive inhibitor of nicotinic acetylcholine receptors;[5] and (−)-pumiliotoxin C **3**, also isolated from dendrobatic frogs,[6] which has been shown to be a reversible blocker of the nicotinic acetylcholine receptor channel (Chart 1).[7]

CHART 1



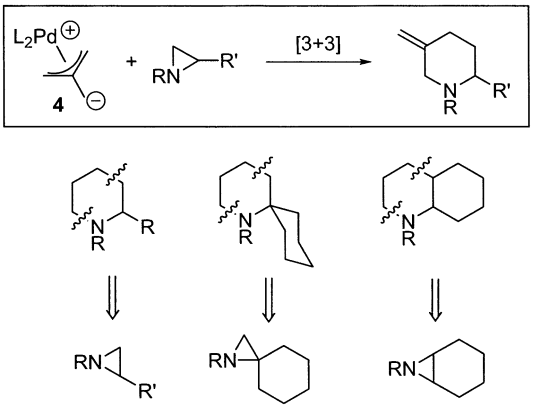
From a synthetic viewpoint, we wished to develop a new strategy to obtain the piperidine ring system. Additionally, we considered the following to be important factors in our approach: (1) The piperidine moiety should be assembled efficiently and with scope for stereocontrol. (2) The products should be endowed with functionality, which would allow them to be transformed to specific target compounds. (3) The technique should exhibit sufficient flexibility so as to allow the assembly of a wide number of skeletal types. In this context, cycloaddition reactions are among the most effective methods for the rapid synthesis of functionalized cyclic systems in a stereocontrolled manner. With regard to six-membered-ring formation, the Diels−Alder reaction holds a uniquely prominent position and formally comprises a [4+2] assembly strategy.[8] In contrast, the employment of a [3+3] cycloaddition approach has been much less widely studied.[9] Nonetheless, the employment of Pd-catalysis has led to techniques for the assembly of pyran derivatives[10] whereas piperidine systems have been prepared

[†] University of Sheffield.
[‡] Pfizer Central Research.

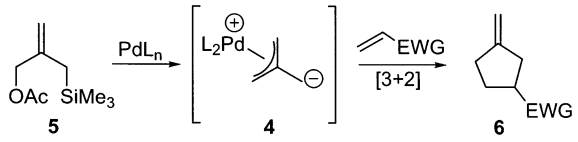
(1) (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem Commun* **1998**, 633. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
(2) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
(3) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1−90.
(4) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.
(5) Takahashi, K.; Witkop, B.; Brossi, A.; Malque, M. A.; Alburquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.
(6) Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebigs Ann. Chem.* **1969**, *729*, 198.
(7) (a) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Alburquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565. (b) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Schultz, A. G.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207.
(8) For a review on [4+2] cycloaddition processes see: Oppolzer, W. In *Comprehesive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, p 315.
(9) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.
(10) (a) Huang, Y.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 6219. (b) van der Louw, J.; van der Baan, J. L.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 9901.

10.1021/jo030002c CCC: $25.00
Published on Web 04/22/2003

SCHEME 1



SCHEME 2



by a formal [3+3] cycloaddition reaction of 1,3-cyclic sulfates with *C*,*N*-dianions,[11] vinylogous amides with α,*β*-unsaturated iminiums,[12] and α,α′-dimethoxylated amides with allyltrimethylsilane.[13] We envisaged that an effective [3+3] cycloaddition approach to piperidines that would encompass our objectives stated would be highly desirable, and anticipated that it would complement existing [4+2] approaches. More specifically, we opted to study the cycloaddition reaction of palladium−trimethylenemethane (Pd-TMM) complexes **4** with aziridines with a view to accessing common piperidine-containing structural types, such as those exhibited in the natural products shown in Chart 1 (vide supra). This general strategy is summarized in Scheme 1.

Trost has carried out extensive studies on the utilization of Pd-TMM complexes in the synthesis of five-membered rings via a [3+2] cycloaddition reaction with electron-deficient alkenes.[14] Crucial to the development of this methodology was the observation that Pd-TMM complexes **4** can be generated in situ as fleeting reactive intermediates by heating 2-[(trimethylsilyl)methyl]-2-prop-1-enyl acetate **5** in the presence of a palladium catalyst (Scheme 2).[15] Pd-TMM complexes have also been reported to undergo [3+2] cycloaddition reactions with aldehydes to provide methylenetetrahydrofurans[16] and imines to provide methylenepyrrolidines,[17] and undergo a [4+3] cycloaddition reaction with pyrones.[18] Thus, Pd-TMM complexes such as **4** have been shown to be powerful and versatile synthetic tools.

TABLE 1. Optimization of the [3+3] Cycloaddition Reaction[a]

entry	catalyst system	solvent	yield, %
1	10% $Pd(PPh_3)_4$	THF	17
2	10% $Pd(OAc)_2$, 40% PPh_3, 20% ^{n}BuLi	THF	49
3	10% $Pd(OAc)_2$, 40% $P(O^iPr)_3$, 20% ^{n}BuLi	THF	59
4	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% ^{n}BuLi	THF	82
5	10% $Pd(OAc)_2$, 80% $P(O^iPr)_3$, 20% ^{n}BuLi	THF	43
6	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% 1-hexene	THF	53
7	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$	THF	24
8	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% ^{n}BuLi	toluene	52
9	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% ^{n}BuLi	dioxan	28
10	10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% ^{n}BuLi	benzene	47

[a] Reactions carried out in 0.1 M refluxing solvent with 1.5 equiv of **7**.

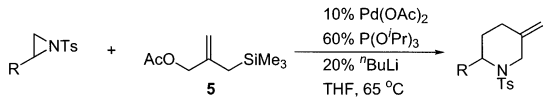
Results and Discussion

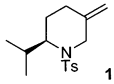
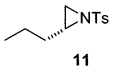
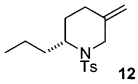
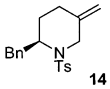
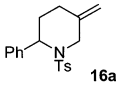
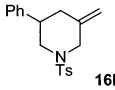
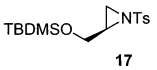
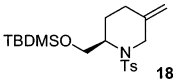
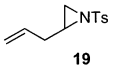
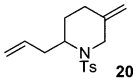
At the outset of our investigations, only a single example of the cycloaddition reaction of Pd-TMM complexes with aziridines was present in the literature.[19] Additionally, the employment of enantiomerically enriched aziridines had not received any attention and therefore the potential of this reaction to furnish piperidine products in a stereocontrolled fashion was unknown. With these issues in mind, we set out to establish the scope of the Pd-catalyzed [3+3] cycloaddition reaction for the stereocontrolled synthesis of functionalized piperidines.

Cycloaddition Reactions of Monosubstituted Aziridines. To act as effective electrophiles, aziridines require either an electron-withdrawing activating group attached to nitrogen or catalysis by Lewis or protic acids.[20] We decided to utilize *p*-toluenesulfonyl (Ts) as the *N*-substituent as *N*-tosylaziridines readily undergo nucleophilic ring cleavage with a range of nucleophiles, and also reacts chemospecifically due to the poor electrophilicity of the sulfonyl group.[21] Enantiomerically pure monosubstituted *N*-tosylaziridines were conveniently prepared in three steps by the method of Craig.[22] With the requisite substrates in hand, we began our studies by investigating the effects of the catalyst system on the efficiency of the [3+3] cycloaddition reaction of **5** and (*S*)-*N*-tosyl-2-methyl-aziridine **7**; the results are outlined in Table 1. The use of $Pd(PPh_3)_4$ (freshly prepared or generated in situ) proved ineffective in promoting piperidine formation, with the desired product **8** only isolated in low to moderate yield (Entries 1 and 2). Inspired by Trost's Pd-TMM [3+2] cycloaddition studies,[14] we opted to investigate the use of phosphite ligands. Indeed, the cycloaddition reaction proved to be more efficient and reproducible with this ligand system. In the event, the use of six catalyst equivalents of $P(O^iPr)_3$ with

(11) Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360.
(12) (a) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. *Org. Lett.* **2000**, *2*, 1161. (b) Slkenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-I.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435.
(13) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.
(14) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1 and references therein.
(15) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.
(16) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408.
(17) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778.
(18) Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213.
(19) Bambal, R. B.; Kemmitt, R. D. W. *J. Organomet. Chem.* **1989**, *362*, C18.
(20) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 1A, pp 1−60.
(21) (a) Stamm, H.; Weiss, R. *Synthesis* **1986**, 392, 395. (b) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *Chem. Commun.* **1987**, 153.
(22) Berry, M. B.; Craig, D. *Synlett* **1992**, 41.

TABLE 2. Exploring the Scope of the [3+3] Cycloaddition Reaction



Entry	Aziridine	Product	Yield
1	 **7**	 **8**	82%
2	 **9**	 **10**	72%
3	 **11**	 **12**	44%
4	 **13**	 **14**	79%
5	 **15**	 **16a**  **16b**	68%[a] (1:1.6)
6	 **17**	 **18**	52%
7	 **19**	 **20**	65%[a]

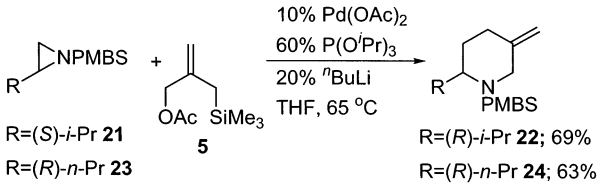
[a] Reaction carried out on racemic aziridine.

[n]BuLi as a reductant provided the best balance of reactivity and catalyst stability[23] (Entries 3−7) while THF was found to be the solvent of choice (Entries 4 and 8−10).

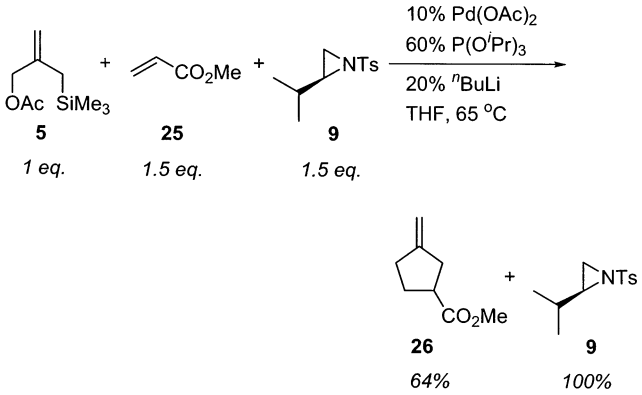
Having uncovered conditions which gave consistently high yields of cycloadduct **8**, we turned our attention to the investigation of the scope of the [3+3] cycloaddition process with a range of monosubstituted *N*-tosylaziridines, our results are outlined in Table 2.[24]

In all cases the [3+3] cycloaddition reaction proceeded to furnish the desired piperidines in good to excellent yield. Notably, these aziridines underwent regioselective addition at the less hindered site and furnished the products in enantiomerically pure form, confirming that the cycloaddition process did not cause unwanted epimerization at the remote stereogenic center.[25] One exception to this trend was observed when *N*-tosyl-2-phenylaziridine **15** (Entry 5) was employed, in which case an almost equal mixture of regioisomeric products **16a** and **16b** was observed. This result is unsurprising as the tendency for a phenyl substituent to promote aziridine cleavage at the benzylic site is well documented.[26] Finally, we were

SCHEME 3



SCHEME 4



pleased to find that more useful functionality could be incorporated into the piperidine products: silyl protected alcohols (Entry 6) and allyl groups (Entry 7) were both well tolerated in the reaction.

To date we have been unable to successfully employ aziridines which do not have an arylsulfonamide activating group.[27] Nonetheless, we have found that *N*-*p*-methoxy-benzenesulfonyl (PMBS) aziridines **21** and **23** smoothly undergo [3+3] cycloaddition reaction to provide **22** and **24** respectively, in good yield (Scheme 3). Notably, **24** was used further in the stereoselective synthesis of (−)-pseudoconhydrine.[24]

This study demonstrates the need for a strongly activating group to be present on the aziridine substrate. Indeed, we have found further evidence for the sluggish nature of this process from a control experiment, which is outlined in Scheme 4. The addition of 1 equiv of **5** to a mixture containing equimolar quantities of methyl acrylate **25** (a typical substrate used in [3+2] cycloaddition reactions)[28] and **9** results in a selective cycloaddition at **25** to produce **26** in good yield with complete recovery of the aziridine. This result suggests that the development of promoter systems to facilitate the reaction with aziridines would be highly beneficial, and studies toward this end are currently under investigation in our laboratories.

Cycloaddition Reactions of 2,2-Disubstituted Aziridines. We next turned our attention to the synthesis of more substituted piperidine products. We postulated that the spiropiperidine core of naturally occurring and biologically active targets such as **2** could be accessed by our methodology and therefore decided to examine the potential of the [3+3] cycloaddition reaction toward this end. A rapid route to aziridines has been achieved by

(23) Good yields of piperidine product could be obtained by using 40 mol % P(OPr-*i*)$_3$; however, the reaction was capricious due to problems associated with precipitation of Pd-metal.

(24) For a preliminary report of this work see: Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596.

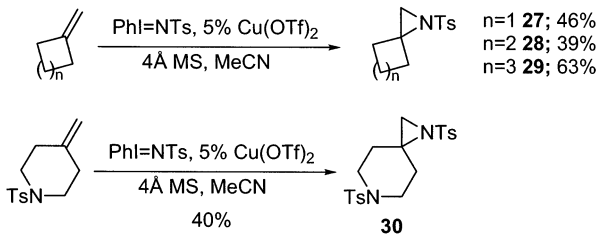
(25) As judged by chiral HPLC analysis of **10** and **14**. The enantiomeric purity of compounds **8**, **12**, and **18** was inferred from these data.

(26) For a recent example see: Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344.

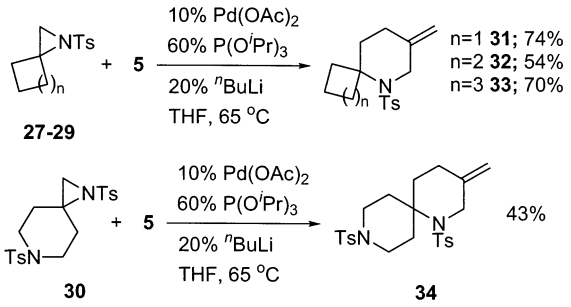
(27) Aziridines bearing SES, Boc, Cbz, and Dpp *N*-substituents do not undergo cycloaddition and are recovered from the reaction mixture unchanged. In contrast, the more highly activated Ns-protected aziridines furnish a complex mixture of products possibly because of competing addition of the Pd-TMM complex to the aromatic ring: Holzapfel, C. W.; van der Merwe, T. *Tetrahedron Lett.* **1996**, *37*, 2307.

(28) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315.

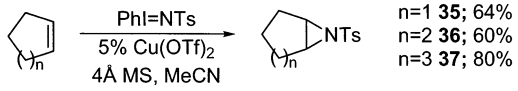
SCHEME 5



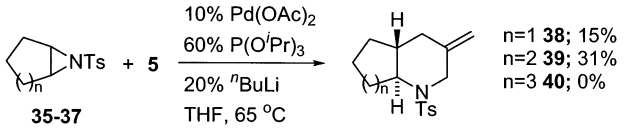
SCHEME 6



SCHEME 7



SCHEME 8



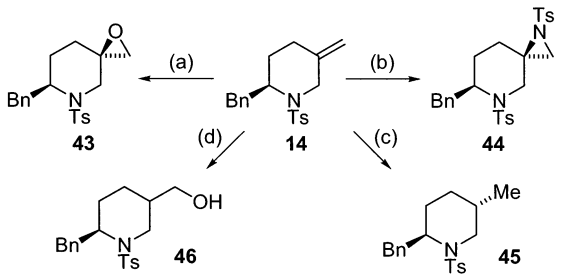
Evans via a copper-catalyzed nitrene transfer to alkenes using [*N*-(4-toluenesulfonyl)imino]phenyliodinane.[29] Therefore, we reasoned that spirocyclic aziridines **27**−**30** could be prepared by this method in a one-step process from the corresponding *exo*-methylene carbocycles (Scheme 5).

The optimum conditions for the [3+3] cycloaddition reactions of monosubstituted aziridines were employed directly for substrates **27**−**30** (Scheme 6), and we were pleased to find that the cycloaddition reaction proceeded smoothly in all cases to furnish the corresponding spiropiperidines **31**−**34** in good yield. The employment of this strategy toward the synthesis of analogues of **2** is currently underway and will be reported in due course.

Cycloaddition Reactions of 2,3-Disubstituted Aziridines. As described in Table 2, ring opening of aziridines generally proceeds via nucleophilic attack at the least hindered site. We decided to examine the possibility of Pd-TMM addition at tertiary centers by utilizing 2,3-disubstituted aziridines. Additionally, this methodology would provide an expedient route to bicyclic piperidines. Once again, we applied the copper-catalyzed aziridination protocol to rapidly generate bicyclic aziridines **35**−**37** from the corresponding cycloalkenes (Scheme 7).

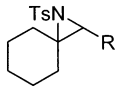
The results of our attempted cycloaddition to bicyclic aziridines **35**−**37** are shown in Scheme 8. In general, the reactions were very sluggish but we were pleased to find that compounds **38** and **39** could be isolated, albeit in low yield. However, no piperidine product **40** was observed from reaction of **37** and starting material was recovered in quantitative yield from the reaction mixture.

SCHEME 9[a]



[a] Reagents and conditions: (a) DMDO, DCM, 25 °C, 16 h; 91% (2.8:1). (b) PhIO, $TsNH_2$, $Cu(MeCN)_4PF_6$ (10 mol %), MeCN, 4Å MS, 25 °C, 16 h; 34% (100:0). (c) 10% Pd/C, 1 atm of H_2, MeOH, 16 h; 88% (9:1). (d) (i) 9-BBN, 3 h. (ii) H_2O_2, NaOH(aq), 20 min; 85% (2:1).

Cycloaddition Reactions of 2,2,3-Trisubstituted Aziridines. Despite the low reactivity of 2,3-disubstituted aziridines, we were interested in whether 2,2,3-trisubstituted aziridines would participate in the [3+3] cycloaddition process. With this in mind, we prepared **41** and **42** via the copper-catalyzed aziridination. In the case



R=Me **41**
R=Ph **42**

of **42**, we hoped that benzylic activation would promote nucleophilic ring-opening. However, on subjecting these aziridines to the established reaction conditions, no piperidine products were isolated, and the starting aziridines were recovered quantitatively.

Finally, we have carried out some representative alkene functionalization reactions to uncover the potential of the piperidine intermediates for further diastereselective elaboration. Accordingly, piperidine **14** was subjected to standard epoxidation, hydroboration, aziridination, and hydrogenation reactions. As outlined in Scheme 9, the levels of diastereoselectivity were found to vary considerably, with epoxidation and hydroboration processes providing the corresponding products **43** and **46** in high yield but with modest levels of stereoselectivity. In contrast, the aziridination and hydrogenation reactions provided **44** and **45** respectively with excellent levels of stereocontrol. Interestingly, the major diastereomers isolated in products **43**−**45** all result from reagent addition across the *Si*-face of the alkene.[30] We have

(29) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.

(30) Only the major diastereomer is shown in each case in Scheme 7. The stereochemical assignment of *cis*- and *trans*-**46** was not carried out due to the poor levels of selectivity observed in this case. The major epoxide diastereomer **43a** was assigned based on the characteristic long-range coupling observed with one of the epoxide CH_2 protons and a ring methylene proton (J = 1.5 Hz): Vedejs, E.; Dent, W. H., III; Kendall, J. T.; Oliver, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 3556. Assignment of **44** is based on 2D ROESY, which is provided in the Supporting Information. Assignment of the major diastereomer of **45** is based on the coupling constants of the protons at C-5 and C-6, see Supporting Information for more details.

previously invoked the importance of the Ts-group for controlling stereochemistry in related functionalization reactions at this position;[24] however, factors which are important in determining the level of selectivity are still unclear and are currently the subject of further studies.

Conclusions

In conclusion, we have developed a rapid and effective approach to enantiomerically pure 2-substituted piperidines from the corresponding enantiomerically pure aziridines and Pd-TMM complex **4**. Additionally, the piperidine products are furnished with an *exo*cyclic methylene group, which provides the opportunity for further functionalization. We have also demonstrated the use of this methodology in the synthesis of spirocyclic and fused bicyclic piperidines although the latter substrates are found to exhibit diminished reactivity, likely because of increased steric hindrance at the electrophilic site. Finally, we have examined some common alkene functionalization reactions and found these to proceed efficiently but with variable levels of diastereoselectivity.

Experimental Section

General experimental methods and literature references to known compounds are reported in the Supporting Information.

Representative Procedure for [3+3] Cycloaddition Reactions—Synthesis of (*S*)-2-Methyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (8): Preparation of 0.14 M Palladium Catalyst. To a suspension of $Pd(OAc)_2$ (50 mg, 0.22 mmol, 1 equiv) in THF (1.6 mL) was added $P(O^iPr)_3$ (0.33 mg, 1.34 mmol, 6 equiv) then ^{n}BuLi (2.5 M in hexanes, 0.18 mL, 0.45 mmol, 2 equiv), and the resultant yellow solution was stirred for 15 min before use.

A solution of **7** (150 mg, 0.71 mmol, 1.5 equiv) in THF (3 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (0.34 mL, 0.05 mmol, 10 mol %) and **5** (0.10 mL, 0.47 mmol, 1 equiv) and the reaction mixture was heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography to yield **8** as a white solid (102 mg, 82%), mp 68−69 °C. $[\alpha]^{25}_D$ −10.10 (*c* 1.19, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (3H, d, J = 7.0 Hz), 1.35−1.62 (2H, m), 2.05 (1H, dt, J = 13.0, 4.5 Hz), 2.22−2.31 (1H, m), 2.44 (3H, s), 3.72 (1H, d, J = 14.5 Hz), 4.02−4.19 (2H, m), 4.74 (1H, br), 4.83 (1H, br), 7.29 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.2, 21.4, 27.0, 30.5, 46.2, 48.3, 110.4, 127.2, 129.5, 137.8, 141.3, 142.9. FTIR (CH_2Cl_2): 2944 (w), 1598 (w), 1338 (m), 1268 (s), 1162 (s) cm^{-1}. *m*/*z* (CI) 266 (MH^+, 60%), 250 (100%), 155 (32%), 110 (43%), 91 (63%). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.36; H, 7.32; N, 5.09.

(*R*)-2-Isopropyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (10). Following the representative procedure, **10** was isolated as a white solid, mp 83−84 °C. $[\alpha]^{25}_D$ −45.09 (*c* 1.12, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz), 1.02−1.27 (1H, m), 1.52−1.70 (1H, m), 1.74−2.25 (3H, m), 2.33 (3H, s), 3.31−3.47 (1H, m), 3.58 (1H, d, J = 16.0 Hz), 4.23 (1H, d, J = 16.0 Hz), 4.55 (1H, br), 4.66 (1H, br), 7.17 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.6, 20.0, 21.5, 25.0, 26.6, 27.2, 47.0, 59.1, 110.2, 127.4, 129.3, 138.3, 141.0, 142.7. FTIR (CH_2Cl_2): 2964 (m), 2874 (w), 1598 (w), 1337 (s), 1269 (s), 1160 (s) cm^{-1}. *m*/*z* (CI) 294 (MH^+, 100%), 250 (75%), 155 (9%). Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.49; H, 7.84; N; 4.77.

(*R*)-2-Propyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (12). Following the representative procedure, **12** was isolated as a colorless oil, $[\alpha]^{25}_D$ 23.80 (*c* 0.90, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.0 Hz), 1.15−1.47 (5H, m), 1.57−1.73 (1H, m), 1.89 (1H, dt, J = 14.0, 3.5 Hz), 2.16 (1H, m), 2.34 (3H, s), 3.58 (1H, d, J = 15.5 Hz), 3.80−3.90 (1H, m), 4.17 (1H, d, J = 15.5 Hz), 4.58 (1H, br), 4.68 (1H, br), 7.19 (2H, d, J = 8.5 Hz), 7.64 (2H, d, J = 8.5 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 19.5, 21.5, 27.3, 28.0, 32.3, 46.5, 52.5, 110.3, 127.3, 129.4, 138.2, 141.2, 142.8. FTIR (CH_2Cl_2): 3055 (m), 2962 (w), 1336 (m), 1270 (s), 1162 (s), 1094 (m) cm^{-1}. *m*/*z* (TOF ES): 294 (MH^+, 100%). HRMS (TOF ES) Calcd for $C_{16}H_{24}NO_2S$ (MH^+): 294.1528. Found: 294.1519.

(*R*)-2-Benzyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (14). Following the representative procedure, **14** was isolated as a white solid (79%), mp 85−86 °C. $[\alpha]^{25}_D$ −15.56 (*c* 0.90, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.12−1.46 (2H, m), 1.99 (1H, dt, J = 14.5, 4.0 Hz), 2.07−2.23 (1H, m), 2.44 (3H, s), 2.95 (2H, d, J = 7.5 Hz), 3.74 (1H, d, J = 15.0 Hz), 4.09−4.21 (1H, m), 4.26 (1H, d, J = 15.0 Hz), 4.71 (1H, br), 4.82 (1H, br), 7.23−7.34 (7H, m), 7.63 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 26.4, 27.1, 36.9, 46.8, 54.3, 110.6, 126.5, 127.3, 128.6, 129.2, 129.5, 137.7, 138.2, 141.1, 143.0. FTIR (CH_2Cl_2): 2952 (w), 1599 (w), 1339 (m), 1272 (s), 1160 (s) cm^{-1}. *m*/*z* (FAB): 342 (MH^+, 68%), 250 (100%), 186 (19%), 155 (39%). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.26; H, 6.68; N, 4.04.

2-Phenyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (16a). Following the representative procedure, **16a** was isolated as an impure mixture with **16b**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45−1.65 (1H, m), 1.45−1.55 (1H, m), 2.00−2.20 (1H, m), 2.28−2.36 (1H, m), 2.44 (3H, s), 3.67 (1H, d, J = 15.5 Hz), 4.32 (2H, d, J = 15.5 Hz), 4.65 (1H, br), 4.76 (1H, br), 5.04−5.12 (1H, m), 7.13−7.45 (7H, m), 7.72 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 27.7, 47.6, 55.2, 66.8, 110.3, 127.1, 127.4, 127.9, 128.6, 129.5, 137.8, 138.7, 141.0, 143.1.

3-Phenyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (16b). Following the representative procedure, **16b** was isolated as a white solid from recrystallization of the mixture of **16a** and **16b**, mp 142−143 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.12−2.24 (1H, m), 2.44 (3H, s), 2.53 (1H, m), 2.87 (1H, tt, J = 13.5, 2.0 Hz), 2.98 (1H, d, J = 12.5 Hz), 3.90 (1H, m), 4.23 (1H, d, J = 12.5 Hz), 4.91 (1H, br), 5.00 (1H, br), 7.16 (2H, d, J = 8.0 Hz), 7.2−7.4 (5H, m), 7.65 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.6, 39.0, 42.6, 51.9, 52.2, 112.6, 127.1, 127.2, 127.8, 128.7, 129.7, 133.2, 139.8, 141.6, 143.6. FTIR (CH_2Cl_2): 3068 (w), 3032 (w), 2951 (m), 1599 (m), 1496 (m), 1450 (m), 1341 (s), 1163 (s), 1095 (s). HRMS (CI) calcd for $C_{19}H_{22}NO_2S$ (MH^+) 328.1371, found 328.1382.

(*R*)-2-(*tert*-Butyl-dimethyl-silanoxymethyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine (18). Following the representative procedure, **18** was isolated as a white solid, mp 74−76 °C. $[\alpha]^{25}_D$ +8.3 (*c* 0.61, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.31−1.48 (2H, m), 1.76−1.92 (2H, m), 2.17−2.34 (1H, m), 2.41 (3H, m), 3.69−3.88 (4H, m), 4.24 (1H, d, J = 15.5 Hz), 4.68 (1H, br), 4.77 (1H, br), 7.25 (2H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.5, −5.4, 21.5, 24.4, 25.9, 27.2, 47.8, 53.6, 62.9, 110.1, 127.3, 129.4, 137.6, 141.4, 143.0. FTIR (CH_2Cl_2): 2956 (m), 2931 (m), 2858 (m), 1472 (w), 1340 (m), 1263 (s), 1160 (s), 1103 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_3SSi$: C, 60.72; H, 8.41; N, 3.54. Found: C, 60.69; H, 8.52; N, 3.46.

2-Allyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (20). Following the representative procedure, **20** was isolated as a white solid, mp 77−78 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21−1.42 (1H, m), 1.47−1.73 (1H, m), 1.94 (1H, dt, J = 14.5, 4.0 Hz), 2.10−2.48 (3H, m), 2.38 (3H, s), 3.65 (1H, d, J = 15.5 Hz), 3.92−4.05 (1H, m), 4.22 (1H, d, J = 15.5 Hz), 4.65 (1H, br), 4.75 (1H, br), 4.99−5.11 (2H, m), 5.73 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.66 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 27.0, 27.1, 34.9, 46.7, 52.3, 110.5, 117.4, 127.3, 129.4, 134.6, 138.0, 141.0, 142.9. FTIR (CH_2Cl_2): 3075 (w), 2926 (w), 2854 (w), 1642 (w), 1598 (w), 1445 (w), 1340 (m), 1159 (s), 1092 (m) cm^{-1}. *m*/*z* (TOF

ES): 292 (MH^+, 100%), 250 (38%). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.71; H, 7.44; N, 4.77.

(*R*)-2-Isopropyl-1-(4-methoxy-benzenesulfonyl)-5-methylene-piperidine (22). Following the representative procedure, **22** was isolated as a white solid, mp 115−117 °C. $[\alpha]^{25}_D$ −43.33 (*c* 0.60, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.5 Hz), 1.05−1.26 (1H, m), 1.55−1.74 (1H, m), 1.82−2.24 (3H, m), 3.35−3.49 (1H, m), 3.58 (1H, d, J = 16.0), 3.80 (3H, s), 4.22 (1H, d, J = 16.0), 4.56 (1H, br), 4.66 (1H, br), 6.84 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.6, 20.1, 25.0, 26.7, 27.3, 47.0, 55.5, 59.1, 110.2, 113.8, 129.4, 133.0, 141.2, 162.4. FTIR (CH_2Cl_2): 3052 (w), 2929 (w), 1598 (w), 1499 (w), 1421 (w), 1336 (w), 1260 (s), 1158 (w), 1094 (w) cm^{-1}. *m/z* (FAB): 310 (MH^+), 266 (60%), 171 (100%), 138 (25%), 123 (61%). Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 61.84; H, 7.66; N, 4.33.

(*R*)-2-Propyl-5-methylene-1-(4-methoxy-benzenesulfonyl)-piperidine (24). Following the representative procedure, **24** was isolated as a white solid, mp 112−113 °C. $[\alpha]^{25}_D$ 39.52 (*c* 0.99, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 7.5 Hz), 1.19−1.52 (5H, m), 1.62−1.76 (1H, m), 1.97 (1H, dt, J = 14.0, 4.0 Hz), 2.05−2.26 (1H, m), 3.68 (1H, d, J = 15.5 Hz), 3.81−3.99 (1H, m), 3.86 (3H, s), 4.20 (1H, d, J = 15.5 Hz), 4.66 (1H, br), 4.75 (1H, br), 6.93 (2H, d, J = 9.0 Hz), 7.73 (d, 2H, J = 9.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 19.5, 27.3, 28.0, 32.3, 46.5, 52.4, 55.5, 110.3, 113.9, 129.4, 132.9, 141.3, 162.4. FTIR (CH_2Cl_2): 3077 (w), 2960 (w), 2874 (w), 1598 (m), 1498 (m), 1338 (m), 1265 (s), 1157 (s), 1094 (m) cm^{-1}. *m/z* (EI): 309 (M^+, 4%), 266 (100%), 171 (39%), 107 (12%). HRMS (EI) calcd for $C_{16}H_{23}NO_3S$ (M^+) 309.1399, found 309.1388.

7-Methylene-5-(toluene-4-sulfonyl)-5-aza-spiro[3.5]-nonane (31). Following the representative procedure, **31** was isolated as a white solid, mp 109−110 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.55−1.72 (2H, m), 1.69 (2H, t, J = 6.5 Hz), 1.90−2.03 (2H, m), 2.27 (2H, t, J = 6.5 Hz), 2.40 (3H, s), 2.44 (2H, ddd, J = 20.5, 10.0, 3.0 Hz), 3.90 (2H, s), 4.75(1H, br), 4.88 (1H, br), 7.23 (2H, d, J = 8.5 Hz), 7.68 (2H, d, J = 8.5 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.6, 21.5, 29.2, 31.6, 33.6, 49.5, 60.3, 110.8, 127.3, 129.4, 140.2, 141.1, 142.7. FTIR (CH_2Cl_2): 2940 (m), 1598 (w), 1443 (w), 1337 (s), 1156 (s), 1091 (m) cm^{-1}. *m/z* (EI): 291 (M^+, 4%), 198 (91%), 155 (5%), 136 (17%). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.90; H, 7.42; N, 4.82.

8-Methylene-6-(toluene-4-sulfonyl)-6-aza-spiro[4.5]-decane (32). Following the representative procedure, **32** was isolated as a white solid, mp 95−97 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.43−1.87 (8H, m), 1.94−2.20 (2H, m), 2.34 (2H, t, J = 6.5 Hz), 2.41 (3H, s, ArCH_3), 4.19 (2H, s, C7−*H*), 4.83 (1H, br, C=C*H*H), 4.94 (1H, br, C=CH*H*), 7.24 (2H, d, J = 8.0 Hz, Ar*H*), 7.70 (2H, d, J = 8.0 Hz, Ar*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 22.6, 29.4, 34.7, 36.0, 51.2, 68.0, 110.6, 127.2, 129.3, 140.7, 142.1, 142.5. FTIR (CH_2Cl_2): 2951 (m), 1598 (w), 1450 (w), 1328 (s), 1156 (s), 1091 (s) cm^{-1}. *m/z* (EI): 305 (M^+, 1%), 198 (79%), 155 (100%), 150 (58%). HRMS calcd for $C_{17}H_{23}NO_2SNa$ (MNa^+) 328.1336, found 328.1341.

3-Methylene-1-(toluene-4-sulfonyl)-1-aza-spiro[5.5]-undecane (33). Following the representative procedure, **33** was isolated as a white solid**,** mp 98−100 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.16−1.39 (2H, m), 1.53−1.65 (4H, m), 1.70−1.86 (4H, m), 2.02−2.17 (2H, m), 2.25 (2H, t, J = 6.0 Hz), 2.41 (3H, s), 4.20 (2H, s), 4.81 (1H, br), 4.89 (1H, br), 7.24 (2H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 22.8, 25.2, 27.2, 31.2, 33.5, 48.2, 62.2, 109.7, 126.8, 129.3, 141.4, 142.3, 142.8. FTIR (CH_2Cl_2): 2933 (m), 1599 (w), 1452 (w), 1317 (m), 1152 (s), 1091 (m) cm^{-1}. *m/z* (CI): 320 (MH^+, 9%), 199 (21%), 164 (25%), 149 (100%). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.38. Found: C, 67.80; H, 7.99; N, 4.42.

3-Methylene-1,9-bis(toluene-4-sulfonyl)-1,9-diaza-spiro-[5.5]undecane (34). Following the representative procedure, **34** was isolated as a white solid, mp 185−187 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.55 (2H, t, J = 6.5 Hz), 1.80−1.91 (2H, m), 2.21 (2H, t, J = 6.5 Hz), 2.29−2.39 (2H, m), 2.42 (3H, s), 2.46 (3H, s), 2.60−2.73 (2H, m), 3.37 (2H, dt, J = 12.0, 4.5 Hz), 4.12 (2H, s), 4.80 (1H, br), 4.89 (1H, br), 7.23 (2H, d, J = 8.0 Hz), 7.33 (2H, d, J = 8.0 Hz), 7.62 (4H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 21.6, 27.3, 31.6, 33.1, 42.5, 48.6, 58.9, 111.1, 127.1, 127.7, 129.6, 129.7, 133.1, 140.2, 140.9, 143.1, 143.6. FTIR (CH_2Cl_2): 2925 (m), 2854 (m), 1596 (w), 1456 (w), 1330 (m), 1166 (s), 1091 (m) cm^{-1}. *m/z* (FAB): 475 (MH^+, 12%), 155 (34%). HRMS (FAB) calcd for $C_{24}H_{31}N_2O_4S_2$ 475.1725, found 475.1746.

3-Methylene-1-(toluene-4-sulfonyl)-octahydro-[1]pyridine (38). Following the representative procedure, **38** was isolated as a white solid, mp 127−129 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.80−2.25(8H, m), 2.20−2.31 (1H, m), 2.39−2.52 (1H, m), 2.45 (3H, s), 2.87 (1H, d, J = 12.0 Hz), 4.27 (1H, d, J = 12.0 Hz), 4.86 (1H, br), 4.96 (1H, br), 7.34 (2H, d, J = 8.0 Hz), 7.67 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.5, 21.5, 27.4, 38.0, 46.1, 54.7, 64.2, 112.3, 128.0, 129.6, 132.9, 141.1, 143.5. FTIR (CH_2Cl_2): 2952 (m), 1600 (w), 1494 (w), 1454 (w), 1351 (s), 1168 (s), 1094 (m) cm^{-1}. *m/z* (EI): 291 (M^+, 82%), 262 (65%), 155 (33%), 136 (74%), 91 (100%). HRMS (EI) calcd for $C_{16}H_{21}NO_2S$ (M^+) 291.1293, found 291.1295.

3-Methylene-1-(toluene-4-sulfonyl)-decahydroquinoline (39). Following the representative procedure, **39** was isolated as a white solid, mp 92−93 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.82−1.01 (1H, m), 1.09−1.77 (8H, m), 2.03−2.20 (1H, m), 2.20−2.31 (1H, m), 2.38 (3H, s), 2.78 (1H, td, J = 10.5, 3.5 Hz), 3.94 (1H, d, J = 16.0 Hz), 4.10 (1H, d, J = 16.0 Hz), 4.77 (1H, br), 4.77 (1H, br), 7.25 (2H, d, J = 8.0 Hz), 7.66 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 25.6, 25.7, 33.0, 33.4, 36.4, 39.5, 49.1, 62.9, 109.8, 127.6, 129.3, 142.3, 143.0. FTIR (CH_2Cl_2): 3055 (m), 2930 (m), 1737 (w), 1450 (m), 1422 (m), 1339 (m), 1272 (s), 1161 (s), 1091 (m) cm^{-1}. *m/z* (EI): 305 (M^+, 65%), 262 (98%), 155 (32%), 150 (37%), 91 (100%). Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59. Found: C, 66.86; H, 7.65; N, 4.54.

6-Benzyl-5-(toluene-4-sulfonyl)-1-oxa-5-aza-spiro[2.5]-octane (43). A 0.062 M solution of dimethyldioxirane in acetone (11.77 mL, 0.73 mmol, 5 equiv) was added to a solution of **14** (50 mg, 0.15 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C via syringe. The reaction was stirred at 0 °C for 1 h and then allowed to warm to room temperature overnight. The reaction mixture was then concentrated in vacuo and purification by flash chromatography providing epoxides **43a** (35 mg, 67%) and **43b** (12 mg, 24%) as colorless oils.

(2*R*,6*S*)-6-Benzyl-5-(toluene-4-sulfonyl)-1-oxa-5-aza-spiro[2.5]octane (43a): $[\alpha]^{25}_D$ −31.79 (*c* 0.98, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26−1.38 (1H, m), 1.67−1.92 (2H, m), 2.23 (1H, td, J = 13.0, 5.0 Hz), 2.43 (3H, s), 2.63 (1H, dd, J = 4.5, 1.5 Hz), 2.74−2.81 (1H, m), 2.74−2.79 (2H, m), 2.82−2.96 (2H, m), 3.33 (1H, d, J = 14.0 Hz), 3.49 (1H, app dd, J = 14.0, 1.5 Hz), 4.30−4.41 (1H, m), 7.16 (2H, d, J = 8.0 Hz), 7.21−7.32 (5H, m), 7.56 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 26.4, 26.5, 35.7, 45.8, 53.7, 55.7, 118.8, 126.6, 127.1, 128.7, 129.1, 129.7, 137.4, 137.9, 143.3. FTIR (CH_2Cl_2): 3024 (w), 2948 (w), 2862 (w), 1599 (w), 1495 (w), 1453 (w), 1338 (m), 1158 (s), 1095 (m), 966 (m) cm^{-1}. *m/z* (TOF ES): 358 (100%, MH^+). HRMS (TOF ES) calcd for $C_{20}H_{24}NO_3S$ (MH^+) 358.1477, found 358.1480.

(2*S*,6*S*)-6-Benzyl-5-(toluene-4-sulfonyl)-1-oxa-5-aza-spiro[2.5]octane (43b): $[\alpha]^{25}_D$ −2.55 (*c* 0.98, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.04−1.17 (1H, m), 1.36−1.60 (2H, m), 2.25 (1H, td, J = 13.5, 5.0 Hz), 2.38 (3H, s), 2.67 (1H, d, J = 4.5 Hz), 2.75 (1H, d, J = 4.5 Hz), 2.98 (2H, d, J = 8.0 Hz), 3.48 (1H, d, J = 14.5 Hz), 3.73 (1H, d, J = 14.5 Hz), 4.06−4.19 (1H, m), 7.14−7.34 (7H, m), 7.78 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.6, 22.8, 25.4, 36.1, 47.1, 51.7, 53.7, 55.3, 126.7, 127.5, 128.7, 129.2, 129.5, 137.7, 138.1, 143.1. FTIR (CH_2Cl_2): 3028 (w), 2951 (w), 2862 (w), 1599 (w), 1496 (w), 1454 (w), 1335 (m), 1159 (s), 1097 (m), 964 (m) cm^{-1}. *m/z*

(EI): 357 (M^+, 4%), 266 (100%), 155 (19%), 91 (38%). HRMS (EI) calcd for $C_{20}H_{23}NO_3S$ (M^+) 357.1399, found 357.1403.

(2*R*,6*S*)-6-Benzyl-1,5-bis(toluene-4-sulfonyl)-1,5-diazaspiro[2.5]octane (44). To a solution of $Cu(MeCN)_4PF_6$ (55 mg, 0.15 mmol, 0.1 equiv), **14** (500 mg, 1.45 mmol, 1 equiv), and 4-toluenesulfonamide (351 mg, 2.03 mmol, 1.4 equiv) in MeCN (5.0 mL) in the presence of 1.00 g of activated 4Å molecular sieves was added, at 0 °C under nitrogen, iodosylbenzene (451 mg, 2.03 mmol, 1.4 equiv). The reaction mixture was stirred at 0 °C for a further 2 h and then at room temperature overnight. The solution was diluted with EtOAc and filtered through Celite. The volatiles were removed in vacuo and the resultant residue purified by flash chromatography on silica gel to give aziridine **44** as a white solid (250 mg, 34%), mp 175−176 °C. $[\alpha]^{25}_D$ −7.50 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75−1.96 (3H, m), 2.39 (3H, s), 2.44 (3H, s), 2.48 (1H, app s), 2.53 (1H, app s), 2.60 (1H, m), 2.80 (1H, dd, J = 13.5, 7.0 Hz), 2.87 (1H, dd, J = 13.5, 9.0 Hz), 3.43 (1H, d, J = 14.0 Hz), 3.64 (1H, d, J = 14.0 Hz), 4.39 (1H, m), 7.11 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.22−7.27 (3H, m), 7.35 (2H, d, J = 8.0 Hz), 7.46 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5, 21.6, 24.8, 27.0, 35.3, 41.7, 45.9, 48.9, 53.8, 126.6, 127.1, 127.4, 128.7, 129.1, 129.7, 137.2, 137.3, 137.9, 143.3, 144.3. FTIR (CH_2Cl_2): 2924 (w), 1598 (w), 1454 (w), 1321 (m), 1157 (s), 1092 (m) cm^{-1}. *m*/*z* (EI): 510 (M^+, 5%), 419 (100%), 355 (6%), 155 (52%). HRMS (TOF ES) calcd for $C_{27}H_{30}N_2O_4S_2$ (MH^+) 511.1720, found 511.1708.

2-Benzyl-5-methyl-1-(toluene-4-sulfonyl)-piperidine (45). To a solution of **14** (89 mg, 0.26 mmol, 1 equiv) in MeOH (1.5 mL) under nitrogen was added 10% Pd/C (27 mg, 0.026 mmol, 0.1 equiv). A balloon filled with H_2 gas was attached to the flask and the nitrogen atmosphere was purged through a needle. The reaction mixture was left to stir for 16 h at room temperature. The volatiles were removed in vacuo and the resulting residue was purified by flash chromatography to give **45**, an inseparable mixture of diastereomers, as a colorless oil (86 mg, 88%). Spectroscopic data for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz), 1.23−1.32 (2H, m), 1.59−1.69 (1H, m), 1.81−1.99 (2H, m), 2.39 (3H, s), 2.60 (1H, dd, J = 13.0, 4.0 Hz), 2.86 (1H, dd, J = 13.0, 11.5 Hz), 3.22 (1H, dd, J = 13.0, 3.5 Hz), 3.45 (1H, d, J = 13.0 Hz), 4.11−4.17 (1H, m), 7.10 (2H, d, J = 7.0 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.24 (2H, d, J = 7.0 Hz), 7.26 (2H, d, J = 7.5 Hz), 7.71 (2H, d, J = 8.5 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.8, 20.7, 21.5, 24.2, 27.4, 35.0, 46.2, 54.8, 126.3, 127.0, 128.5, 129.2, 129.6, 138.3, 138.7, 142.9. FTIR (CH_2Cl_2) 3055 (s), 2987 (s), 2306 (m), 1422 (s), 1261 (s), 1164 (m) cm^{-1}. HRMS (TOF ES) calcd for $C_{20}H_{26}NO_2S$ (MH^+) 344.1684, found 344.1696.

[6-Benzyl-1-(toluene-4-sulfonyl)-piperidin-3-yl]-methanol (46). To a stirred solution of **14** (60 mg, 0.18 mmol, 1 equiv) in THF (0.5 mL) at 0 °C under nitrogen was added 0.5 M 9-BBN (0.35 mL, 0.18 mmol, 1 equiv). After 3 h, aqueous 1 M NaOH solution (0.35 mL, 0.35 mmol, 2 equiv) and 30% H_2O_2 solution (0.04 mL, 0.35 mmol, 2 equiv) were added and stirring continued for 20 min. The resulting mixture was extracted with ethyl acetate and dried over $MgSO_4$, and the volatiles were removed in vacuo. Purification by flash chromatography provided **46**, an inseparable mixture of diastereomers, as a colorless oil (53 mg, 85%). Spectroscopic data for the major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15−1.91 (5H, m), 2.32 (3H, s), 2.66−2.82 (2H, m), 3.40 (1H, dd, J = 10.5, 5.0 Hz), 3.40 (1H, dd, J = 10.5, 7.0 Hz), 3.72−3.89 (2H, m), 4.17−4.31 (1H, m), 6.95−8.24 (7H, m), 7.52 (2H, m, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.5, 22.3, 35.5, 38.2, 43.3, 54.1, 65.6, 126.4, 126.7, 127.0, 128.6, 129.2, 129.6, 138.5, 142.9. FTIR (CH_2Cl_2) 3618 (m), 3537 (br), 3065 (m), 3030 (m), 2938 (s), 2869 (s), 1600 (s), 1496 (s), 1456 (s), 1336 (s), 1153 (s), 1091 (s) 1032 (s) cm^{-1}. HRMS (TOF ES) calcd for $C_{20}H_{26}NO_3S$ (MH^+) 360.1633, found 360.1617

Acknowledgment. We are grateful to the EPSRC for studentships (S.J.H. and W.J.M.), Pfizer for a CASE award (S.J.H.), and the University of Sheffield.

Supporting Information Available: Experimental procedures for the synthesis of aziridines and ^{1}H and ^{13}C spectra for select piperidine compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030002C