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Diastereocontrolled Synthesis of *trans*- and *cis*-*meso*-Cyclopentene Aziridines

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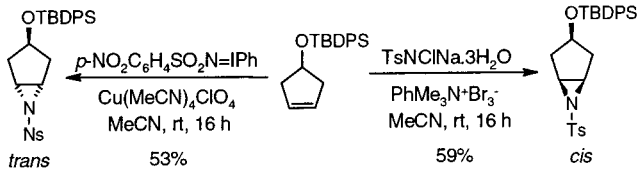
ABSTRACT

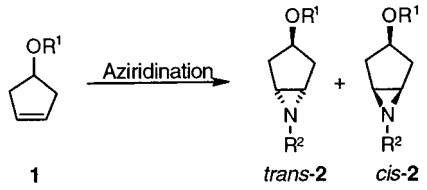


The synthesis of novel substituted *meso*-aziridines is described: aziridination of 4-*tert*-butyldiphenylsilyloxy-cyclopent-1-ene is trans selective using Cu(I)/PhI=NSO_2Ar and cis selective using $PhNMe_3^+Br_3^-$/Chloramine-T.

The synthesis of enantiomerically enriched chiral building blocks via asymmetric desymmetrization of meso cyclic and acyclic epoxides is a well-established and widely studied method in organic synthesis.[1,2] In contrast, much less attention has been devoted to the asymmetric desymmetrization of *meso*-aziridines. The following are the only examples reported to date: (i) Scheffold and da Zhang's Vitamin B_{12}-mediated rearrangement of *N*-acyl aziridines to allylic amides with up to 95% enantioselectivity;[3] (ii) Jacobsen et al.'s ring opening of *N*-alkyl aziridines with Me_3SiN_3 in the presence of a Schiff base−chromium complex to give azido amines in up to 94% ee;[4] (iii) Oguni and coworkers' reaction of thiols with *N*-acyl aziridines and a diethyl zinc-tartrate catalyst to generate amino sulfides in up to 93% ee;[5] (iv) Müller and Nury's use of a Schiff base−copper catalyst to promote the addition of a Grignard reagent to *N*-sulfonyl aziridines with up to 91% enantioselectivity;[6] and (v) Müller and Nury's desymmetrization of *N*-sulfonyl aziridines using an alkyllithium and (−)-sparteine.[6]

With this current interest in desymmetrization reactions of *meso*-aziridines, we decided to investigate some methods for the direct conversion of alkenes into substituted meso cyclic aziridines (Scheme 1). There are a handful of reports on the synthesis of substituted *meso*-aziridines. For example, Zalkow and Hill, Gassman and Schaffhausen, and Ganem et al. have all made contributions in this area, but their approaches are not general.[7] In addition, we have reported the synthesis of *meso*-cyclohexene aziridines *trans*- and *cis*-**3**

Scheme 1



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(1) For reviews, see: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(2) For recent examples of this strategy in synthesis, see: Hodgson, D. M.; Cameron, I. D. *Org. Lett.* **2001**, *3*, 441. de Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett.* **2001**, *42*, 8081.

(3) da Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602.

(4) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611.

(5) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817.

(6) Müller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662.

(7) Zalkow, L. H.; Hill, R. H. *Tetrahedron* **1975**, *31*, 831. Gassman, P. G.; Schaffhausen, J. G. *J. Org. Chem.* **1978**, *43*, 3241. Schoenfeld, R. C.; Lumb, J.-P.; Ganem, B. *Tetrahedron Lett.* **2001**, *42*, 6447.

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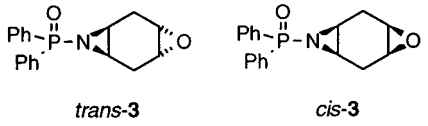
by epoxidation of the corresponding aziridino cyclohexene (Scheme 2).[8]

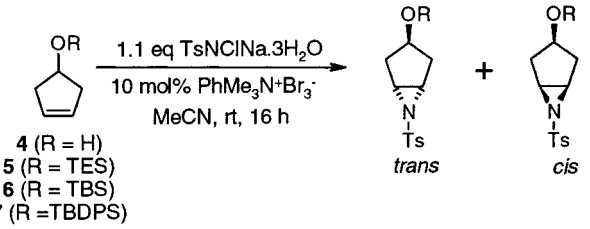
Scheme 2



To develop a general route to substituted *meso*-aziridines, our starting point and the subject of this Letter is a study of the aziridination of free and protected hydroxy substituted cyclopentenes **1** as a way of preparing *meso*-aziridines *trans*- and *cis*-**2** (Scheme 1). Two routes for direct aziridination of alkenes have been utilized in the present study: (i) reaction involving the use of Chloramine-T ($TsNClNa\cdot 3H_2O$) and phenyltrimethylammonium tribromide, introduced by Sharpless et al.,[9] and (ii) reaction using an iodinane $PhI{=}NSO_2$-Ar and copper(I) or copper(II) salts, introduced by Evans et al.[10] and developed further by Andersson and co-workers.[11] Although the diastereoselectivity of functionalizing alkenes has been widely studied for many reactions (e.g., epoxidation, dihydroxylation, cyclopropanation),[12] it is interesting to note that there are only a few examples of the diastereoselective aziridination of alkenes.[13,14] The main aim of our study was the discovery of conditions and/or substrates for the diastereocontrolled preparation of each of the aziridines *trans*-**2** and *cis*-**2** from alkenes **1**.

A range of substituted hydroxyl-protected cyclopentenes **5**−**7** were readily prepared by standard protection of known[15] 3-cyclopenten-1-ol **4**. All four cyclopentenes **4**−**7** were aziridinated under standard Sharpless conditions (1.1 equiv of commercial Chloramine-T,[16] 10 mol % of phenyltrimethylammonium tribromide, acetonitrile, room temperature, 16 h) (Scheme 3), and the results are presented in Table 1.

Scheme 3

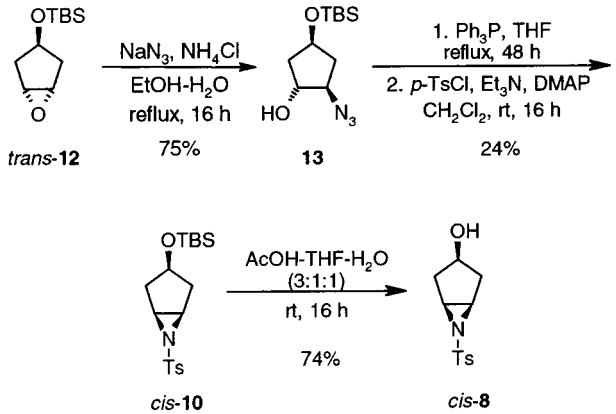


The degree of diastereoselectivity was established by ^1H NMR spectroscopy on the crude product mixtures, and the aziridines were isolated by chromatography. The relative stereochemistry of the aziridines was established by synthesis from an epoxide of known stereochemistry (vide infra).

The mechanism of the Sharpless aziridination involves the initial formation of a bromonium ion and subsequent attack by a nitrogen source before ring closure to form the aziridine.[8] Thus, we anticipated that *cis*-aziridines would be the major diastereoisomers obtained via preferred formation of the bromonium ion trans to the OR substituent. As can be seen from the results in Table 1, this was indeed the case with *cis*-aziridines predominating (around 70:30 cis:trans diastereoselectivity). Surprisingly, there was little change in the diastereoselectivity when varying the size of the substituent from OH to OTBDPS (compare entries 1 and 4 in Table 1). From a synthetic point of view, we note that the hydroxyl-substituted aziridines *cis*- and *trans*-**8** were formed in a high 86% yield (Table 1, entry 1) but were not separable by chromatography, and the total yield of aziridines increased as the stability of the hydroxyl protecting group increased to a maximum 96% yield of aziridines *cis*- and *trans*-**11** (Table 1, entry 4, TBDPS protecting group). Thus, a synthetically useful cis selective aziridination result has been achieved: starting from alkene **7** (TBDPS protecting group), Sharpless aziridination afforded a 59% isolated yield of aziridine *cis*-**11** (Table 1, entry 4).

The relative stereochemistry of the aziridines was established as outlined in Scheme 4. Starting from epoxide *trans*-

Scheme 4



12 of known[17] stereochemistry, ring opening with sodium azide gave azido alcohol **13**, which was converted into aziridine *cis*-**10** by treatment with triphenylphosphine and

(8) O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett*. **1999**, *40*, 8427.

(9) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1998**, *120*, 6844. Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett*. **1999**, *1*, 783. For a different ammonium salt used in the same type of aziridination protocol, see: Ali, S. I.; Nikalje, M. D.; Sudulai, A. *Org. Lett*. **1999**, *1*, 705.

(10) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc*. **1994**, *116*, 2742.

(11) Söndergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett*. **1997**, *38*, 6897.

(12) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307.

(13) For examples of diastereoselective aziridination reactions using PhI=NTs, see: Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc*. **1996**, *118*, 10752. White, R. D.; Wood, J. L. *Org. Lett*. **2001**, *3*, 1825.

(14) For examples of diastereoselective aziridination reactions not involving iodinanes, see: Fioravanti, S.; Luna, G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1997**, *53*, 4779. Atkinson, R. S.; Kelly, B. J. *Chem. Commun*. **1998**, 624.

Table 1. Diastereoselective Aziridination of Alkenes **4**−**7** Using Sharpless Conditions

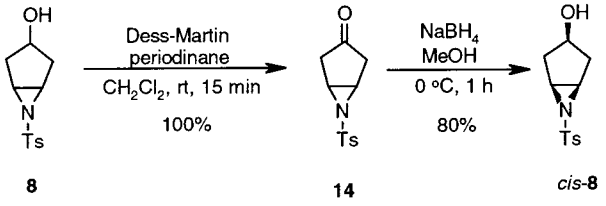
entry	R	alkene	aziridine	trans:cis[a]	total yield (%)[b]	yield of trans (%)[c]	yield of cis (%)[c]
1	H	**4**	**8**	29:71	86[d]		
2	TES	**5**	**9**	31:69	58	22	36
3	TBS	**6**	**10**	35:65	79	31	48
4	TBDPS	**7**	**11**	37:63	96	37	59

[a] By ^{1}H NMR spectroscopy on the crude product mixture. [b] Total isolated yield of *trans*- and *cis*-aziridines after chromatography. [c] Isolated yield of pure *trans*- or *cis*-aziridine after chromatography. [d] An 86% yield of a 28:72 mixture of *trans*- and *cis*-**8** after chromatography.

then *p*-toluenesulfonyl chloride. Deprotection of the TBS group in aziridine *cis*-**10** then gave hydroxy aziridine *cis*-**8**. Further protection or deprotection reactions, together with introduction of a *p*-nitrobenzenesulfonyl substitutent on nitrogen in the sequence shown in Scheme 4, enabled us to prove the stereochemistry of all of the aziridines depicted in this paper. Furthermore, our results have led to a useful ^{1}H NMR spectroscopy correlation, which allows quick identification of the relative stereochemistry of aziridines of the general structure **2**.[18]

The Sharpless aziridination route was only moderately cis diastereoselective, affording around 70:30 mixtures of *cis*- and *trans*-aziridines (see Table 1). Consequently, we investigated an alternative approach for the synthesis of *cis*-aziridines as outlined in Scheme 5. Oxidation of the 72:28

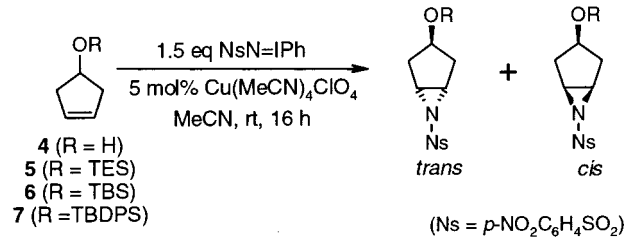
Scheme 5



mixture of hydroxy aziridines *cis*- and *trans*-**8** (obtained in a high 86% yield by Sharpless aziridination of alcohol **4**) using Dess−Martin periodinane[19] gave keto aziridine **14** in quantitative crude yield. Although potentially prone to β-elimination, keto aziridine **14** proved to be a sufficiently stable compound (provided that it was not subjected to silica gel). Reduction of the crude keto aziridine **14** with sodium borohydride in methanol at 0 °C then gave a single diastereoisomeric hydroxy aziridine *cis*-**8** (as judged by ^{1}H NMR spectroscopy on the crude product), which was isolated in 80% yield. Presumably, the hydride attacks the carbonyl group from the least hindered exo face of the bowl-shaped keto aziridine **14**. This two-step oxidation−reduction sequence is the best approach to *cis*-aziridines.

In developing a diastereoselective entry into the corresponding *trans*-aziridines, we anticipated using an iodinane (e.g., PhI=NTs) in the presence of copper(I) or copper(II) salts since there are two reports of aziridination on the least hindered face of an alkene using these conditions.[12] However, to obtain high yields in Evans' aziridinations, it is necessary to use either a large excess of the alkene or very dilute conditions.[9] Instead, we were attracted to the use of *p*-$NO_2C_6H_4SO_2N$=IPh in the presence of $Cu(MeCN)_4ClO_4$, as described by Andersson et al.,[10] for three reasons: (i) Andersson reported much improved yields when using *p*-$NO_2C_6H_4SO_2N$=IPh compared with using PhI=NTs;[10] (ii) the *p*-nitrobenzenesulfonyl group can be conveniently deprotected using thiols, as reported by Fukuyama et al.;[20] and (iii) *p*-nitrobenzenesulfonyl-substituted aziridines show increased reactivity to nucleophilic opening,[21] which could be important in subsequent desymmetrization reactions. Hence, all four cyclopentenes **4**-**7** were aziridinated under Andersson conditions (1.5 equiv of *p*-$NO_2C_6H_4SO_2N$=IPh, 5 mol % of $Cu(MeCN)_4ClO_4$, acetonitrile, room temperature, 16 h) (Scheme 6), and the diastereoselectivity was ascertained in

Scheme 6



a fashion analogous to that described previously. The results are shown in Table 2.

Using the Andersson conditions, the highest combined yields of diastereoisomeric aziridines were obtained with a

(15) Crandall, J. K.; Banks, D. B.; Coyler, A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423.

(16) All of the aziridination reactions using Sharpless conditions reported in this paper have been carried out with the commercially available trihydrate of Chloramine-T ($TsNClNa\cdot 3H_2O$).

(17) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402.

(18) For aziridines *trans*-**2**, the diastereotopic CH_AH_B appear at δ_H 2.42−2.17 and 1.81−1.63; for aziridines *cis*-**2**, the diastereotopic CH_AH_B appear at δ_H 2.09−2.03 and 1.99−1.89. That is, aziridines *trans*-**2** have "more separated" diastereotopic CH_AH_B groups than aziridines *cis*-**2**. Furthermore, for aziridines *trans*-**2** (R≠H), the CHO signal appears as a quintet (J = 7.5 Hz) at δ_H 4.06−4.17; for aziridines *cis*-**2** (R≠H), the CHO signal appears as a broad triplet (J = 6.5−7.0 Hz) at δ_H 4.36−4.41.

(19) Dess, D. B.; Martin, J. C. *J. Am. Chem.* Soc. **1991**, *113*, 7277.

(20) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373. Nihei, K−i.; Kato, M. J.; Yamane, T.; Palma, M. S.; Konno, K. *Synlett* **2001**, 1167.

(21) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett*. **1997**, *30*, 5253.

Table 2. Diastereoselective Aziridination of Alkenes **4**−**7** Using Andersson Conditions

entry	R	alkene	aziridine	trans:cis[a]	total yield (%)[b]	yield of trans (%)[c]	yield of cis (%)[c]
1	H	**4**	**15**	30:70	67		
2	TES	**5**	**16**	84:16	34[d]	27	7
3	TBS	**6**	**17**	86:14	40	40	0
4	TBDPS	**7**	**18**	87:13	64	53	11

[a] By ^{1}H NMR spectroscopy on the crude product mixture. [b] Total isolated yield of *trans*- and *cis*-aziridines after chromatography. [c] Isolated yield of pure *trans*- or *cis*-aziridine after chromatography. [d] In this case, 3.0 equiv of NsN═IPh were used.

free hydroxyl group (67% yield, Table 2, entry 1) and the robust TBDPS hydroxyl protecting group (64% yield, Table 2, entry 4). As expected, steric factors ensured that *trans*-aziridines were the major diastereoisomers with the silyl-protected alkenes **5**−**7**, although the diastereoselectivity was essentially independent of the steric size of the silyl group (Table 2, entries 2−4). In this way, a synthetically useful trans selective aziridination has been accomplished: starting from alkene **7** (TBDPS protecting group), Andersson aziridination afforded a 53% yield of aziridine *trans*-**11** (Table 2, entry 4). Interestingly, we found that aziridination of hydroxy alkene **4** was cis diastereoselective: an inseparable 70:30 mixture of aziridines *cis*- and *trans*-**8** was generated in a good 67% yield (Table 2, entry 1). Even though this is the sterically least demanding substituent, the cis diastereoselectivity is still surprising. We speculate that this is an example of a transition metal-catalyzed hydroxyl-directed aziridination that clearly merits further investigation.[22]

In summary, we report a range of diastereoselective aziridination reactions of alkenes in which it is possible to control the sense of the diastereoselectivity by changing the reaction conditions. For example, starting from alkene **7**, it is possible to obtain either aziridine *cis*-**11** (59% yield) via a Sharpless protocol or aziridine *trans*-**18** (53% yield) via an Andersson protocol. Alternatively, reduction of keto aziridine **14** furnishes an 80% yield of hydroxy aziridine *cis*-**8**. Thus, via a series of different reaction sequences, reagents, and protecting groups, we have shown that it is possible to synthesize the previously unknown substituted *meso*-aziridines **2**. Convenient access into these types of substituted *meso*-aziridines should now facilitate studies into their asymmetric desymmetrization.

Acknowledgment. We thank the EPSRC and GlaxoSmithKline for a CASE award (to C.M.R.).

Supporting Information Available: Full details on the synthesis and characterization of trans and cis isomers of compounds **8**−**11**, cis and trans isomers of compounds **15**−**18**, and compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For an example of a hydroxyl-directed aziridination, see: Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1515.