Tetrahedron Letters, Vol.32, No.22, pp 2533-2536, 1991
Printed in Great Britain

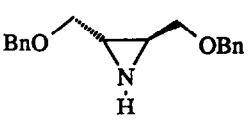
0040-4039/91 $3.00 + .00
Pergamon Press plc

C_2-Symmetric Aziridines as Efficient Chiral Auxiliaries

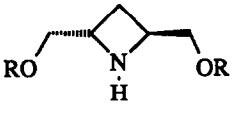
David Tanner* and Carin Birgersson
Department of Organic Chemistry, University of Uppsala
Box 531, S-751 21 Uppsala, Sweden

Abstract: The C_2-symmetric aziridines **1** and **1'** (available from (+)- and (-)-tartaric acid, respectively) are excellent chiral auxiliaries for asymmetric alkylation and aldol reactions.

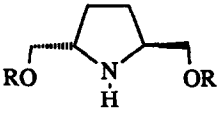
In 1977, Whitesell observed good asymmetric induction in the alkylation of a chiral cyclohexanone enamine, and the discussion of competing transition states presented in his paper[1] included the perspicacious observation: *"Clearly what is needed is an amine with a C_2 axis of symmetry"*. The chiral auxiliary introduced at that time was (+)-*trans*-2,5-dimethylpyrrolidine, and since then the importance of molecular C_2-symmetry in a variety of chemical[2] and physical[3] processes has become widely appreciated. Of the series of C_2-symmetric[4] cyclic amines **1** - **4** , the pyrrolidine **3** (or its enantiomer) has been used extensively for substrate-controlled asymmetric synthesis by Katsuki and Yamaguchi[5] while piperidine **4** and its enantiomer have been introduced by Kurth[6].



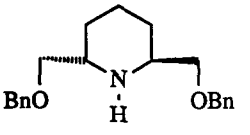
1



2



3 R = Me , MOM

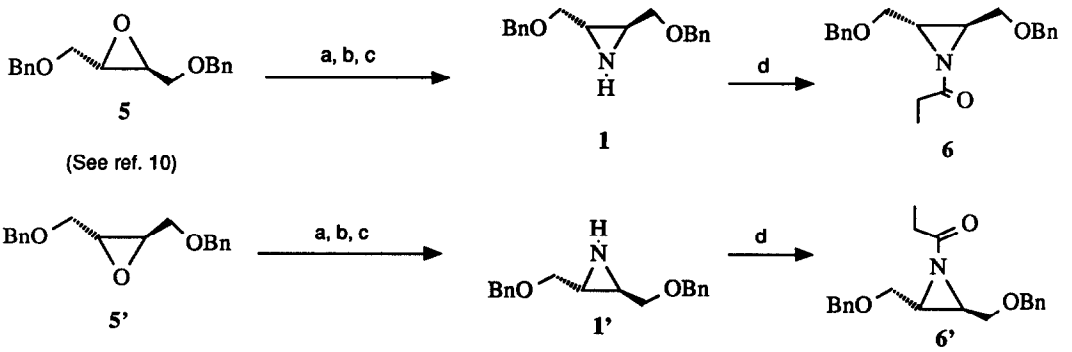


4

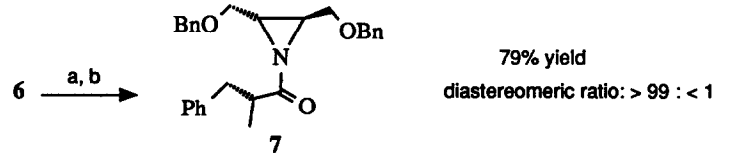
Our own interest in chiral small-ring systems, particularly aziridines[7], has now turned toward amines **1** and **2**. In the context of asymmetric amide enolate chemistry (e.g. based on **6**) the aziridine **1** was felt to be a particularly promising candidate as a chiral auxiliary, for the following reasons: (i) **1** and its enantiomer **1'** are readily available in multi-gram quantities from (+)- and (-)-tartaric acid, respectively (Scheme 1 and ref. 10); (ii) inspection of molecular models suggested that the enolate derived from the corresponding amide **6** (or **6'**) might undergo diastereoselective processes (such as asymmetric akylation and aldol reactions) with the side-chain oxygens playing a key role (chelation to the metal counter-ion); (iii) the expected relative ease of non-destructive removal of the aziridine auxiliary by hydrolytic[8] or other[9] methods.

In this Letter we describe the preparation of **1** and **1'** and report that the lithium enolates of **6** and **6'** do indeed display high levels of diastereoselectivity in asymmetric alkylation and aldol reactions. We also present attempts to probe the stereochemical factors responsible for our results. The synthesis of the two enantiomeric pairs of aziridines **1/1'** and **6/6'** is shown in Scheme 1.

Epoxides **5** or **5'** are readily available[10] on a large scale from (+)- and (-)-tartaric acid, respectively, and provide straightforward access to optically pure **1** or **1'**; these were tested as chiral auxiliaries (following acylation to **6** or **6'**) in a standard enolate alkylation (shown for **6** in Scheme 2).

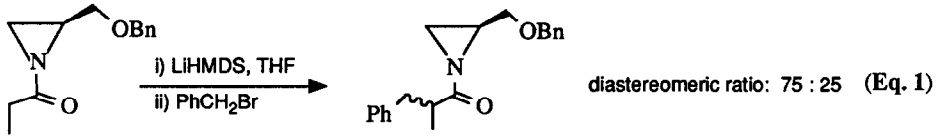


Scheme 1: (a) NaN_3, NH_4Cl, $MeO(CH_2)_2OH/H_2O$, 94%; (b) MsCl, NEt_3, CH_2Cl_2, 89%; (c) $LiAlH_4$, THF, 79%; (d) propionic anhydride, NEt_3, DMAP (cat.), CH_2Cl_2, 91%

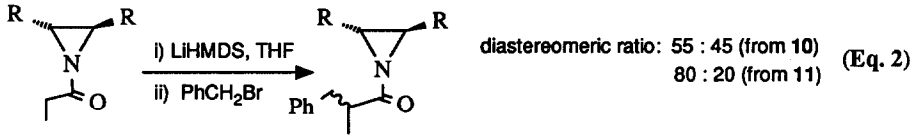


Scheme 2: (a) LiHMDS, THF, -78°C; (b) $PhCH_2Br$, -78°C to RT

According to ^{13}C NMR spectroscopic analysis (75 MHz, S/N ratio 500:1) the crude product **7** was a single diastereomer[11] with the absolute configuration shown . The importance of auxiliary C_2-symmetry was then probed,as shown in Eq.1, optically pure **8** being derived from commercially available (*S*)-(-)-glycidol.



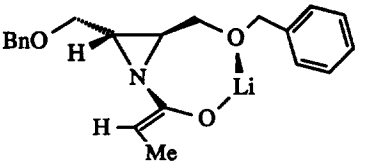
The absolute configuration of the major diastereomer of **9** was assigned by analogy with **7**. These results show that the C_2-symmetry element[4] is truly important in the alkylation of **6**. Steric effects and the chelation/non-chelation question were then addressed, as shown in Eq. 2. For this purpose,it was sufficient to use racemic **10** and **11**.



10 (R = Ph)
11 (R = ^{n}Bu)

The diphenylaziridine moiety of **10** was a poor chiral inducer,while **11** gave more respectable results. The higher d.e. values obtained using **6**, as compared to **11**, may be due mainly to steric effects, but it is also plausible to invoke internal chelation in the enolate of the former to explain the results. While we are aware that (i) it may be naive to rationalize the stereochemical outcome of enolate chemistry on the basis of monomeric structures[12], and (ii) subtle stereoelectronic factors[13] may be

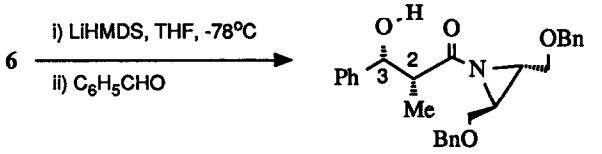
operative, we nevertheless offer the "working model" depicted below:



The importance of the ring geometry[4b] and the C_2-symmetry of the auxiliary have already been pointed out; we have also good grounds for the assumptions that (i) the *Z*-enolate is formed under our reaction conditions[14] and (ii) the enolate nitrogen is markedly pyramidalized[13,15]. Chelation of the lithium cation, as depicted, then directs the incoming electrophile to the "lower" face of the enolate, resulting in the (*R*) absolute configuration at C_α of **7** shown in Scheme 2. A more systematic study of possible chelation effects (variation of metal ion and ethereal side-chains) is now under way.

The good leaving-group ability of nitrogen in aziridino-amides is the basis of Brown's aldehyde synthesis[9] and we have exploited this to remove the auxiliary from **7** with only slight epimerization[16]. Details of other (hydrolytic) procedures to remove/recover the auxiliaries will be presented elsewhere, as will the results of our synthetic efforts directed towards the chiral azetidine **2** shown in the introduction.

Finally, preliminary studies indicate that the enolate of **6** undergoes a highly *syn*-selective aldol reaction[14] with benzaldehyde (Eq. 3).



73% yield
syn aldol ratio: 98 : 2
$J_{2,3}$ = 2.8 Hz
no anti aldols detected

(Eq. 3)

The *syn* geometry of the aldol product (expected from the reaction of a *Z*-enolate if the Zimmerman-Traxler transition state model[14] is invoked) was confirmed by the coupling constant analysis[14] shown above. The diastereomeric pair of *anti* aldols (if at all present) could not be detected by ^{13}C NMR spectroscopic analysis[17] of the crude product. Further results, including rigorous assignments of absolute stereochemistry, will be reported in due course.

Acknowledgements. We thank the *Swedish Natural Science Research Council* for financial support, and Dr. Stefan Sjöberg for generous gifts of optically pure carboxylic acids[11].

References and notes

1. Whitesell, J.K.;Felman, S.W. *J.Org.Chem.* **1977** *42* 1663.

2. (a) the pioneering studies were made by: Kagan, H.B.;Dang, T.P. *J.Am.Chem.Soc.* **1972** *94* 6429. (b) for an excellent review, see: Whitesell. J.K. *Chem.Rev.* **1989** *89* 1581. Some more recent uses of C_2-symmetric amines: (c) Corey, E.J. *Pure & Appl.Chem.* **1990** *62* 1209; (d) Hanessian, S.;Bennani, Y.L. *Tetrahedron Lett.* **1990** *31* 6465; (e) Fuji, K.;Node, M.;Naniwa, Y.;Kawabata, T.

ibid. **1990** *31* 3175.

3. Isaksson, R.;Wennerström, H.;Wennerström, O. *Tetrahedron* **1988** *44* 1697.
4. (a) As pointed out[2b,6] amines such as **3** and **4** are not strictly C_2-symmetric in their (non-planar) ground state conformations with pyramidal nitrogen. They do however, possess "functional"[6b] C_2-symmetry. (b) The faces of aziridine **1** are homotopic, and the nitrogen atom is chirotopic but nonstereogenic.
5. See: Uchikawa,M.;Hanamoto, T.;Katsuki,T.;Yamaguchi, M. *Tetrahedron Lett.* **1986** *27* 4577 and references therein.
6. (a) Najdi, S.;Kurth, M.J. *Tetrahedron Lett.* **1990** *31* 3279;/(b) Najdi, S.;Reichlin, D.;Kurth, M.J. *J.Org.Chem.* **1990** *55* 6241.
7. Tanner, D.;Birgersson, C;Dhaliwal, H.K. *Tetrahedron Lett.* **1990** *31* 1903 and references therein.
8. See: Bennet, A.J.;Wang, Q.-P.;Slebocka-Tilk, H.;Somayaji, V.;Brown, R.S.;Santarsiero, B.D. *J.Am.Chem.Soc.* **1990** *112* 6383.
9. Brown, H.C.;Tsukamoto, A. *J.Am.Chem.Soc.* **1961** *83* 4549.
10. Nicolaou, K.C.;Papahatjis, D.P.;Claremon, D.A.;Magolda, R.L.;Dolle, R.E. *J.Org.Chem.* **1985** *50* 1440.
11. The diastereomers of **7**, prepared independently from **1** and the relevant enantiomeric acid chlorides, were very readily distinguished by ^{13}C NMR spectroscopy at 75 MHz.
12. Seebach, D. *Angew.Chem.Int.Ed.Engl.* **1988** *27* 1624 (review of Li-enolates).
13. See, e.g., Matassa, V.G.;Jenkins, P.R.;Kumin, A.;Damm, L.;Schreiber, J.;Felix,D.;Zass, E.;Eschenmoser, A. *Israel J.Chem.* **1989** *29* 321,/and references therein; see also: Oppolzer, W.;Poli, G.;Starkemann, C.;Bernardinelli, G. *Tetrahedron Lett.* **1988** *29* 3559.
14. See, e.g., Evans, D.A.;Nelson, J.V.;Taber, T.R. in *Topics in Stereochemistry, vol 13, chap. 1.* (Allinger, N.L.;Eliel, E.L.;Wilen, S.H., *Eds.*)Wiley-Interscience, New York, **1982.**
15. See, e.g., Laube, T.;Dunitz, J.D.;Seebach, D. *Helv.Chim.Acta.* **1985** *68* 1373. The relatively high-frequency carbonyl band in the IR spectrum of **6** (1690 cm^{-1}) is evidence for N-pyramidality/decreased amide resonance also in the enolate precursor. (See also ref. 9).
16. Reduction[9] of **7** (H_2O work-up) and chromatography re-delivered the auxiliary and gave (*R*)-2-methyl-3-phenylpropanal (70%) of 97% e.e., $[\alpha]_D$ -4.75° (c = 0.40, acetone). See: Enders, D.; Eichenauer, H. *Chem. Ber.* **1979** *112* 2933.
17. Heathcock, C.H.;Pirrung, M.C.;Sohn, J.E. *J.Org.Chem.* **1979** *44* 4294.

(Received in UK 4 March 1991)