Stereocontrolled synthesis via chiral aziridines

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Abstract. The use of chiral, non-racemic, aziridines for stereochemical control in diastereo- and enantioselective synthesis is described. Such aziridines are readily available in quantity from the corresponding chiral epoxides, and can be utilised: (i) as chiral *substrates*, e.g. for the enantioselective synthesis of carbapenem antibiotics and non-proteinogenic amino acids; (ii) as efficient chiral *auxiliaries* for diastereoselective enolate alkylation and aldol reactions; (iii) as chiral *ligands*, e.g. for enantioselective OsO₄-mediated 1,2-dihydroxylation of olefins.
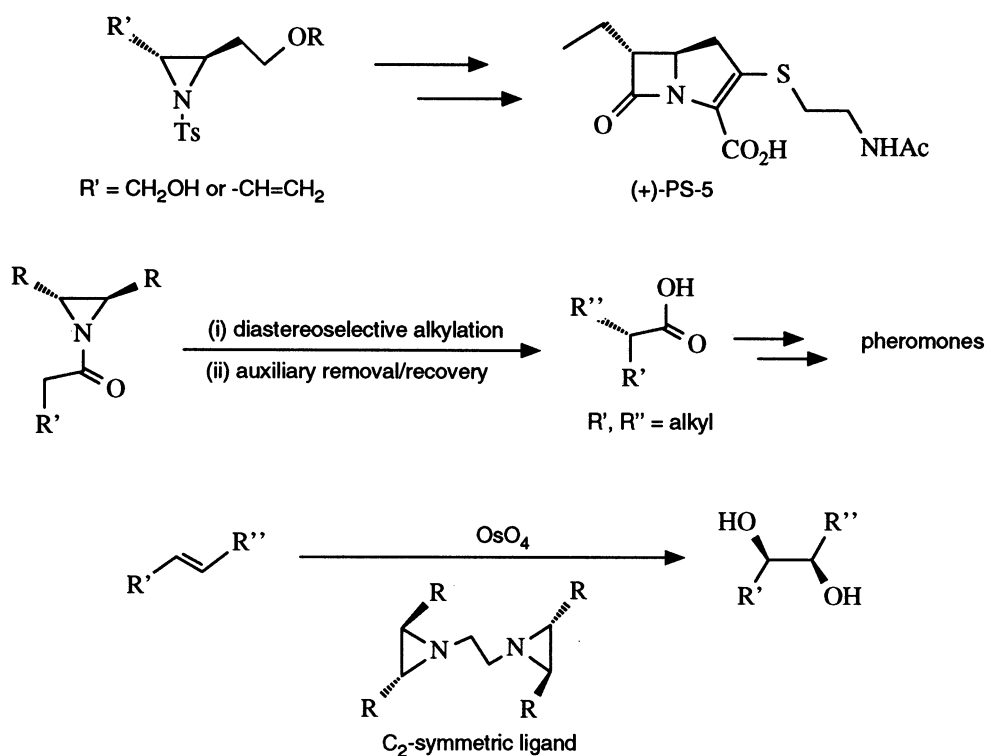
INTRODUCTION

Our interest in aziridines began a few years ago (ref. 1) in the course of a stereoselective total synthesis of the spirocyclic alkaloid perhydrohistrionicotoxin, **1**. We found that the side-chain of the key spirocycle **2** could be introduced *via* a substitution reaction for which the aziridinium ion shown below was postulated as the reactive intermediate.
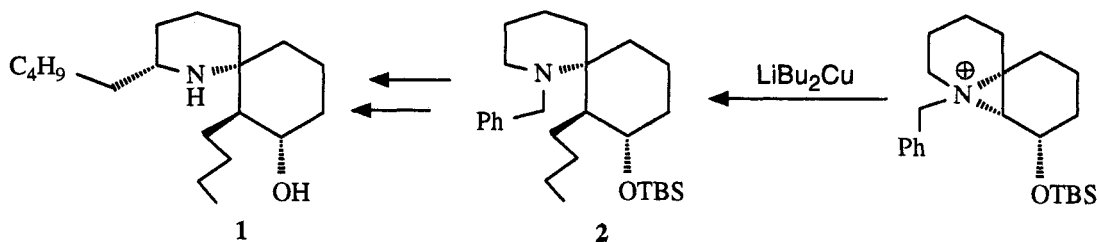
Although the yield of the reaction was modest, we were sufficiently encouraged by the results of our first encounter with aziridine chemistry to initiate a research program to explore the possible uses of chiral aziridines for stereochemical control in diastereo- and enantioselective synthesis.

Our aziridine project consists of three major lines of research, the first being the use of these heterocycles as chiral starting materials for the asymmetric synthesis of natural products (e.g. β-lactam antibiotics). The second goal is the development of aziridines as chiral auxiliaries for diastereoselective enolate chemistry (e.g. alkylation, aldol and Michael reactions). Thirdly, we have begun to explore the potential of C_2-symmetric bis(aziridines) as chiral ligands in syntheses mediated by organotransition metal species (e.g. dihydroxylation of olefins by OsO₄).

R' = CH₂OH or -CH=CH₂   (+)-PS-5

(i) diasterioselective alkylation

(ii) auxiliary removal/recovery

R', R'' = alkyl → pheromones

C₂-symmetric ligand

These three variations on the aziridine theme will be discussed separately below, after a short description of some of the methods by which enantiomerically pure (or highly enriched) aziridines can be obtained.
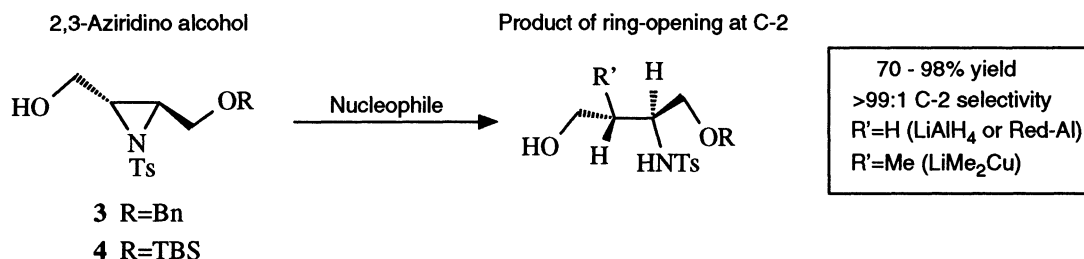
SYNTHESIS OF CHIRAL AZIRIDINES

Among the more obvious sources of chiral aziridines are 1,2-amino alcohols derived from amino acids (ref. 2) or carbohydrates (ref. 3). These methods are usually enantiospecific, but have the disadvantage that normally only one of the enantiomeric series is easily and cheaply available. An enzymatic transformation of a suitably functionalised *meso* aziridine has also been reported (ref. 4), as have methods for the direct enantioselective aziridination of prochiral olefins (ref. 5).

Asymmetric versions of Blum's stereospecific synthesis of aziridines from epoxides (ref. 6) have been developed by Depezay (from carbohydrates, ref. 7) and by ourselves (via Sharpless asymmetric epoxidation, refs. 8-12). Our general scheme is shown below for the *trans* series only, but this methodology provides equally easy access to all four aziridine stereoisomers of excellent optical purity.

trans   trans   trans

Sharpless AE   i) NaN₃   ii) PPh₃

>95% e.e. (or enantiomer)   >95% e.e. (or enantiomer)
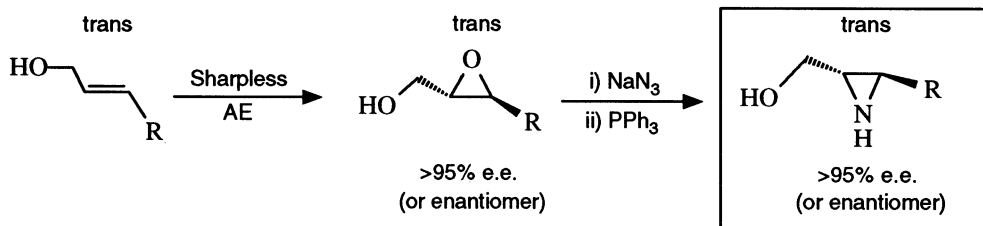
AZIRIDINES AS CHIRAL SUBSTRATES

The utility of chiral 2,3-aziridino alcohols in asymmetric synthesis is based largely upon our ability to perform highly stereo- and regioselective ring-opening reactions which provide enantiomerically pure amino alcohol derivatives suitable for further elaboration. We use a tosyl group both to protect the nitrogen and to activate the ring towards nucleophilic attack (ref. 13) and we have found that the behaviour of N-tosyl 2,3-aziridino alcohols towards nucleophiles is in many ways reminiscent of that of their well-explored epoxy alcohol precursors. Some representative examples from the *trans* series are shown below (ref. 11).

2,3-Aziridino alcohol   Product of ring-opening at C-2

70 - 98% yield
>99:1 C-2 selectivity
R'=H (LiAlH$_4$ or Red-Al)
R'=Me (LiMe$_2$Cu)

3 R=Bn
4 R=TBS

Ring-opening occurs with clean inversion, and the excellent regioselectivity can be explained in terms of co-ordination of the reagent to the free C-1 hydroxyl prior to intramolecular delivery of the nucleophile to the proximal ring carbon.

As illustrated below for *trans* aziridine **3**, completely regioselective ring-opening at C-3 is possible by use of AlMe$_3$ in a non-coordinating solvent, and we have demonstrated (ref. 12) that the Lewis basic nature of the benzyloxy substituent is responsible for the regiochemical outcome. Similar levels of C-3 regioselectivity are attainable with the *cis* isomer.

Product of ring-opening at C-3

80-90% yield
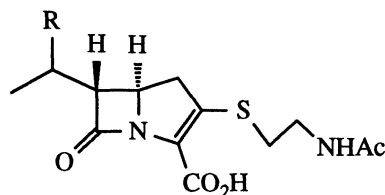>99:1 C-3 selectivity
(also for cis isomer)
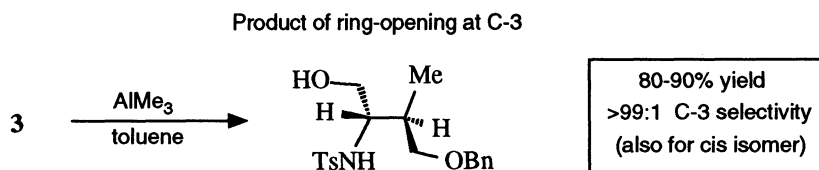
We have used such ring-opening reactions as key steps in enantioselective routes to some members of the important family of carbapenem antibiotics (refs. 9,10,12).

Targets: Carbapenem antibiotics
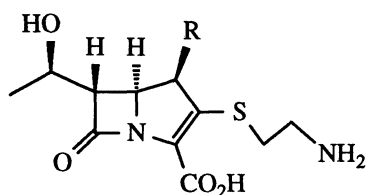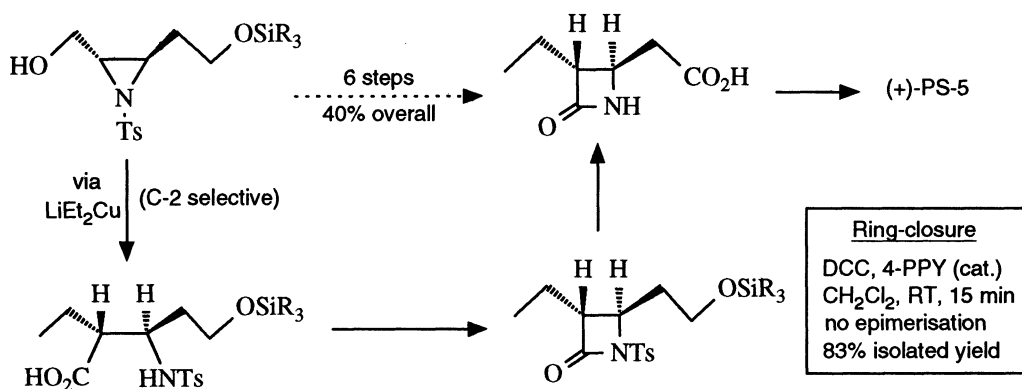

Thienamycin: R = H
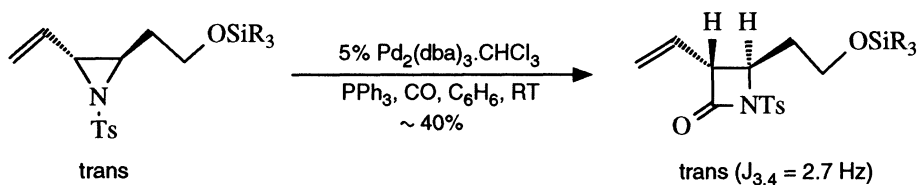1β-Methylthienamycin: R = Me

PS-5: R = H
PS-6: R = Me

Based on the pioneering studies done in the Merck Sharp & Dohme laboratories (ref. 14a) suitably substituted monocyclic β-lactams can be defined as key intermediates, and an apposite retrosynthetic analysis reveals the possibility of using 2,3-aziridino alcohols as chiral starting materials.

trans carbapenem   trans β-lactam

trans allylic alcohol   trans epoxide   trans aziridine
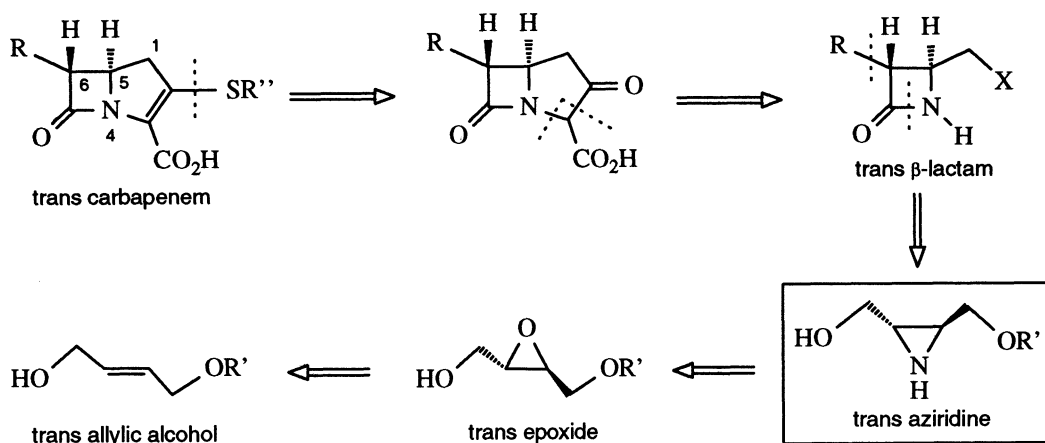
The requisite aziridino alcohols were readily available from the corresponding Sharpless epoxides in excellent overall yield and in >95% enantiomeric purity. Protection/activation by N-tosylation was followed by application of our C-2 selective ring-opening methodology with Red-Al or LiEt$_2$Cu to afford intermediates suitable for transformation to the natural forms of the carbapenems (+)-thienamycin and (+)-PS-5, respectively. The route to the latter antibiotic also featured a new, efficient and mild β-lactam ring-closure reaction which has been developed in our laboratory.

6 steps
40% overall

(+)-PS-5

via
LiEt$_2$Cu (C-2 selective)

Ring-closure
DCC, 4-PPY (cat.)
CH$_2$Cl$_2$, RT, 15 min
no epimerisation
83% isolated yield

Swern oxidation and Wittig methylenation of the aziridino alcohol shown above gives the corresponding *trans* vinyl aziridine which can be transformed in one pot to a *trans* 3-vinyl β-lactam. The reaction, which presumably occurs via insertion of CO into a π-allyl complex formed by ring-opening of the aziridine by Pd(0), is apparently stereoselective (ref. 15) and a closer study is under way.

5% Pd$_2$(dba)$_3$.CHCl$_3$
PPh$_3$, CO, C$_6$H$_6$, RT
~ 40%

trans   trans (J$_{3,4}$ = 2.7 Hz)

The β-lactam syntheses described above thus involve the C-2 selective ring-opening of *trans* aziridines. However, we have also used the C-3 selective ring-opening of *cis* species (ref. 12) to develop routes to 1β-methylthienamycin, reported (ref. 14b) to have even higher biological activity than thienamycin itself. In both syntheses shown below, the 1β-methyl group is introduced with the correct relative and absolute stereochemistry via completely regioselective ring-opening by AlMe$_3$. The second route, which features chiral aziridines at two stages in the reaction sequence, furnishes diastereomerically and enantiomerically pure **5** from the readily available **6** in five steps and 35% overall yield.
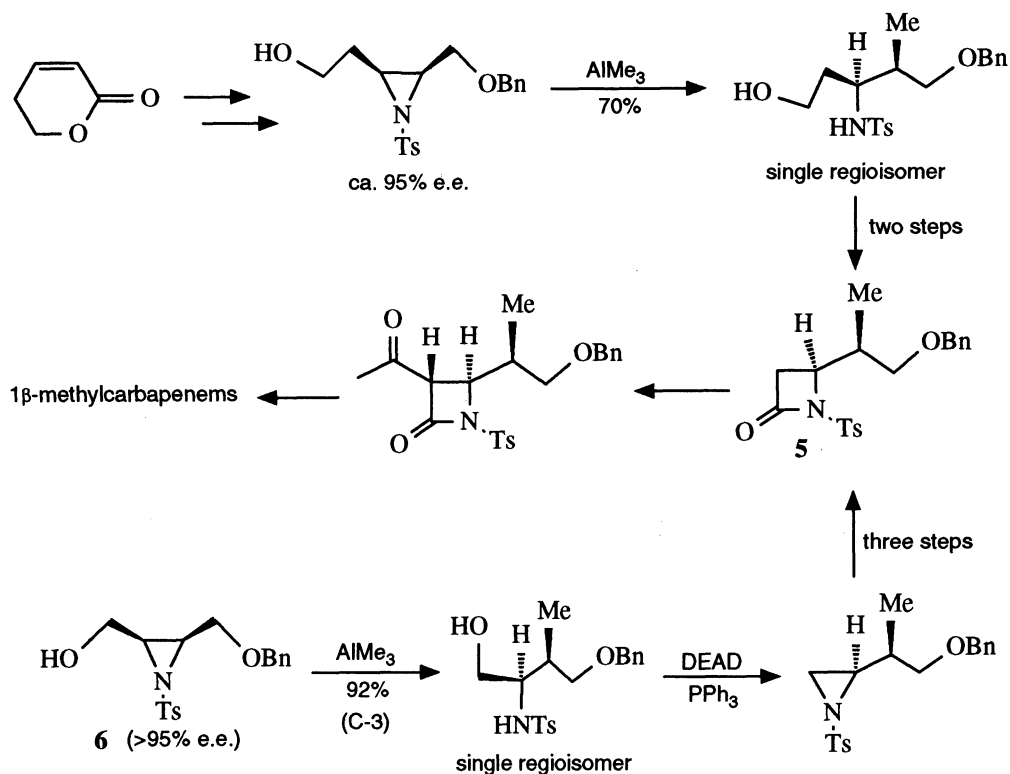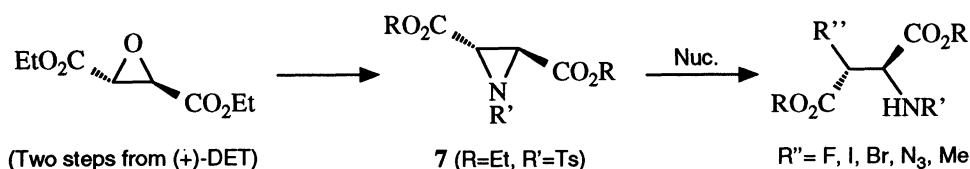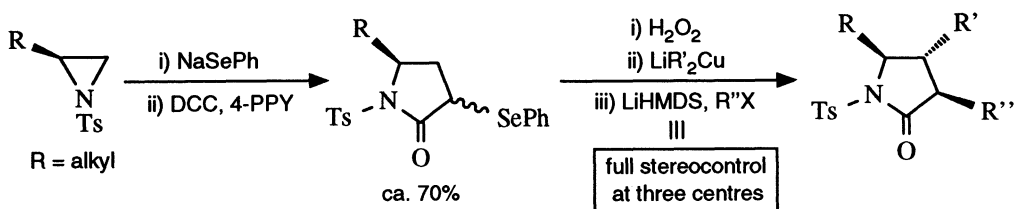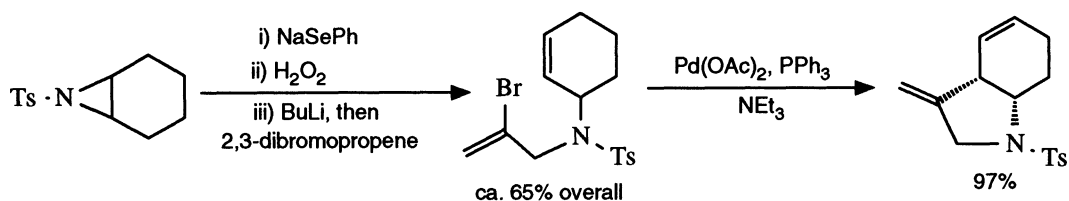

In summary, the "aziridine route" to carbapenems is characterised by *stereocontrol* which is the result of enantioselectivity in the Sharpless epoxidation (which furnishes both enantiomers with equal ease), stereospecificity in the epoxide-to-aziridine transformation, and regioselectivity in the aziridine ring-opening. This allows us to produce, at will, any desired carbapenem diastereomer from very simple starting materials.

In ongoing work directed towards the total synthesis of alkaloids, we have found (ref. 16a) that aziridine chemistry can be used as in the the model studies depicted in the first two equations below. Asymmetric versions of the first process are currently being studied. (Selenium intermediates of the type shown in the middle equation are, of course, also available from glutamic acid (ref. 16b) and we have used these in an alternative enantioselective route to carbapenems).

The C$_2$-symmetric aziridine **7**, which is readily available in both enantiomeric forms from (+)- or (-)-diethyl tartrate (DET), can be regarded as a synthetic equivalent for the β-cation of aspartic acid. Nucleophilic ring-opening of this highly reactive aziridine gives access to a variety of non-proteinogenic amino acid derivatives (ref. 17).

It may be noted that **7** (R=R'=H) is a natural product synthesised recently by Zwanenburg (ref. 18) using chemistry very similar to that used in our earlier route to the N-tosyl diester shown below.


i) NaSePh
ii) H_2O_2
iii) BuLi, then
2,3-dibromopropene

ca. 65% overall

$Pd(OAc)_2$, PPh_3
NEt_3

97%

R = alkyl

i) NaSePh
ii) DCC, 4-PPY

ca. 70%

i) H_2O_2
ii) LiR'_2Cu
iii) LiHMDS, R''X
III

full stereocontrol
at three centres

EtO_2C ... CO_2Et

(Two steps from (+)-DET)

7 (R=Et, R'=Ts)

Nuc.

R''= F, I, Br, N_3, Me

AZIRIDINES AS CHIRAL AUXILIARIES

The synthesis of **7** and its use as a chiral substrate prompted our interest in the development of C_2-symmetric aziridines as chiral auxiliaries for asymmetric synthesis (ref. 19a,b). Once again, the starting materials were (+)- or (-)-DET, and the chiral epoxide precursors to the C_2-symmetric aziridines **8** are easily prepared in quantity by the method of Nicolaou (ref. 19c).

(from (+)-DET)

R=Bn, Me, etc.

8   R'=alkyl, alkenyl, etc.   **9**

(from (-)-DET)

8'   **9'**
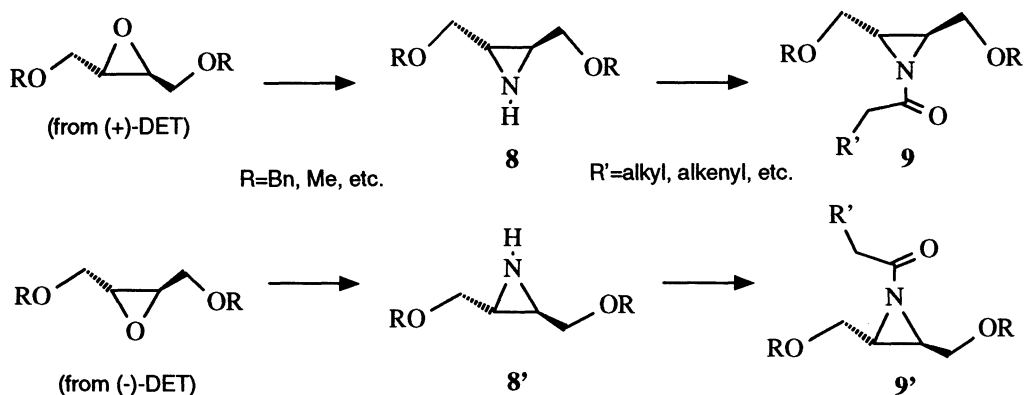
Another advantage of using aziridines such as **8** as removable chiral auxiliaries is the relative ease of hydrolysis or reductive cleavage of the corresponding amides. We hoped that specific enolates derived from **9** or **9'** would enjoy internal coordination of the cation to both the enolate oxygen and the ethereal
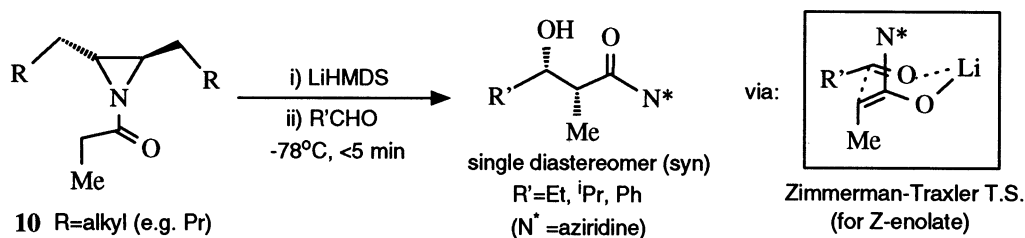
oxygen of the side-chain, thus allowing for diastereofacial differentiation in subsequent reactions such as alkylation. Some of the results are shown below.

Z-enolate (9 + LiHMDS)
R=Bn or Me

70-80% yield
80 to >98% d.e.

X=H (via LiAlH$_4$)
X=OH (via LiOOH)
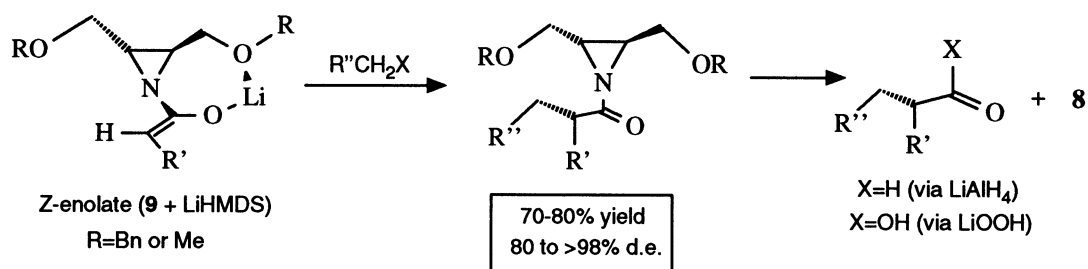
In line with our reasoning, the absolute configuration of the products is as shown above, there being no apparent difference in the performances of the benzyl and methyl bis(ethers). We have also demonstrated that both the C$_2$-symmetry of the auxiliary and the ability of the cation to coordinate to the side-chain are indeed important. (Mono-substituted aziridines, use of cations such as Na$^+$ or K$^+$, and C$_2$-symmetric aziridines lacking the side-chain oxygen all give poorer results). The auxiliary can be removed either by reaction with LiAlH$_4$ to give a chiral aldehyde (ref. 19a) or by hydrolysis with lithium hydroperoxide which yields the chiral acid (ref. 20); little or no epimerisation occurs under these conditions. This type of enolate methodology is very useful for the diastereo- and enantioselective synthesis of a wide variety of natural products, including insect pheromones (ref. 21a), amino acids (ref. 21b) and macrolide antibiotics (ref. 21c).

During the past decade, few organic transformations have received so much attention as the stereoselective aldol reaction (ref. 22) and the importance of this process in the diastereo- and enantioselective construction of highly complex natural products is now well documented. It was therefore of interest to test our aziridine auxiliaries in this respect, and our preliminary results are promising.

Although auxiliaries such as **8** perform well in the aldol reaction with relatively bulky electrophiles (ref. 19a) we have more recently found (ref. 23) that better results can be obtained for a wider range of aldehydes by use of aziridines **10**, which lack side-chain oxygens.

10 R=alkyl (e.g. Pr)

i) LiHMDS
ii) R'CHO
-78°C, <5 min

single diastereomer (syn)
R'=Et, ^{i}Pr, Ph
(N* =aziridine)

via:

Zimmerman-Traxler T.S.
(for Z-enolate)

The results are consistent with formation of the Z-enolate and reaction via a Zimmerman-Traxler transition state in which the R' group is "equatorial". The side-chains of **10** (in contrast to those of **9**) cannot compete with the electrophile in coordination to the cation and thus, in the presumed transition state, they exert purely steric diastereofacial control effects akin to those proposed for the Evans oxazolidinone auxiliaries (ref. 22d). It is noteworthy that the aldol reactions shown above can be simply carried out with the *lithium* enolates, without the need to form, e.g., boron or titanium species. The scope

of these aziridine auxiliaries in other diastereoselective processes such as the Michael and Diels-Alder reactions is currently under scrutiny.

AZIRIDINES AS CHIRAL LIGANDS

The third part of our project deals with the development of C_2-symmetric bis(aziridines) as chiral ligands for transition metals, the ultimate goal being enantioselective homogeneous catalysis of organometallic reactions. Our choice of C_2-symmetric species was based on both studies of molecular models and ample literature precedent (ref. 24a). We have worked out the simple and general synthesis of the desired bis(aziridines) shown below, and the first reaction we have studied is the OsO_4-mediated *syn*-1,2-dihydroxylation of prochiral olefins (ref. 24b).
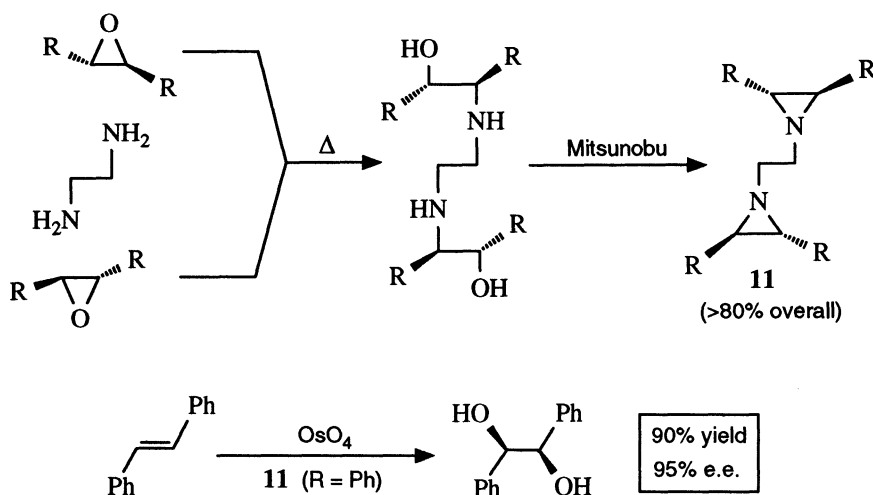
These initial results from the stoichiometric process are encouraging - a rapid reaction at -78°C gives an excellent isolated yield of optically active stilbene diol (95% e.e.). The "fine tuning" of the above reaction and the application of these ligands to other asymmetric processes such as epoxidation, cyclopropanation and (of course!) *aziridination* will be the subject of future studies.

Acknowledgements

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