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STUDIES TOWARD THE APPLICATION OF OXAZOLINE-EPOXIDE EQUIVALENCY IN 1,3-ASYMMETRIC INDUCTION

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SUMMARY: Synthetically versatile epoxy alcohols **8a** and **8s** have been prepared from a common intermediate, chiral aldehyde **5**, through a sequence involving diastereoselective allylation followed by stereospecific transformation of the oxazoline to an epoxide.

Chiral oxazolines, readily prepared from numerous naturally available vicinal amino alcohols, have shown considerable utility in asymmetric synthesis.[1] Most often, the chirality of the heterocycle is exploited in an asymmetric operation on the substituent at the 2-position of the oxazoline (R^1 in **1** → **2**, figure 1) which is followed by release of the modified fragment as a carboxylic acid (X = OH) or an aldehyde (X = H) through hydrolytic or reductive methods of cleaving the heterocycle, respectively (**2** → **3**).[1a] Less commonly, the asymmetry of the oxazoline has been used to direct modification of the substituent at the 4-position (R^2 in **1** → **2**). In this instance, the modified cleavage product of the oxazoline retains the original amino alcohol functionality (**4**), offering the opportunity for further elaboration. Previously, we have reported the successful exploitation of this strategy using an oxidative cleavage of the resultant amino alcohol (R^3 = H) to afford a chiral aldehyde.[2] In this Letter, we wish to describe an extension of this approach wherein an oxazoline is exploited as an epoxide surrogate capable of effective, stereodivergent 1,3-asymmetric induction.

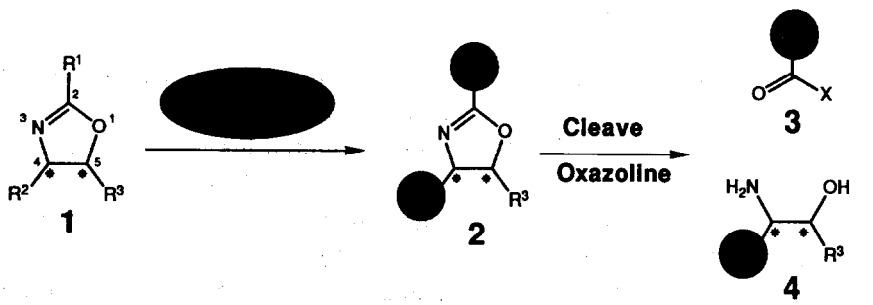
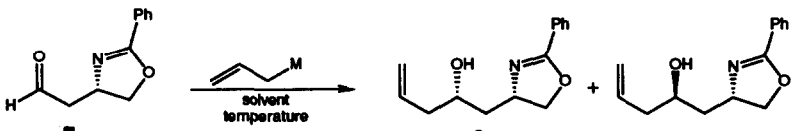


Figure 1.

In connection with efforts to develop a general synthetic strategy to polyacetate carbon frameworks, we have examined the asymmetric addition reactions of aldehyde **5**, which is readily available from L-aspartic acid.[2] When aldol condensations using a variety of simple achiral acetate enolates exhibited disappointingly low levels of stereoselection,[3] an investigation into the

diastereoselective allylation of this aldehyde was surveyed. As the results in the Table indicate, allylation could be controlled to select for either the *syn* isomer **6s** or the *anti* isomer **6a** (see highlighted entries 6 and 8). Of significant practical note, the diastereomerically pure products could be easily obtained by simple chromatographic removal of the minor, undesired isomer in either case.

TABLE

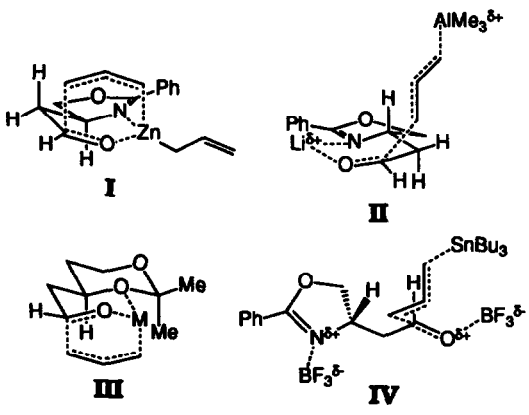


5 **6s** **6a**

Entry	M	Solvent/Temp.	**6s:6a**[a] (Yield[b])
1	MgBr	ether/-78°	59:41
2[c]	ZnCl/LiCl	ether/-78°	70:30
3[d]	ZnCl/MgBrCl	ether/-78°	76:24
4[d]	ZnCl/MgBrCl	THF/-78°	84:16 (82%)
5[d]	ZnCl/MgBrCl	THF/0°	92:8
6[c]	***Zn(allyl)/LiCl***	***THF/0°***	***98:2 (70%)***
7[d]	$AlMe_3MgBr$	ether/-78°	44:56
8[c]	***$AlMe_3Li$***	***ether/-78°***	***16:84 (78%)***
9	$SnBu_3/BF_3$	CH_2Cl_2/-78°	80:20 (77%)

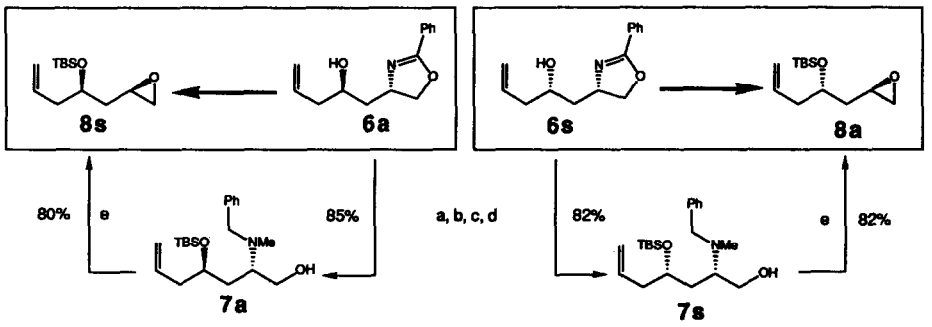
[a]determined by ^1H NMR integration[4]
[b]isolated yield after chromatographic purification
[c]reagent prepared from allyllithium
[d]reagent prepared from allylmagnesium bromide

This remarkable diastereofacial control can be rationalized via transition states **I** and **II**, which attribute these contrasting stereoselectivities to preferences for intramolecular and intermolecular delivery of the allyl group to the chelated aldehyde. It is interesting to note that the observed stereoselection for the zinc-mediated allylation is *opposite* the sense of diastereoselection observed for the allylation of related β-alkoxy aldehydes.[5] It is speculated that the sp^2 nature of the chelated nitrogen biases the transition state toward a boat conformation (**I**) in contrast to the chair geometry suggested to explain the *anti*



selectivity seen in oxygen analog (**III**). Interestingly, it was observed that this reaction was significantly more *syn*-selective at 0° than at -78° (entries 4 and 5) and the diallylzinc reagent gave higher levels of selectivity than the allylzinc chloride species (entries 5 and 6). The *anti* selective allylaluminate reaction was found to be very sensitive to the nature of the counter ion, as demonstrated by entries 7 and 8 in the Table. This may be the result of a kinetic or thermodynamic preference for the lithium chelate relative to the magnesium bromide chelate in promoting a transition state geometry such as **II**.[6] Finally, it is noteworthy that respectable levels of *anti* selection are found in the BF_3-mediated allylstannane reactions (entry 9), consistent with an extended transition state of the type **IV** which bears analogy to previous suggestions.[7]

With access to the diastereomeric allylated oxazolines (**6a** and **6s**) from a common precursor **5** in hand, attention was turned to the manipulation of the heterocycle. In order to establish the desired asymmetric 1,3-relationship between oxygenated centers required for polyacetate targets, we sought a means for the stereospecific replacement of the nitrogen by an oxygen. This was realized through application of the methodology reported by Castedo and co-workers as shown in figure 2.[8] Specifically, routine protection of the homoallylic alcohols as *t*-butyldimethylsilyl ethers (TBSO-) was followed by reductive cleavage of the oxazolines to the corresponding benzylamino alcohols,[1a] then N-methylation to efficiently afford the diastereomeric tertiary amines **7a** and **7s**. Exposure of these compounds to dichlorocarbene generated under the conditions employed by Castedo (1 hour at RT) cleanly affords the synthetically versatile epoxy alcohols **8a**[9] and **8s** with complete stereochemical control (within the limits of detection).[10]



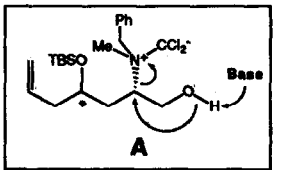
Reagents: (a) TBSOTf, Et_3N, 0°; (b) DIBAL, $PhCH_3$, 0°; (c) HCHO, PhH, Dean-Stark ($-H_2O$); (d) DIBAL, $PhCH_3$, -78°; (e) $CHCl_3$, 50% NaOH (aq.), Bu_4NCl (cat.).

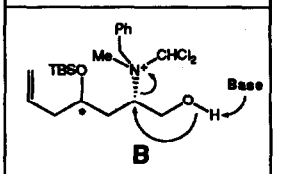
Figure 2.

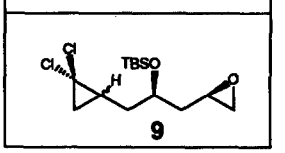
This surprisingly efficient epoxide-forming reaction apparently proceeds through intramolecular displacement of either the intermediate nitrogen ylide (**A**), as previously suggested,[8] or via the corresponding tetraalkyl ammonium species (**B**). In the present case, it is clearly possible that the ylide may act as an internal base to promote an intramolecular deprotonation to lead to the observed products (base = CCl_2^- in **A**). The chemical selectivity of the reaction is noteworthy. Potential competitive side reactions, including the insertion of the dichlorocarbene into the benzylic

C-H bonds or the carbon-carbon double bond, were not problematic. In fact, dichlorocarbene adduct **9** could be isolated in trace quantities only after prolonged reaction times (i.e., greater than 6 hours).

As a result of the diastereoselective control available in the allylation reactions of β-amino aldehyde **5** and the efficient and stereospecific conversion of vicinal amino alcohols to epoxides, synthetically useful access to both diastereomers of the versatile building blocks **8a** and **8s** are available from a single precursor. With the availability of numerous chiral amino alcohols, most notably from α-amino acids, it can be anticipated that this methodology will offer attractive means to the synthesis of a wide variety of asymmetric polyoxygenated arrays. Along these lines, our efforts to exploit intermediates **8a** and **8s** will be reported in due course.







ACKNOWLEDGEMENT: The financial support of the National Institutes of Health is gratefully acknowledged.

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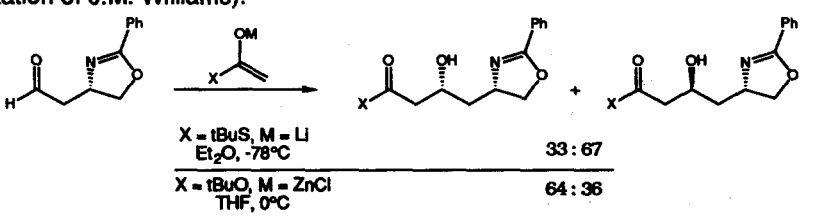

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8. Castedo, L.; Castro, J.L.; Riguera, R. *Tetrahedron Lett.* **1984**, *25*, 1205.
9. For the synthesis of a similar epoxy ether, see: Manfield, E.; Steel, P.G.; Thomas, E.J. *J. Chem. Soc., Chem. Commun.* **1987**, 1826.
10. Compounds **8a** and **8b** were found to be homogeneous by ^{1}H NMR (300 MHz) and tlc analysis (SiO_2, 80% hexanes : 20% ether).

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