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Stereocontrolled Synthesis of *R* or *S*, *E* or *Z* Unsaturated α–Amino Acids by Enantio- and Diastereoselective Epoxidation of δ-Hydroxy Allylic Phosphine Oxides

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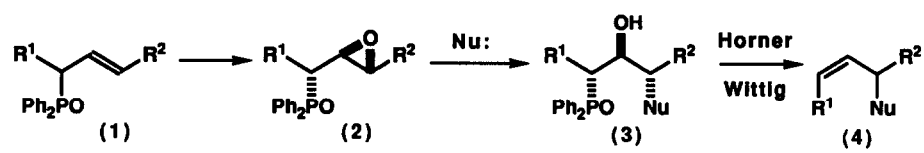
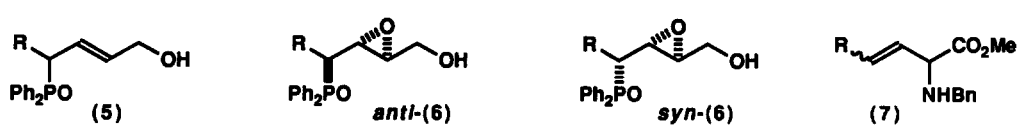
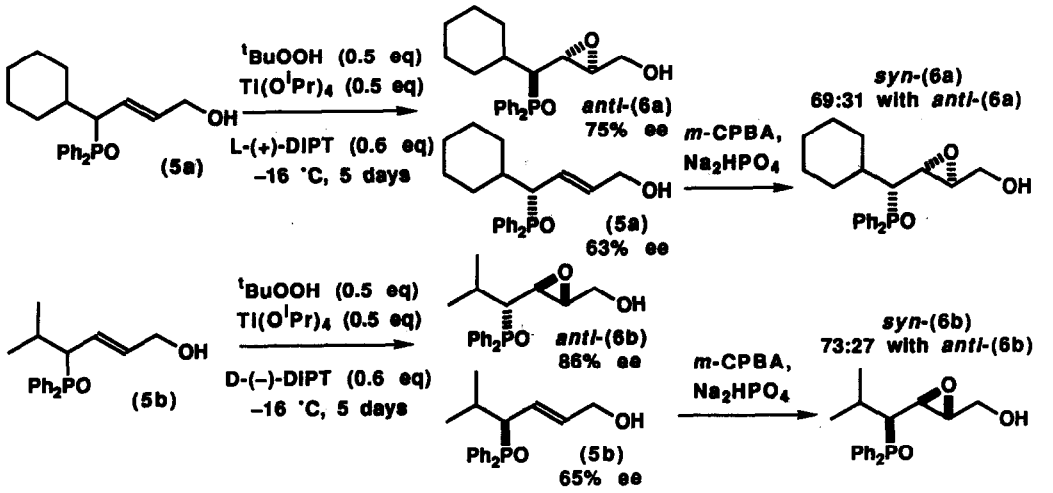
Abstract: *Epoxidation of δ-hydroxy allylic phosphine oxides* **5** *with* m-*CPBA can be* syn *selective. All stereoisomers of epoxy alcohols* **6** *are available when this method is used in tandem with an* anti *selective Sharpless kinetic resolution. The stereoisomers of epoxy alcohols* **6** *can be transformed stereospecifically into single isomers of unsaturated α–amino acids* **7**. *A mechanistic explanation for the stereoselectivity observed in the* m-*CPBA epoxidation is proposed.*

We are currently making use of the epoxides **2** of allylic phosphine oxides **1** as regio- and stereocontrolled allyl cation equivalents.[1] Nucleophilic opening of the epoxide, followed by Horner-Wittig elimination of the resulting alcohol **3**, leads to allylic compounds **4** with controlled double bond geometry. Because of the stereospecific nature of both the epoxide opening and Horner-Wittig elimination, the relative stereochemistry of the epoxide **2** is reflected in the geometry of the final double bond in **4**. Stereocontrol in this sequence therefore depends on the stereoselectivity of the epoxidation of the allylic phosphine oxide **1**.

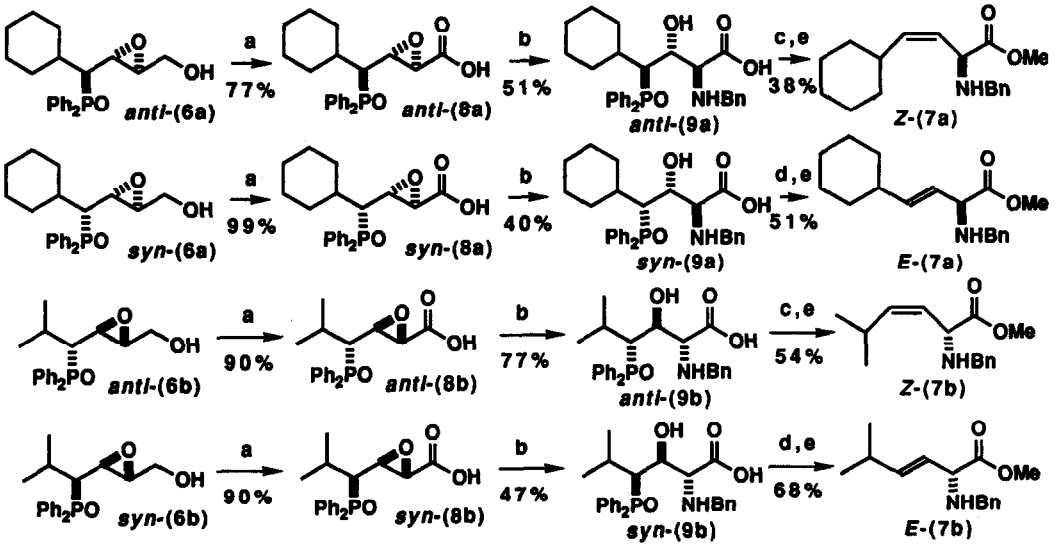


We have recently published a synthesis of homochiral *anti* epoxides *anti*-**6** by Sharpless kinetic resolution of δ-hydroxy allylic phosphine oxides **5**.[2] In this paper we describe the general asymmetric synthesis of any of the four stereoisomers of epoxides **6** (either enantiomer of *syn*-**6** or *anti*-**6**) by a combination of asymmetric (Sharpless) and diastereoselective (peracid) epoxidation. The synthetic importance of these epoxides, and this stereocontrolled route to them, is demonstrated by using them as starting materials in the synthesis of any isomer (*E* or *Z*, *R* or *S*) of the class of protected unsaturated amino acids **7**





Sharpless kinetic resolution[3] of **5a** and **5b**[4] using L-(+)-DIPT and D-(–)-DIPT respectively gave *anti* epoxides *anti*-**6a** and *anti*-**6b** with high enantiomeric excess.[2] The kinetic resolution also returned the starting allylic alcohols enantiomerically enriched. *m*-CPBA Epoxidation of this material was, conversely, *syn*-selective, and gave optically active *syn* epoxy alcohols *syn*-**6d** and *syn*-**6e**. The epoxide diastereomers **6** were separated from each other and from the allylic alcohol **5** by HPLC. By choosing which enantiomer of tartrate is used in the kinetic resolution, any stereoisomer of **6** may be made.



Reagents: a. RuO_4, $NaIO_4$, MeCN, CCl_4; b. $BnNH_2$, H_2O; c. KOH, DMSO; d. NaH, DMF; e. CH_2N_2

Oxidation ($RuCl_3$, $NaIO_4$, MeCN)[5] of the epoxy alcohols **6** gave, in excellent yield, the epoxy acids **8**. Regioselective nucleophilic opening of these epoxides with benzylamine[6] gave protected α-amino acids **9**. Stereospecific Horner-Wittig elimination[7] of the sodium or potassium dianions of **9** gave unsaturated amino acids which were isolated as their N-protected methyl esters **7**. Chiral shift experiments with Pirkle's reagent[8]

showed that the enantiomeric excesses of **7b** were the same as those of **6b**.[9] Unsaturated amino acids are of interest as anti-microbial agents or as tools in the elucidation of the structure and function of proteins.[10]

The diastereoselectivity of the *m*-CPBA epoxidation was further investigated by treating racemic δ-hydroxy allylic phosphine oxides[4] **5** with *m*-CPBA. The ratios of diastereomers obtained are presented in the table. The stereoselectivity of the reaction is markedly dependent on the substituent R. When R is a branched alkyl group (entries **a** and **b**), the epoxidation is *syn* selective. When R is an unbranched alkyl group (entries **c** and **d**), the reaction is only very marginally *syn* selective, and when R is small (entry **e**) the reaction swings to being *anti* selective.

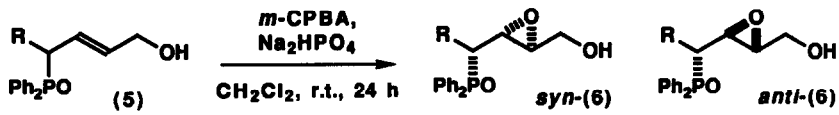
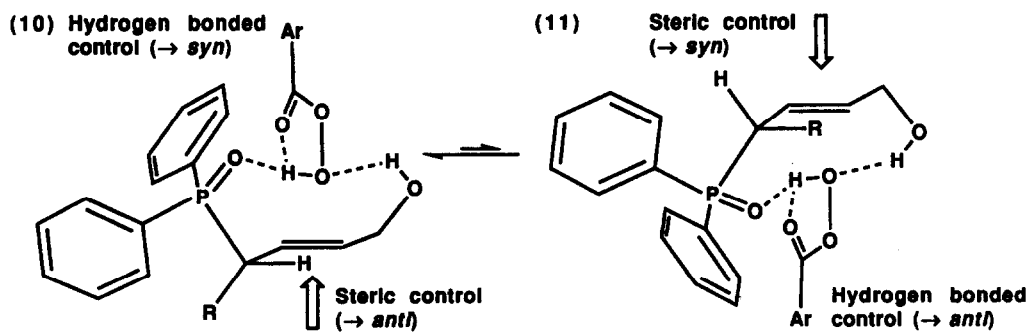


Table: Diastereoselectivity in the *m*-CPBA Epoxidation of **5**

entry	R =	ratio *syn*-**6** : *anti*-**6**
a	cyclohexyl	69:31
b	^{i}Pr	73:27
c	n-pentyl	54:46
d	Et	53:47
e	Me	29:71

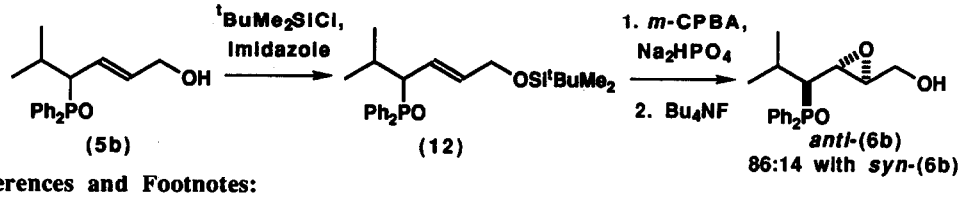
Epoxidations of simple allylic phosphine oxides **1** (R^1, R^2 = alkyl) usually give good yields of *anti* epoxides **2**, because of the steric directing effect of the bulky diphenylphosphinoyl group, which shields one face of the double bond.[1,11] We have previously suggested,[1] however, that a free δ hydroxyl may induce the diphenylphosphinoyl group to direct epoxidation *syn* by hydrogen bonding to the incoming peracid.

The results presented in the table confirm that the diphenylphosphinoyl group can be a *syn* director in the epoxidation of δ-hydroxy allylic phosphine oxides **5**, but only when R is branched. This can be understood in terms of a transition state **10**,[12] in which the hydroxyl group and the phosphoryl oxygen co-operate in a cyclic hydrogen-bonded structure, favouring approach of the peracid *syn* to the diphenylphosphinoyl group. A similar co-operative effect has been observed in the epoxidation of allylic alcohols bearing benzyloxy, silyloxy or amide groups.[13]



The two most probable lowest energy reactive conformations of **5** are represented as **10** and **11**.[12,14] When R is branched, conformation **10** is greatly favoured over conformation **11** because of the crowding experienced when R moves into the plane of the double bond. Epoxidation therefore takes place solely in conformation **10**, largely from the top face (which gives *syn* epoxide) but also to some extent from the sterically favoured bottom face (giving *anti*). For smaller R, conformation **11** is also populated. Hydrogen bonding directed epoxidation of **11** gives *anti* epoxide. Moreover, the bottom face of **10** is less shielded by small R. The combined result of these effects is overall *anti*-selective epoxidation of **5e** when R is small.

Allylic alcohol **5b** was protected as the silyl ether **12**. Epoxidation of **12**, followed by deprotection of the silylated epoxy alcohols, gave predominantly the *anti* epoxide *anti*-**6b**. Clearly, without the free hydroxyl, cyclic structure **10** cannot form, and the diphenylphosphinoyl group reverts to a steric *anti* directing rôle.[6a]



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