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Asymmetric Epoxidations and Kinetic Resolutions of δ-Hydroxy Allylic Phosphine Oxides

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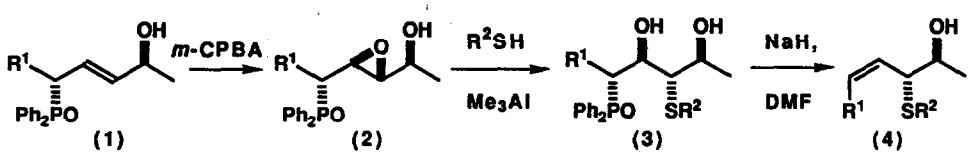
Abstract: *δ-Hydroxy allylic phosphine oxides 5 undergo asymmetric epoxidation to yield epoxy alcohols 6 with high enantio- and diastereoselectivity. Kinetic resolutions are also successful, even with a chiral centre remote from the allylic hydroxyl, if that chiral centre bears a diphenylphosphinoyl group. The diphenylphosphinoyl group then exerts a novel* anti-*directing effect on the epoxidation.*

Diphenylphosphinoyl-substituted epoxides[1] (such as **2**) have been used as intermediates in the stereocontrolled connective synthesis of allylically and homoallylically substituted compounds, such as the hydroxy alkenyl sulphide **4**.[2] Nucleophilic attack on the epoxide introduces a substituent into 2 γ to phosphorus, and unmasks the hydroxyl group necessary to generate the controlled-geometry double bond of **3** in the final stereospecific Horner-Wittig elimination step.



Our published stereocontrolled approach[1] to epoxides **2** involves peracid epoxidation of δ-hydroxy allylic phosphine oxides **1**, directed *syn* by the hydroxyl group. Since the Ph_2PO group was used to set up the 1,4 relative stereochemistry in **1**, the chiral centre bearing OH is functioning as a "relay" centre in the transfer of stereochemical information from the Ph_2PO group to the epoxide.

We now report the asymmetric synthesis of epoxides **6** from allylic phosphine oxides **5**[3] using the enantio- and diastereoselective Sharpless epoxidation,[4] both in simple, achiral cases ($R^1 = R^4 = H$) and in cases requiring a kinetic resolution (R^1 or $R^4 \neq H$). In the case of $R^1 \neq H$, $R^4 = H$, we have discovered a remarkable, and, to our knowledge, unique example of an effective Sharpless kinetic resolution of a chiral centre *trans* to the allylic hydroxymethyl group. This allows us to control both absolute and relative stereochemistry in **6** without the use of a "relay" centre carrying the hydroxyl group.

Treatment of achiral δ-hydroxy allylic phosphine oxides **7a-c**[3d] with an excess of *tert*-butyl hydroperoxide in the presence of titanium tetraisopropoxide (1 eq), L-(+)-diethyl tartrate (1.2 eq) and 4Å molecular sieves gave the epoxy alcohols **8a-c** in good yields and with high enantiomeric excesses.[5,8]

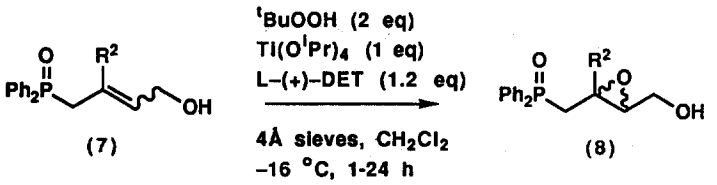


Table 1. Asymmetric Epoxidations of Achiral δ-Hydroxy Allylic Phosphine Oxides

Entry	Starting Material 7:			Product 8:	
	R^2	geometry	yield (%)	stereochemistry[a]	e.e. (%)[5]
a	H	E	76	(2*S*, 3*R*)	82
b	Me	E	91	(2*S*, 3*R*)	96
c	Me	Z	85	(2*S*, 3*S*)	92

[a]Absolute configurations were inferred from the established rules for enantioselectivity in the asymmetric epoxidation.[8]

When secondary allylic alcohols **9** (bearing a chiral centre δ to phosphorus) were epoxidised using only 0.5 equivalents of hydroperoxide and L-(+)-DIPT (diisopropyl tartrate) a kinetic resolution was observed, allowing both remaining starting material **9** and product epoxy alcohol **10** to be isolated (after h.p.l.c.) in good e.e. In accordance with the established rule[8] for the kinetic resolution, we assume that with L-(+)-DIPT the *S* allylic alcohol is the faster-reacting enantiomer. The reaction is also diastereoselective, producing the *anti* epoxide ***anti*-10** only, unless there is a substituent *cis* to the hydroxymethyl group.[9] This *anti*-directing effect of an allylic hydroxyl group in transition metal-catalysed epoxidations is well documented.[8]

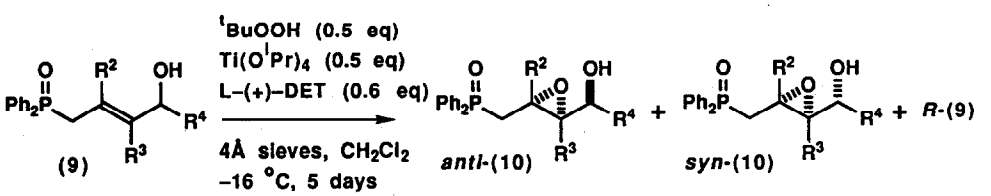


Table 2. Kinetic Resolutions with a Chiral Centre δ to Phosphorus

Entry	R^2	R^3	R^4	Completion[a] (%)	Ratio[a] *anti*-**10**:*syn*-**10**	e.e. *anti*-**10**[5] (%)	e.e. *R*-**9**[5] (%)
a	H	H	Me	50	100:0	>95	95
b	H	Me	Me	50	100:0	>95	91
c	Me	H	^{n}Pr	45	50:50	85-95	80

[a]% Completion of reactions and ratios of diastereomers were all determined by integration of the NMR spectrum of the crude mixture or by analytical h.p.l.c.

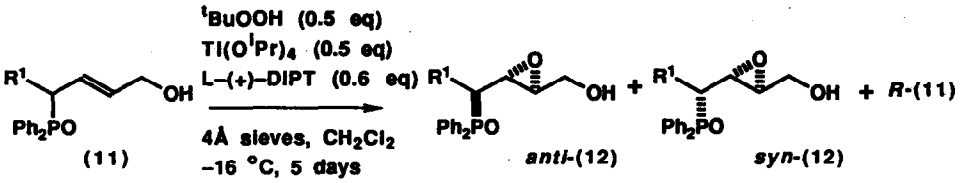
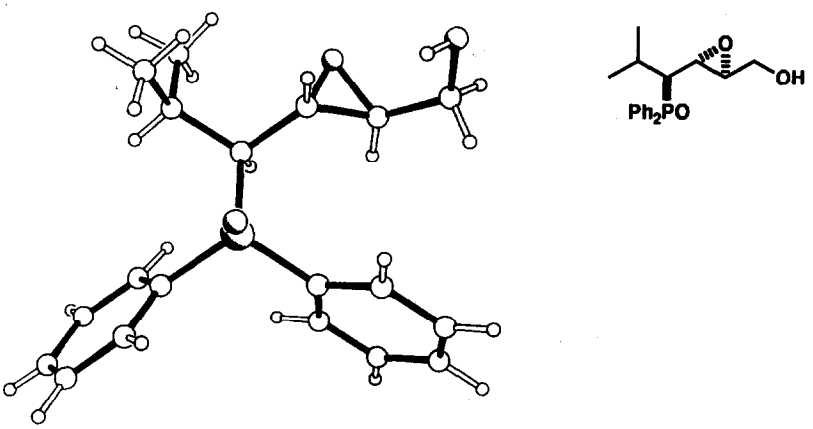


Table 3. Kinetic Resolutions with a Chiral Centre α to Phosphorus

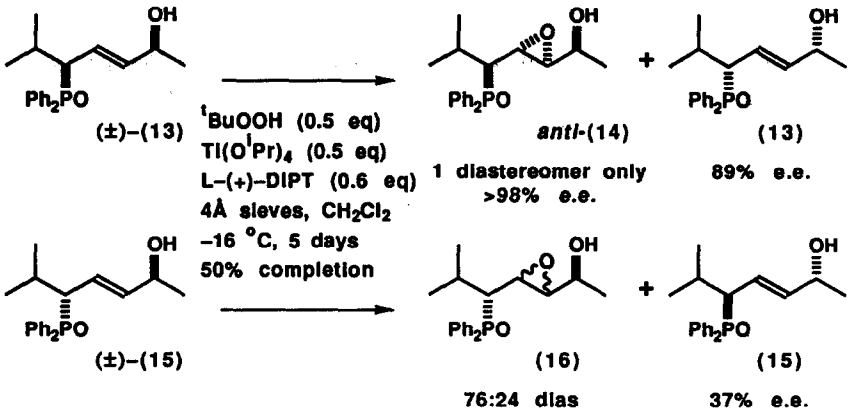
Entry	R^1	Completion (%)	Ratio *anti*-12:*syn*-12	e.e. *anti*-12[5] (%)	e.e. *R*-11[5] (%)
a	Me	57	54:46	–	10
b	Et	54	65:35	82	31
c	n-Pentyl	52	68:32	–	36
d	i-Pr	47	93:7	85	65
e	Cyclohexyl	42	90:10	75	65

The efficiency of the kinetic resolution of primary allylic alcohols **11**, which have a chiral centre α to phosphorus, is highly dependent on the nature of R^1 (Table 3). When R^1 is small (entry **a**), the chiral centre passes almost unnoticed by the chiral catalyst: both enantiomers epoxidise at the same rate, leading to a mixture of diastereomers and little enantiomeric enrichment of the remaining starting material. On the other hand, when R^1 is branched (entries **d** and **e**), one enantiomer epoxidises significantly more rapidly than the other, and an efficient kinetic resolution is observed. This is, to our knowledge, the first example of a Sharpless kinetic resolution at a chiral centre *trans* to the allylic hydroxymethyl in an acyclic system: the only previous example gave remaining starting material of only 6% e.e. at 60% completion.[10] This effect is presumably due to the exceptional bulkiness of the Ph_2PO group.[3b] The relative stereochemistry of the major epoxide products *anti*-**12** was determined by an X-ray crystal structure of *anti*-**12d** (Figure 1), and the other *anti* epoxides identified by similarities in their NMR spectra. Absolute configurations were inferred from the general rule[8] for enantioselectivity in the Sharpless epoxidation.

Figure 1. X-ray Crystal Structure of *anti*-12d



The two diastereomers **13** and **15**, with chiral centres both α and δ to phosphorus, showed a marked match-mismatch effect in the kinetic resolution. When the *anti*-directing effects of the OH and Ph_2PO groups co-operate, as in **13**, the reaction is highly enantio- and diastereoselective. When the directing effects compete with one another, as in **15**, the selectivities drop substantially.



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References and Footnotes:

1. McElroy, A. B.; Warren, S. *Tetrahedron Lett.*, 1985, **26**, 2119-2122.
2. McElroy, A. B.; Warren, S. *Tetrahedron Lett.*, 1985, **26**, 5709-5712.
3. (a) Brown, P. S.; McElroy, A. B.; Warren, S. *Tetrahedron Lett.*, 1985, **26**, 249-252; (b) McElroy, A. B.; Warren S. *Tetrahedron Lett.*, 1985, **26**, 1677-1680; (c) Brown, P. S.; Greeves, N.; McElroy, A. B.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, 1991, 1485-1492; (d) Clayden, J.; Collington, E. W.; Warren, S. *Tetrahedron Lett.*, preceding paper.
4. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.*, 1980, **102**, 5974-5976; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.*, 1987, **109**, 5765-5780.
5. Enantiomeric excesses were determined either by integration of the ^{19}F or ^{1}H NMR spectra of the Mosher's ester derivatives (ref. 6) or by integration of the ^{1}H NMR spectrum in the presence of Pirkle's chiral solvating agent, R-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (ref. 7).
6. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, **34**, 2543-2549.
7. Pirkle, W. H.; Sikkenga, D. L.; Parkin, M. J. *J. Org. Chem.*, 1977, **42**, 384-387.
8. (a) Finn, M. G.; Sharpless, K. B. in *Asymmetric Synthesis*, Academic Press (1985), ed. Morrison, J. D., vol. 5, ch. 8; (b) Johnson, R. A.; Sharpless, K. B. in *Comprehensive Organic Synthesis*, Pergamon (1991), ed. Trost, B. and Fleming, I., vol. 7, pp 389-436; (c) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Synlett.* 1991, 548-550.
9. (a) Rossiter, B. E. in *Asymmetric Synthesis*, Academic Press (1985), ed. Morrison, J. D., vol. 5, ch. 7, p. 212; (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda M.; Sharpless, K. B. *J. Am. Chem. Soc.*, 1981, **103**, 6237-6240.
10. Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takeiani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.*, 1983, **55**, 589-604.

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