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Asymmetric Dihydroxylations of Allylic Phosphine Oxides

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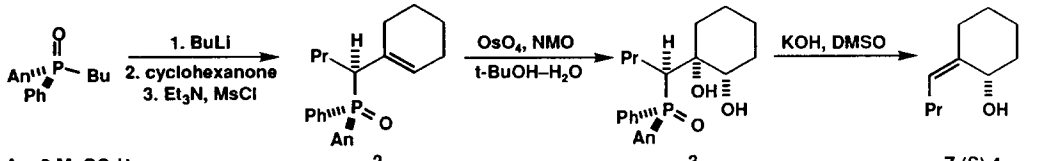
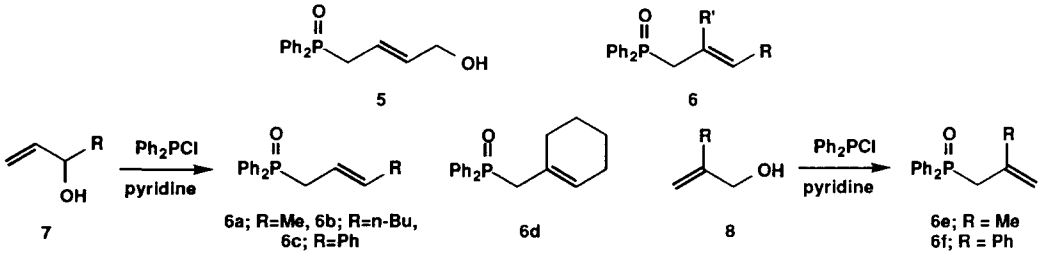
Abstract: Allylic phosphine oxides **6** undergo asymmetric dihydroxylation to yield 1,2 diols **9**. The enantioselectivity of these reactions depends critically on the class and quantity of chiral ligand used. A model to explain the sense and degree of asymmetric induction is proposed.

We have previously described the use of homochiral (*ortho*-methoxyphenyl)phenylphosphinoyl 1,2 diols (such as **3**) in the synthesis of optically active allylic alcohols, e.g. *Z*-(*S*)-**4**.[1] In this sequence of reactions stereochemical information is transferred from phosphorus to carbon by the addition of lithiated phosphine oxide **1** to cyclohexanone. *Anti*-selective dihydroxylation of the allylic phosphine oxide **2** introduces the hydroxyl group β to phosphorus which is necessary to generate the controlled-geometry double bond of **4** in the final stereospecific Horner-Wittig elimination step.

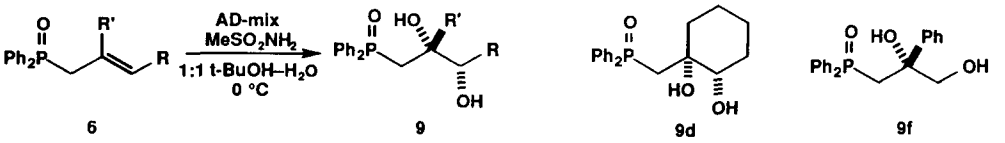


We have also synthesised optically active allylic alcohols[2] using a reagent based strategy, namely the Sharpless asymmetric epoxidation of δ-hydroxy allylic phosphine oxides[3] (such as **5**). A more flexible approach to homochiral allylic alcohols would be the asymmetric dihydroxylation of allylic phosphine oxides **6** which need not contain the pendant hydroxyl group necessary for asymmetric epoxidation. In this paper, we report the results of a study into the scope and limitations of the Sharpless asymmetric dihydroxylation of allylic phosphine oxides. A model which rationalises our results is also described.



We synthesised cyclic allylic phosphine oxide **6d** by dehydration of the corresponding tertiary alcohol[4] and open chain allylic phosphine oxides **6a-c** and **6e-f** using the [2,3] Arbusow rearrangement[5] of allylic alcohols **7** and **8**. Allylic phosphine oxides **6a-c** were produced with good *E* selectivity (**6a**, 95:5; **6b**, 97:3; **6c**, 94:6) as *E*:*Z* mixtures easily separable by crystallisation.

Allylic phosphine oxides **6** were dihydroxylated[6] using commercially available AD-mixes[7] at 0 °C with added methanesulfonamide (except for terminal alkenes **6e-f**). Diols **9** were obtained in good yields but with somewhat disappointing enantiomeric excesses (table 1) when compared with other diols reported by Sharpless in his extensive study.[6]



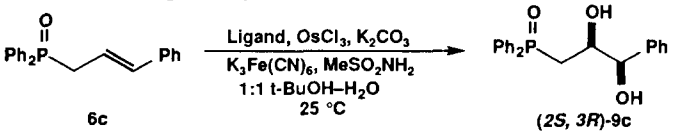
6 9 9d 9f

Table 1 : Asymmetric dihydroxylations of Allylic Phosphine Oxides using AD-mixes

Entry	Starting material	R	R'	AD-mix		Product Yield (%)	Stereochemistry[a]	ee[b] (%)
1	**6a**	Me	H	α	**9a**	84	—[c]	10
2	**6b**	n-Bu	H	α	**9b**	61	(2R, 3S)	49
3	**6c**	Ph	H	α	**9c**	66	(2R, 3S)	74
4	**6d**	—$(CH_2)_4$—		α	**9d**	73	—[c]	18
5	**6e**	H	Me	β	**9e**	75	R	55
6	**6f**	H	Ph	β	**9f**	74	R	86

[a] Our assignment of absolute stereochemistry is discussed later in this paper. [b] Ref 8. [c] The enantiomeric excess is too low for reliable assignment of absolute stereochemistry.

In an attempt to increase the enantiomeric excesses of the diols **9** obtained in the dihydroxylation reaction, we developed a new set of asymmetric dihydroxylation conditions based on our racemic dihydroxylation protocol:[9] treatment of allylic phosphine oxide **6c** with catalytic quantities of $DHQD_2$-PHAL ligand and osmium (III) chloride in the presence of potassium ferricyanide, potassium carbonate and methanesulfonamide in 1:1 tertiary butanol–water at room temperature gave diol **9c** with 84% ee (entry 2; table 2). This improves upon the 74% ee of diol **9c** obtained using AD-mix α (entry 1; table 2). We found that varying the concentration of the chiral amine accelerator had an insignificant effect on the enantioselectivity of the reaction but gave improved yields (entries 2-4; table 2).



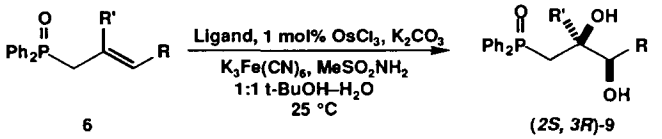
6c (*2S, 3R*)-**9c**

Table 2 : Comparison between AD-mix and our new dihydroxylation conditions with phosphine oxide **6c**

Entry	Ligand (mol%)	Source of OsO_4 (mol%)	Yield (%)	Product Stereochemistry	ee (%)
1	DHQ_2-PHAL (1.0)	$K_2OsO_2(OH)_4$ (0.2)	66	(2R, 3S)	74
2	$DHQD_2$-PHAL (2.5)	$OsCl_3$ (1.0)	72	(2S, 3R)	84
3	$DHQD_2$-PHAL (5.0)	$OsCl_3$ (2.0)	49	(2S, 3R)	85
4	$DHQD_2$-PHAL (7.5)	$OsCl_3$ (1.0)	94	(2S, 3R)	85

We have also investigated the effect of different ligands with our asymmetric dihydroxylation conditions. Sharpless originally reported the use of ligands DHQD-CLB and DHQD-PHN in the asymmetric dihydroxylation reaction.[10] These ligands contain only one quinuclidine unit and we were pleased to observe higher enantioselectivity using these ligands than with the generally superior "dimeric" ligand $DHQD_2$-PHAL used in AD-mix β (table 3: compare entries 2 and 3 in table 3 with entry 2 in table 1 and compare

entries 6 and 7 in table 3 with entry 4 in table 1). Sharpless and Sato have reported a similar trend in enantioselectivity in the asymmetric dihydroxylation of allylic trimethylsilanes.[11] We suggest that the steric bulk of the diphenylphosphinoyl and trimethylsilyl groups hinders efficient asymmetric dihydroxylation with the more crowded "dimeric" ligands.



6 (2S, 3R)-9

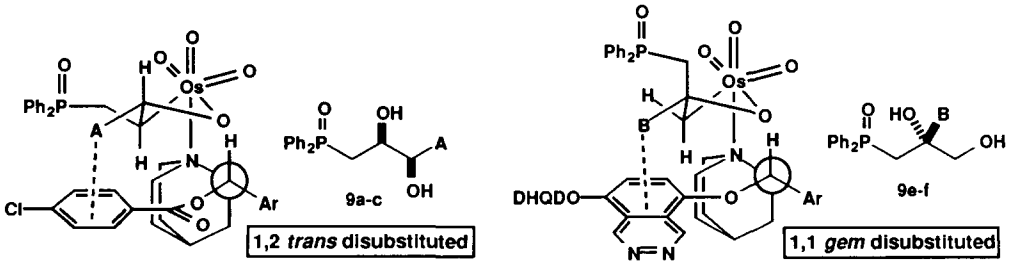
Table 3 : Asymmetric dihydroxylation using DHQD-PHAL and DHQD-PHN

Entry	Starting material			Ligand (mol%)[a]	Product			
		R	R'			Yield (%)	Stereochemistry[b]	ee (%)
1	**6b**	n-Bu	H	DHQD-CLB (2.0)	**9b**	64	(2S, 3R)	58
2	**6b**	n-Bu	H	DHQD-CLB (13.0)	**9b**	70	(2S, 3R)	76
3	**6b**	n-Bu	H	DHQD-PHN (25.0)	**9b**	70	(2S, 3R)	75
4	**6c**	Ph	H	DHQD-CLB (13.0)	**9c**	79	(2S, 3R)	86
5	**6c**	Ph	H	DHQD-PHN (25.0)	**9c**	69	(2S, 3R)	88
6	**6d**	—$(CH_2)_4$—		DHQD-CLB (13.0)	**9d**	62	—[c]	60
7	**6d**	—$(CH_2)_4$—		DHQD-PHN (25.0)	**9d**	62	—[c]	38

[a] 13 mol% of DHQD-CLB and 25 mol% of DHQD-PHN were the quantities originally used by Sharpless and Sato.[11] [b] Our assignment of absolute stereochemistry is discussed later in this paper. [c] No reliable prediction of absolute stereochemistry can be made.

Allylic phosphine oxide **6b** was dihydroxylated with lower enantioselectivity when we decreased the amount of ligand DHQD-CLB from 13 mol% to 2 mol% (entries 1-2; table 3). Interestingly, similar enantiomeric excesses were obtained using DHQD-CLB and DHQD-PHN as ligands with 1,2 *trans* disubstituted allylic phosphine oxides **6b** (entries 2-3; table 3) and **6c** (entries 4-5; table 3) whereas appreciably different enantiomeric excesses were observed with trisubstituted allylic phosphine oxide **6d** (entries 6-7, table 3). Sharpless and Sato have also noted a similar effect with the corresponding trisubstituted allylic trimethylsilane.[11]

Sharpless has recently proposed a model which rationalises the sense and degree of asymmetric induction in the asymmetric dihydroxylation reaction.[12] We have used a modified version of this model to rationalise the preferred formation of (*R*)-1,2 diols **9e-f**[13] and also to predict the sense of asymmetric induction in the dihydroxylation of 1,2 *trans* disubstituted allylic phosphine oxides **6a-c**.



The model considers the lowest energy metallaoxetane which is the first intermediate in the proposed [2+2] cycloaddition pathway. Sharpless suggests that the substitutent on the alkene which can best be stabilised by solvophobic and π-interactions occupies the pseudoequatorial position directly above the

aromatic ring of the ligand. We believe that it is substituent A (in 1,2 *trans* disubstituted alkenes **6a-c**) or substituent B (in 1,1 *gem* disubstituted alkenes **6e-f**) which is positioned as shown in the diagrams and that *the diphenylphosphinoyl group is too large to occupy this position.* We suggest this because changing substituent A in allylic phosphine oxides **6a-c** from methyl to butyl to phenyl increased the enantiomeric excess from 10% ee to 49% ee to 74% ee (entries 1-3; table 1) and changing substituent B in allylic phosphine oxides **6e-f** from methyl to phenyl increased the enantiomeric excess from 55% ee to 86% ee (entries 5-6; table 1).

When considering the Sharpless mnemonic, it is important to realise that our modification of the model proposed by Sharpless predicts the same sense of asymmetric induction for the asymmetric dihydroxylation of 1,2 *trans* disubstituted allylic phosphine oxides **6a-c** but the opposite sense of asymmetric induction with 1,1 *gem* disubstituted allylic phosphine oxides **6e-f**. Others have noted a reversal in the sense of asymmetric induction in the Sharpless asymmetric dihydroxylation of 1,1 *gem* disubstituted alkenes.[14]

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7. AD-mix-β and AD-mix-α are available from Aldrich Chemical Company Limited. The conversion of 1 mmol of alkene requires 1.4 g of AD-mix-β which contains potassium ferricyanide (3.0 mmol), potassium carbonate (3.0 mmol), $(DHQD)_2$-PHAL (0.01 mmol) and $K_2OsO_2(OH)_4$ (0.02 mmol).
8. Enantiomeric excesses were determined by integration of the ^1H NMR spectrum of the bistrimethylsilyl derivatives in the presence of Pirkle's chiral solvating agent, (R)-(–)-2,2,2,-trifluoro-1-(9-anthryl)ethanol: Pirkle, W. H.; Sikkenga, D. L.; Parkin, M. S. *J. Org. Chem.*, **1977**, *42*, 384-387.
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