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Diastereoselective Reactions of Optically Active γ-Substituted Vinyl Phosphine Oxides

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Abstract: Dehydration of diphenylphosphinoyl diols (synthesised by asymmetric dihydroxylation of allylic phosphine oxides) gives γ-hydroxy vinyl phosphine oxides. Some diastereoselective reactions of vinyl phosphine oxides with hydrogen, carbon and heteroatomic nucleophiles are discussed.
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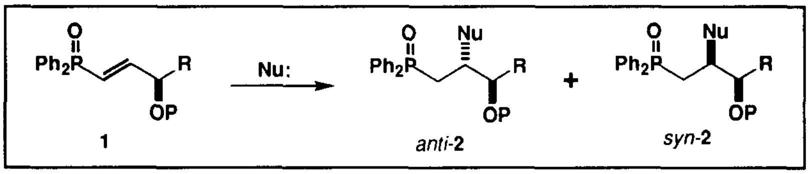
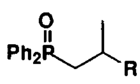
The chemistry of vinyl phosphine oxides has received little attention compared to that of vinyl phosphonates.[1] Previously, amines,[2] amides,[3] organocuprates,[4] silyl cuprates,[5] 1,3-dipoles[6] and dienes[1] have been combined with simple vinyl phosphine oxides but the diastereoselectivity of these transformations has not been addressed in detail. In this paper, we report the results of the first ever study to focus on the reactions of nucleophiles with optically active vinyl phosphine oxides like **1**.

We have previously shown that chiral phosphine oxides **3** can be used to synthesise allylic alcohols (e.g. **4**),[7] alkenyl oxazolidinones (e.g. **5**)[8] and allylic sulfides (e.g. **6**)[9] with remote chiral centres across double bonds of controlled geometry. The aim of the study reported in this paper was to provide an efficient route to optically active phosphine oxides **2** which, by analogy with **3**, are potential precursors of allylically functionalised molecules like **4-6**. We have already shown that phosphine oxides **2** (Nu = Me) are useful intermediates in the synthesis of optically active cyclopropyl ketones such as **7**.[10]





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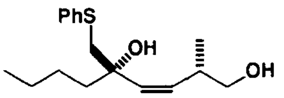

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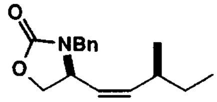

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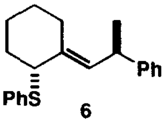

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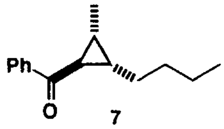


7

Vinyl phosphine oxides **10** were easily synthesised using a two-step sequence inspired by the work of Sharpless.[11] Diphenylphosphinoyl diols **8**, synthesised by asymmetric dihydroxylation of the corresponding allylic phosphine oxides,[12] were activated as mixtures of cyclic sulfites **9** and eliminated using DBU (Table 1).[13] The eliminations were highly *E*-selective presumably because the reaction proceeded mainly *via* conformation **11** even when $R^2 \neq H$. Alcohols **10c-d** could be protected in excellent yield as silyl ethers (TBDMSCl / imidazole) and MOM acetals ($MeOCH_2Cl$ / Et_3N) using mild reaction conditions.[14]

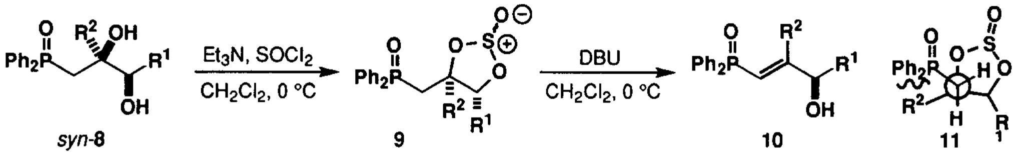
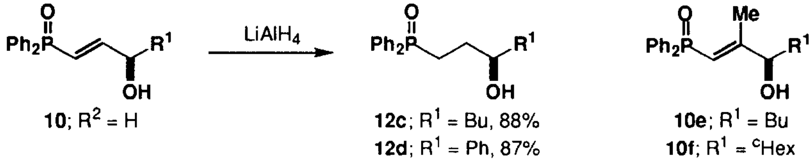


Table 1: Synthesis of vinyl phosphine oxides **10**

Entry	Starting material	R^1	R^2	Product	ee (%)	*E*:*Z*	Yield (%)
1	*syn*-**8a**	Me	H	**10a**	46	>95:5	58
2	*syn*-**8b**	Et	H	**10b**	76	>95:5	65
3	*anti*-**8b**	Et	H	**10b**	22	>95:5	78
4	*syn*-**8c**	Bu	H	**10c**	76	>95:5	99
5	*syn*-**8d**	Ph	H	**10d**	86	>95:5	89
6	*syn*-**8e**	Bu	Me	**10e**	74	83:17	81
7	*syn*-**8f**	cyclo-Hex	Me	**10f**	84	88:12	91

Treatment of vinyl phosphine oxides **10c-d** with lithium aluminium hydride gave alcohols **12** in good yield. Optically active γ-hydroxy phosphine oxides like **12** have been synthesised before by classical resolution and are useful intermediates in the synthesis of *Z* homoallylic alcohols.[15] Unfortunately, reduction of methyl-substituted vinyl phosphine oxides **10e-f** was not very diastereoselective, giving at best 60:40 mixtures of alcohols *anti*- and *syn*-**13**.



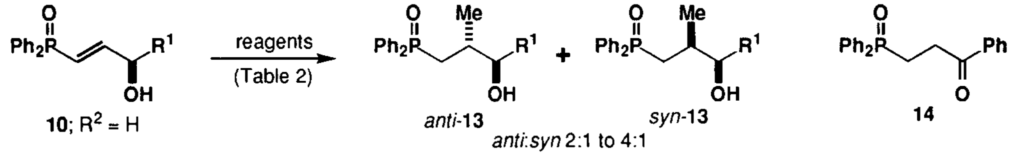


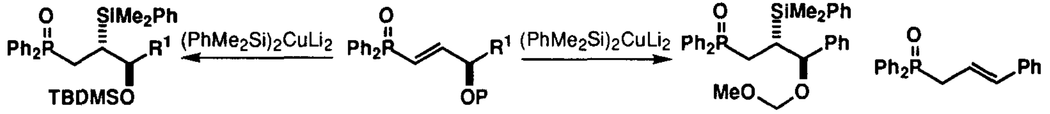
Table 2: Reaction of vinyl phosphine oxides **10** (R^2 = H) with methyl cuprates

Entry	Starting material	R^1	Reagent	Solvent	*anti*:*syn*[a]	Yield (%)
1	**10a**	Me	Me_3CuLi_2	ether	63:37	60[b]
2	**10c**	Bu	Me_3CuLi_2	ether	78:22	41 + 22[c]
3	**10c**	Bu	$Me_2(CN)CuLi_2$	ether	78:22[d]	*e*
4	**10d**	Ph	Me_3CuLi_2	ether	74:26[f]	22 + 10[c]
5	**10d**	Ph	Me_3CuLi_2	THF	*g*	–

[a] By 400 MHz ^1H NMR. [b] Isolated as a 63:37 mixture of *anti*- and *syn*-**13a**. [c] Yields of pure *anti* and *syn* isomers. [d] 19:63:18 mixture of starting material and *anti*- and *syn*-**13c**. [e] Not isolated. [f] 30:52:18 mixture of **14**, *anti*- and *syn*-**13d**. [g] Mainly **14** by ^1H NMR.

An alternative approach to alcohols **13** was to add a methyl group to vinyl phosphine oxides **10** (R^2 = H). Reaction of phosphine oxides **10** with methyl cuprate reagents was moderately *anti* selective,[16] giving alcohols **13** (which were separable by HPLC) in reasonable yield (entries 1-4, table 2).[18] Unlike the reactions of similar sulfones,[19] the reaction of **10c** was equally diastereoselective with Me_3CuLi_2 and $Me_2(CN)CuLi_2$ (compare entries 2 and 3). Unfortunately, phenyl-substituted **10d** rearranged under the rather basic reaction conditions to give achiral ketone **14** (entries 4-5, table 2).[20]

Next, we turned our attention to the reactions of Fleming's silyl cuprate[21] with vinyl phosphine oxides. For example, silyl ethers **15a-b** and MOM acetal **16** reacted with $(PhMe_2Si)_2(CN)CuLi_2$ to give β-silyl phosphine oxides *anti*-**17a-b** and **18** with moderate to excellent stereoselectivity. Treatment of acetal **18** with acidic methanol gave allylic phosphine oxide *E*-**19** in 82% yield:[22] the reliable *anti* stereospecificity of the Peterson elimination[23] confirmed the sense of the stereoselectivity of the addition reaction.



17a; R = Bu, 84%, 70:30
17b; R = Ph, 58%, >95:5

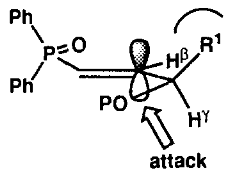
15; P = TBDMS
16; P = CH_2OMe

18; 71%, 88:12

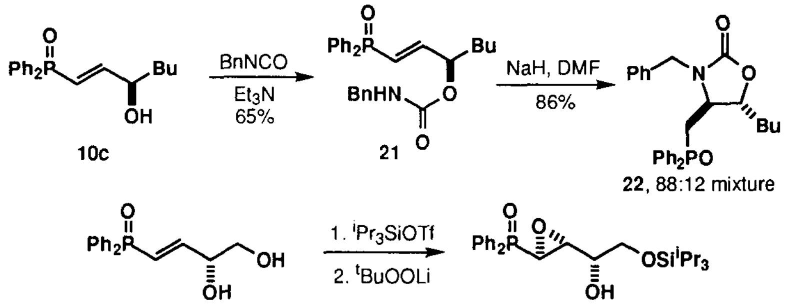
19

The reactions of methyl and silyl cuprates with vinyl phosphine oxides **10**, **15** and **16** were more *anti* selective with larger R^1 substituents.[24] The small coupling constant (3.5-4.7 Hz) between H^β and H^γ suggests that phosphine oxides **10**, **15** and **16** mainly populate the conformation shown in the Figure. We suggest that the reactions are more stereoselective with larger R^1 simply because the top face of **20** is more effectively shielded.

Figure



20 → *anti* product



10c

21

22, 88:12 mixture

23

24, 57:43 mixture

We also looked at the reactions of vinyl phosphine oxides with oxygen and nitrogen nucleophiles. For example, treatment of urethane **21** with sodium hydride triggered the formation of oxazolidinone **22** in excellent yield. Alternatively, diol **23** (synthesised by working up a Sharpless epoxidation with aqueous sodium hydroxide[26]) could be protected and epoxidised with the nucleophilic agent lithium *tert*-butyl hydroperoxide. We have assigned the sense of the stereoselectivity of these reactions by analogy with similar reactions of vinyl sulfones.[27]

In summary, we have shown that optically active vinyl phosphine oxides **10** can be produced by dehydration of diphenylphosphinoyl diols **8** (synthesised by Sharpless asymmetric dihydroxylation). γ-Substituted vinyl phosphine oxides such as **10**, **15** and **16** react cleanly and often diastereoselectively with a range of carbon, hydrogen and heteroatomic nucleophiles. The synthetic value of the products of these nucleophilic additions will be reported in due course.

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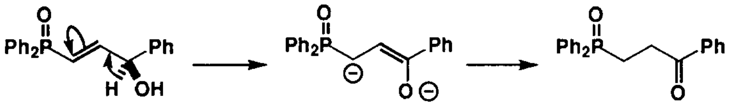
14. Attempted protections of vinyl phosphine oxides (e.g. **10d**) using strongly basic reaction conditions precipitated tautomerisation to the corresponding γ-keto phosphine oxides (e.g. **14**).



10b **14**

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