# Chiral 2-Vinyl-1,3,2-oxazaphospholidin-2-ones: New Dienophiles for Asymmetric Diels–Alder Reactions

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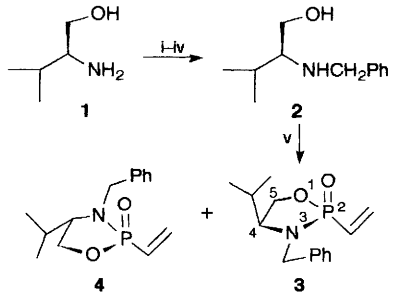
Diels–Alder reactions of chiral dienophiles: (2*R*,4*S*)- and (2*S*,4*S*)-2-vinyl-1,3,2-oxazaphospholidin-2-ones (**3** and **4**) derived from (*S*)-valinol with cyclopentadiene led to mixtures of *endo*- and *exo*-adducts with high diastereofacial selectivity (>90% for **3** and 80 and 88% respectively for **4**); an explanation is proposed based on X-ray crystallographic structures for the dienophile and the derived *endo*-cycloadduct **5**.

Despite the enormous amount of work on vinyl sulphoxides,[1] relatively few studies have been concerned with asymmetric induction reactions involving chiral substrates of the phosphine oxide type.[2] Because high asymmetric induction has been observed in the 1,3-dipolar cycloaddition of chiral vinyl sulphoxides with acyclic nitrones and in Diels–Alder reactions with cyclopentadiene or furan,[3] we have been interested in investigating the Diels–Alder reaction using chiral vinylphosphonates as the dienophiles.[4] We have chosen vinylphospholidines **3** and **4** as our initial substrates.

Treatment of vinylphosphonic dichloride† with 1 equiv. of (*S*)-*N*-benzylvalinol‡ **2** and 9 equiv. $Et_3N$ in toluene at −78 °C for 1 h and at 20 °C for 12 h gave an 82% yield of (2*R*,4*S*)-2-vinyl-1,3,2-oxazaphospholidin-2-one **3**§ {m.p. 94–96 °C, $[\alpha]_D$ −44.2° (*c* 1.25)}¶ and the diastereoisomeric (2*S*,4*S*)-**4** {m.p. 33–34 °C, $[\alpha]_D$ −29.8° (*c* 1.25)} in a *ca.* 1:1 ratio (Scheme 1). Phospholidines **3** and **4** were separated readily by silica gel column chromatography (AcOEt–hexane). The assignment of the relative and absolute configuration of the more polar oxazaphospholidine **3** follows from X-ray crystallographic analysis (Fig. 1; see later). Accordingly, the less polar isomer has to possess the absolute structure **4**.

When **3** was treated with cyclopentadiene (neat, room temp., 3 days), a mixture of *endo*- and *exo*-adducts (*ca.* 10:19) was formed in 96% yield. Two adducts were separated readily by silica gel column chromatography and the optical purity of each adduct was determined by 500 MHz $^1H$ NMR spectroscopy or HPLC (μ-Porasil, n-hexane–1,4-dioxane, 88:12) to



**Scheme 1** *Reagent and conditions*: i, $Bu^tMe_2SiCl$, $Et_3N$, tetrahydrofuran (THF); ii, PhCHO, benzene, $MgSO_4$; iii, $NaBH_4$, MeOH; iv, $Bu^n{}_4NF$, THF; v, $CH_2{=}CHPOCl_2$, $Et_3N$, toluene, initially at −78 °C and then at room temp.

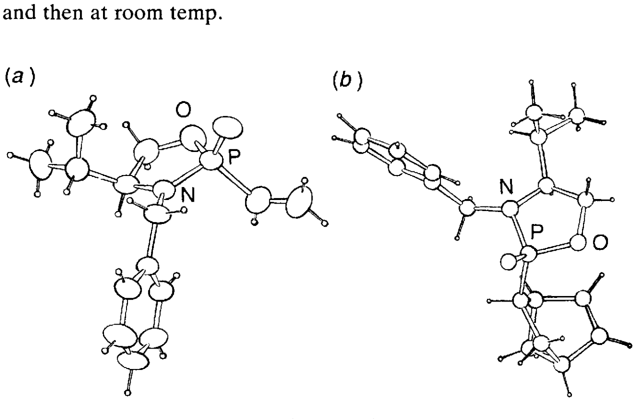


**Fig. 1** ORTEP diagrams of (*a*) (2*R*,4*S*)-vinyl-1,3,2-oxazaphospholidin-2-one **3**; (*b*) the *endo*-adduct **5**

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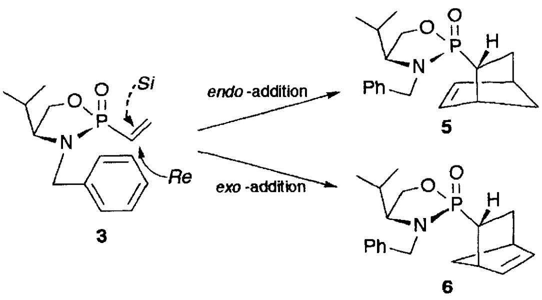
† This compound was prepared *in situ* from 2-chloroethylphosphonic dichloride and $Et_3N$ in toluene (−78 °C to room temp.).

‡ This compound was synthesized by silylation of (*S*)-valinol with $Bu^tMe_2SiCl$, benzylation and desilylation.

§ All enantiomers are depicted with absolute stereochemistry indicated. All new compounds displayed satisfactory $^1H$ NMR spectra (500 MHz) and elemental analyses (for crystalline compounds) or high-resolution mass spectra (for oil).

¶ Specific rotations were determined in $CHCl_3$ at room temperature.



Scheme 2 *Si*-face attack

be >90% for both adducts. Because of the highly crystalline nature of the adducts, the diastereoisomeric purity of each adduct {*endo*: m.p. 91–93 °C, $[\alpha]_D$ +28.0° (*c* 0.32) and *exo*: m.p. 125–126 °C, $[\alpha]_D$ −17.0° (*c* 0.18)} can be conveniently raised to >99% by simple recrystallization from hexane–diethyl ether.

The absolute structure of the *endo*-adduct **5** thus obtained was determined by X-ray crystallographic analysis shown in Fig. 1.‖ This shows that cyclopentadiene approaches from *Si*-face of **3** with high preference (Scheme 2).

In order to clarify the origin of this diastereoselectivity,[5,6] the X-ray crystallographic analysis of **3** was undertaken and revealed two interesting structural features: (*i*) the carbon–carbon double bond and the P=O group are *syn* planar (s-*cis*) and (*ii*) the oxazaphospholidine ring is almost flat and its nitrogen atom is in sp$^2$ hybridization.‖ It is obvious that the *Re*-face is shielded by the benzyl group. This conformation (Fig. 1) of the isomer **3**, having the phosphonyl oxygen *anti* to the phenyl group though *cis* to the isopropyl group, might also explain why **3** is more polar than **4**. High diastereofacial selectivity was also observed in the Diels–Alder reaction of (2*S*,4*S*)-**4** with cyclopentadiene to give two adducts (*endo*/*exo* = 0.67, diastereoisomeric excess 80% for *endo*- and 88% for *exo*-adducts).

This remarkable Diels–Alder reaction of the vinyl phospholidine **3** with cyclopentadiene (without addition of chelating agents) complements and advances the related chemistry explored with vinyl sulphoxides.[1] The potential utility of these reactions in natural product synthesis is clear, since the resulting phospholidine derivatives can be manipulated by the Horner–Emmons reaction. A wide range of application for asymmetric synthesis seems to be possible and is now being intensively pursued in this laboratory.

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‖ *Crystal data* for **5**: $C_{19}H_{26}NO_2P$, $M$ = 331.40, monoclinic, space group $P2_1$, $a$ = 16.669(1), $b$ = 17.590(2), $c$ = 6.144(1) Å, $\beta$ = 97.89(1)°, $U$ = 1784.4 Å$^3$, $D_c$ ($Z$ = 4) = 1.234 g cm$^{-3}$, $F(000)$ = 712, $\mu$ = 14.22 cm$^{-1}$, $\lambda$(Cu-K$\alpha$) = 1.5418 Å. Reflections were measured with an Enraf-Nonius CAD-4 four-circle diffractometer. The structure was solved by direct methods (MULTAN) and refined by full-matrix least-squares analysis to $R$ = 0.065 for 3068 $F$ [$I$ >2$\sigma$($I$)]. The positional parameters of hydrogen atoms were calculated stereochemically and added in the calculation of structure factors. All non-hydrogen atoms were refined anisotropically.

*Crystal data* for **3**: $C_{14}H_{20}NO_2P$, $M$ = 265.30, orthorhombic, space group $P2_12_12_1$, $a$ = 8.3324(8), $b$ = 9.0550(4), $c$ = 18.951(1) Å, $U$ = 1429.8 Å$^3$, $D_c$ (Z = 4) = 1.232 g cm$^{-3}$, $F(000)$ = 568, $\mu$ = 16.56 cm$^{-1}$, $\lambda$(Cu-K$\alpha$) = 1.5418 Å. The structure was solved and refined as for **5**; $R$ = 0.057 for 1680 $F$ [$I$ >2$\sigma$($I$)].

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.