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Synthesis and Diels-Alder Reactivity of Chiral 2-(Alk-1-enyl)-1,3,2-diazaphospholidine 2-oxides

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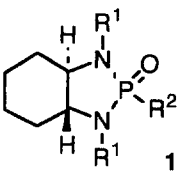
Abstract: 2-(Alk-1-enyl)-1,3,2-diazaphospholidine 2-oxides **4**, containing the *trans-N,N'*-dibenzylcyclohexane-1,2-diamine chiral auxiliary, may be prepared by palladium(0)-mediated coupling of the phosphorous acid derivative **3** with alkenyl halides. The X-ray crystal structure of the prop-1-enyl compound **4b** has been determined. Some stereoselectivity has been observed in Diels-Alder reactions of the compounds **4**. For example, the substituted (*E*)-acrylate ester **4c** acts as a dienophile towards cyclopentadiene in hot toluene to give the four possible diastereoisomeric adducts in a 62:17:15:6 molar ratio; it has been shown that the structure of the main product **5c** is consistent with attack of the diene on the less hindered face of the dienophile and that the methoxycarbonyl, rather than the diazaphospholidinyl group, has the *endo*- orientation. The dienyl-1,3,2-diazaphospholidine 2-oxide **4f** acts as a diene in the reaction with 4-phenyl-1,2,4-triazoline-3,5-dione to give a 70:30 mixture of adducts.

Keywords: *Phosphorus heterocycles; Palladium and compounds; Asymmetric reactions; Diels-Alder reactions.*

Phosphonic acids, $RP(O)(OH)_2$ and their derivatives are of growing importance as targets for synthesis, largely because of their ability to mimic biologically significant functional groups such as phosphate esters, carboxylic acids and the transition states for ester and amide hydrolysis.[1] Established methods for the enantioselective synthesis of phosphonic acid derivatives commonly involve the use either of a phosphorus nucleophile or of a carbanion nucleophile which is stabilised by an adjacent phosphorus atom. The reactions of 1,3,2-diazaphospholidine-2-oxides (**1**; R^2 = H or alkyl) derived from *trans-N,N'*-dialkylcyclohexane-1,2-diamines are particularly notable;[2] dialkyl phosphites may also act as *P*-nucleophiles in asymmetric reactions catalysed by chiral Lewis acids.[3]



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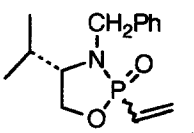

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We have begun to explore the chemistry of chiral, unsaturated phosphonic acid derivatives **4** in which the C=C bond of an alkenyl group is attached directly to phosphorus. These systems offer the possibility of performing asymmetric cycloaddition and conjugate addition reactions on the alkenyl group. Because the heterocycles are derived from the C_2-symmetric *trans*-cyclohexane-1,2-diamine chiral auxiliary, the phosphorus atom is not stereogenic: thus we avoid the difficulties encountered by Katagiri *et al.*, who obtained diastereoisomeric mixtures when preparing the 2-vinyl-1,3,2-oxazaphospholidine 2-oxides **2**.[4]

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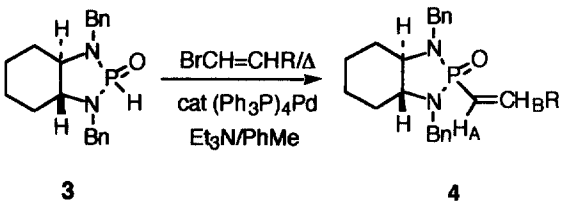
We selected the readily available[2c] *N,N'*-dibenzyldiazaphospholidine derivative (±)-**3** as our starting material.[5] The palladium(0)-catalysed coupling of dialkyl phosphite esters with aryl and vinyl halides is known[6] and was recently proposed as a possible method for the vinylation of diazaphospholidines.[2c] We now confirm that it is a useful method of preparing our desired *P*-alkenyl compounds **4** (Table 1).[7] A control experiment, in which the preparation of **4c** was attempted in the absence of the $Pd(PPh_3)_4$, did not yield any of the coupled product and led to the recovery of most of the starting material **3**.



3 **4**

Scheme 1

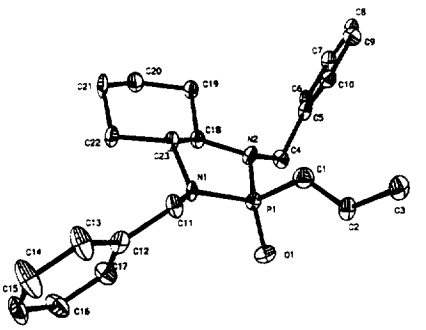


Fig 1. X-ray crystal structure of **4b** (R = Me)

Compound (*note a*)	R	Yield from **3**	mp/°C	δ_P (note *b*)	$J_{HA,P}$ /Hz	$J_{HB,P}$ /Hz	$J_{HA,HB}$ /Hz
4a	(*E*)-Ph	77%	155-158	31.0	19	(*note c*)	16
4b	(*E*)-Me (note *d*)	41%	136-138	30.5	22	20	16
4c	(*E*)-CO_2Me	90%	162-164	26.9	19	19	17
4d	(*Z*)-CO_2Me	76%	147-150	25.1	17	42	14
4e	(*Z*)-SO_2Tol	23%	204-206	20.7	10	39	13
4f	(*E,E*)-CH=CHPh	33%	212-214	31.0	20	(*note c*)	16

Table 1. 2-Alkenyl-1,3,2-diazaphospholidine-2-oxides prepared according to Scheme 1.
Notes: [a]Satisfactory combustion microanalyses (CHN ± 0.3%) and high resolution mass spectra have been obtained for compounds **4a-f**. [b]$CDCl_3$ solvent, δ_P relative to 85% H_3PO_4. [c]*J* not determined as ^1H NMR signals overlap. [d]The 1-bromopropene was a commercial (Lancaster) mixture of the (*E*)- and (*Z*)- isomers and gave a mixture of (*E*)- and (*Z*)- products, but the yield quoted refers to recrystallised, pure (*E*)- product.

An X-ray crystal structure of the *P*-prop-1-enyl compound (±)-**4b** was determined.[8] The asymmetric unit contains two crystallographically independent, but conformationally similar molecules, one of which is illustrated in Fig 1. The nitrogen atoms were found to have a flattened pyramidal geometry with Σ(bond angles at N) in the range 347-349°. The *N*-benzyl groups adopt pseudoequatorial orientations, as has been observed in the *P*-alkyl compounds of Hanessian.[2a] The O-P-C=C torsion angle is close to 0°, as in the crystal structure of (2*R*, 4*S*)-**2**;[4] this contrasts with the 180° O-P-C-C torsion angle proposed by Hanessian to account for stereoselectivity in nucleophilic reactions of anions derived from **1** (R^2 = *n*-alkyl).

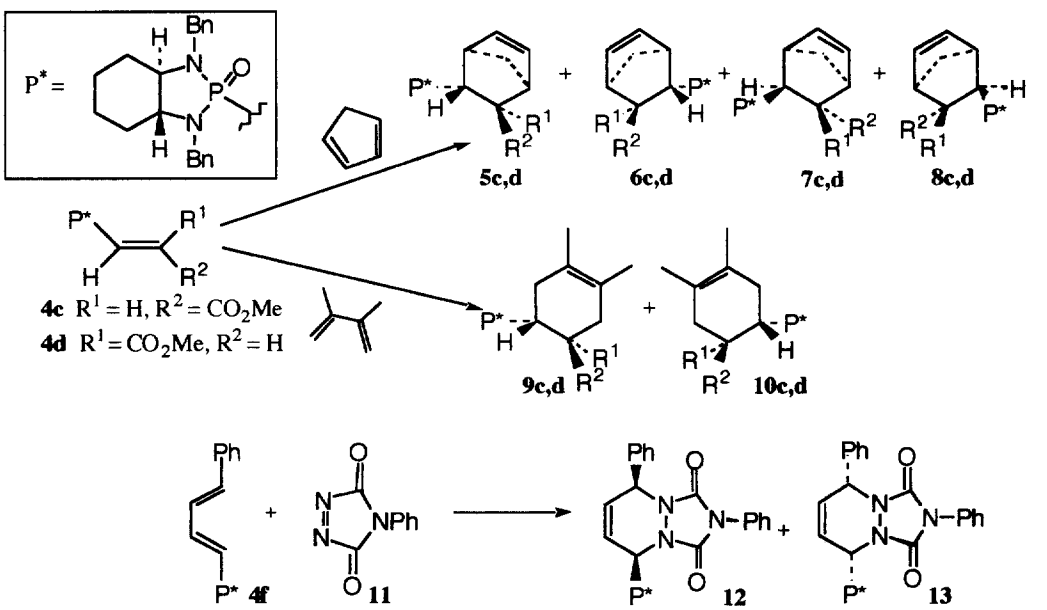
The *P*-styryl and prop-1-enyl compounds **4a** and **4b** were unreactive as dienophiles and were recovered unchanged after heating for several days at 110 °C with excess cyclopentadiene in toluene. However, the phosphorus-substituted acrylates **4c** and **4d** underwent Diels-Alder reactions with both

cyclopentadiene and 2,3-dimethylbuta-1,3-diene to form mixtures of diastereoisomeric cycloadducts as indicated in Table 2 and Scheme 2.

Entry	Diene (equivalents)	Dienophile	Reaction conditions	% Conversion of dienophile into adducts	δ_P of adducts (% of total product)[a]
1	Cyclopentadiene (10)	**4c**	PhMe, 100 °C, sealed tube, 3 d	100[b]	43.6 (62), 43.4 (15), 43.1 (6), 42.6 (17)
2	Cyclopentadiene (10)	**4d**	PhMe, 100 °C, sealed tube, 3 d	87[b]	42.5 (32), 42.0 (29), 41.2 (20), 40.6 (19)
3	2,3-Dimethylbuta-1,3-diene (30)	**4c**	PhMe, 110 °C, sealed tube, 7 d	100[a,b]	42.9 (58), 42.9 (42) *(notes b,c)*
4	2,3-Dimethylbuta-1,3-diene (30)	**4d**	PhMe, 110 °C, sealed tube, 7 d	44[a,b]	42.4 (63), 42.0 (37)
5	**4f** (0.8)	**11**	CH_2Cl_2, -40 to +20 °C over 2 h	>90[a,b]	30.3 (70), 29.7 (30)

Table 2. Diels-Alder reactions of alkenyl and dienyl diazaphospholidines.

Notes: [a] Estimated by integration of the 101 MHz ^{31}P NMR spectrum of the crude product. [b] Estimated by integration of the 250 MHz ^1H NMR spectrum of the crude product. [c] The two diastereoisomeric products were distinguished by their ^1H NMR spectra, *e.g.* CO_2Me at δ3.72 (major product) and 3.71 (minor product).



Scheme 2

In each case the observed number of diastereoisomeric products was consistent with reaction having occurred at both faces of the alkenyldiazaphospholidine C=C bond. For adducts derived from cyclopentadiene the phosphorus heterocycle could adopt either an *exo* or an *endo* orientation with respect to the norbornene nucleus. The major diastereoisomer from the reaction of the (*E*)-acrylate **4c** with cyclopentadiene (Table 2, entry 1) was isolated by flash chromatography [CH_2Cl_2 to CH_2Cl_2-Et_2O (3:1); gradient elution]. NMR coupling constants indicated that the CO_2Me group had an *endo*- orientation, whereas the phosphorus-containing substituent was *exo*- and so the structure of the main product must be

either **5c** or **6c**. NOESY studies (Fig 2) supported the structure **5c**. The preferential formation of this product is consistent with approach of the diene from the less hindered face of the C=C bond in the conformer of **4c** having a 0° O-P-C=C torsion angle (Fig. 3).

The (*Z*)-dienophile **4d** showed lower stereoselectivity in its reaction with cyclopentadiene than did **4c**. Similar observations concerning *exo/endo* preferences have been made for the reactions between cyclopentadiene and achiral (*E*)- and (*Z*)- β-phosphonoacrylate esters;[9] in these systems the electronic *endo*-directing effect of the methoxycarbonyl group and the steric effect of the phosphorus-based groups act in opposition. The dienyldiazaphospholidine **4f** was able to act as a Diels-Alder diene and upon treatment with 4-phenyl-1,2,4-triazoline-3,5-dione **11** readily yielded a 70:30 mixture of the two possible diastereoisomeric adducts.

Thus we have developed a route to new unsaturated phosphonic acid derivatives in which the two faces of the C=C bond are diastereotopic to one another. We are currently investigating the variation in diastereoselectivity of addition reactions at the C=C double bond as the *N*-substituents are changed and we are extending these studies to include conjugate addition reactions of phosphorus-substituted acrylates.

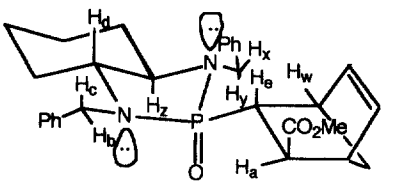


Fig 2. Structure of major cycloadduct **5c** by 2D NMR. H_e and H_w are not *J* -coupled. NOESY correlations are observed between H_a-H_b, H_c-H_d, H_d-H_e, H_w-H_x and H_y-H_z.

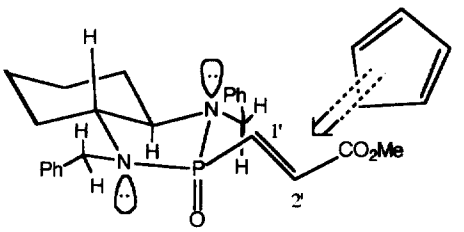


Fig 3. Attack on the less hindered (1'-*Re*, 2'-*Si*) face of the C=C of **4c**, thus minimising repulsions from the *N*-benzyl groups.

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1. See *e.g.* Bartlett, P. A.; Giangiordano, M. A. *J. Org. Chem.* **1996**, *61*, 3433; DeClercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. *Nature* **1986**, *323*, 464; Bandini, E.; Martelli, G.; Spunta, G.; Panunzio, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2127 and references therein.
2. See *e.g.* (a) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837; (b) Bennani, Y. L.; Hanessian, S. *Chem Rev.* **1997**, *97*, 3161; (c) De la Cruz, A.; Koeller, K. J.; Rath, N. P.; Spilling, C. D.; Vasconcelos, I. C. F. *Tetrahedron* **1998**, *54*, 10513 and references therein.
3. See *e.g.* Groaning, M.D.; Rowe, B.J.; Spilling, C.D. *Tetrahdron Lett.* **1998**, *39*, 5485 and references therein.
4. Katagiri, N.; Yamamoto, M.; Iwaoka, T.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1429.
5. All diazaphospholidines prepared by us and referred to in this Letter are racemic; for clarity only the (*R,R*)-cyclohexane-1,2-diamine derivatives are shown. However, both enantiomers of the diamine are available commercially.
6. Hirao, T.; Masunaga, T; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
7. Typical procedure for Pd-mediated coupling: The 1,3,2-diazaphospholidine 2-oxide **3** (1 mmol) was suspended in PhMe (10 ml). β-Bromostyrene (1.5 mmol), Et_3N (1.5 mmol) and $(Ph_3P)_4Pd$ (0.05 mmol) were added and the mixture was stirred under N_2 at 80 °C for 20 h. The cooled reaction mixture was filtered through anhydrous $MgSO_4$ and the solvent was evaporated. Flash chromatography [CH_2Cl_2-Et_2O (9:1)], then recrystallisation from CH_2Cl_2-Et_2O gave **4a** (77 %).
8. Atomic co-ordinates, thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
9. Öhler, E.; Haslinger, E.; Zbiral, E. *Chem. Ber.* **1982**, *115*, 1028.