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# AMINE-DIRECTED LITHIATION IN ALIPHATIC ORGANOPHOSPHORUS SYSTEMS. AN APPROACH TO α-MONOALKYLATION OF α,ß-UNSATURATED PHOSPHINE OXIDES [1]

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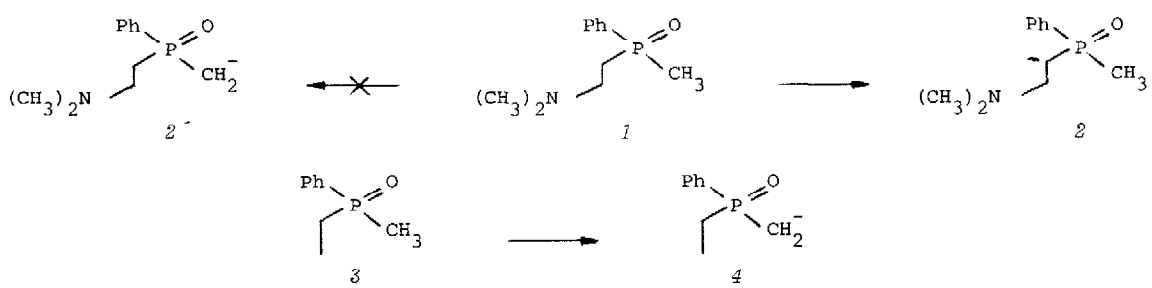
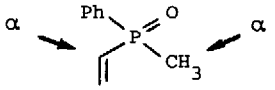
*Abstract:* Novel optically active α,ß-unsaturated phosphine oxides are prepared in one pot via regioselective alkylation of amine protected homochiral vinyl phosphine oxides.

The concept of using heteroatoms as directing elements in selective lithiation reactions has found widespread application in contemporary synthetic chemistry.[2] We wish to demonstrate here that control of this type can also be exercised in simple aliphatic organophosphorus systems. We have found that deprotonation of (ß-aminoethyl)methylphenylphosphine oxide *1* by n-butyllithium or lithium diisopropylamide leads to the formation of the carbanion *2* rather than of the expected carbanion *2'*.[3] To compare, a related oxide *3* which lacks the amine director gives carbanion *4* exclusively.[4]

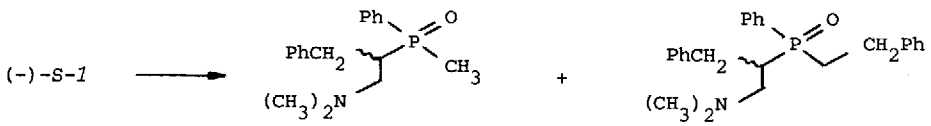



In fact, the prime objective of our study was to explore the possibility of direct alkylative elaboration of the homochiral methylphenylvinylphosphine oxide (-)-S-*5*.[5] It was our desire to introduce carbon electrophiles in either of its two α positions,[6] for we had envisioned that the achievement of this goal would provide an expedient access to many novel virtually homochiral α,ß-unsaturated phosphine oxides of known configuration.[7]



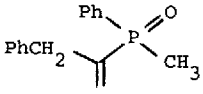
(-)-S-*5*

The use of the homochiral (-)-S-*1*[8] as a vinyl protected equivalent of (-)-S-*5* suggested itself after all the attempts to directly metalate (-)-S-*5* without polymerizing it, failed. Thus, the treatment of oxide (-)-*1* (1.5 mmol in tetrahydrofuran) with 1.1 equivalent of n-butyllithium (-70°C, 2h), followed by quenching with benzyl bromide (1.1 equivalent, -70°C → room temperature), led to the formation of ca. 1.2:1 mixture of two diastereomeric monoalkylated oxides *6*, along with some dialkylated products *7* in 56 and 24% yield, respectively, as assayed by $^{31}P$ NMR.



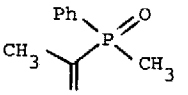
*6* *7*

The proof for structures *6* and *7* came from examination of the isolated compounds itself,[9] and for *6*, also from its conversion to the desired α,ß-unsaturated phosphine oxide (+)-*8*, via sequential quaternization-elimination reactions (1-$CH_3I$ in THF; 2-aqueous $Na_2CO_3$ in THF; 79%).[10] Apparently, the amine controls effectively the site of the first alkylation only.



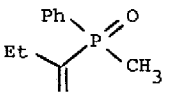
(+)-*8* (41%)

$[\alpha]_{589}=+6^{\circ}(CHCl_3)$
$\delta^{31}P = 31.5 (CHCl_3)$



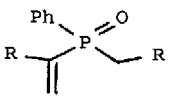
(-)-*9* (42%)

$[\alpha]_{589}=-18.9^{\circ}(CHCl_3)$
$\delta^{31}P = 31.8 (CHCl_3)$



(-)-*10* (38%)

$[\alpha]_{589}=-1.5^{\circ}(CHCl_3)$
$\delta^{31}P = 31.6 (CHCl_3)$

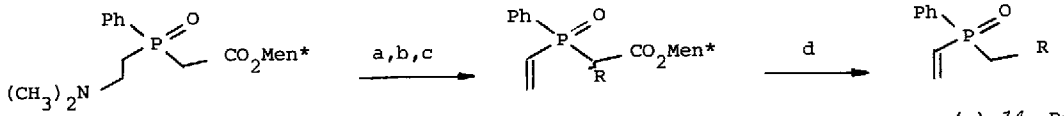


*11*

R = $CH_3$, Et

Analogous syntheses carried out in one pot, i.e., without the isolation of intermediates of type *6* and *7*, and utilizing methyl iodide and ethyl iodide as alkylating agents, gave equally satisfactory results and furnished two other α-monoalkylated optically active α,ß-unsaturated phosphine oxides *9* and *10*, respectively, in useful overall (isolated) yields.[10,11] Since the applied deprotonation[12] and quaternization-elimination[8] conditions were demonstrated not to affect the chirality at phosphorus, the high optical purity of the synthesized oxides could reasonably be assumed. The observation of only single pattern of lines in the $^1H$ NMR (300 MHz) spectra of *9* and *10* recorded in the presence of 1 equivalent of (R)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine *12* used as a chiral shift reagent,[13] suggests similar conclusion.[14]

Thus, it appears, that the presented synthetic protocol constitutes a practical, albeit not fully optimized yet, solution to the problem of α-monoalkylation of vinyl phosphine oxides. In addition, to accomplish sole α'-monoalkylation of (-)-*5*, a complementary procedure starting from readily available amino phosphine oxide (-)-R-*13*[8,15] was developed and was typified by the synthesis of optically active oxides (-)-*14* and (-)-*15* in 47.2 and 54.6% overall yields, respectively.[10]




Men* = L-menthyl

(-)-R-*13*

a - NaH, THF, room temp.

b - RX, THF, 0°C

c - $CH_3I$, aqueous $Na_2CO_3$, THF, 60°C

d - $LiCl/H_2O$, DMSO, 180°C, 4h

(-)-*14*: R=$CH_3$

$[\alpha]_{589}$=-77.3°(c,4.5,$CHCl_3$)

$\delta^{31}P$ =30.3 ($CHCl_3$)

(-)-*15*: R=$CH_2Ph$

$[\alpha]_{589}$=-58.6°(c,3.7,$CHCl_3$)

$\delta^{31}P$ =28.4 ($CHCl_3$)

*Acknowledgement.*

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4. In checking experiment, deprotonation of *3* with n-butyllithium at -70°C, followed by quenching with benzyl bromide gave the known ethylphenyl(2-phenylethyl)phosphine oxide[5] in 89% isolated yield (quantitative by $^{31}P$ NMR).

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See also references 1,5 and 8.

8. Pietrusiewicz, K.M.; Zablocka, M. *Tetrahedron Lett.* 1988, *29*, 1991.

9. *6* (~1.2:1 mixture of diastereomers): mp 65-72°C, $[\alpha]_{589}$=+30.1° (c,3.6,$CHCl_3$). MS, m/e 301 ($M^+$), 161 (base). $^1$H NMR ($CDCl_3$) δ: P-$CH_3$: 1.72 (d,J=13.3 Hz,major) and 1.77 (d,J=13.1 Hz, minor); N$(CH_3)_2$: 2.0 (s,major) and 2.08 (s,minor); 2.0-3.45 (mm,5H), 6.9-778 (mm,10H). $^{13}$C NMR ($CDCl_3$) δ (aliphatic region): P-$CH_3$ 16.05 (d,J=67.4 Hz,minor) and 16.45 (d,J=67.9 Hz, major); Ph-$CH_2$ 32.38 (major) and 32.73 (minor); P-CH 40.38 (d,J=69.4 Hz,minor) and 40.82 (d, J=69.3 Hz,major); N$(CH_3)_2$ 45.19; N-$CH_2$ 57.59 (minor) and 58.35 (major). $^{31}$P NMR ($CHCl_3$) δ 42.0.
*7* (~2.5:1) mixture of diastereometers: mp 110-112°C, $[\alpha]_{589}$=+1.7° (c,1.8,$CHCl_3$). MS, m/e 391 ($M^+$), 161 (base). $^1$H NMR ($CDCl_3$) δ (no P-$CH_3$ hydrogens) N$(CH_3)_2$: 2.03 (s,major) and 2.13 (s, minor); 2.08-3.55 (mm,9H), 6.99-7.83 (mm,15H). $^{13}$C NMR ($CDCl_3$) δ (aliphatic region) Ph-$CH_2$ 27.64 (major) and 29.71 (minor): P-$CH_2$ 30.93 (d,J=63.9 Hz,minor) and 31.27 (d,J=64.3 Hz, major); Ph-$CH_2$ 32.29 (major) and 32.92 (minor); P-CH 39.74 (d,J=65.4 Hz); N$(CH_3)_2$ 45.3; N-$CH_2$ 57.4 (minor) and 58.4 (major). $^{31}$P NMR ($CHCl_3$) δ 44.3.

10. All the products were adequately characterized by $^1$H, $^{13}$C and $^{31}$P NMR and MS.

11. In these syntheses, small quantities of the corresponding α,α'-dialkylated products *11* were also isolated.[10]

12. Treatment of a THF solution of (-)-*S*-*1* [211 mg, 1 mmol, $[\alpha]_{589}$=-24.7°(c,2.6,$CHCl_3$)] with 0.75 mL of 1.3 N solution of n-BuLi in hexane at -70°C, followed by quenching with water (-70°C → r.t.), resulted in the isolation of (-)-S-*1* unchanged [92%, $[\alpha]_{589}$=-24.8°(c,2.1, $CHCl_3$)].

13. Dunach, E.; Kagan. H.B. *Tetrahedron Lett.* 1985, *26*, 2649.

14. In a reference spectrum recorded with our instrument the P-$CH_3$ doublet (δ=1.63, $J_{PH}$=12.2 Hz) of racemic *tert*-butylmethylphenylphosphine oxide was cleanly resolved by (-)-R-*12* into two 1:1 doublets separated by 5.7 Hz, in full agreement with the original report.[13]

15. Direct alkylation of unprotected (-)-$S_P$-[(menthoxycarbonyl)methyl]phenylvinylphosphine oxide[5] with the assistance of NaH or DBU/LiCl[16] proved again unsuccessful.

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