*Tetrahedron: Asymmetry* Vol. 4, No. 10, pp. 2143-2146, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

# Synthesis of Enantiomerically Pure Styryl and Dienyl Phosphine Oxides *via* Pd-catalyzed Heck Coupling Reaction[1]

**K. Michał Pietrusiewicz*, Maciej Kuźnikowski and Marek Koprowski**

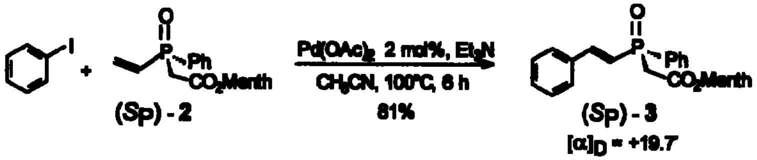
*The Polish Academy of Science, Centre of Molecular and Macromolecular Studies,*
*ul.Sienkiewicza 112, 90-363 Łódź, Poland*

(*Received in UK 25 July* 1993)

**Abstract:** (S)-Methylphenylvinylphosphine oxide (1) undergoes facile Pd-catalyzed coupling with functionalized aryl and vinyl halides to provide new enantiomerically pure styryl and dienyl phosphine oxides including also the corresponding symmetrical and nonsymmetrical bisphosphine derivatives.

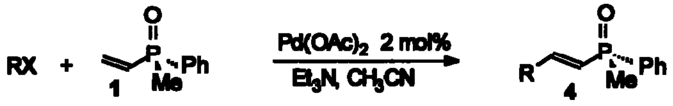
Since the pioneering reports in 1968 by Horner[2] and by Knowles[3] on chiral modification of the Wilkinson's hydrogenation catalyst [$RhCl(PPh_3)_3$], the use of chiral phosphine ligands to induce asymmetry in catalytic processes under homogeneous conditions has become an indispensable tool in contemporary synthetic laboratory and industrial practice.[4] Functionalized nonracemic P-chiral phosphine derivatives which could be easily elaborated to the desired ligand structures are however difficult to obtain and new synthetic methodologies in this area are in constant demand.[5] Recently, it has been demonstrated that enantiomeric vinyl phosphine oxides can be successfully used as synthons for the preparation of novel P-chiral ligands[6] as well as as the reagents for effecting P → C chirality transfer in stoichiometric addition and cycloaddition processes.[7] Of similar synthetic potential would be analogous enantiomeric vinyl phosphorus compounds bearing terminal carbon substituents or having extended unsaturation chain, but to date these are virtually unknown.[8] In this communication we wish to demonstrate that a range of enantiomeric styryl and dienyl phosphine oxides can be conveniently prepared from a single enantiomerically pure (-)-(*S*)-methylphenylvinylphosphine oxide (1)[9] and various aryl and vinyl halides by employment of the Pd-catalyzed Heck coupling reaction.[10]

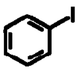
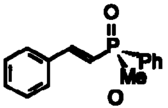
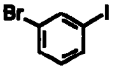
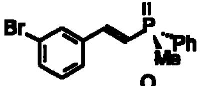
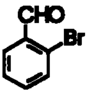
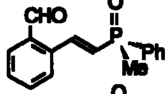
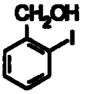
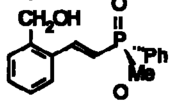
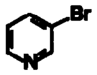
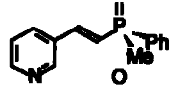
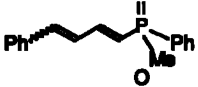
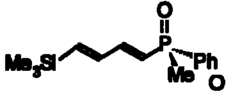
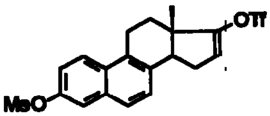
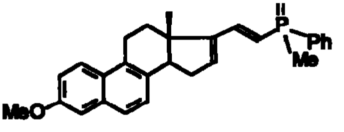
Heteroatom substituted olefins find common use as acceptors in the Heck reaction, but it is also frequently observed that the adjacent heteroatom affects markedly the overall reaction course as well as the ultimate product structure.[11] However, we have found that under typical Heck conditions[10] a model P-chiral vinyl phosphine oxide (*S*p)-2[9] reacted with iodobenzene readily and cleanly to afford the expected coupling



product 3 in 81% isolated yield. Due to the presence of the menthyl chiral auxiliary in the substrate structure this experiment served us also to establish that the starting configurational homogeneity of the phosphorus stereogenic center of 2 was fully preserved under the studied conditions as the preserved diastereomeric purity of 3 was confirmed. It was therefore possible at the outset to assume that the analogous reactions utilizing enantiomerically pure (*S*)-1 were most likely to lead similarly to enantiomerically pure coupling products of the unchanged configuration at phosphorus.[12] A series of such reactions was performed. The overall synthetic transformation and the resulted styryl and dienyl phosphine oxides are listed in the Table.[13]

**Table:**



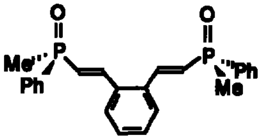
| RX | Reaction temp, time (added phosphine) | 4 | Isolated yield, %[a] | $\delta_P$ ppm[b] | $[\alpha]_D$[c] |
|---|---|---|---|---|---|
|  | 100°C, 22 h |  | 91 | 27.6 | +19.9 |
|  | 100°C, 22 h |  | 78 | 27.2 | +33.1 |
|  | 100°C, 2 h<br>(4% *o*-tol₃P) |  | 73 | 28.3 | +21.2 |
|  | 100°C, 16 h |  | 92 | 29.0 | -7.8 |
|  | 100°C, 11 h<br>(4% *o*-tol₃P) |  | 67 | 28.3 | +6.5' |
|  | 100°C, 52 h<br>(4% Ph₃P) |  | 72[d] | 27.3 | -[e] |
|  | 100°C, 24 h<br>(4% *o*-tol₃P) |  | 31 | 27.6 | -54.5 |
|  | 100°C, 82 h<br>(4% *o*-tol₃P)<br>*n*-Bu₄N⁺Br⁻ |  | 36[e,f] | 28.5[g] | -[h] |

[a] Not optimized [b] In $CH_3Cl$; relative to $H_3PO_4$. [c] In $CH_3Cl$ , c 0.6 + 2. [d] Mixture of E and Z isomers in a 65:35 ratio corresponding exactly to the isomeric composition of the starting β-bromostyrene. [e] Racemic 1 was used in this experiment. [f] 1:1 mixture of the two P-epimers. [g] Only one line observed. [h] P-epimers not separated.

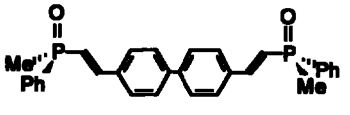
As can be seen from the collected examples several unprotected organic functions could be readily introduced into the phosphine oxide structure in this way. These included also a chiral ketone residue (last entry), which can potentially be used for resolution of the P-center in the products derived from racemic vinyl phosphine oxides.

Multiple coupling reactions[14] were also studied to test the possibility of placing two (or more) chiral vinyl phosphinyl residues on one aromatic core in either proximal or distal positions. These were found similarly efficient (Chart I) although, in the former case, they required somewhat modified conditions [2% $Pd(OAc)_2$, 8% $Ph_3P$, $Et_3N$, DMF, 135°C, 36 h] as well as the use of the corresponding aryl dibromides instead of the diiodides. In addition, by taking advantage of the known difference in reactivity of aryl iodides vs. aryl bromides in the absence of the phosphine cocatalyst in such reactions[15] (cf. second entry in the Table) analogous disubstituted benzene derivatives bearing two different chiral phosphinyl moieties could be obtained. This is exemplified by the syntheses of **8** and **9**, in which racemic benzylphenylvinylphosphine oxide and *o*-anisylphenylvinylphosphine oxide were allowed to react in the presence of $Ph_3P$ (under otherwise typical conditions) with the *m*-bromostyryl phosphine oxide **4** derived earlier chemoselectively from 3-bromoiodobenzene to afford pairs of diastereomeric dioxides **8**(~1:1)[16] and **9**(~1:1),[16] respectively, in which one phosphorus stereogenic center can serve to resolve another.[17]

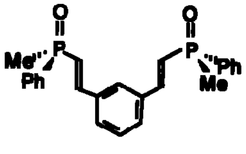
**Chart I**



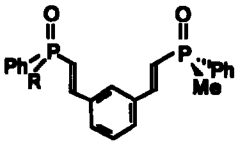
**5** 65%, $\delta_P$ 27.3
$[\alpha] = -12$ (c1.0, $CHCl_3$)



**6** 85%, $\delta_P$ 27.9
$[\alpha] = +117$ (c 2.4, $CHCl_3$)



**7** 92%, $\delta_P$ 27.7
$[\alpha] = +53.8$ (c 2.3, $CHCl_3$)



**8** R=$CH_2Ph$, 44%, $\delta_P$ 27.4, 27.5
**9** R=o-MeOPh, 48%, $\delta_P$ 23.0, 28.5

Use of enantiomerically pure compounds **4**-**9** as precursors to novel ligands and as chiral reagents is underway.

**Acknowledgment.** This project was financially supported by the State Committee on Scientific Research, Poland, Grant No. 2.13079101. We are also very grateful to Prof. Sandro Cacchi, Rome, for a sample of estrone triflate, and to Prof. Vito Fiandanese, Bari, for a gift of (2-bromovinyl)trimethylsilane.

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12. This assumption has also been unambiguously verified by chiral HPLC measurements on two of the products **4**, i.e., methylphenylstyrylphosphine oxide and methylphenyl(*o*-hydroxymethylstyryl)phosphine oxide. We thank Prof. F. Gasparrini, Rome, for these measurements.
13. All new compounds were characterized by $^1$H, $^{13}$C and $^{31}$P NMR and elemental analysis and/or high resolution MS.
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16. Ratio estimated from $^1$H NMR spectrum; diastereomers not distinct in $^{31}$P NMR.
17. For previous "selfresolving" diphosphorus systems see references 6b, 8d.