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A Novel Displacement Route to P-Chiral Phosphine Oxides of High Enantiomeric Purity[1]

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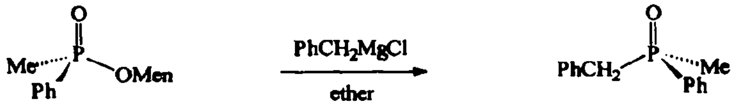
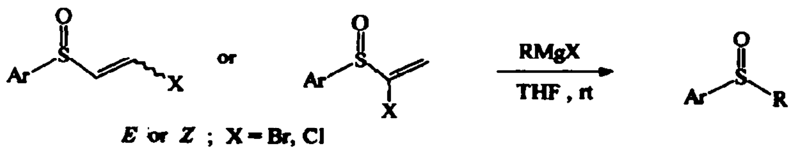
Abstract: Reactions of (*R*)-(1-chlorovinyl)methylphenylphosphine oxide with aryl and alkenyl Grignard reagents result in highly stereoselective displacement of the halovinyl group and afford virtually enantiomerically pure arylmethylphenyl and alkenylmethylphenylphosphine oxides of inverted configuration at phosphorus.

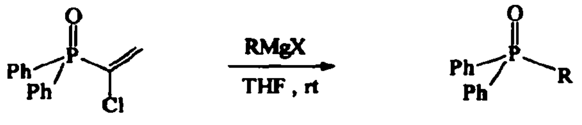
Since the pioneering work of Mislow and coworkers[2] and Nudelman and Cram,[3] on stereoselective reactions of diastereomeric menthyl phosphinates with Grignard reagents (e.g. Equation 1), synthetic routes to scalemic[4] P-chiral phosphine oxides and other P-chiral phosphine derivatives based on nucleophilic displacement reactions of P-resolved phosphorus esters with organometallic reagents have attracted much attention.[5] Yet, despite their continued practical importance and development,[5] syntheses in which virtually complete stereoselectivity in the displacement steps can be accomplished are still rare and not easily predictable. As noted early by Mislow[2] and later experienced by others,[6] such displacements are very sensitive to variation of groups at phosphorus and magnesium as well as to the nature of the ester leaving group. Recent discoveries that halovinyl groups at sulfur[7,8] and at phosphorus[9] can act as effective leaving groups for substitution by Grignard reagents (Equations 2 and 3) turned our attention to the possibility of probing utility of these groups for the stereoselective synthesis of scalemic phosphine oxides. It could be



(1)



(2)



(3)

reasonably expected that mild reaction conditions (cf. Equation 3) and possible matching of carbon nucleophiles with carbon centered leaving groups would create advantageous situation in terms of facility and potential stereochemical homogeneity of the substitution process. As it has been recently established,[8] Grignard substitutions of halovinyl groups in enantiomeric halovinyl sulfoxides proceed with clean inversion of configuration at sulfur. In this communication we wish to demonstrate that reactions of (*R*)-(1-chlorovinyl)methylphenylphosphine oxide (**1**)[10] with Grignard reagents result analogously in the stereospecific displacement of the halovinyl group in **1** and afford displaced phosphine oxides of inverted configuration at phosphorus.

The starting oxide (*R*)-**1** was synthesized from (*S*)-methylphenylvinylphosphine oxide[11] by the published procedure[10] and was subjected to reactions with various aryl and alkenyl Grignard reagents under nitrogen in THF at room temperature. Under these conditions a series of scalemic arylmethylphenyl and alkenylmethylphenylphosphine oxides was readily obtained. Their structures and physical data are collected in the Table together with the overall equation.

The effectiveness of the new route is well illustrated by the synthesis of the industrially important PAMP oxide **2**[12] in 83% isolated yield (entry 1). The measured specific rotation of **2** was found to match well the known value reported for the enantiomerically pure compound and designated also its absolute configuration as *S*.[5c] Similarly straightforward comparison and assignment of absolute configuration based on the literature data were also possible for oxides **3**,**4**,**6**,**7** and they indicated unequivocally that the studied displacements of the chlorovinyl group in (*R*)-**1** occurred with very high stereoselectivity and with inversion of configuration. The virtually complete enantiomeric purity of all the products was independently confirmed by the NMR determination with a chiral shift reagent (see Table). The absolute configurations assigned to oxides **5** and **8** are based on the established displacement stereocourse.

To summarize, it has been demonstrated that the halovinyl group at the resolved P-center, as in (*R*)-**1**, can be displaced by Grignard reagents under mild conditions and with clean inversion of configuration. Considering that access to quantities of enantiomerically pure 1-halovinyl phosphine oxides is straightforward,[10] the developed procedure shows promise for the synthesis of a wide range of structurally diversified P-chiral phosphine oxides of very high enantiomeric purity.

A typical procedure is exemplified below.

Table. Reactions of (*R*)-(1-chlorovinyl)methylphenylphosphine Oxide (1) with Grignard Reagents.

Entry	R	Product	% Yield[a]	$[\alpha]_D$[b]	% ee[c]	Conf.	Ref.
1	*o*-Anisyl	2	83	-25.4	>98	S	5c
2	*p*-Anisyl	3	58	-7.9	>98	S	2
3	*p*-Tolyl	4	61	-8.3	>98	S	13
4	2-Thienyl	5	72	-3.8[d]	>98	S	-
5	4-Biphenylyl	6	90	-12	>98	S	5c
6	(*E*)-2-Phenylethenyl	7	57	-20[d]	>98	R	1
7	(*E*)-2-(Trimethylsilyl)ethenyl	8	51	+34.7[d]	>98	R	-

(a) Yields refer to pure isolated products. (b) c = 0.55 -1.75, methanol. (c) Ee values determined by NMR using [(*R*)-3,5-dinitro-*N*-(1-phenylethyl)benzamide] as the chiral shift reagent.[14] (d) In chloroform

Synthesis of Methylphenyl(2-thienyl)phosphine Oxide (5). 1.6 mL of a 0.75 N solution of 2-thienylmagnesium bromide in THF, under N_2, was added dropwise to a stirred solution of 0.16 g (0.8 mmol) of 1 in 10 mL of THF. After 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and was extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried (Na_2SO_4), and then evaporated *in vacuo*. The residue was chromatographed on silicagel using ethyl acetate/petroleum ether 3:1 and ethyl acetate/methanol 2:1 as eluents and afforded 5 in 72% yield. MS (70 eV): m/e (relative intensity) 222 (50) 221 (47) 207 (100) 139 (7) 77 (36). NMR (500 MHz, $CDCl_3$) 7.77-7.93 (m, 2H), 7.66 (ddd, J = 1.0, 3.9, 4.8 Hz, 1H), 7.54-7.43 (m, 4H), 7.15 (ddd, J = 1.7, 3.6, 4.8 Hz, 1H), 2.04 (d, J = 13.6 Hz, 3H) ppm.

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