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Efficient Synthesis of Benzylphosphine Oxides and *E*-Stilbenes

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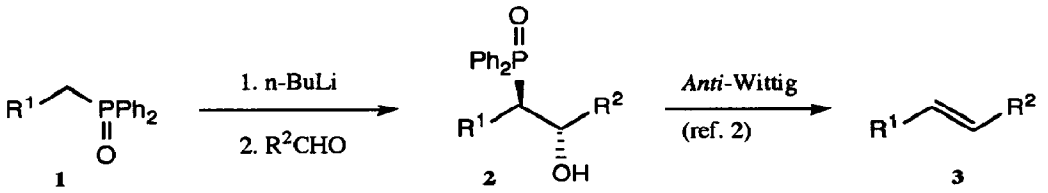
Abstract: A series of substituted benzylphosphine oxides has been synthesised by reduction of the corresponding (α-chlorobenzyl)phosphine oxide, derived from the benzaldehyde and chlorodiphenylphosphine, with either sodium borohydride (DMSO, 60–70 °C, 12 h) or tributyltin hydride and AIBN (C_6H_6, 80 °C, 2 h). Reaction of the (α-lithiobenzyl)phosphine oxide with aldehydes gave exclusively *E*-alkenes.

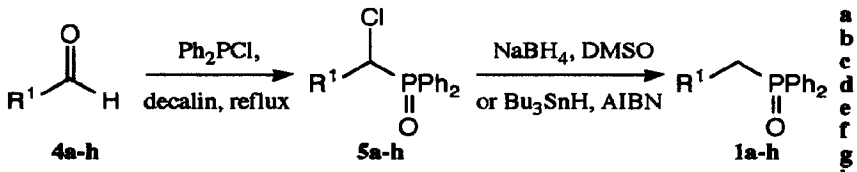
Several simple stilbene natural products have been shown to possess anti cancer properties.[1] We are currently pursuing a study to apply our recently discovered *anti*-Wittig methodology[2] to the synthesis of this type of stilbene. For this purpose we required an efficient synthesis of the substituted benzyl phosphine oxide **1** in order to study the *anti* Horner Wittig reaction **2** → **3**. We outline, herein, a new synthesis of benzylphosphine oxides and their subsequent stereoselective conversion to *E*-stilbenes.



The synthesis of benzyldiphenylphosphine oxides is somewhat problematical. The usual method of synthesis of diphenylphosphine oxides — the thermolysis of triphenylphosphonium hydroxides[3] — is not successful since the benzyl group is preferentially expelled. Benzyldiphenylphosphine oxide **1a** has been made by reaction of the benzylmagnesium chloride with diphenylphosphinoyl chloride.[4] We were unable to make **1h** — the benzylphosphine oxide we first required — efficiently by this method which, in any case, requires a large excess of the Grignard reagent. The coupling of lithium diphenylphosphide[5] with the 3,4,5-trimethoxybenzylchloride was also inefficient. We finally chose to attempt the reduction of α-chlorobenzyl phosphine oxide **5a**. We synthesised a range of substituted α-chlorobenzylphosphine oxides **5a-h** by reaction of chlorodiphenylphosphine and the corresponding benzaldehyde.[6] The reduction with sodium borohydride in

DMSO[7] in most cases proved facile providing the benzyl phosphine oxide cleanly after several hours at 70 °C. The only reduction that proved troublesome was that of α-chloro-(3,4,5-trimethoxybenzyl)phosphine oxide **5h** which resists reaction, even at temperatures above 70 °C. However, the required phosphine oxide can be obtained very easily by radical dechlorination by the reaction of **5h** with tributyltin hydride. The reduction of **5d** with sodium borohydride gave a dimeric product[8] (20 %) in addition to **1d** (51%). But again the radical dechlorination proved efficient. We were unable to obtain high yields of the *p*–chloro derivative **5f**, since it was always contaminated with the phosphine oxide **1f**. Phosphine oxides have been reported as by-products in the reaction **4** → **5**, however we found that the slow reduction to **1f** occurs, rather surprisingly, by simply refluxing pure **5f** in decalin.

Our two-step procedure compares well with the three step process normally required for the synthesis of benzylphosphonium salts and benzylphosphonate esters (aldehyde → alcohol → bromide → phosphorus reagent).



R
a Phenyl
b 2–Methylphenyl
c 4–Methylphenyl
d 2–Methoxyphenyl
e 4–Methoxyphenyl
f 4–Chlorophenyl
g 3,4,–Dimethoxyphenyl
h 3,4,5–Trimethoxyphenyl

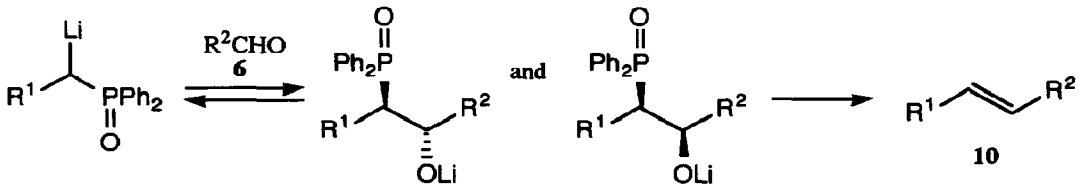
Table 1. Synthesis of phosphine oxides **1a-h**

	R	**4** → **5** yield (%)	**5** → **1** yield (%)
a	Phenyl	68	78[a]
b	2–Methylphenyl	70	75[a]
c	4–Methylphenyl	82	75[a]
d	2–Methoxyphenyl	78	51[a], 80[b]
e	4–Methoxyphenyl	73	53[a]
f	4–Chlorophenyl	—	67[a]
g	3,4–Dimethoxyphenyl	61	63[a]
h	3,4,5–Trimethoxyphenyl	64	78[b]

(a) By reduction with $NaBH_4$, DMSO, 70 °C, 12 h; (b) By reduction with Bu_3SnH, AIBN, C_6H_6, 80 °C, 2 h.

With the benzyl phosphine oxides **1** in hand we attempted the synthesis of the *erythro* phosphinyl alcohol **2** by sequential treatment of **1** with n-butyllithium and aromatic aldehyde **6**. However, to our surprise, we isolated not an alcohol but the *E*-stilbene **10**. The reaction is general — a variety of aldehydes give *E*-stilbenes in essentially quantitative yield (table 2). After addition of the aldehyde **6** to the red solution of the phosphine oxide anion **7**, the solution immediately turned colourless. After 15-20 minutes a white precipitate of lithium diphenyl phosphinate formed. Presumably the *erythro* and *threo* derivatives **8** and **9** equilibrate via **7** and **6**, whilst elimination of the *threo* lithium salt **9** is much faster than elimination of the *erythro* adduct **8**. Although it is odd to observe elimination of the lithium alkoxide — normally this only occurs with the sodium or potassium

alkoxides — it is not an unprecedented finding. Direct elimination from the lithium alkoxide occurs when the phosphine oxide bears an alpha sulfide group,[9] or an alpha isoxazole ring.[10] Kallmerten *et al.* have also observed direct elimination when the phosphine oxide bears an alpha phenyl group as part of their synthesis of oudemansin A.[11] In all these cases the *E*-alkene is formed exclusively. The formation of stilbene by the Horner-Wittig reaction is well documented. Warren, Whitham *et al.* have shown that the *erythro* and *threo* adducts do indeed equilibrate via the starting materials, leading eventually to mixtures of *cis* and *trans* stilbene.[12] They showed that the *threo* adduct gives an approximately 1:1 mixture of *E*-stilbene and benzyldiphenylphosphine oxide **1a** when treated with n-butyllithium in THF at room temp. for three hours. In addition, they demonstrated that alcohols from **8** and **9** are obtained in poor yield (31%) from reaction of metallated **1** with benzaldehyde when the reaction is quenched immediately at 0 °C after warming from –78 °C. We have observed that if the alcohol is required the quench must be carried out at low temperature (–78 °C).



7a-h *erythro* **8** *threo* **9**

Table 2. Synthesis of *E*-Stilbenes **1a-h** → **10**

1	R^2	yield (%) **1a-h** → **10**
a	Phenyl	95
a	2–Methylphenyl	98
a	4–Methylphenyl	99
a	2–Methoxyphenyl	98
a	4–Methoxyphenyl	91
a	3,4,5–Trimethoxyphenyl	89
b	2–Methylphenyl	99
b	4–Chlorophenyl	78
c	4–Methylphenyl	79
c	4–Methoxyphenyl	83
c	3,4,5–Trimethoxyphenyl	78

1	R^2	yield (%) **1a-h** → **10**
c	2–Methoxyphenyl	73
e	4–Chlorophenyl	66
e	2–Methoxyphenyl	62
g	4–Methoxyphenyl	90
g	3,4–Dimethoxyphenyl	99
g	3,5–Dimethoxyphenyl	78
h	2–Methoxyphenyl	91
h	4–Methoxyphenyl	70
h	3,4,5–Trimethoxyphenyl	99
h	3–OTBS–4–$OMeC_6H_3$	70

The *E*:*Z* selectivity in all cases is > 95:5 as determined from the ^1H nmr spectrum of the crude reaction mixture

Standard procedures:

Syntheses of (α-chlorobenzyl)phosphine oxides **5**. A mixture of the aldehyde **4** (70 mmol) and chlorodiphenylphosphine (70 mmol) and decalin (100 ml) was heated under reflux for 3 hours. After cooling to room temperature the decalin was decanted from the brown

oil that had separated from the reaction mixture. The (α-chlorobenzyl)phosphine oxides **5** was obtained by dissolving the oil in hot isopropanol and cooling. The crystals obtained were generally pure enough for the next reaction.

Syntheses of benzylphosphine oxides 1. To a stirred solution of the (α-chlorobenzyl)phosphine oxide **5** (29.3 mmol) in dry DMSO (250 ml) was added sodium borohydride (80 mmol). The mixture was stirred at 70 °C for 2-4 h (until reaction is complete by tlc). The mixture is poured into ice/hydrochloric acid (3 M)(1.5 l) and extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were washed with water (500 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate) or recrystallisation. Alternatively, a mixture of (α-chlorobenzyl)phosphine oxide **5** (28.9 mmol), tributyltin hydride (37.5 mmol) and AIBN was heated under reflux in benzene (200 ml). After 2 h the solvent was evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate) or recrystallisation.

Syntheses of stilbenes. To a stirred mixture of phosphine oxide **1** (1 mmol) in dry THF (3 ml) at 0 °C was added dropwise n-butyllithium (1 mmol of a 2.5 M solution in hexanes) under nitrogen. The solution was stirred at 0 °C for 10 min. and the aldehyde **6** (1 mmol) in dry THF (1 ml) added. The solution was stirred at room temperature for 12 h. Water (50 ml) was added and the mixture extracted with dichloromethane (3 × 25 ml). The organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2, hexane).

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Notes and References

1 Gill, M. T.; Bajaj, R.; Chang, C. J.; Nichols, D. E.; McLaughlin, J. L. *J. Nat. Prod.*, 1987, **50**, 36-40; Ferrigni, N. R.; McLaughlin, J. L.; Powell, R. G.; Smith, Jr, C. R. *J. Nat. Prod.*, 1984, **47**, 347–353; Castro, O.; Lopez, J.; Vergara, A.; Stermitz F. R.; Gardner, D. R. *J. Nat. Prod.*, 1986, **49**, 680-683; Cardona, L.; Fernández, I.; Garcia, B.; Pedro, J. R. *Chem. and Ind.*, 1985, 759–760; Pettit, G. R.;Singh, S. B.; Hamel, E.; Lin. C. M.; Alberts, D. S.; Garcia–Kendall, D. *Experientia*, 1989, **45**, 209–211

2 Lawrence, N. J.; Muhammad, F. *J. Chem. Soc., Chem. Commun.*, 1993, 1187–1188.

3 Fenton, G. W.; Ingold, C. K. *J. Chem. Soc.*, 1929, 2342–2357; Meisenheimer, J.; Casper,J.; Horing, M.; Lauter, W.; Lichtenstadt, L.; Samuel, W. *Justus Leibigs Ann. Chem.*, 1926, **449**, 213–248; Zanger, M.; Vander Werf, C. A.; McEwen, W. E. *J. Am. Chem. Soc.*, 1959, **81**, 3806–3807.

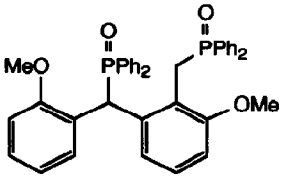
4 Morrison, D. C. *J. Am. Chem. Soc.*, 1950, **72**, 4820–4821.

5 Aguiar, A. M.; Beisler, J.; Mills, A. *J. Org. Chem.*, 1962, **27**, 1001–1005.

6 De' ath, N. J.; Miler, J. A.; Nunn, M. J.; Stewart, D. *J. Chem. Soc., Perkin Trans. 1*, 1981, 776–784.

7 Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.*, 1969, **34**, 3923–3926.

8 The structure of the dimer is tentatively assigned as



9 Grayson, J. I.; Warren, S.; Zaslona, A. T. *J. Chem. Soc., Perkin Trans. 1*, 1987, 967–976; Juaristi, E.; Gordillo, B.; Valle, L. *Tetrahedron*, 1986, **42**, 1963–1970.

10 Collington, E. W.; Knight, J. G.; Wallis, C. J.; Warren, S. *Tetrahedron Lett.*, 1989, **30**, 877–880.

11 Wittman, M. D.; Kallmerten, J. *J. Org. Chem.*, 1987, **52**, 4303–4307.

12 Buss, A. D.; Warren, S.; Leake, J. S.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1*, 1983, 2215–2218.

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