

THE STEREOCHEMISTRY OF WITTIG REACTIONS OF YLIDE-ANIONS DERIVED FROM SEMI-STABILIZED PHOSPHONIUM YLIDES

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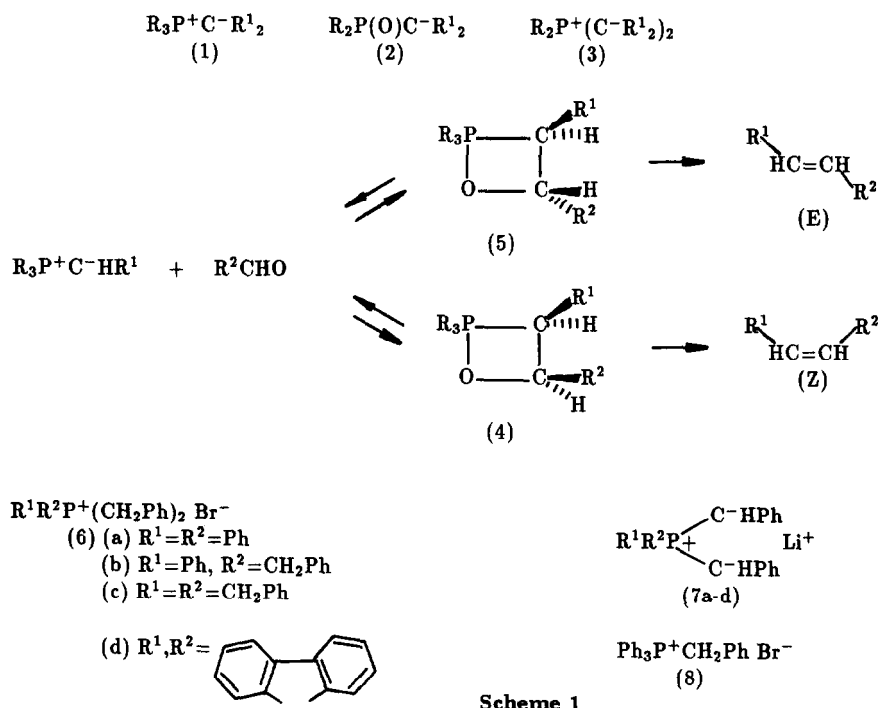
Abstract: Ylide-anions derived from a variety of benzylphosphonium salts react with one or two equivalents of benzaldehyde to give excellent yields of stilbene. Reactions of these ylide-anions with one equivalent of aldehyde usually lead to increased E-stereoselectivity compared to the reactions of analogous ylides.

Phosphorus-based olefin syntheses fall into two groups; those involving ylides (1) (Wittig reaction) and those involving phosphoryl-stabilised carbanions (2). Although the complementary nature of these methods mean that a wide range of alkenes can be synthesised, major problems remaining are the low reactivity of ylides towards ketones, the absence of a satisfactory route to (Z)-alkenes carrying conjugating electron-withdrawing substituents, and the low level of stereochemical control in reactions of phosphoryl-stabilised carbanions (which otherwise are generally superior to the Wittig reaction). Ylide-anions (3) are analogues of phosphoryl-stabilised carbanions and would be expected to retain the high reactivity of the latter compounds. Reactivity of ylides has long been recognised as a key factor in the stereochemistry of the Wittig reaction¹; under "salt-free" conditions oxaphosphetane formation from reactive ylides is irreversible and olefin stereochemistry is *kinetically-controlled* through preferential formation (for reasons still not clear) of the cis-oxaphosphetane (4) which collapses to (Z)-alkene. With stable ylides oxaphosphetane formation is reversible and the *thermodynamically-preferred* trans-oxaphosphetane (5), and hence (E)-alkene, predominates.

The predominance of trans-alkene from reactions of phosphoryl-stabilised anions has been attributed partially to the reduced driving force for collapse of the pentacoordinate intermediates in these cases compared to that for the equivalent intermediates in the Wittig reaction leading to greater betaine reversibility and hence the thermodynamic product². We reasoned that ylide-anions would display the increased reactivity of phosphoryl-stabilised anions while maintaining the strong driving force of P=O formation for collapse of the pentacoordinate intermediate, leading to an increase in the proportion of (Z)-alkene while retaining the advantages of phosphoryl-stabilised anions³.

In spite of the elegant work of Schmidbaur and his co-workers⁴ on ylide-anions as ligands in organometallic compounds their use as synthetic reagents had scarcely been investigated until a recent report⁵ by Cristau's group, which shows that these reagents undergo the Wittig reaction, but provides no information on alkene stereochemistry. In this letter we report reactions of ylide-anions derived from semi-stabilized ylides; reactions of ylide-anions derived from stabilised ylides will be reported elsewhere.

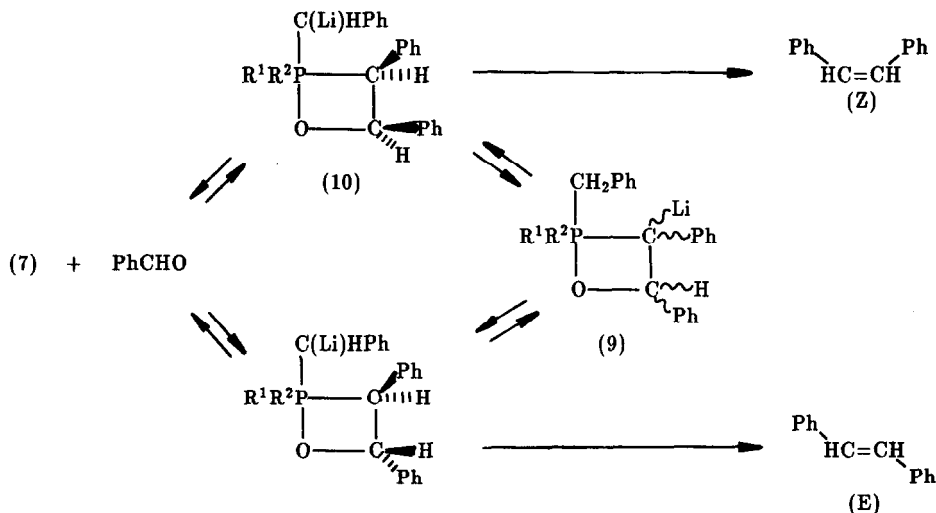
Our initial investigations have involved benzylidene ylide-anions and benzaldehyde; synthetic strategies known to improve stereoselectivity in other systems have been singularly

**TABLES.****REACTION A:** $\text{R}_4\text{P}^+ \text{Br}^-$ with *n*-BuLi and PhCHO**REACTION B:** $\text{R}_4\text{P}^+ \text{Br}^-$ with 2 x *n*-BuLi and PhCHO**REACTION C:** $\text{R}_4\text{P}^+ \text{Br}^-$ with 2 x *n*-BuLi and 2 x PhCHO**TABLE 1:** Yields¹³ and stereochemistry of stilbenes obtained from the reactions of ylides and ylide-anions with benzaldehyde at 20°C.

SALT	REACTION A		REACTION B		REACTION C	
	Z/E	% Yield	Z/E	% Yield	Z/E	% Yield
$\text{Ph}_3\text{P}^+\text{CH}_2\text{Ph}$	57/43	99				
$\text{Ph}_2\text{P}^+(\text{CH}_2\text{Ph})_2$	15/85	87	15/85	96	6/94	144
$\text{PhP}^+(\text{CH}_2\text{Ph})_3$	32/68	92	17/83	96	5/95	160
$\text{P}^+(\text{CH}_2\text{Ph})_4$	37/63	100	14/86	95	7/93	134
$\begin{array}{c} \text{Ph} \\ \\ \text{P}^+(\text{CH}_2\text{Ph})_2 \\ \\ \text{Ph} \end{array}$	15/85	100	9/91	100	21/79	190

TABLE 2: Yields¹³ and stereochemistry of stilbenes obtained from the reactions of ylides and ylide-anions with benzaldehyde at -98°C.

SALT	REACTION A		REACTION B		REACTION C	
	Z/E	% Yield	Z/E	% Yield	Z/E	% Yield
$\text{Ph}_3\text{P}^+\text{CH}_2\text{Ph}$	68/32	86				
$\text{Ph}_2\text{P}^+(\text{CH}_2\text{Ph})_2$	13/87	86	12/88	92	18/82	176
$\text{PhP}^+(\text{CH}_2\text{Ph})_3$	24/76	81	30/70	81	5/95	155
$\text{P}^+(\text{CH}_2\text{Ph})_4$	48/52	96	12/88	91	4/96	121



unsuccessful in the synthesis of stilbenes (Schlosser's β -oxido ylide approach⁶ has little effect on alkene stereochemistry; however see reference 7). Ylide-anions (7a-d) were generated from salts (6a-d) by reaction in dry THF with two molar equivalents of *n*-BuLi⁸ followed by the addition of one or two molar equivalents of benzaldehyde. The results of these experiments, and those of normal Wittig reactions⁹ of the salts (6a-d) and (8) carried out under similar conditions with one molar equivalent of *n*-BuLi and benzaldehyde, are shown in Table 1.

In all cases reactions of ylide-anions with a molar equivalent of benzaldehyde occurred to give excellent yields of stilbene *generally with significantly enhanced amounts of (E)-isomer compared to the equivalent reaction with ylide* to the extent that the proportions of (E)-stilbene are amongst the highest reported. The use of dibenzophosphole-derived stabilized ylides¹⁰ and phosphine oxides¹¹ is reported to enhance the proportion of (Z)-alkene; in view of this the results from reactions of the salt (6d) are noteworthy. Although the use of (6d) gives the highest yields of alkene obtained in any of our reactions, neither ylide or ylide-anion reactions lead to an increased proportion of (Z)-alkene (in fact a *decreased* proportion is observed in the latter case¹²). However, reaction of the ylide-anion (7d) with two equivalents of benzaldehyde does give a substantial increase in the proportion of (Z)-alkene as well as an increased overall yield when compared to the acyclic examples. This last result (through comparison of the stereochemistry with that observed in a Horner-Wittig reaction of the anion of benzyl(dibenzophosphole) oxide with benzaldehyde) provides support for a simple two-step mechanism involving a phosphoryl-stabilised anion in the second step. However, a variety of mechanisms can be envisaged for these reactions depending on the relative reactivities of the ylide-anion and the anion-containing intermediates; the simplest of these is shown in scheme 2.

It seems unlikely that the increase in (E)-isomer derives from the same reason (slow intermediate decomposition to alkene) that causes high (E)/(Z) ratios in phosphoryl-based reactions. Possible alternative explanations are Schlosser-type equilibration (perhaps enhanced by intramolecular proton-transfer) through the oxaphosphetane-anion (9) and/or Maryanoff's anionic group effect mechanism⁷.

The yields of stilbene obtained from reactions of (7a-c) where two molar equivalents of benzaldehyde were used indicate that a second olefination (presumably involving the corresponding phosphoryl-stabilized anion, although reaction with an oxaphosphetane-anion (e.g.10) is also possible) occurs. The extent of the increase in (E)/(Z) ratios in these reactions indicates that this second olefination is (E)-stereospecific.

All these reactions occur readily at -98°C ; although, as can be seen from the results in Table 2, the effect on alkene stereochemistry of lowering the reaction temperature is small.

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References and Notes.

1. I Gosney and A G Rowley, "The Wittig Reaction", in *Organophosphorus Reagents in Organic Synthesis* (ed. J I G Cadogan), Academic Press, NY, 1979, p.26ff.
2. B J Walker, "PO-Activated Olefinations", in reference 1, p.167ff.
3. Some support for this view is available from reactions of the stabilized ylide $\text{Ph}_3\text{P}=\text{CHCOCH}_2\text{COOEt}$ and its anion, designated as $\text{Ph}_3\text{P}=\text{CHCOCH}^-\text{COOEt}$; the former being highly unreactive even to aldehydes, while the latter reacts readily with aliphatic aldehydes to give largely Z-alkenes (K M Pietrusiewicz and J Monkiewicz, *Tetrahedron Lett.*, 1986, 27, 739). However, these results can be interpreted in ways other than that given in this reference.
4. H Schmidbaur, *Angew. Chem. Int. Ed. Engl.*; 1983, 22, 907.
5. H-J Cristau, Y Ribeill, F Plenat, and L Chiche, *Phosphorus and Sulfur*, 1987, 30, 135.
6. M Schlosser and K F Christmann, *Angew. Chem. Int. Ed. Engl.*, 1966, 26, 311.
7. (a) H Daniel and M le Corre, *Tetrahedron Lett.*, 1987, 28, 1165; (b) B E Maryanoff, A B Reitz, and B A Duhl-Emswiler, *J. Am. Chem. Soc.*, 1985, 107, 217.
8. The colour changes observed during slow addition of BuLi indicate that substantial amounts of ylide-anion (dark red) is formed initially, even when the phosphonium salt is still in great excess. This equilibrates with ylide (lighter red) until one equivalent of base has been added, after which ylide anion is always present.
9. The addition of one equivalent of LiBr to these reactions before benzaldehyde was added had no observable effect on alkene stereochemistry.
10. I F Wilson and J C Tebby, *J. Chem. Soc. Perkin I*, 1972, 2713.
11. T G Roberts and G H Whitham, *J. Chem. Soc. Perkin I*, 1985, 1953; the use of dibenzophosphole-derived phosphine oxides in olefinations leads to greater enhancement of (Z)-alkene than use of the corresponding ylides.
12. A recent publication (E Vedejs and C Marth, *Tetrahedron Lett.*, 1987, 28, 3445) reports that reactive ylides based on dibenzophosphole give alkenes with high (E)-selectivity and provides convincing evidence that this derives from the *trans-oxaphosphetane intermediate* being kinetically-preferred in these cases. It is tempting to speculate that the increased proportion of (E)-alkene obtained from reaction of one mole of benzaldehyde with the ylide-anion derived from (6d) is derived from a similar inversion of the kinetic preference of the oxaphosphetane intermediates.
13. Yields are based on phosphonium salt in all cases and were determined by gc on SGR (2.5%) at 200° using hexamethylbenzene as an internal standard.

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