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Crown Ether Catalyzed Stereospecific Synthesis of Z- and E-Stilbenes by Wittig Reaction in a Solid-Liquid Two-Phases System[#]

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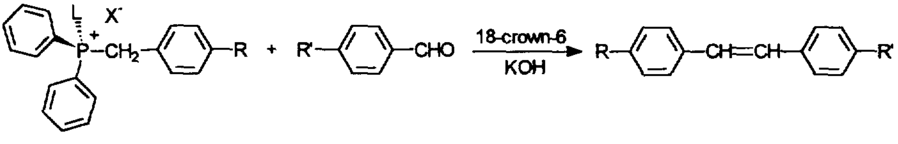
Abstract: Potassium hydroxide and a catalytic amount of 18-crown-6 are used, in alternative to the classical Wittig conditions, to prepare very rapidly and stereoselectively Z- and E-stilbenes. In particular, the use of benzyltriphenylphosphonium iodides always leads to a complete Z-stereospecificity, while benzyldiphenylchlorophosphonium salts give a complete E-stereospecificity.

The Wittig reaction is one of the most important methods for the synthesis of alkenes because of the certainty with which the position of the newly formed double bond can be established, and has therefore attracted much attention both from the synthetic and the mechanistic point of view.[1] As far as the stereochemistry is concerned, the configuration of the introduced double bond is less easy to control, being governed by the nature of the ylide: stabilized ylides, bearing π-acceptor groups at the α carbon, like $Ph_3P{=}CHX$ with X = ester, acyl, vinyl, etc., generally react with high (E)-olefin selectivity,[2-4] while non-stabilized ylides, bearing α alkyl group, give Z alkenes.[5,6] Semi-stabilized ylides, like benzyl ylides, usually yield mixtures of Z and E isomers.[7] In particular, the reactions of benzylidenetriphenylphosphoranes with aryl aldehydes to prepare substituted stilbenes are, especially in the absence of the Li^+ cations, practically non-stereoselective, giving nearly 50:50 mixtures of the Z-E isomers.[7]

In this paper we are reporting convenient reaction conditions, alternative to those usually employed in the classical Wittig reaction (anhydrous aprotic solvents, hydride or organometal base and inert atmosphere), to prepare very rapidly substituted Z and E stilbenes with complete stereoselectivity.

The benzyltriphenylphosphonium chlorides, bromides, and iodides (**1**) and benzyldiphenylchlorophosphonium bromides (**2**) were prepared according to the standard procedure. The reactions of **1** or **2** with the benzaldehydes **3** were carried out in a solid-liquid two-phase system consisting of dichloromethane and a twofold molar excess of solid potassium hydroxide, containing 5~10 mole % of 18-crown-6.[8] The results obtained using differently substituted benzaldehydes and different benzyltriphenylphosphonium halides, as well as benzylchlorodiphenylphosphonium bromides, are reported in Table 1.



(1)

1 L = Ph; **2** L = Cl **3** **4**

[#] Dedicated to the memory of Professor Giuseppe Bellucci (d. March 3, 1996).

Table 1. Diastereoisomeric Ratios of Stilbenes **4**.[a]

Run	Phosphonium halide			Aldehyde		
		R	X^-	R'	T (°C)	Z : E[a]
1	**1**	*p*-CH_3O	Cl^-	H	-70	85 : 15
2	**1**	H	Br^-	*p*-CH_3O	-70	70 : 30
3	**1**	*p*-CH_3O	Cl^-	*p*-CH_3O	-70	85 : 15
4	**1**	*p*-CH_3O	I^-	*p*-CH_3O	-70	>98 : <2
5	**1**	*p*-CH_3	Cl^-	H	-70	85 : 15
6	**1**	H	Br^-	*p*-CH_3	-70	83 : 17
7	**1**	H	Br^-	*p*-CH_3	0	70 : 30
8	**1**	H	I^-	*p*-CH_3	-70	>98 : <2
9	**1**	*p*-CH_3	Cl^-	*p*-CH_3	-70	85 : 15
10	**1**	*p*-CH_3	Br^-	*p*-CH_3	-70	85 : 15
11	**1**	*p*-CH_3	I^-	*p*-CH_3	-70	>98 : <2
12	**1**	H	Br^-	H	-70	75 : 25
13	**1**	H	Br^-	H	0	65 : 35
14	**1**	H	I^-	H	-70	>98 : <2
15	**1**	*p*-CF_3	Br^-	H	-70	85 : 15
16	**1**	H	Br^-	*p*-CF_3	-70	83 : 17
17	**1**	H	Br^-	*p*-CF_3	0	70 : 30
18	**1**	*p*-CF_3	Br^-	*p*-CF_3	-70	82 : 18
19	**1**	*m*-CF_3	I^-	*m*-CF_3	-70	>98 : <2
20	**1**	*p*-CN	Br^-	*p*-CN	-70	>98 : <2
21	**2**	H	Br^-	*p*-OCH_3	25	1 : 99
22	**2**	H	Br^-	*m*-OCH_3	25	1 : 99
23	**2**	H	Br^-	*p*-CH_3	25	2 : 98
24	**2**	H	Br^-	H	25	2 : 98
25	**2**	H	Br^-	*p*-CF_3	25	4 : 96
26	**2**	*p*-CF_3	Br^-	*p*-CF_3	25	1 : 99
27	**2**	H	Br^-	*p*-NO_2	25	1 : 99

[a] Determined by HPLC. Yields ≥ 90%.

All reactions of **1** or **2** with **3** were very fast (typically about 10-15 min) even at -70 °C when R in **1** or **2** was hydrogen or an electron donating group, while longer times (typically 2-3 h) were required when this substituent was an electron withdrawing group. It is noteworthy that neither anhydrous conditions nor an inert atmosphere were necessary. Furthermore, all reactions were stereoselective and both the Z and E stilbenes with a stereoisomeric ratio ≥ 98:2 could be obtained in > 90% yield, using appropriate conditions.

The temperature effect was investigated using benzyltriphenylphosphonium bromides and unsubstituted, *p*-methyl and *p*-(trifluoromethyl)substituted benzaldehydes. The Z : E ratio was always found to increase moderately with decreasing temperature, in agreement with earlier reports relative to reactions carried out under the usual Wittig condition[9] (compare: runs 6-7, 12-13 and 16-7).

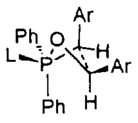
The data of Table 1 show that the electronic effects of para substituents on the benzaldehyde phenyl ring on the stereoselectivity of the olefin formation are rather modest and independent of their electron withdrawing or electron donating character (compare: runs 2, 6, 12 and 16). The effects of substituents at the para position on the benzyl substituent of **1** are likewise small or null (compare runs 1, 5 and 12, 15). On the other hand, the reaction is markedly affected by the nature of the counteranion of the phosphonium salt, the stereoselectivity increasing on passing from chloride or bromide to iodide. In fact, all benzyltriphenylphosphonium iodides reacted with benzaldehydes bearing both electron withdrawing and electron donating substituents to produce the practically pure Z isomers. An increase in the Z-selectivity due to the addition of I^- ions had been observed also in Wittig reactions carried out under classical conditions when Na^+ was present, while little or no effect was found in the presence of K^+ or Li^+.[10]

Finally, pure E stilbenes can be obtained through the same procedure, using benzylchlorodiphenylphosphonium bromides at room temperature, regardless of the nature of para substituents on the benzyl group of **2** or at the para position of benzaldehyde phenyl ring (runs 18-23).

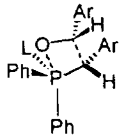
Although the first attempts at rationalizing the stereochemistry of the Wittig reaction were based on a stepwise mechanism, involving a reversible nucleophilic addition step to generate a betaine intermediate, whose stereochemical equilibration was considered to determine the final outcome of the reaction,[11] more recent studies cast doubt on the intermediacy of betaines,[12,13] and indicate that the reaction actually occurs through a cycloaddition mechanism leading to oxaphosphetane intermediates (**5**).[7,13,14] In this framework the stereochemistry of the olefin formation should be determined by a combination of 1,2 and 1,3 steric interactions and by the degree of rehybridization at phosphorus in the four center transition state (TS) for the formation of intermediate **5**.

Different geometries have been then proposed for this TS, depending on its position on the reaction coordinate and on the nature on the phosphorous substituents.[1,15] A puckered cis-selective geometry of type **6**, in which the 1,2-interactions of the ylide α substituent with the aldehyde group and with the adjacent phosphorous substituent are smaller than in the corresponding trans form, has been proposed for early TS such as those corresponding to non-stabilized ylides. A planar trans-selective 4-center TS of type **8**, in which the 1,3-interactions are relieved since phosphorous is closed to trigonal bipyramidal geometry and 1,2-interactions control the selectivity, have been instead postulated for late TS as those of stabilized ylides. Finally, a nearly planar trans-selective 4-center geometry of type **7**, in which phosphorous has still an essentially reactant-like hybridization, has also been hypothesized for early TS, when the 1,3-interactions between the phosphorous ligand, L, and the aldehyde substituent are minimized reducing the steric requirements of L.

Early TS

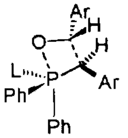


cis-**6**



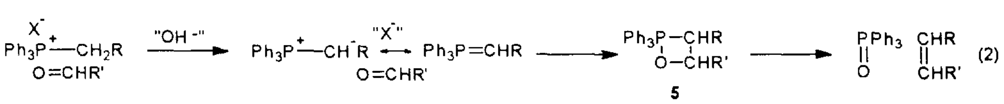
trans-**7**

Late TS



trans-**8**

In our condition the presence of a catalytic amount of crown ether, able to solvate cations,[16] produces very reactive "naked" OH^- ions which greatly accelerate the first step of the reaction. Furthermore, the ylide



$$\underset{O=CHR'}{\overset{X^-}{Ph_3\overset{+}{P}-CH_2R}} \xrightarrow{\text{"}OH^-\text{"}} \underset{O=CHR'}{Ph_3\overset{+}{P}-\overset{-}{C}HR} \overset{\text{"}X^-\text{"}}{\longleftrightarrow} Ph_3P=CHR \longrightarrow \underset{\mathbf{5}}{\begin{matrix}Ph_3P-CHR\\ |\qquad |\\ O-CHR'\end{matrix}} \longrightarrow \begin{matrix}PPh_3 & CHR\\ \| & \|\\ O & CHR'\end{matrix} \qquad (2)$$

formation is accompanied by a release of "naked" X^- anions which, before diffusing away, may affect the reactivity of the ylide towards the carbonyl compound, e.g. enhancing its zwitterionic character, and make the related TS earlier. A puckered TS of type cis-**6** can in fact explain the Z-selectivity observed in particular when benzyltriphenylphosponium iodides were used. On the other hand, the presence of the crown ether should again result in an early TS also for reactions carried out with the benzyldiphenylchlorophosphonium bromides **2**. In this case, however, the substitution of a phenyl group at phosphorous with a much less sterically demanding chlorine atom, which is moreover linked to phosphorous by a bond longer than the P-Ph bond,[17,18] can shift the TS to a nearly planar 4-center one of type trans-**7**, leading stereospecifically the E-isomers of stilbenes.

In conclusion, the results of the present investigation provide a convenient and safe alternative method to perform Wittig reactions of semi-stabilized benzyl ylides with benzaldehydes, leading to either Z- or E-stilbenes with a very considerable time saving and, most importantly, with an easily determined Z or E stereospecificity, that till now had never been achieved in these reactions.

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8. Typical procedure: to 1 mmol of the phosphonium salt **1** or **2**, dissolved in 2 ml of dichloromethane, the aryl aldehyde **3** (1 mmol) and 18-crown-6 (0.05-0.1 mmol) were added. The mixture was led to the proper temperature and freshly powdered potassium hydroxide (2 mmol) was added under magnetic stirring. When the colour, immediately formed, faded to a pale yellow, the mixture was diluted with dichloromethane and filtered off, and the filtrate was washed with water. The organic phase was dried ($MgSO_4$) and evaporated to give the crude product, which was analysed by HPLC (Spherisorb S5 ODS2, 25 cm; methanol:water, 80:20; flow rate 1ml/min) in order to establish the Z:E ratio, and purified by column chromatography over alumina, using hexane or hexane:ethyl acetate as the eluent. Yield $\geq$ 90% .
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