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# Lithium Cation-Catalyzed Wittig Reactions

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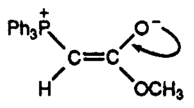
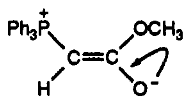
The condensation of stabilized phosphorane 1 with benzaldehyde is catalyzed by $Li^+$ ion. In the presence of a large quantity of $Li^+$, ylide 1 adds slowly to ketones with which it does not react under the usual reaction conditions. On the other hand, pretreatment of the ylide solution with trace amounts of BuLi tends to slow the reactions with aldehydes, probably by removing any traces of water and conjugate acid, the sources of protons that catalyzed these condensations.

## Introduction

Stabilized phosphorane 1, in $CDCl_3$ solution, resolves at −20 °C into two isomeric forms (in the ratio 3:1) which were identified as **1-cis** and **1-trans**.[1] Upon addition of benzaldehyde the two forms coalesce and Wittig condensation product starts to appear within minutes at −20 °C.[1,2]



**1-cis**



**1-trans**

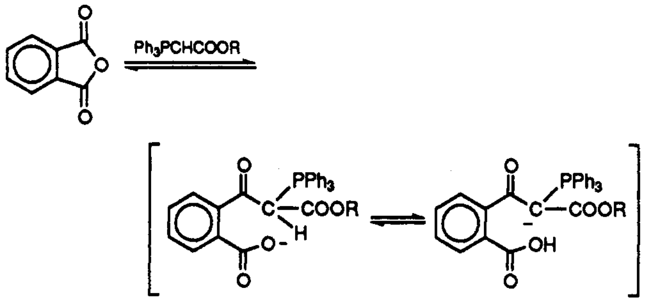
When the same reaction is carried out under scrupulously anhydrous conditions and any acidic contaminants (including traces of the ylide's conjugate acid, the phosphonium salt) are removed by pretreating the ylide solution with a trace quantity of butyllithium (1.6 M solution in hexanes), the two isomeric forms of the phosphorane remain distinct after the addition of benzaldehyde; the ensuing condensation reaction is considerably slower even at room temperature, Figure 1.[2]

On the basis of these observations, we concluded that interconversion of the two isomeric forms of the ylide and the condensation reaction are both catalyzed by trace amounts of protons.[2]

This conclusion was further supported by the observations made during reactions of phosphorane 1 with cyclic anhydrides, where an initial addition of the ylide to an anhydride generates protons, as shown in Scheme 1. In these reactions, the pretreatment of the ylide solution with trace amounts of BuLi did not result in slowing down the rates of reactions.[2]

It was not possible to determine from the above observations if the two catalytic processes were related, that is, if the rapid interconversion of the two isomeric forms of the ylide contributed in any way to the increase in the rate of condensation with the carbonyl group. In an attempt to resolve this problem and to assess the role of cations other than protons, we carried out a series of condensation reactions under anhydrous and acid-free conditions but in the presence of $Li^+$.

### Scheme 1



## Results and Discussion

As a baseline study, the reaction of benzaldehyde with ylide 1 (fresh sample from Aldrich) was monitored by $^{31}P$ NMR for 180 min at −20 °C (experiment 1) and an identical reaction was monitored at 0 °C (experiment 2). The protocol followed was similar in all reactions. The initial spectrum of ylide 1 in $CDCl_3$, recorded at room temperature, showed both isomeric forms. The signals were broadened significantly, indicating a slow interconversion. The temperature was then lowered to 0 °C (or −20 °C) and a solution of benzaldehyde in $CDCl_3$, cooled to −5 °C (or −20 °C) was added to the ylide (0 °C) with vigorous shaking. After 5 min of equilibration at 0 °C (or −20 °C), the $^{31}P$ NMR spectrum was recorded. The reaction was monitored at an appropriate temperature for 90 min to 180 min.

To explore the role of $Li^+$, we followed the condensation of 1 (fresh sample) with benzaldehyde in $CDCl_3$ saturated with LiBr (experiment 3). When ylide 1 was dissolved in $CDCl_3$ saturated with LiBr, **1-cis** and **1-trans** appeared immediately, their ratio unchanged at about 3:1. Upon addition of benzaldehyde, the rate of condensation carried out at 0 °C was significantly greater than that in the absence of $Li^+$ (experiment 3).

For all experiments the increase in the product $Ph_3PO$ was measured and the plots of the integrated ratios $Ph_3PO/Ph_3PO$ + ylide versus time are shown in Figure 2.

The results shown in Figure 2 indicate that the presence of $Li^+$ increases the rate of condensation of the stabilized ylide 1 with benzaldehyde. However, since the presence

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[1] Bestmann, H. J.; Joachim, G.; Lengyel, T.; Oth, J. F.; Merenyi, R.; Weitkamp, H. *Tetrahedron Lett.* 1966, 3355. Bestmann, H. J.; Snyder, J. P. *J. Am. Chem. Soc.* 1967, *89,* 3963. Randall, F. J.; Johnson, A. W. *Tetrahedron Lett.* 1968, *24,* 2841. Crews, P. *J. Am. Chem. Soc.* 1968, *90,* 2961. Snyder, J. P. *Tetrahedron Lett.* 1971, 215.

[2] Kayser, M. M.; Hooper, D. L. *Can. J. Chem.* 1990, *68,* 2123.

0022-3263/94/1959-1126$04.50/0

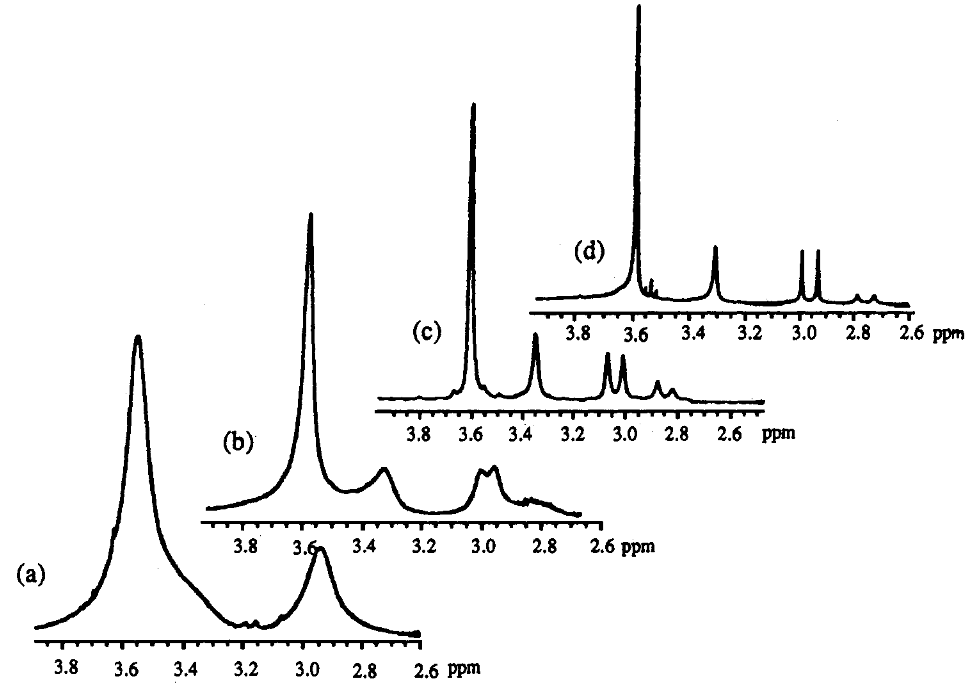

**Figure 1.** Proton NMR spectra of phosphorane 1: (a) unpurified ylide, 20 °C; (b) purified ylide, 20 °C; (c) unpurified ylide, −30 °C; (d) unpurified ylide + BuLi, 20 °C.

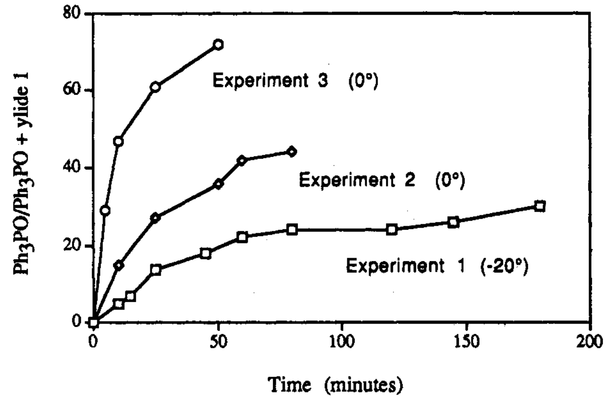

**Figure 2.** Wittig reactions of benzaldehyde with stabilized phosphorane 1 monitored by $^{31}$P NMR.

of trace amounts of BuLi, sufficient to deprotonate the reaction medium, results in a much slower reaction, it appears that $Li^+$ must be present in more than trace quantities to cause an increase in reaction rates. One may conclude that under these conditions the complexation of $Li^+$ ion with the carbonyl group of benzaldehyde facilitates nucleophilic attack in a manner similar to that in proton catalysis. Nonetheless, the degree and the manner in which $Li^+$ interacts with the ylide required further investigation.

Lithium bromide is considerably more soluble in acetone than it is in $CDCl_3$. A series of solutions was prepared with various ratios of ylide to $Li^+$ ion in acetone-$d_6$ solution. All solutions showed separation of cis and trans signals in the $^1$H spectrum. The separations of the cis and trans doublets as a function of the ratio [ylide]/[$Li^+$] are shown in Table 1.

Presumably, much of the $Li^+$ ion in these solutions is associated with the solvent (acetone); nevertheless, there is also evidence for the association of $Li^+$ ion with the ylide. Increasing separation of doublets would normally be correlated with a decrease in the rate of interconversion, and if all other conditions are constant, an increase in the barrier to cis/trans interconversion. The results shown in Table 1 would then indicate a decreasing barrier with increasing concentration of $Li^+$ ion. This is certainly not expected. The effect of metal ions on cis/trans interconversion in amides, which may serve as analogues to the ylides, has been extensively investigated. Only $Ag^+$ was found to decrease the barrier to interconversion for amides. The standard interpretation of these results is that $Ag^+$ complexes with the nitrogen atom of amides, while $Li^+$ and other cations complex with the oxygen, increasing the barrier.[3] It seems very unlikely that complexation of $Li^+$ ion with the oxygen of the ylide would decrease the barrier to internal rotation. An alternative explanation for the decrease in doublet separation with increasing $Li^+$ concentration is differential interaction between $Li^+$ and the oxygen atom in cis and trans forms of 1. Due to the repulsion between $Li^+$ and the positively charged phosphorus atom, we could expect that the complexation of $Li^+$ with **1-trans** would be at a shorter range than that with **1-cis** and thus lead to differential chemical shifts.

**Table 1. Separation of Cis and Trans Doublets in the $^1$H NMR Spectra of Ylide as a Function of [ylide]/[$Li^+$] Ratio**

| [ylide]/[$Li^+$] | separation, ppm |
|---|---|
| 0.50 | 0.054 |
| 1.01 | 0.085 |
| 1.42 | 0.121 |
| 1.83 | 0.161 |
| 3.47 | 0.221 |

We were surprised to find that, in the presence of $Li^+$, the stabilized ylide slowly reacts with the acetone solvent, forming the $\alpha,\beta$-unsaturated ester, as shown by the appearance of an olefinic carbon, the proton bonded to that carbon, and the formation of triphenylphosphine oxide as monitored, respectively, by the $^{13}$C, $^1$H and $^{31}$P NMR spectra of the reaction mixture. After a few hours, all signals expected for the $\alpha,\beta$-unsaturated ester were

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[3] Egan, W.; Bull, T. E.; Forsen, S. *J. Chem. Soc. Chem. Commun.* 1972, 1099.

clearly visible. Thus, when a solution of ylide in $d_6$-acetone was saturated with LiBr (approximately a molar ratio of LiBr to ylide of 1.5), reaction of the ylide and solvent, as monitored by the loss of ylide $^{31}P$ signal and increase in the $^{31}P$ signal of triphenylphosphine oxide, was 50% complete in 15 h at 20 °C. The same solution, without added $Li^+$, showed no reaction after 5 days at 20 °C.

Stabilized ylides are often characterized, among other criteria, by their failure to react with ketones, although it has been reported that acids were used to activate ketonic carbonyl groups toward reactions with stabilized ylides.[4] This must now be revised to say that such condensations will not occur in the absence of a catalyst, and that $Li^+$ ion is a good catalyst for these reactions.

From these results we can be certain that $Li^+$ interacts with one or all of the species, acetone, the ylide, or the betaine intermediate in this Wittig reaction. Our evidence for chemical shift change in the ylide upon adding $Li^+$ (Table 1) strongly suggests that the ylide must be involved in this interaction.

To avoid the complication of interaction of $Li^+$ with acetone solvent, a solution was prepared where complexation, if it does happen, occurs with the ylide. This solution was prepared to contain approximately 2% of the ylide dissolved in $CDCl_3$ saturated with LiBr. This corresponded to a ratio of at least 100:1 of ylide to LiBr. The barrier to cis/trans interconversion for this solution was determined from the measurement of $^{31}P$ NMR spectra between −40 °C and +40 °C. Actual values were calculated using the method of Shanan-Atidi and Bar-Eli for the calculation of barriers to conversion between species giving unequal single peaks.[5]

For the transformation cis to trans, the free energy of activation $\Delta G^{\ddagger}$, was found to be 69.2 kJ mol$^{-1}$ and the value for the reverse transformation was found to be 68.6 kJ mol$^{-1}$. For a solution with no $Li^+$ ion, the value of $\Delta G^{\ddagger}$ is reported to be 43.1 kJ mol$^{-1}$. Thus the effect of a trace of $Li^+$ is an increase of 60% in the barrier.

Upon standing over a period of 5 days, the solution of ylide in $CDCl_3$ with LiBr in $CDCl_3$ slowly absorbed water, with an increase in a signal assigned to $H_2O$ at 1.6 ppm. This was accompanied by a breaking down of the doublet splitting in the $^1H$ NMR spectrum, followed by a loss of the cis/trans separation. The rate of this process was very much slower than the control process in a solution of ylide in dried $CDCl_3$ with a molecular sieve in the tube.

Addition of $Li^+$, as LiBr, achieved the same resolution of the two isomeric forms as the addition of a trace quantity of BuLi. In both cases there was no change in the chemical shift of the ylide carbon in the $^{13}C$ NMR spectrum of the phosphorane. This would suggest that LiBr, which, as the solid, is quite hygroscopic, serves as a drying agent removing any water molecules that might be present and thus slowing the interconversion of the two forms, whereas BuLi removes traces of conjugate acid and water by reaction.

We may conclude that the interconversion of **1-cis** and **1-trans** is proton-catalyzed but is not affected by a trace amount of $Li^+$. On the other hand, Wittig reaction is catalyzed by both Lewis acids: proton and lithium cation. From the practical point of view, it appears that small quantities of these Lewis acids facilitate the condensation reaction, perhaps by providing a lower energy route via $Li^+$-stabilized betaine. When a large excess of $Li^+$ is present in the reaction medium (as in the experiment carried out in acetone-$d_6$) a possible increase in the concentration of charge on the ylide's carbanion may also contribute to the increase in the reaction rates.

## Experimental Section

In all reactions studied, ylide was largely free from its conjugate acid, benzaldehyde was freshly distilled, and deuterated chloroform (used as a solvent during the reactions) was treated with molecular sieves. The NMR tubes used in all experiments were oven-dried at 150 °C for at least 3 h. Butyllithium used was 1.6 M solution in hexanes (Aldrich).

The general procedure used was as follows. Ylide 1 (0.3 mmol) dissolved in dry $CDCl_3$ (0.5 mL) was placed in an oven-dried, nitrogen-swept NMR tube and the spectrum was recorded. It was recorded again when an appropriate temperature was reached, 0 °C or −20 °C, depending on the experiment. In the experiments with BuLi an appropriate volume of BuLi was then added and the spectrum was taken again. Benzaldehyde (0.3 mmol) dissolved in precooled $CDCl_3$ (0.2 mL) was then added and the total volume adjusted to approximately 1 mL with $CDCl_3$. The reaction was then followed at constant temperature with spectra taken at 15–20-min intervals.

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[4] Ruchardt, C.; Eichler, S.; Panse, P. *Angew. Chem. Int. Ed. Engl.* **1963**, *21*, 619. Bose, A. K.; Manhas, M. S.; Ramer, R. M. *J. Chem. Soc. (C)* **1969**, 2728.

[5] Shanan-Atidi, H.; Bar-Eli, K. H. *J. Chem. Phys.* **1970**, *40*, 961.