Practical Guidance for Obtaining Optimum *cis*-Selectivities in Wittig Reactions with Triphenylphosphonio-alkanides**

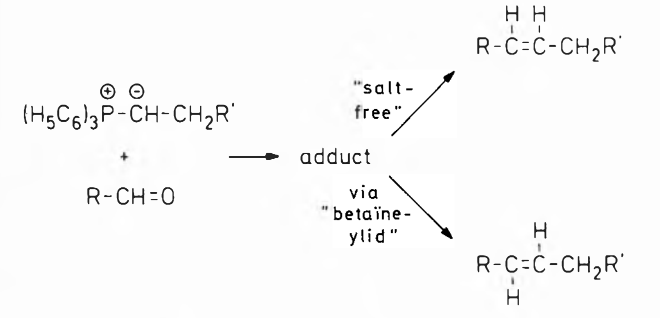
Manfred Schlosser*, Bruno Schaub, Jose de Oliveira-Neto, and Suruliappa Jeganathan

This and the following communication are dedicated to Professor Vladimir Prelog on the occasion of his 80th birthday

Abstract: Attention is drawn to the crucial role played by the base, the solvent, and the temperature in determining the stereochemical outcome of «salt-free» olefination reactions. Under optimized conditions unprecedented *cis*-selectivities are observed.

Precisely 20 years ago, *cis*- and *trans*-selective modifications of the Wittig reaction were disclosed[1]. Both are restricted to the use of «reactive»[2] ylids***, i.e. triphenylphosphonio-alkanides without a hetero-substituent nor an unsaturated hydrocarbon moiety (1-alkenyl or aryl) attached to the α-position. On the other hand, the carbonyl component may be randomly chosen among branched or unbranched aliphatic, unsaturated or aromatic aldehydes[2,3].

Whereas the *trans*-selectivity attained is 99.5% in typical[4] and 98% in difficult[5] cases, so far the *cis*-selectivity of «salt-free» Wittig reactions averages only 95%. Though laborious, new carbon-carbon linking methods such as the carbocupration of acetylene[6] or the palladium-promoted alkylation of 1-alkenylboranes[7] offered a superior *cis*-selectivity in olefin synthesis. Therefore, we have scrutinized all parameters which may improve stereocontrol in ylid reactions. The present communication focuses on the reaction conditions and restates some principles which were already previously[1–3] recognized as being essential.



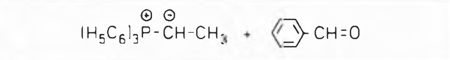
1. *Salt Effects*

Ether-soluble lithium salts or, in liquid ammonia, even sodium salts[4] may affect the stereochemical outcome of Wittig reactions in two ways[3]: they diminish the *erythro*(*cis*)-selectivity of the adduct-forming step, when present from the beginning, and they catalyze an epimerization process[8] which progressively increases the proportion of the *threo*(*trans*)-component, even if they are added only after oxaphosphetane formation[3]. Thus, it is a prerequisite for high *cis*-selectivities to exclude lithium salts or any other *soluble*[9] metal halide from the reaction medium. The «instant ylid» technique[10] allows this goal to be achieved most conveniently. Upon addition of an ethereal solvent, mixtures of an alkyltriphenylphosphonium bromide and sodium amide[11], inert towards each other in the solid state, immediately begin to evolve ammonia, the generation of the ylid being complete after 15–30 min of vigorous stirring at 25°C. Replacement of the ethereal solvent by toluene or of sodium amide by sodium and potassium hydride (in tetrahydrofuran) gives particularly pure ylids but requires longer reaction times (2–10 h).

2. *Solvent and Complexand Effects*

Compared with sodium amide, the «Rochow bases» sodium or potassium bis(trimethylsilyl)amide offer no particular advantage but lead to somewhat diminished yields and selectivities (see Table 1). Potassium *tert*-butyl alcoholate in ethereal

Table 1. Wittig reaction of triphenylphosphonio-ethanide with benzaldehyde: (*Z*/*E*)-ratios of 1-phenylpropene depending on which complexing NH- or OH-acid, if any, had been added either before or after oxaphosphetane formation[a)].



complexand	2 equiv. added to the ylid	1 equiv. added to the ylid	1 equiv. added to the oxaphosph.
-	91.5 : 8.5	91.5 : 8.5	91.5 : 8.5
$((H_3C)_3Si)_2NH$	90.5 : 9.5	91.5 : 8.5	90 : 10[b)]
NH_3 [c)]	90.5 : 9.5	91.0 : 9.0	91.5 : 8.5
H_3CSOCH_3	89.5 : 10.5	90.5 : 9.5	90.0 : 10.0
$(H_3C)_3COH$	80.0 : 20.0	84.0 : 16.0	86.0 : 14.0
H_3COH	43.5 : 56.5	68.5 : 31.5	72.0 : 28.0

[a)] In this and the following communication all (*Z*/*E*)-ratios are rounded to half-percentage points although both the analytical accuracy (gas chromatography on $AgNO_3$, where possible, or silicon rubber and polyester loaded columns; at least 3 injections per run) and the synthetic reproducibility (at least 3, sometimes up till 10 individual runs for each reaction) proved to be better. There remains, however, some ambiguity concerning the temperature profile when the reaction mixture being at −75°C is allowed to reach 25°C. In general, it appears to be beneficial for *cis*-selectivities if this warm-up period is kept as short as possible.

[b)] This mixture gives rise to some erratic behavior. In one experiment we found a (*Z*/*E*)-ratio of only 61.5:38.5.

[c)] The appropriate amount of liquid ammonia was transferred by means of a pipet to the ylid or oxaphosphetane solution cooled to −75°C.

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* *Correspondence:* Prof. Dr. M. Schlosser
Institut de Chimie organique de l'Université
Rue de la Barre 2, CH–1005 Lausanne

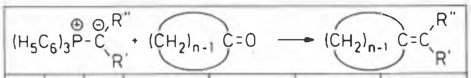
** The work described in this and the following communication was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (grant No 2.446-0.84).

*** Following the example of eminent researchers (A.W. Johnson, H.J. Bestmann, H. Schmidbaur, and G. Wittig among others) we prefer the spelling «ylid» over «ylide». As a hybrid rather than piece of consistent nomenclature, the word «yl*id*» ends with a syllable which is not the same as in chlor*ide*. Actually, ylid is pronounced like «rid» and not like «ride».

solvents[12] or *tert*-butyl alcohol[13] and sodium *tert*-pentyl alcoholate in benzene[14] must not be taken into consideration unless one is willing to sacrifice the stereoselectivity of the olefination reaction (see Table 1).

Toluene[15] may prove to be the most suitable solvent for the olefination of carbonyl compounds (such as phenylacetaldehyde) which show a high propensity for enolate formation. In general, however, tetrahydrofuran (THF), ethylene glycol dimethyl ether (EGME), diethyl ether (DEE), and *tert*-butyl methyl ether (tBME) are the solvents of choice, the latter two often leading to slightly better yields and selectivities. Like protic solvents (alcohols), dimethyl sulfoxide (DMSO) should be strictly avoided because it is detrimental for both yields and stereoselectivities (see Tables 2 and 3).

Table 2. Reaction of triphenylphosphonio-methanide, -butanide, and -isopropanide with cyclopentanone, cyclohexanone, or cycloheptanone: yields of olefins as a function of the base and the solvent.

						
R'	R"	n	$NaNH_2$ THF [a)]	$NaN(tms)_2$ THF [b)]	Nadmso DMSO [c)]	LiC_4H_9 DEE [d)]
H	H	6	92%	57%	86%[17]	52%[19]
		7	90%	85%	<10%[18]	-
C_3H_7	H	5	86%	32%	15%	-
		6	91%	80%	53%	-
CH_3	CH_3	5	71%	58%	26%	-
		6	83%	52%	30%	37%

a) The ketone was added to the ylid solution at 0 °C and the mixture kept 2 h at 25 °C.
b) $NaN(tms)_2$ = sodium bis(trimethylsilyl)amide. The new reactions were performed in analogy to a literature procedure[16].
c) Nadmso = methylsulfinylmethyl sodium. The new reactions were performed in analogy to a literature procedure[17].
d) The new reaction was performed in analogy to a literature procedure[19].

Table 3. Reaction of triphenylphosphonio-propanide with hexanal or benzaldehyde: yields and, in parentheses, (*Z*/*E*)-ratios of olefins as a function of the base and the solvent.

$(H_5C_6)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-C_2H_5 + R-CH=O \longrightarrow R-CH=CH-C_2H_5$				
R	$NaNH_2$ THF [a)]	$NaN(tms)_2$ THF [b)]	Nadmso DMSO [c)]	LiC_4H_9 DEE [d)]
$H_{11}C_5$	95% (97 : 3)	70% (96 : 4)	60% (91 : 9)	81% (50 : 50)
H_5C_6	97% (94 : 6)	97% (85 : 15)	68% (73 : 27)	80% (86 : 14)

a) The aldehyde was added to the ylid solution at −75 °C and the mixture was kept 15 min at 25 °C.
b) See footnote b) to Table 2.
c) See footnote c) to Table 2.
d) See footnote d) to Table 2.

3. *Temperature Effects*

The *cis*-selectivities depend heavily on the temperature at which the ylid and the aldehyde combine to afford the adduct[3]. What is frequently overlooked is the exceptionally high exothermicity of the oxaphosphetane-forming step. Thus, the aldehyde has to be added dropwise under efficient cooling and the temperature inside the reaction vessel must be continuously monitored. If such precautions are taken, optimum *cis*/*trans*-ratios are attained around −75 °C or −100 °C (see Table 4).

Table 4. Reaction of triphenylphosphonio-ethanide with hexanal or benzaldehyde and of triphenylphosphonio-butanide with benzaldehyde: (*Z*/*E*)-ratios of olefins as a function of the temperature at which the aldehyde was added to the solution of the ylid in THF[a–c)].

$(H_5C_6)_3\overset{\oplus}{P}-\overset{\ominus}{C}H-R' + R-CH=O \longrightarrow R-CH=CH-R'$			
T	R' = CH_3	R' = CH_3	R' = C_3H_7
[°C]	R = $H_{11}C_5$	R = 	R = 
+25	87.0 : 13.0	85.5 : 14.5	91.0 : 9.0
0	90.0 : 10.0	88.5 : 11.5	94.0 : 6.0
-25	92.0 : 8.0	89.0 : 11.0	95.5 : 4.5
-50	93.5 : 6.5	91.0 : 9.0	96.0 : 4.0
-75	95.5 : 4.5	91.5 : 8.5	96.5 : 3.5
-100	96.5 : 3.5	92.0 : 8.0	97.0 : 3.0

a) See footnote a) to Table 1.
b) Yields, like (*Z*/*E*)-ratios, were determined by gas chromatography using an «internal standard» and calibration coefficients. They fell in the range of 83–95%.
c) Temperatures below ordinary were adjusted by means of an ice bath (0 °C), a cryogenic unit (−25 °C and −50 °C), a dry ice/methanol bath (−75 °C), and a methylcyclohexane/liquid nitrogen mixture (−100 °C).

General working procedure: A suspension of the alkyltriphenylphosphonium salt (100 mmol) and sodium amide[20] (100 mmol) in DEE, tBME, EGME/hexane (1:1 by volume), or THF (200 mL) is vigorously stirred during 20 min at 25 °C, the evolving ammonia being swept out by a gentle stream of nitrogen. The brick-red solution is cooled to −75 °C and the aldehyde (100 mmol) added dropwise, in the course of about 15 min. After leaving the reaction mixture 15 or 120 min at 25 °C (depending on whether the carbonyl compound was an aldehyde or ketone), the olefin can be directly isolated by distillation or chromatography on silica gel. In the latter case it is advantageous first to precipitate the bulk of the triphenylphosphane oxide which is produced together with the olefin by adding 300 mL of cold (< −20 °C) hexane and to remove it by filtration or centrifugation.

Received: June 18, 1986 [FC 73]

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[8] The dominant epimerization mode is the reversible decomposition of the oxaphosphetane intermediate to the precursors ylid and aldehyde. Reversibility is substantial with aromatic and less important with aliphatic aldehydes. Thus, consecutive addition of *p*-methylbenzaldehyde (1.1 equiv.) and benzaldehyde (2.0 equiv.) to triphenylphosphonio-butanide at −75 °C and warming up to 25 °C gives rise to 53% 1-phenyl-1-pentene (besides 38% 1-*p*-tolyl-1-pentene) while only 14% of 1-phenyl-1-pentene (besides 79% of 4-octene) result when the *p*-methylbenzaldehyde is replaced by butanal.

[9] Although it can be done there is no need to remove, by filtration, the sodium bromide which is produced together with the ylid when a phosphonium bromide is treated with sodium amide in an ethereal solvent. Being entirely insoluble under such conditions, the salt does not interfere with any of the reagents nor reaction intermediates.

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[11] The necessity of employing high-quality sodium amide should be emphasized again. A content of as little as 10% of sodium hydroxide may suffice to drastically lower the yields due to Ingold- or Haller-Bauer-type degradation of the phosphonium salt which is converted to benzene and alkyldiphenylphosphane oxide.

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[20] In general we use the 50% sodium amide suspension in toluene which is supplied by Fluka AG, Buchs. The solvent is removed by filtration through a sinter-glass frit and the amide particles are washed with DEE, dried, and stored under nitrogen.