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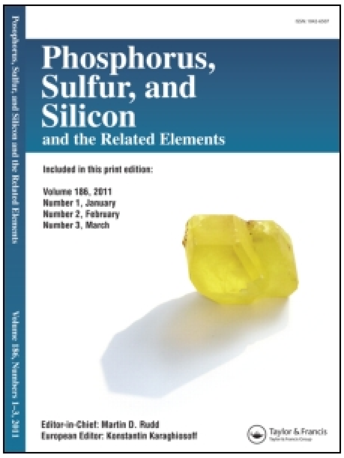

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The Wittig Reaction : 30 Years Later

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THE WITTIG REACTION : 30 YEARS LATER

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Abstract : New and old ylid reactions are described and their mechanisms examined.

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The Wittig reaction [1, 2] belongs to the most prominent methods for organic synthesis. It can be performed under very mild and essentially neutral conditions, is absolutely reliable as far as the regioisomeric homogeneity of the alkene product is concerned and has an immensely wide scope of application, which was still expanded by the introduction of useful modifications such as the Wittig/Horner-procedure in which "PO ylids" (derived from phosphine oxides or phosphonates) replace the ordinary phosphonio ylids.

Other modifications helped to establish stereoselective versions of the Wittig reaction. Thus, mainly cis-olefins form when triphenyl--phosphonio-alkylids react with aldehydes in the absence of soluble lithium salts. Prerequisites are a solvent of low polarity and low temperatures at the moment when the ylid and the aldehyde combine. Ylids carrying an unbranched, primary alkyl group at the carbanionic center give rise to cis/trans ratios ranging from 94 : 6 to 99 : 1 [3, 4]. On the other hand, when the ylid is allowed to react with an aldehyde in the presence of soluble lithium salts and the adduct is epimerized in an α-deprotonation/reprotonation sequence, the initially formed diastereomeric mixture of the intermediate is converted to the essentially pure threo form. Upon completion of the reaction by elimination of triphenylphosphine oxide an olefin results the cis/trans-ratio of which averages 1 : 99 [3, 5]. Using the same α-deprotonated adducts as key intermediates, an entry to trisubstituted and functionalized ethylenic compounds has been opened ("SCOOPY-procedure", "three-dimensional Wittig reaction" [3, 6]).

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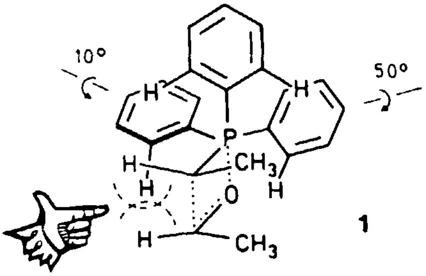
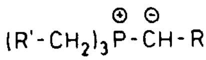
Although these stereoselective modifications of the Wittig reaction became very popular in the past decade and found wide application, their mechanistic basis remained obscure. Only recently the *cis*-selectivity of salt-free ylids found a rational explanation which is compatible with all experimental findings [7]. According to this model, the propeller-like conformational arrangement of the phenyl groups at the transition state (1) sterically impedes the formation of a *trans*-3,4-disubstituted oxaphosphetane, the precursor to a *trans*-olefin. In contrast, the aldehyde can readily combine with the ylid in a "leeward approach". The ylid side-chain forces the neighboring phenyl ring out of the way and the organic moiety of the aldehyde does not experience much of repulsion when it advances on the same side thus generating a *cis*-oxaphosphetane leading finally to the *cis*-alkene.



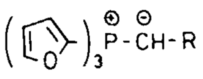
1

Variations of the "stationary" groups at the phosphorus atom allow to "tune" the steric interactions and thus optimize the resulting stereoselectivity. Compared with the common phenyl substituents, primary alkyl groups (2a) as well as furyl rings (2b) diminish the steric bulk while *ortho*-substituted aryl groups (2c and 2d) increase it [8].

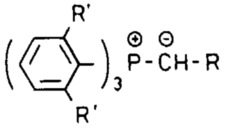


$$(R'\text{-}CH_2)_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H\text{-}R$$

$[R' = H, H_7C_3]$



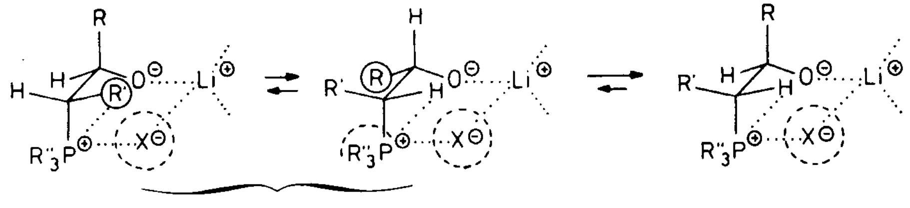
2b



2c $[R' = CH_3, R'' = H]$

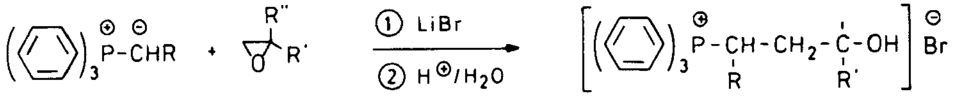
2d $[R' = R'' = F]$

The *trans*-selectivity in the presence of lithium salts and under equilibrating conditions merely reflects the enhanced thermodynamic stability of the *threo*-betaine-LiX adduct (*threo*-3) with respect to its *erythro*-isomer. These intermediates contain two bulky groups : besides the triphenyl-phosphonio moiety also the OLi function which in aprotic solvents is subject to complexation and notably aggregation. As a conformational analysis [8] reveals, only the *threo*-configuration offers the possibility to place both organic substituents R and R' in an *anti*-periplanar position relative to the space-demanding phosphonio and, respectively, alcoholate group at the adjacent center.



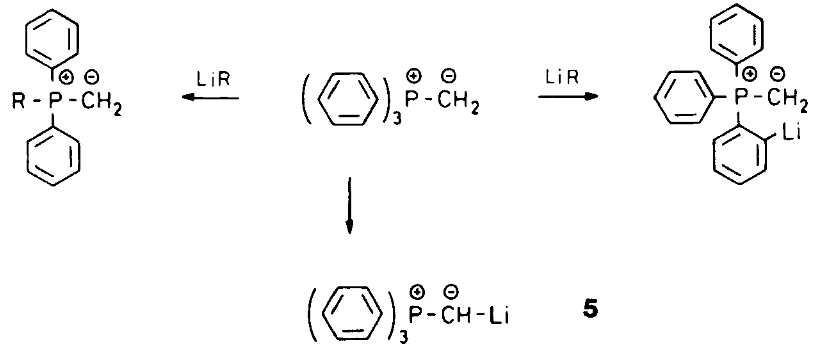
erythro-3 **threo-3**

Lithium salts also affect the outcome of ylid reactions with electrophiles other than aldehydes or ketones. Whereas oxiranes are practically inert towards salt-free ylids, they readily undergo ring-opening, affording, after hydrolysis, γ-hydroxyalkyl-tri-phenylphosphonium salts (4) when lithium bromide is present [9]. The very strong O-Li linkage in the intermediate, constitutes the major driving force for this adduct formation.



4

A different means of activation exists to make again phosphonio ylids react with electrophiles as weak as oxiranes. The ylid nucleophilicity may be drastically increased by metalating the ylid center, thus producing an α-lithio-ylid (5) [9, 10]. Though quite appealing in principle, this approach suffers from severe practical drawbacks. Even with most powerful metalating agents such as *sec*- and *tert*-butyllithium the hydrogen/metal exchange occurs only sluggishly and, worse, is accompanied by side reactions. A thorough ^{1}H-, ^{2}H- and ^{31}P-nmr investigation of the reaction mixtures and the products obtained upon quenching with deuterium chloride helped to identify two of these competing reactions : a phenyl/alkyl exchange and the metalation of one of the phenyl rings at the *ortho*-position [11].



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Finally, the practical execution of Wittig reactions has found a most remarkable improvement and simplification by the recent introduction of "instant ylid" powders [12]. As long as dry, these homogeneous mixtures of a phosphonium salt with a stoichiometric amount of sodium amide may be stored almost indefinitely. They generate, however, immediately the corresponding ylid when suspended in tetrahydrofuran or diethyl ether. These "instant ylids" exhibit highest reactivities towards aldehydes, ketones and methyl formiates. While the reaction may be performed in a minimum time and without even requiring inert gas protection, excellent yields and extreme stereoselectivities are obtained.

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References

1 G. Wittig & G. Geißler, Justus Liebigs Ann. Chem. 580 (1953), 44.

2 M. Schlosser, Chemie Lab. Betr. 33 (1982), 259.

3 M. Schlosser, Topics Stereochem. 5 (1970), 1.

4 M. Schlosser, G. Müller & K.F. Christmann, Angew. Chem. 78 (1966), 677; Angew. Chem. Int. Ed. Engl. 5 (1966), 667.

5 M. Schlosser & K.F. Christmann, Angew. Chem. 78 (1966), 115; Angew. Chem. Int. Ed. Engl. 5 (1966), 126.

6 M. Schlosser & K.F. Christmann, Synthesis 1969, 38.

7 M. Schlosser & B. Schaub, J.Am. Chem. Soc. 104 (1982), 5821.

8 R. Oi, B. Schaub & M. Schlosser, unpublished.

9 M. Schlosser, Huynh Ba Tuong, J. Respondek & B. Schaub, Chimia 37 (1983), 10.

10 M. Schlosser, G. Steinhoff & T. Kadibelban, Angew. Chem. 78 (1966), 1018; Angew. Chem. Int. Ed. Engl. 5 (1966), 968; Justus Liebigs Ann. Chem. 743 (1971), 25.

11 T. Jenny, B. Schaub & M. Schlosser, unpublished.

12 M. Schlosser & B. Schaub, Chimia 36 (1982), 396.