

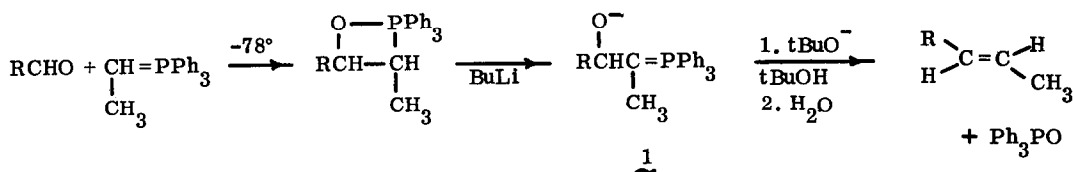
ON THE ORIGIN OF STEREO- AND POSITION SELECTIVITY
IN THE SYNTHESIS OF ALLYLIC ALCOHOLS FROM β -OXIDO YLIDES

E. J. Corey, Peter Ulrich and A. Venkateswarlu

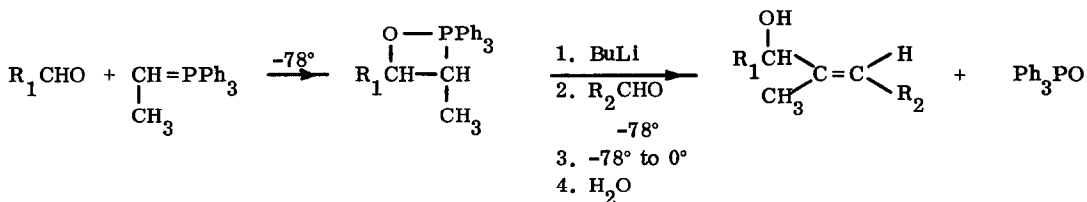
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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β -Oxido ylides, e.g., 1, were first prepared by Schlosser¹, and applied by him to the synthesis of trans-1,2-disubstituted olefins as shown in Scheme I.² Subsequently it was shown³ that β -oxido ylides could be used to advantage in the stereoselective synthesis of trisubstituted olefins as illustrated in Scheme II. As



Scheme I



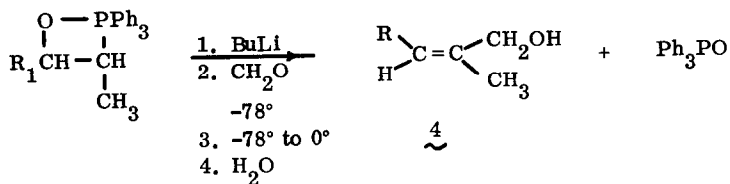
R_1 and R_2 are alkyl or aryl.

Scheme II

indicated in Scheme II, the β -oxido ylide route to olefins allows the joining of the carbons of three components in one operation in such a way that the oxygen of the first aldehyde component is retained whereas that of the second aldehyde is eliminated as phosphine oxide. This position specificity for the olefin synthesis could even be demonstrated for the case of benzaldehyde and 1-deutero benzaldehyde as the aldehyde components.³ With benzaldehyde as the first component and deuterio-benzaldehyde as the second the product was exclusively 2, whereas reversal of the aldehyde order gave only 3. A different type of behavior was noted when formaldehyde



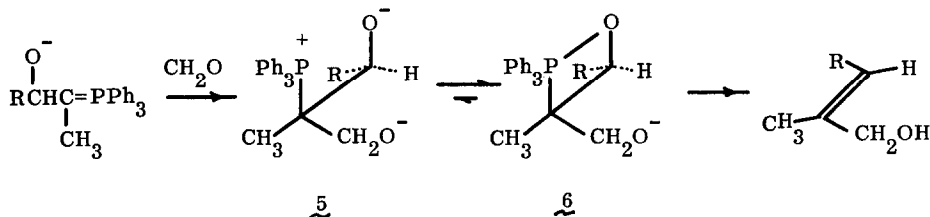
was used as the second aldehyde component, as is outlined in Scheme III. The special behavior of formaldehyde as the second aldehyde component, i.e., retention of its oxygen in the product, results in a different



Scheme III

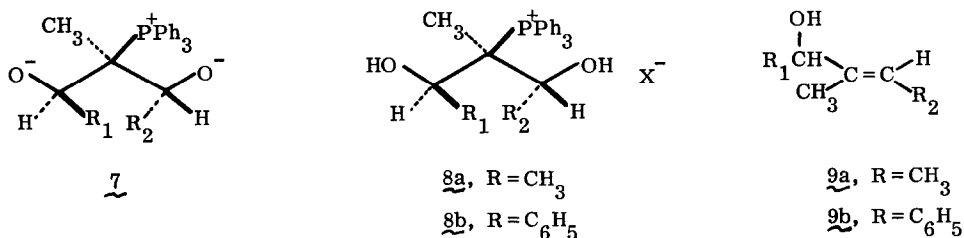
location of the double bond in the final product (4) relative to the starting components. The formaldehyde based process shown in Scheme III generates the olefinic linkage of *Z*-stereochemistry with high stereoselectivity, and this has proved extremely useful for the synthesis of a variety of substances including α -santalol^{3a}, farnesol^{4a} and insect juvenile hormone.^{4b,5}

The reaction of a β -oxido ylide (1) with either a proton donor, mercuric ion^{3b} or iodobenzene dichloride^{3b} obviously occurs in the same stereochemical sense since *trans*-olefin is produced in each case. The attack of the carbonyl electrophile formaldehyde with 1 follows the same stereochemical course to give the primary adduct 5, which goes on to product through the presumably more stable² oxaphosphetane 6. The suggestion that β -oxido ylides react with aldehydes by way of oxaphosphetanes only² is clearly untenable in this



Scheme IV

instance. Since there seems to be little reason to assume that the reaction of a β -oxido ylide with formaldehyde should be different than that with other aldehydes we prefer the original suggestion³ that the structural and stereochemical selectivity observed in the reaction of a β -oxido ylide with a higher aldehyde is due to the intermediacy of a primary adduct with the stereorelationships expressed in formula 7.⁶ In this note we present additional evidence in support of this earlier proposal and a more detailed explanation of the basis for



the remarkable stereoselection involved.

Reaction of the β -oxido ylide derived from acetaldehyde and ethylenetriphenylphosphorane (1, R = CH₃) in tetrahydrofuran (THF) at -78° under argon with acetaldehyde followed by treatment of the reaction mixture with acetic acid in THF at the same temperature produced a colorless precipitate which could be obtained in crystalline form (mp 214.5-215°) from methylene chloride-ether as the bromide salt in 56-63% yield. The structure of this solid was revealed as the racemic isomer 8a by proton magnetic resonance (pmr)

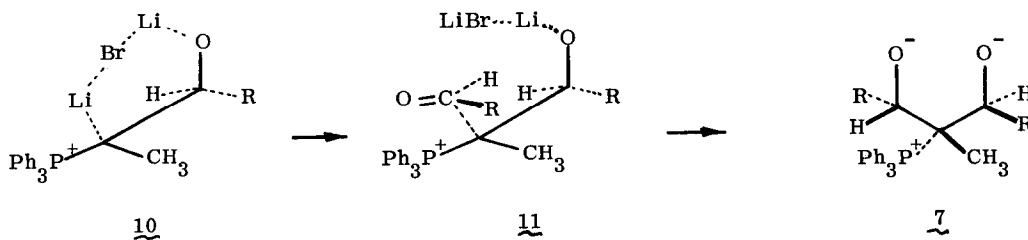
spectroscopy which clearly shows the non-equivalence of the methine, hydroxyl and methyl protons of the two acetaldehyde-derived CH_3CHOH moieties. Obviously, these units would be diastereotopic only in a racemate form; i. e., not in a meso form. Treatment of **8a** with 2 equiv of methyllithium in ether to regenerate the dioxido intermediate **7**, $\text{R}=\text{CH}_3$, followed by stirring at 25° to effect elimination of triphenylphosphine oxide and isolation afforded the E-allylic alcohol **9a** and the corresponding Z isomer in a ratio of 93:7 by pmr analysis (65% yield). Authentic samples of these isomeric olefins were prepared for direct comparison.⁷

Examination of the mother liquors from the isolation of **8a** revealed the presence of an additional 3% of this substance (total 66%), ca. 6% of an isomer which appears to be the meso form (decomposition of which as above leads mainly to the Z isomer of **9a**), and 5-10% of the E-alcohol **9a**. Thus the stereoselectivity of formation of **7**, $\text{R}_1=\text{R}_2=\text{CH}_3$, from the β -oxido ylide **1**, $\text{R}=\text{CH}_3$, and acetaldehyde at -78° is approximately 10 to 1. The smaller size of methyl relative to higher alkyl or aryl indicates that this is the minimum stereoselectivity to be expected for the reaction of a β -oxido ylide **1** with an aldehyde.

Reaction of the β -oxido ylide **1**, $\text{R}=\text{C}_6\text{H}_5$, in THF at -78° with benzaldehyde afforded after protonation (HOAc or Bu_3NHCl) and precipitation with ether a chromatographically homogeneous dihydroxy phosphonium salt (**8b**, $\text{X}=\text{Cl}$) in 80% yield.⁸ Treatment of this dihydroxy phosphonium adduct with 2 equiv of *n*-butyllithium at -78° followed by storage at 25° for 2 hr to effect elimination afforded exclusively E-1,3-diphenyl-2-methyl-2-propen-1-ol (**9b**), the same product obtained in the normal β -oxido ylide process with benzaldehyde as the first and second aldehyde components.

Taken together these results indicate that the reaction of a β -oxido ylide with an aliphatic or aromatic aldehyde affords stereoselectively a racemic dioxido phosphonium adduct with high stereoselectivity and further that it is the preference of this intermediate to form E-olefin which determines that the oxygen of the second aldehyde component⁹ is lost. All known experimental data can be accommodated by this scheme.

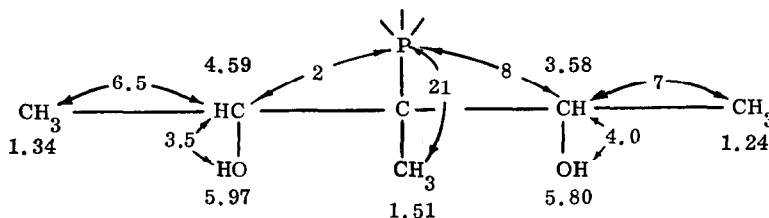
The question of why β -oxido ylides (**1**) react with aldehydes (or other electrophiles) with such selectivity is most intriguing but far from answerable at present in view of the total lack of knowledge of the nature of β -oxido ylides in solution. One interesting and not unreasonable possibility (Scheme V) is that β -oxido ylides possess a cyclic structure with a strong preference for the diastereomeric form **10**. Reaction of **10** with an aldehyde so as to minimize steric interferences between groups (geometry as in **11**) would then lead to the stereochemistry demonstrated for the intermediate adduct **7**.^{10, 11}



Scheme V

References and Notes

1. M. Schlosser and K. F. Christmann, *Angew. Chem. Int. Ed. Eng.*, **5**, 126 (1966); *Ann. Chem.*, **708**, 1 (1967).
2. For evidence that the oxaphosphetane structure is more stable than the betaine form of the ylide-aldehyde adduct in the Wittig reaction see E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, **95**, 5778 (1973). See also, M. Schlosser, A. Piskala, C. Tarchini and H. B. Tuong, *Chimia*, **29** (1975).
3. (a) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226, 3523 (1970); (b) E. J. Corey, J. I. Shulman and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).
4. (a) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6637 (1970); (b) *idem.*, *ibid.*, **92**, 6636 (1970).
5. For application of the β -oxido ylide method according to scheme II to the synthesis of prostaglandins F_2 and E_3 see E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaaf, *J. Am. Chem. Soc.*, **93**, 1490 (1971).
6. In our view the dioxido phosphonium structure is probably in mobile equilibrium with the mono-oxido oxaphosphetane structure² corresponding to the final product (*vide infra*).
7. The *E* isomer was obtained by reaction of methylolithium with tigaldehyde at 0° in ether. The *Z* isomer was prepared by the method of H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958).
8. Unfortunately the pmr spectrum of this product did not allow a distinction between racemic and meso geometry.
9. With the exception of formaldehyde which understandably favors the reaction course outlined in Schemes III and IV.
10. The experimental procedure for the preparation of 3-(2,4-dihydroxy-3-methylpentyl)triphenylphosphonium bromide (8a) is as follows: To a suspension of $Ph_3PEt^+Br^-$ (1.86g, 5.0mmol) in THF (20ml) at 0° under argon was added *n*-BuLi in hexane (5.0mmol). After stirring for 30 min at 0° to 25° the clear orange solution was cooled to -78° and treated with acetaldehyde (5mmol) for 10 min. The yellow solution was treated with *n*-BuLi in hexane (5.0mmol) and the resulting deep red solution was stirred 5 min at -78°, 2 min at 0° and then recooled to -78°. A 2.5-fold excess of acetaldehyde was added and then after 5 min, HOAc in THF (10mmol) producing a dense precipitate. Ether (30ml) was added to complete precipitation, and the mixture was warmed to 25° and stirred for 10 min. The colorless solid was collected by filtration and washed with 1:1 Et_2O -THF, benzene and Et_2O , the washings being combined with the above filtrate. The resulting powder was digested with CH_2Cl_2 , filtered and concentrated to give 2.17g of colorless solid (99% crude). A solution of this solid in 3ml of 4:1 CH_2Cl_2 - Et_2O deposited colorless crystals of 8a $\cdot CH_2Cl_2$ (63% yield): pmr (100 MHz, 1:1 $CDCl_3$ / $DMSO-d_6$) δ 7.60 (m, 15H, Ph), other pmr peaks (δ values) and coupling constants (Hz) are summarized in the following diagram:



11. This research was assisted financially by a grant from the National Science Foundation.