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ANIONIC ACTIVATION OF STABILIZED YLIDES. A HIGHLY Z-STEREOSELECTIVE WITTIG REACTION OF (3-ETHOXYCARBONYL-2-OXOPROPYLIDENE)TRIPHENYLPHOSPHORANE WITH ALIPHATIC ALDEHYDES

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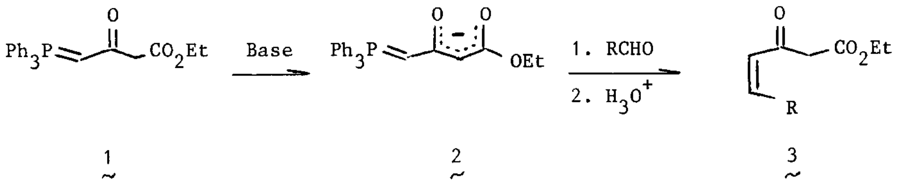
Abstract: *Reaction of stabilized ylide 1 with carbonyl partners can be promoted via anionic activation of the ylide; the presence of charge is responsible for the high Z-selectivity in the direct formation of conjugated enones.*

Despite the fact that efforts to fully understand the mechanism of the Wittig reaction still continue,[1] its application for stereoselective synthesis of alkenes has long ago become of paramount importance in synthetic practice.[2] In general, non-stabilized phosphonium ylides react with aldehydes to produce predominantly Z-olefins whereas stabilized phosphonium ylides afford predominantly E-olefins in such reactions. While in the former case that ramification can be conveniently circumvented via equilibrating procedure of Schlosser,[3] the apparently lacking complementary solution for the reversal of stereoselectivity in the latter case has not been offered as yet. Undoubtedly, direct route to the labile Z-alkenes would be of great synthetic importance. Most of the efforts along this line, however, were diverted rather to the corresponding phosphonate reagents, in which the search for Z-selectivity was focused mainly on the modification of the phosphorus ester groups, and/or judicious choice of reaction conditions.[4] We wish to demonstrate for the first time that high yields of conjugated Z-enones can be achieved directly in reactions involving carbonyl stabilized ylide 1 and aliphatic aldehydes. Our approach takes advantage of changing the reactivity of the ylide via simple *in situ* transformation of the stabilizing carbonyl group into its enolate counterpart 2. The overall conversion is outlined below.



Under neutral conditions ylide **1** is poorly reactive and does not react with aldehydes even after prolonged heating in refluxing tetrahydrofuran .[5] However, when equimolar amounts of the ylide and an aldehyde were mixed together with 2 equivalents of NaH in tetrahydrofuran and a small amount of water was then added to activate NaH,[7] a very facile reaction occured leading to the expected conjugated ß-keto ester 3 with considerable preference for the formation of the Z isomer. A short series of model experiments (Table) revealed further that in such reactions the selectivity was substantially higher for aldehydes bearing large alkyl substituents and was practically complete for the sterically most demanding pivalaldehyde. This observation resembles closely trends previously noted only in reactions of highly reactive (non-stabilized) ylides[1e,j,2,8] and demonstrates explicitly the efficacy of the presented approach.

Table[a]

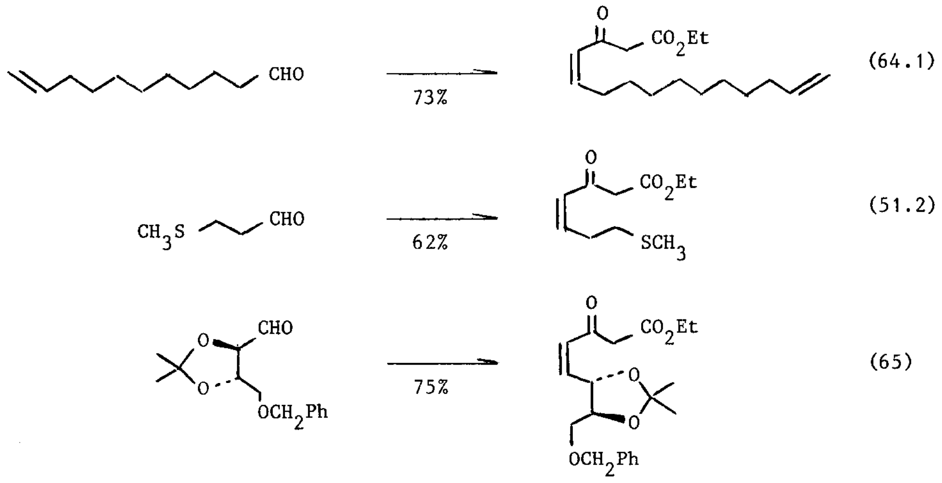
Aldehyde	Yield of **3**, %[b]	Z isomer, %[c]
CH_3CHO	15	60
CH_3CH_2CHO	65	85
$CH_3(CH_2)_9CHO$	91	86
$(CH_3)_2CHCHO$	90	84
$(CH_3)_3CCHO$	42	98

a - Reaction conditions are given in ref. 9. b - Yields are for isolated and distilled material.[10] c - Isomer ratios are GLC values; pure E isomers for comparison were available from our earlier work on the corresponding phosphonate reagent.[11]

Contrary to expectations,[2,12] the addition of HMPA as co-solvent to tetrahydrofuran did not result in the increase of the Z/E ratio although, in this medium, addition of water to promote generation of **2** was no longer necessary. Analogously, admixture of 15-crown-5 which proved advantageous in some annulation reactions of the ylide anion **2**, did not exibit similar effect this time.[13] Some other conditions (K_2CO_3, lower reaction temperatures, DMF) were also briefly examined but eventually the original procedure[9] proved to be the most satisfactory and, at the same time, mild enough to tolerate the presence of additional functionalities in the carbonyl substrate (Scheme). In this context, the stereoselective elaboration of optically active tartaric acid derived aldehyde is noteworthy.[14]

The high efficiency of the ylide anion **2** in producing a preponderance of Z-alkenes is at first sight surprising, considering a formal structural analogy of **2** to the well known ß-oxido ylides.[2,3] However, extensive internal stabilization of the acetoacetate anion in **2** may be suggested to explain this dramatic difference in stereochemical behaviour of the two systems.

In contrast to the above cases, only small percentage of Z-isomers could be detected (GLC) in the crude reaction mixture of products derived from **2** and aromatic aldehydes; the corresponding numbers for benzaldehyde, *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde being 25.5, 10.4 and 13.4%, respectively. The true pattern of selectivity in these reactions is probably obscured by rapid isomerization of the final products[15] and/or by "stereochemical drift" during the reaction.[1a,c]



Scheme[a]

a - In all presented cases the selectivity was ~ 9:1 in favor of the Z isomer. Yields are given for isolated material. The numbers in parentheses represent yields of separated and distilled pure Z isomer.[10]

In summary, it has been demonstrated that poorly reactive phosphonium ylides can be effectively utilized in valuable stereoselective transformations after simple activation by charge.[16] The presented approach complements our previous findings on the E-selective synthesis of substituted Nazarov reagents;[11] both Z and E isomers have now become readily and directly available.

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We are also indebted to Profs. E.L. Eliel and R. Bodalski and Drs. Bruce and Cynthia Maryanoff for advice and comments.

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5. More forcing conditions together with acid catalysis may however induce condensation of **1** with benzaldehyde but they were shown too destructive in the case of simple aliphatic aldehydes.[6] Our experiments with isobutyraldehyde (1 equiv. of **1**, trace of *p*-toluenesulfonic acid, 14 h reflux in tetrahydrofuran or benzene) have confirmed this observation. The yield of conjugated ß-keto ester was less than 10% in both cases with Z isomer content of 18 and 21%, respectively (GLC).
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9. Procedure: To a stirred solution of the ylide **1** (4 mmol) in tetrahydrofuran (ca.30 mL) were added 2 equiv. of NaH followed by addition of an aldehyde (4 mmol). Practically no reaction was observed until 2 drops of water were added to the mixture and then the flask was immersed in a bath preheated to 35-40^{o}C for about 0.5-1 h. When the ylide was completely consumed the reaction was quenched with diluted HCl and then patitioned between ether and brine. The ethereal layer was washed twice with diluted $NaHCO_3$, then twice with distilled water, dried ($MgSO_4$) and evaporated *in vacuo*. The crude products were purified by distillation and separation of isomers was realized by flash chromatography using CH_2Cl_2 or Hexanes-EtOAc as eluents.
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