Reviews

Regio- and stereoselectivity in the addition reactions of CH-acids to aldehydes under the conditions of phase-transfer catalysis

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The regio- and stereoselectivity of the reactions of carbanions, generated from alkanals, carboxylates of the type XYCHCOOEt (X = EtOOC, CN, Ac; Y = H, Br), or derivatives of 3-methyl-4-phosphono-2-butenoic acid using PTC techniques, with aldehydes of various types (alkanals, α,β-enals, cross-conjugated enedials, benzaldehydes, *etc.*) are reviewed. The factors affecting the outcome of these reactions are discussed. The carbanion analogs, triphenylphosphorus ylides, are shown to attack selectively at one of the aldehyde groups of aromatic dialdehydes. The regularities found for the title reactions were used in the syntheses of some biologically active isoprenoids.

Key words: [C_2]- and [C_4]-carbanions; phase transfer catalysis; aldol condensation; the Michael addition; the Knoevenagel condensation; the Darzens reaction; the Horner—Emmons and the Wittig olefination; regioselectivity; stereoselectivity.

The base-catalyzed addition of CH-acids to aldehydes is a process of great synthetic importance since it makes it possible to elongate the carbon chain and introduce various functional groups into the molecule in a single step. However, the traditional conditions under which such reactions used to be carried out (*i.e.*, with the use of alkali metals or their hydrides, hydroxides, amides, or alkoxides in absolute solvents) are sometimes not suitable for aldehydes, since under them numerous side reactions may easily occur. Hence, the techniques of phase transfer catalysis (PTC)[1—4] appear to be rather promising here as they often allow successful performance of even those nucleophile-involving reactions which in their "classical" variants are either ineffective or simply not possible. As regards the theory of organic reactivity, of particular interest here are the factors that affect the regioselectivity of the addition of CH-acids to substrates with two or more electrophilic centers and the stereoselectivity of the reaction if the latter gives rise to two or more geometrical isomers.

This article is intended to show how a systematic study of various aspects of the interaction of nucleophilic reagents with aldehydes under the conditions of PTC helps to control the direction of the addition of carbanions to a given reactive site or the stereochemistry of the resulting unsaturated products.

Aldol condensation

With a view of obtaining geometrically pure *E* isomers of α,β-enals of type A (which are convenient intermediates for the synthesis of allylic alcohols and

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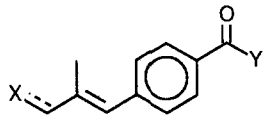
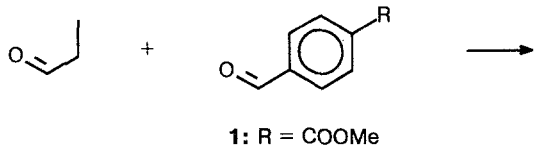
certain biologically active substances)[5–8] we tested the feasibility of selective aldol condensation of aliphatic aldehydes with their aromatic (or heteroaromatic) congeners under PTC conditions. Propanal and 4-(methoxycarbonyl)benzaldehyde (**1**, R = COOMe), a substrate with two different alkali-sensitive functional groups, were used as reference reactants in a search for the optimum conditions of these reactions; the resulting aldehydo ester **2** (R = COOMe) is a valuable bifunctional building block for the synthesis of 4-(nor-polyprenyl)benzoic acids and their derivatives (see also below, in the "Wittig reaction" section).

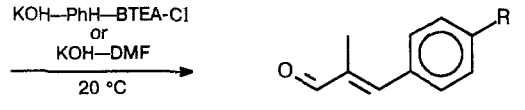


A

The most practiced conventional variants of the condensation of aromatic aldehydes with *n*-alkanals, that is, by using alcoholic or aqueous alcoholic solutions of alkali bases,[9–11] proved to be of little effectiveness, and the yields of the required product did not exceed 15 per cent. The application of the previously reported PTC procedures recommended for the aldol condensation[12,13] was also disappointing: in the system aqueous NaOH—benzene—benzyltriethylammonium chloride (BTEA-Cl) the reaction proceeded slowly to give **2** in no more than 20 % yields, whereas in the systems solid K_2CO_3 (or Na_2CO_3)—benzene (or CH_2Cl_2)—BTEA-Cl compound **2** was not formed.



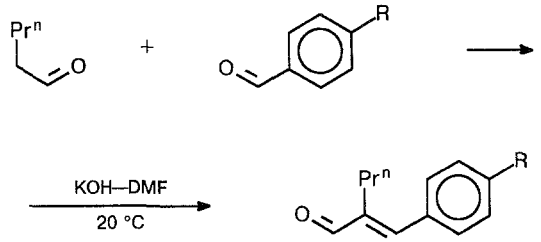
1: R = COOMe



2: R = COOMe

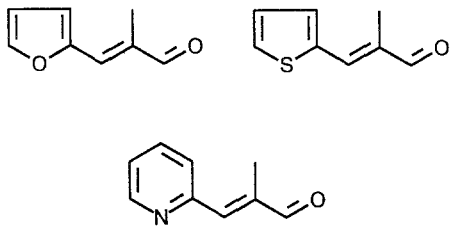
R (yield (%)) = MeO (29,70*), H (62), Cl (73), COOMe (90), NO_2 (84)

Far better results were obtained in two other heterogeneous systems, namely, solid KOH (or NaOH)—benzene—BTEA-Cl and solid KOH (or NaOH)—DMF where the yield of the enal **2** (R = COOMe) amounted to 90 %; for a successful synthesis only catalytic amounts of the base are necessary.[14] The efficiency of the biphasic system solid KOH(cat.)—DMF was demonstrated on a series of related reactions. Under the same conditions benzaldehyde and its derivatives (R = Cl, OMe, NO_2) react with propanal to give the respective enals **2**; electron-withdrawing substituents (CO_2Me, NO_2) accelerate the reaction while the electron-donating MeO group markedly reduces its effectiveness. Similar results were obtained upon condensing *n*-pentanal with benzaldehydes.



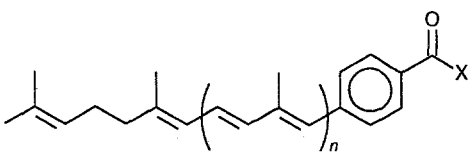
R (yield (%)) = H (62), Cl (64), COOMe (62)

This procedure of aldol condensation was successfully extended to various heterocyclic aldehydes (furfural, 2-thiophene-, and 2-pyridinecarboxaldehyde), which readily react with propanal to afford the respective 3-heterylsubstituted 2-methyl-2-propenals[14] in yields of ~69—71 %:

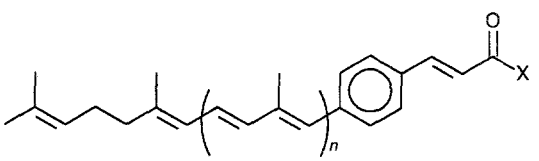


According to the GLC and NMR data, in all these cases the reaction proceeds stereospecifically with the formation of geometrically pure *E* isomers.[5,14]

The aldehyde esters **2** (R = COOMe, COOEt) thus obtained were employed as the bifunctional building blocks in our synthesis of 4-substituted benzoic acids and their derivatives.[5] Among the members of this family certain compounds belonging to the structural types **B** and **C** had been claimed to display promising pharmacological activity of various profiles,[15] *e.g.*, anti-tumor[16] hypolipidaemic[17] and anti-platelet aggregation activity.[18]



B (*n* = 0, 1)



C (*n* = 0, 1)

* Based on the consumed aldehyde.

The patented methods of their synthesis[16,17] involve the Horner—Wadsworth—Emmons (HWE) reaction at the skeleton assemblage stage. This is done by condensing either citral (or its analogs) with the esters of 3-(4-ethoxycarbonyl)phenyl-2-methyl-2-propenylphosphonic acid or pseudoionone (or its analogs) with dialkyl 4-(ethoxycarbonyl)benzylphosphonates. Both approaches involve rather tedious preparation of the required phosphonates and the use of alkali hydrides or alkoxides in srtictly anhydrous solvents, while the yields of the target products are only moderate.

An alternative way of synthesizing compounds of the type **B** or **C** is based on another strategy[5,19] which consists in employing the bifunctional synthons **A** as the key building blocks corresponding to the "eastern" C_{11}(or C_{13}) moiety of the carbon skeleton of **B** (or **C**) and the complementary isoprenoidal C_{10} and C_5 triphenylphosphonium halides.

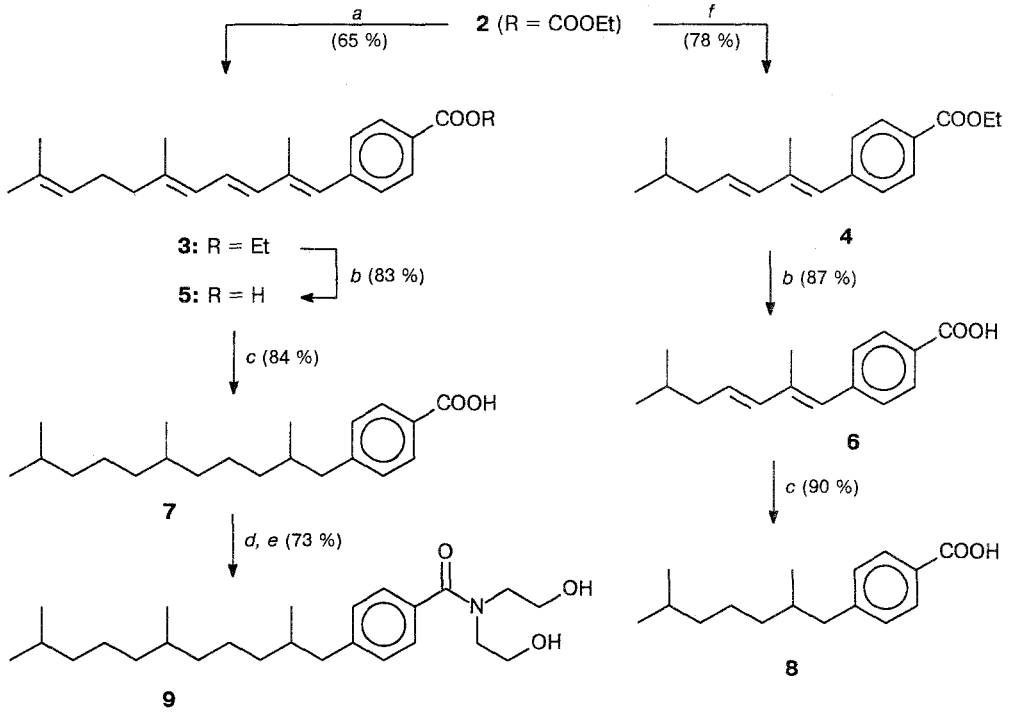
The potentialities of this route to the acid derivatives with nor-isoprenoidal side chaines can be illustrated by a recent synthesis[5] of 4-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)benzoic acid (**5**) (Scheme 1). Previously,[16] the acid **5** had been patented as an anti-tumor substance.

The Wittig olefination of enal **2** with geranyltriphenylphosphonium bromide or 3-methylbutyltriphenylphosphonium bromide in a heterogeneous system gave rise to esters **3** or **4**, respectively, which were transformed to the target acids **5** or **6** upon saponification. Their hydrogenation afforded the "saturated" acids **7** and **8**. The latter displays high hypolipidaemic potency,[17] while the amide **9** inhibits the aggregation of blood platelets.[18] The overall yields of compounds **8** and **9** by the routes depicted in Scheme 1 amounted to 54.3 % and 29.4 %, respectively, whereas the earlier procedures[16—18] provided only for *ca.* 20 % and 15 % yields (based on the limiting starting compound).

Addition of CH-acids to α,β-enals

The base-catalyzed addition of the CH-acids (such as malonic esters and the like) to the α,β-unsaturated aldehydes results in the elongation of the carbon chain by two carbon atoms with concomitant introduction of various functional groups. Due to the delocalization of the π electrons in the molecules of α,β-enals the latter behave in the reactions of this type as the ambident electrophiles, that is, they are prone to accept the nucleophile at the C=C bond (1,4 addition) as well as at the C=O group (1,2 addition). Eventually, this may result in the products of various classes and structural types, such as functionally substituted aldehydes,[19] conjugated dienes,[20] cyclopropanes,[21] epoxides,[22] and dihydrofurans.[23,24] In order to ensure the regioselectivity of a given reaction, and thus the formation of the desirable products, it is necessary to take into account many factors affecting the reactivity, *i.e.* the structure of the CH-acid and enal, the nature of the

Sheme 1



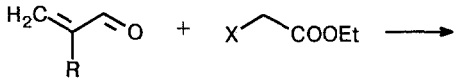
Reagents and conditions: *a.* $[GerPPh_3]^+Br^-$—K_2CO_3—dioxane, Δ; *b.* KOH—H_2O—EtOH; *c.* H_2—Pd/C—EtOH; *d.* $SOCl_2$—PhH, Δ; *e.* $HN(CH_2CH_2OH)_2$—Et_2O, 0 °C; *f.* $[Me_2CH(CH_2)_2PPh_3]^+Br^-$—$K_2CO_3$—dioxane, Δ.

base and solvent, the presence of a catalyst, and so on.[25,26]

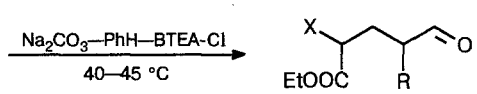
In the practice of organic synthesis, it is the advent of PTC that made it possible to study systematically the chemo- and regioselectivity of addition of malonic ester (ME) and related CH-acids to the α,β-unsaturated aldehydes. By employing various PTC techniques[3] one was able to widen considerably the scope of the Michael reaction. Although conventional variants of the latter give poor results when the enals are used as the electrophiles,[27] a few cases of successful implementation of the Michael addition to enals in heterogeneous systems are presently known. Thus, crotonaldehyde reacts with ME (in the system K_2CO_3—toluene—Bu_4NHSO_4)[28] or with acetoacetic ester (AAE) (in the system LiI—DME)[29] to give the products of 1,4 addition in 36 % and 55 % yields, respectively. Acrolein and AAE react on the dry surface of Al_2O_3, affording the 1,4 adduct in a 90 % yield.[30]

Interaction of enals with CH-acids of the type $XCH_2COOAlk$ (X = COOAlk, Ac, CN) takes place most effectively in systems composed of a solid base and an organic liquid where powdered Na_2CO_3 is the solid phase.[31,32] Under these conditions (solid Na_2CO_3—benzene—BTEA-Cl), the addition of ME, AAE and cyanoacetic ester (CAE) to a large number of various α,β-enals was performed. By applying the PTC technique it became possible to obtain valuable information about the influence of the structure of the both reactants on the outcome of their interaction. Here we observed the following trends in the reactivity:

1. *Enals with no substituents in the β-position* (acrolein, methacrolein) react with ME, AAE, and CAE only in the sense of Michael conjugate 1,4 addition to give the respective saturated aldehydo esters **10**—**15**.



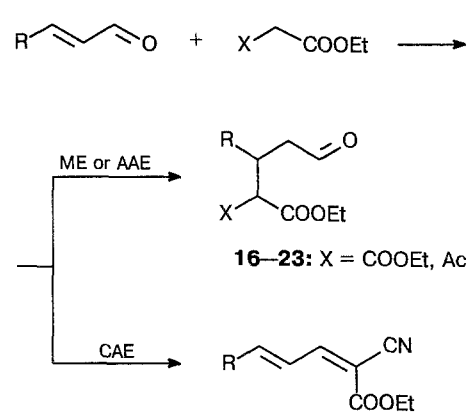
X = COOEt, Ac, CN



10—15

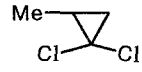
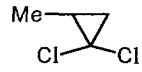
Compound	R	X	Yield (%)
10	H	COOEt	50
11	Me	COOEt	33
12	H	COMe	47
13	Me	COMe	45
14	H	CN	30
15	Me	CN	28

2. β-*Monosubstituted enals*, such as crotonaldehyde, cinnamaldehyde, fumaraldehyde dimethyl monoacetal, and 3-(2-methyl-3,3-dichlorocycloprop-1-yl)acrolein, react with ME and AAE at the C=C bond (the Michael reaction). However, their interaction with CAE takes place at the C=O bond in the 1,2 addition mode which eventually gives rise to the functionally substituted conjugated dienes **24**—**30** (the Knoevenagel reaction).

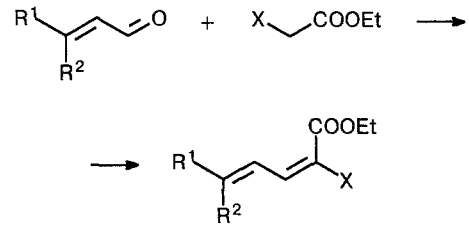


16—23: X = COOEt, Ac

24—30

Compound	R	X	Yield (%)
16	Me	COOEt	60
17	Ph	COOEt	56
18	$(MeO)_2CH$	COOEt	50
19		COOEt	75
20	Me	COMe	48
21	Ph	COMe	55*
22	$(MeO)_2CH$	COMe	64
23		COMe	54

3. β,β-*Disubstituted enals* (3-methyl-2-butenal, β,β-dichloroacrolein, citral) react with ME and CAE only at the carbonyl group (the Knoevenagel reaction).



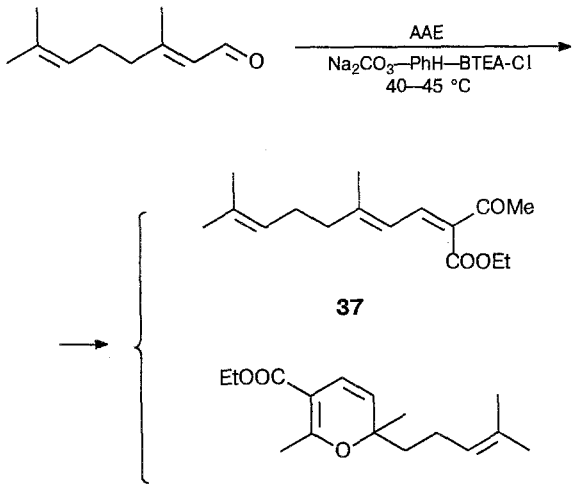
31—36

Compound	R^1	R^2	X	Yield (%)
24	Me	H	CN	15
25	Ph	H	CN	64

* The reaction results in 5-phenyl-2-cyclohexen-1-one.

Compound	R^1	R^2	X	Yield (%)
26	$(MeO)_2CH$	H	CN	47
27	Me(Ph)N	H	CN	85
28	PhCH=CH	H	CN	86
29	CCl_2=CH	H	CN	75
30	CCl_2=CHCH=CH	H	CN	75
31	Me	Me	CN	43
32	Cl	Cl	CN	68
33	Me_2C=$CHCH_2CH_2$	Me	CN	91
34	Me	Me	COOEt	38
35	Cl	Cl	COOEt	48
36	Me_2C=$CHCH_2CH_2$	Me	COOEt	30

Interestingly, the interaction of citral with AAE results in the formation of a 3 : 7 mixture of the acyclic (**37**) and cyclic product (**38**); apparently, the latter is due to the valence isomerization which occurs the during reaction (*cf.* Ref. 33).



4. *Enals of the type* CCl_2=CH—(CH=CH)$_n$CHO can react with ME and AAE both at the C=C and C=O bonds (Table 1).

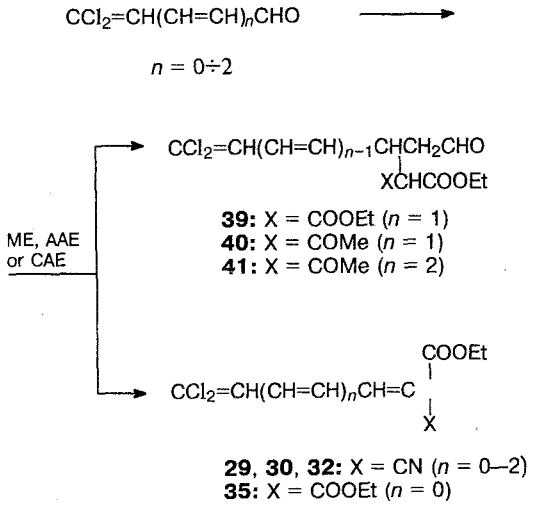


Table 1. Reaction of CCl_2=CH(CH=CH)$_n$CHO aldehydes with CH-acids: relationship between the chain length and the percentage of adducts at the C=C and C=O bonds in the products mixture

CH-acid	n = 0		n = 1		n = 2	
	C=C	C=O	C=C	C=O	C=C	C=O
$CH_2(COOEt)_2$	0	100	75	25	—	—
$EtOOCCH_2COMe$	0	100	45	55	18	82
$CNCH_2COOEt$	0	100	0	100	0	100

As follows from Table 1, the direction of the reaction of aldehydes CCl_2=CH—(CH=CH)$_n$CHO with ME and AAE depends on the chain length in the conjugated polyenals. β,β-Dichloroacrolein (n = 0) reacts exclusively at the C=O bond. This may be due to steric congestion at the C(3) atom of the enal (apparently, just as in the case of other β,β-disubstituted alkenals), which prevents the carbanion from attacking this position in the enal molecule. Naturally, the elongation of the conjugated carbon chain in ω,ω-dichloropolyenals diminishes steric effects of terminal substituents and thus facilitates the formation of the products corresponding to the nucleophilic addition to the C=C bond. This is in fact observed for the reactions of 5,5-dichloro-2,4-pentadienal with ME and AAE, the Michael type 1,4-adduct predominating in the former case. 7,7-Dichloro-2,4,6-heptatrienal does not react with ME, but on treatment with AAE it affords a mixture of 1,4- and 1,2-adducts where the latter predominates.[26]

Obviously, the direction of the nucleophilic addition depends on the nature of the carbanion, enal structure, and reaction conditions. Generally, the energy of interaction between the reactants is the sum of coulombic, orbital, and steric energies. The effects of the solvent and counterion on the outcome of the processes under study need not be discussed here, since all of them took place under identical PTC conditions.

Molecular orbital calculations of electronic parameters of the carbanions and enals showed that a single explanation of all pecularities of the addition of CH-acids to enals cannot be based on the idea of competing orbital and coulombic interactions alone.[26] At the same time, steric effects, which arise from the difference in the volumes of hydrogen atom and methyl group or chlorine atom, can substantially affect the direction of the reaction. The addition of carbanions to enals involves a noticeable change in the geometry of one of the carbon atoms of the enal which drifts from planar (sp^2 state) to pyramidal as the carbanion approaches the reaction center. Relative rehybridization energies for the C(1) and C(3) atoms of acrolein and its methyl- and chloro-substituted derivatives, R^1R^2C=CHCHO, calculated as the energy differences between the sp^3 and sp^2 states (assuming the energy of the structure

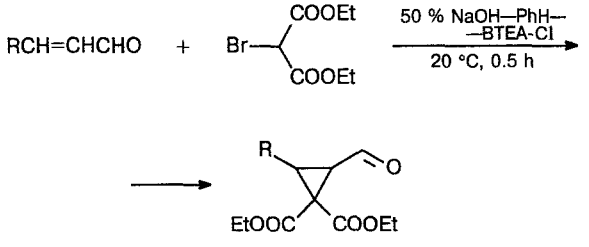
with tetrahedral C(3) atom to be zero),[26] are as shown below:

R^1	H	H	Me	H	Cl
R^2	H	Me	Me	Cl	Cl
ΔE/kcal mol^{-1}	4	−3	−9	−1	−4

This implies that for the parent acrolein the pyramidalization of the terminal C(3) atom of the C=C bond is energetically favored. A qualitative change in the reactivity occurs upon replacing one of the hydrogen atoms at C(3) by a methyl group: for 2-butenal it is pyramidalization of the C(1) atom that is energetically favored. The substitution of another methyl group for the second H atom at C(3) makes this energy difference in 3-methyl-2-butenal as high as 9 kcal mol^{-1}. A similar trend is observed when the hydrogen atoms at C(3) are replaced by chlorine atoms. Thus, it is due mainly to steric factors that the regioselectivity of nucleophilic addition is modified upon substituting Me groups or Cl atoms for H atoms at C(3).

Interaction of halo-substituted CH-acids with α,β-enals can also take place either at the C=O bond (1,2 addition) or at the C=C bond (1,4 addition). In the former case the glycide esters are eventually formed, while in the second case the intermediate Michael adducts undergo cyclization to give cyclopropanes[34,35] or five-membered heterocycles.[23,24] All these transformations are observed upon the addition of bromomalonic ester (BME) to various α,β-enals and dienals under the conditions of PTC. On the whole, the reactions of α,β-unsaturated aldehydes are characterized by the reactivity trends reminiscent of those discussed in the preceding subsection.

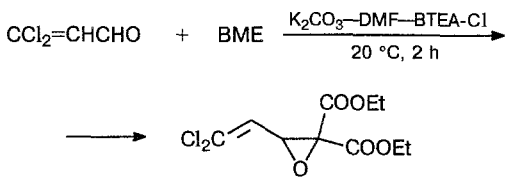
1. *Unsubstituted and β-monosubstituted enals and dienals* react with BME under standard conditions (50 % aqueous NaOH—organic solvent—BTEA-Cl) to give the respective cyclopropanes (**42**); the latter result from a Michael addition reaction followed by 1,3 cyclization:



42a–g

R (yield (%)) = H (49), Me (46), Ph (69), $(MeO)_2CH$ (43), MeCH=CH (75), PhCH=CH (75), CCl_2=CH (78)

2. *ω,ω-Dichloro-substituted mono- and dienals* in the system solid K_2CO_3—DMF—BTEA-Cl react with BME at the carbonyl group to give glycide esters (the Darzens reaction); in the case of 5,5-dichloro-2,4-pentadienal the resulting diene epoxide **44** is accompanied by vinylacetylenic epoxide **45** due to partial dehydrochlorination of **44**.



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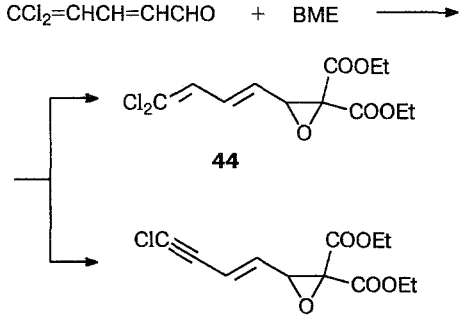
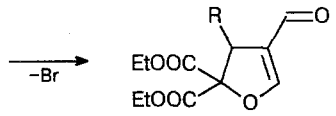


45 (**44** : **45** = 7 : 3)

3. *Ylidenemalonic aldehydes* (**46a–f**)* were found to react with BMF in a hitherto unknown manner, yielding the 2,2,3-trisubstituted 2,3-dihydrofuran-4-carboxaldehydes (**47**). Their formation is the result of the Michael reaction and subsequent 1,5 cyclization of the intermediate 1,4-adduct.[23,24]

46

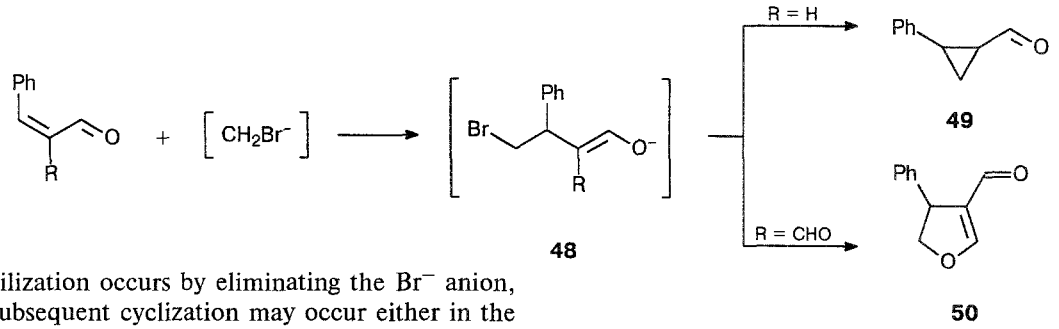


47a–f

46: R (yield (%)) = Ph (51), 4-ClC_6H_4 (60), 4-$MeOC_6H_4$ (74) PhCH=CH (55), 2-thienyl (75), $Me(CH=CH)_2$ (60)

Different behavior of enals and enedials in their reactions with BME corresponds to the two different modes of stabilizing the intermediate oxanion. In both

* Ylidenemalonic aldehydes $RCH=C(CHO)_2$ are a recently discovered, interesting family of β-dicarbonyl compounds. Their synthesis was elaborated by one of us (G. V. K.) in cooperation with Professor Arnold's group at the Institute of Organic Chemistry and Biochemistry in Prague (Czech Republic).[36–39]

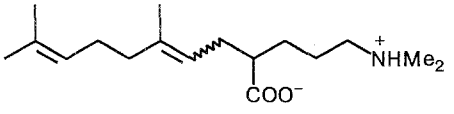


cases stabilization occurs by eliminating the Br^- anion, whereas subsequent cyclization may occur either in the 1,3 or in the 1,5 position.

The relationship between the structure of α,β-unsaturated aldehydes and their behavior in these reactions is in a good agreement with the results of the MO calculations[40] for the elimination of Br^- from the oxanion **48** made by using the potential energy cross-section technique. The process was modelled by the addition of a hypotetical CH_2Br^- carbanion to various enals which gives rise to the intermediates of the type **48**; the elimination of Br^- from the latter was assumed to preceed the cyclization.

The calculation showed the formation energy of cyclopropane **49** to be 6 kcal mol^{-1} higher than that of dihydrofuran **50**. However, in the case of the α-unsubstituted enal (R = H), the reactants are separated from the energetically favored product by a high activation barrier (>20 kcal mol^{-1}), which is insurmountable at normal temperatures (*ca.* 20 °C). Therefore, when R is H, the reaction proceeds under kinetic control to give the thermodynamically unfavored formylcyclopropane. When the α-H atom in the enal is replaced by the CHO group, the activation barrier between the reactants and dihydrofuran **50** becomes much lower, and the product of the thermodynamically controlled 1,5 cyclization is thus formed.

Synthetic application. The heterophasic variant of the Michael reaction was successfully used by the authors in an effective synthesis of Metaprogerol (**51**), a pharmacologically active isoprenoid known to accelerate the healing of the lesions caused by myocardial infarction (see Ref. 15). The key intermediate **52** was obtained in a high yield at the critical stage of the synthesis by acylating geranylacetoacetic ester (easily accessible from linalool) with acrolein under PTC conditions.



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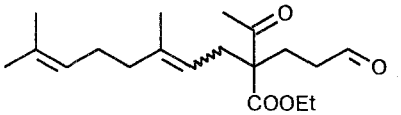


52

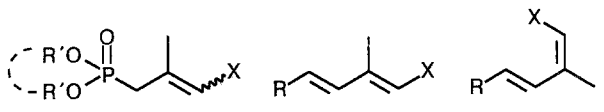
In this way, the yield of Metaprogerol from the starting linalool was raised to 28 % overall,[41] whereas in earlier works it did not exceed 10 %. Thus, it was demonstrated that under the conditions of PTC the alkyl-substituted CH-acids add to acrolein with exactly the same 1,4-regioselectivity as the parent AAE.

Horner—Wadsworth—Emmons reaction of aldehydes with derivatives of 3-methyl-4-phosphono-2-butenoic acid

The reaction of carbonyl compounds with phosphonates bearing a carbanion-stabilizing, electron-withdrawing substituent adjacent to the anionic center (the Horner—Wadsworth—Emmons reaction)* is a very popular and effective tool for the preparation of *vic*-disubstituted and trisubstituted olefins; its mechanistic and synthetic aspects are thoroughly reviewed.[42,43] However, little attention was paid in the reviews to the reaction of aldehydes with the derivatives of 3-methyl-4-phosphono-2-butenoic acid of the general type **53**. Such phosphonates are often used in the synthesis of biologically active polyunsaturated isoprenoids, when the carbon chain is to be extended by a functionalized isoprenoidal C_5 unit.[44—47]

However, the expectation, aroused by the successful application of these allylic phosphonates to the synthesis of isoprenoidal polyenes in the early sixties, faded somewhat later, as it was realized that the configurational integrity of the double bond is invariably lost when the starting **53** is exposed to the base.[44] As a consequence, when this reaction is implemented by employing such conventional deprotonating agents as alkoxides, hydrides, or amides of alkali metals in various organic solvents, the resulting product is always a binary mixture of stereoisomeric dienes. Interestingly, the newly formed double bond of the diene is always *E*-configurated, and geometrical isomerism of the dienes relates only to the α,β-conjugated double which bond, already existed in the starting phosphonate.[45—51]

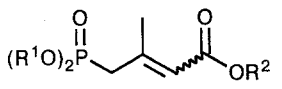
* For brevity, this transformation will hereafter be referred to as the HWE reaction or HWE olefination.



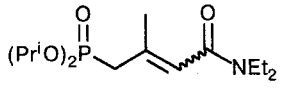
53 (*E* and/or *Z*) 2*E*,4*E* 2*Z*,4*E*

The low stereoselectivity of the HWE reactions involving the allylic phosphonates of the type **53** (usually they give the products of the general type **56** with the ratios of the 2*E*,4*E*- to 2*Z*,4*E*-isomers ranging from 45 : 55 to 75 : 25; only in few particular cases[49,51] this ratio is as high as *ca.* 85 : 15) is a serious obstacle for its application to the synthesis of 3-methyl-2,4-alkadienoic acids and their derivatives, since their biological activity may strongly depend on the configuration of their double bonds. For example, the most potent antikeratotic and immunomodulating drugs related to retinoic acid (Tigason®, Roaccutan®) and juvenile hormone analogs (Methoprene®, Hydroprene®, *etc.*) possess the *all-E* configuration, while the phytohormone abscisic acid and its analogs require the *Z* configuration of the terminal double bond for displaying the maximum potency.[15]

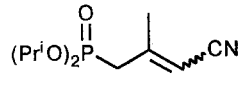
With a view of enhancing the stereoselectivity and controlling stereochemical outcome of the HWE olefination of aldehydes with allylic phosphonates of the type **53**, a systematic study of the factors capable of affecting this process was undertaken.[52–59] The reactions were carried under the PTC conditions, since the latter give both certain preparative advantage and the possibility to affect the course of the reaction by additional factors inherent to heterophasic systems. The progress of the reaction and the ratios of geometrical isomers in the starting phosphonates (**53a—l**) and resulting derivatives of 3-methyl-2,4-alkadienoic acids (binary mixtures of 2*E*,4*E*- and 2*Z*,4*E*-stereoisomers) were monitored by GLC and ^{1}H NMR spectroscopy; both methods gave coinciding data.



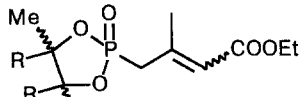
53



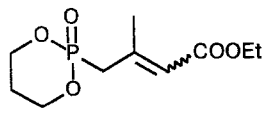
53i



53h



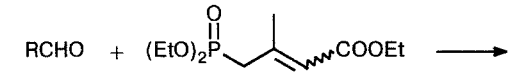
53j: R = H
53k: R = Me



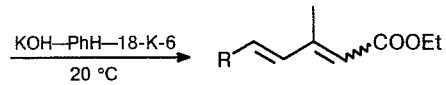
53l

53: R^1 = Me (**a**), Et (**b—d**), Pr^i (**e—g**)
R^2 = Me (**a,b,e**), Et (**c,f**), Pr^i (**d,g**)

Table 2. Yields and stereoisomer composition of the products obtained upon the reaction of phosphonate **53c** with aldehydes **54a—f** and **55**



54a—f, 55 **53c**



56a—f, 57a

Aldehyde	R	Diene	Yield of diene (%)	2*E*,4*E* : 2*Z*,4*E* ratio
54a	Me	**56a**	20	60 : 40
54b	Pr^n	**56b**	40	60 : 40
54c	*n*-C_7H_{15}	**56c**	42	60 : 40
54d	Me_2CH	**56d**	39	61 : 39
54e	Bu^t	**56e**	19	62 : 38
54f	*n*-$C_4H_9CH(Et)$	**56f**	42	58 : 42
55	Me_2CHCH_2	**57a**	67	62 : 38

The effects of the reactants' structure and concentration were studied in the heterophasic catalytic system solid KOH—benzene—18-crown-6 at room temperature. Under these conditions all starting phosphonates **53a—l**, irrespective of their geometrical purity, undergo a rapid stereomutation in the reaction medium to give an equilibrium mixture of *E* and *Z* isomers; its composition is independent of their initial ratio in **53** and remains permanent throughout the reaction.

The effect of the aldehyde structure on the stereochemical outcome of the reaction[55] was studied for the case of the reaction of phosphonate **53c** with a series of aliphatic aldehydes of linear (**54a—c**), α-branched (**54d—f**), and β-branched structure (**55**). Under the conditions indicated in Table 2, in all cases the reaction products were obtained as binary mixtures of the 2*E*,4*E* and 2*Z*,4*E* isomers of the respective ethyl 3-methyl-2,4-alkadienoates (**56a—f, 57a**).

The data in Table 2 show that the isomer composition of all the products in the series is nearly identical. The unbranched (**54a—c**) and α-branched aldehydes (**54d—f**) give the diene esters **56a—f** with nearly the same stereoselectivity as the β-branched aldehyde **55** does. Thus, the structure of aldehydes is of little importance for the ratio of 2*E*,4*E* and 2*Z*,4*E* isomers in the reaction products. On the other hand, this ratio (*ca.* 60 : 40) is practically reversed with respect to the steady-state proportion of *E* and *Z* isomers of the phosphonate **53c** in the reaction mixture (*ca.* 37 : 63).

The effect of the reactants' concentration on the stereoselectivity of the reaction[55] was observed in the case of interaction of 3-methylbutanal (**55**) with phosphonate **53c** under the same PTC conditions as stated in Table 2.

The results presented in the Fig. 1 show that the content of the 2*Z*,4*E* isomer in the dienoate **57a** increases with increasing concentration of the aldehyde. On the other hand, an increase in the concentration of the phosphonate results in enhancing the proportion of the 2*E*,4*E* isomers in the product with respect to that obtained at the equimolar ratio of reactants. When the aldehyde is taken in excess, the plot of the 2*E*,4*E* : 2*Z*,4*E* ratio *vs.* the ratio of **[53c]** to **[55]** becomes linear. The extrapolation of the plot reveals that the limiting ratio of the 2*E*,4*E* to 2*Z*,4*E* isomer is about 0.85 (as can be determined from the intercept on the ordinate axis), that is, *ca.* 46 : 54 = 0.851. It is to be noted that even this limiting ratio between the 2*E*,4*E* and 2*Z*,4*E* isomer remains markedly higher than the steady-state equilibrium ratio of the *E* and *Z* isomers of the phosphonate **53c** in the reaction medium. This ratio stays at ≈37 : 63 both in the absence and in the presence of the aldehyde. It must be stressed here that a prolonged exposure of the isolated mixture of the 2*E*,4*E* and 2*Z*,4*E* isomers of the diene **57a** to powdered KOH under the conditions of the reaction (20 °C, 3—8 h) did not affect their ratio.

These facts imply that the equilibrium mixture of allylic phosphonates (in which the *Z* isomer predominates) may be considered as a "pool" from which the *E* isomer is continuously "hooked" during the reaction with aldehydes. Obviously, when the steady-state equilibrium is reached, the overall rate of the reaction with the aldehyde is markedly higher for the *E* isomer of the phosphonate-derived carbanion than for the respective *Z* carbanion.* Enhanced reactivity of the *E* carbanion toward alkanals (in spite of its being the minor component in the equilibrium *E*/*Z* mixture of carbanions derived from the phosphonate **53**) may be due to its greater steric accessibility. This assumption was corroborated on studiyng the reactions of isovaleraldehyde (**55**) with a series of phosphonates of the type **53** bearing various substituents.

The effect of the phosphonate structure on the stereoselectivity of the reaction.[52,53] Starting from alkyl 3-methyl-2-butenoates and trialkyl phosphites $P(OR^1)_3$, a series of allylic phosphonates (**53a—g**) was prepared by a known procedure.[62] The ratios between the *E* and *Z* isomers in these phosphonates varied from one speciment to another, but in the absence of bases they remained unchanged on prolonged storage at room temperature (both neat and in organic solvents).

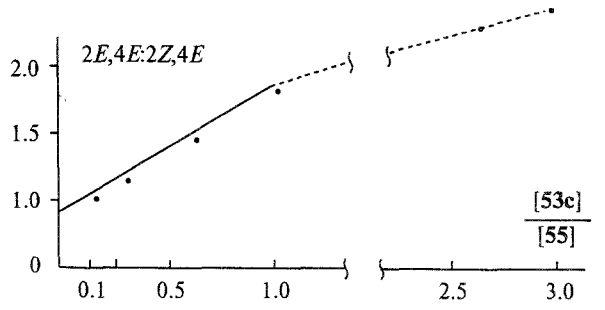


Fig. 1. Dependence of the stereoisomer ratio in ethyl 3,7-dimethyl-2,4-octadienoate (**57a**) on the concentration of aldehyde **55** (hence, on the ratio between **53c** and **55**). The intercept of the ordinate axis corresponds to the limit ratio of the 2*E*,4*E* and 2*Z*,4*E* isomers at infinitely large **[55]** (*i.e.*, at **53c** : **55** → 0).

The phosphonates **53h** and **53i**, in which the ester moieties are replaced by related electron-withdrawing groups of very different volumes, CN and $CONEt_2$, were prepared by modified procedures.[53,59]

The effect of the functional substituent X in the phosphonates of the type **53** on the stereochemistry of the dienes resulting from their interaction with alkanals was demonstrated in the reactions of acyclic phosphonates **53b—i** with 3-methylbutanal.[54] The respective dienes (**57a—e**) were obtained as the binary mixtures of 2*E*,4*E* and 2*Z*,4*E* geometrical isomers; the composition of these mixture tended to be permanent during the reaction and was not changed upon subsequent workup.

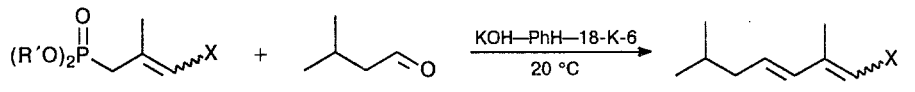
As appears from Table 3, the isomer composition of the products (**57a—e**) varies within a relatively broad range. Just as in the previous series of experiments (*cf.* Table 2), the quantitative ratio between isomeric dienes does not depend on either the isomer ratio in the starting phosphonate or the equilibrium composition of the *E*/*Z* mixture of the carbanions formed from the phosphonates in the basic reaction medium.

The data presented in Table 3 testify to the dependence of the isomer composition of the reaction products (**53a—e**) on the nature of the substituent X in the starting phosphonates. The size of alkoxy groups at the P aton of the phosphonates **53** being equal, the smaller the size of X is, the higher is the content of the 2*E*,4*E* isomer in the diene **57**.

The decisive influence of the steric factor on the stereochemical outcome of the reaction is demonstrated by a correlation between the van der Waals volume (V_w) of substituent X and the stereoselectivity of the process, namely, by the linearity of the plot $\ln[2E,4E]/[2Z,4E] = f(1/V_w)$ (see Fig. 2).

* It is interesting to compare the *E*-stereoselective olefination of aldehydes with allylic phosphonate **53c** (2*E*,4*E* > 2*Z*,4*E*; no detectable amount of the 4*Z* isomers in the resulting diene mixture) with the *Z*-selective olefination of aldehydes with such derivatives of phosphonoacetic acid as 2-(alkoxycarbonyl)methyl-1,3,2-dioxaphospholanes[60] and bis-2,2,2-trifluoroethyl(methoxycarbonyl)methylphosphonate.[61] In the latter case the *Z*-selectivity was associated with a higher reactivity of these cyclic phosphonates with respect to conventional trialkyl phosphonoacetates (which implied a rapid transformation of the *erythro*-configurated "aldolate" oxanions into *Z* alkenes). It appears that in the case of phosphonates **53** their reaction with aldehydes proceeds exclusively *via* the *threo*-oxanion irrespective of the configuration of the phosphonate carbanion.

Table 3. Effect of the substituent X in phosphonates **53b—i** on the stereoselectivity of their reaction with aldehyde **55**



53b—i **55** **57a—e**

Phosphonate	Diene	R'	X	2*E*,4*E*/2*Z*,4*E* ratio in **57**	*E* : *Z* ratio in **53**	
					starting phosphonate	reaction mixture
53b	**57b**	Et	COOMe	65 : 35	52 : 48	35 : 65
53c	**57a**	Et	COOEt	62 : 38	54 : 46	37 : 63
53d	**57c**	Et	$COOPr^i$	58 : 42	70 : 30	38 : 62
53h	**57d**	Pr^i	CN	92 : 8	55 : 45	53 : 47
53e	**57b**	Pr^i	COOMe	84 : 16	68 : 32	42 : 58
53f	**57a**	Pr^i	COOEt	80 : 20	49 : 51	40 : 60
53g	**57c**	Pr^i	$COOPr^i$	74 : 26	52 : 48	41 : 59
53i	**57e**	Pr^i	$CONEt_2$	69 : 31	40 : 60	40 : 60

A parallel study[52] revealed a clear-cut dependence of the stereoselectivity of the reaction on the size of alkoxy groups attached to the P atom of the phosphonates **53**. This dependence is particularly evident in the sub-series of methoxycarbonyl-substituted allylic phosphonates with various phosphorus-containing moieties (**53a,b,e**). In this triad the strongest steric hindrance is created by the bulky isopropoxy groups. As a result, the content of the 2*E*,4*E* isomer in the resulting diene is as high as 84 %. When the phosphorus bears the alkoxy groups of the smallest size, *i.e.*, the MeO groups, the content of the 2*Z*,4*E* diene in the products increases to 43 %) (see Table 4).

Earlier,[64,65] similar effect was observed in the reaction of phosphonates of the type $(R^1O)_2P(O)CHMeCO_2R^2$ with 2-phenylpropanal; however, the content of the *E* isomer in the resulting alkene was decreased rather than increased by diminishing the size of the CO_2R^2 group. Also, the condensation of alkanals with phosphonate **53f** in homogeneous media[46] was reported to give the product with a higher content of the 2*E*,4*E* isomer than in the case of **53c**.

Another way of controlling the stereoselectivity of the reaction between the phosphonates of the type **53** and aldehydes through the nature of alkoxyl ligands in the phosphonate grouping was to employ the respective cyclic analogs (**53j—l**) derived from 1,3,2-dioxaphospholane and 1,3,2-dioxaphosphorinane.[54] The reactions of cyclic phosphonates **53j—l** with 3-methylbutanal **55** under the PTC conditions specified above gave rise to specimens of diene ester **57a** in which the 2*Z*,4*E* isomer was predominant (Table 5).

The highest content of the 2*Z*,4*E* isomer in **57a** was observed in the case of the five-membered phosphonate **53j**, the lowest — in the case of the conformationally more flexible six-membered phosphonate **53l**. Thus, by varying the alkoxy substituent at the phosphorus atom in

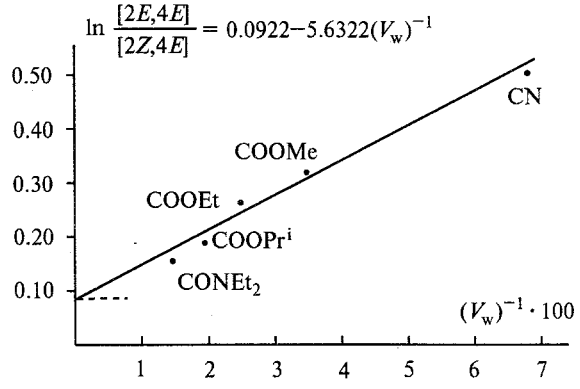


Fig. 2. Dependence of ln[2*E*,4*E*]/[2*Z*,4*E*] on the inverse van der Waals volume of the functional substituent X in the diisopropyl phosphonates **53e—i**. The values of V_w (cm^3 mol^{-1}), calculated according to Bondy,[63] are as follows: CN — 14.70, COOMe — 28.85, COOEt — 38.80, $COOPr^i$ — 57.08, $CONEt_2$ — 63.61.

Table 4. Effect of the substituents at the phosphorus atom in phosphonates **53a—g** on the stereochemistry of the products of their reaction with 3-methylbutanal (**55**)

Phosphonate	Diene	R'	X	Yield of diene (%)	2*E*,4*E* : 2*Z*,4*E* ratio
53a	**57b**	Me	COOMe	70	57 : 43
53b	**57b**	Et	COOMe	64	65 : 35
53e	**57b**	Pr^i	COOMe	67	84 : 16
53c	**57a**	Et	COOEt	67	62 : 38
53f	**57a**	Pr^i	COOEt	69	80 : 20
53d	**57c**	Et	$COOPr^i$	70	58 : 42
53g	**57c**	Pr^i	$COOPr^i$	65	74 : 26

compounds of type **53**, one can change the ratio of geometrical isomers in the diene products (**57**) toward the predominance of either the 2*E*,4*E* diene (when

R'O = OPr^i, as in **53e**) or the 2*Z*,4*E* diene (when $(R'O)_2P$ = $(MeCHO)_2P$, as in **53j**).

The controlling of stereoselectivity in the HWE reactions of allylic phosphonates of the type **53** with aldehydes by slight structure modifications of the former (that is, by varying the ligands at the phosphorus atom and/or the functional substituent X in the γ-position) appears to be a promising approach to the synthesis of stereodefined derivative of 3-methyl-2,4-alkadienoic acids. In other words, the phosphonates of the type **53** may be considered as isoprenoidal C_5 synthons with "regulated" configuration, suitable for elongating the carbon chain by an *E* or *Z* isoprenoidal unit.

The multistep nature of the HWE reaction, in particular, the existence of reversible steps involving the formation and dissociation of oxanions,[41,42,48] may be the reason of substantial effect exerted by the nature of the solvent, base, and phase transfer catalyst upon the stereoselectivity of olefination. Similar effects were observed previously for the reactions of aldehydes with the structurally simpler phosphonates.[66,67]

The effects of temperature and the medium.[56] At the temperatures ranging from +22 °C to −65 °C the base-induced equilibrium between the *E* and *Z* forms of the phosphonate **53c** in the system solid KOH—toluene—18-crown-6 is reached at the same *E* : *Z* ratio, namely, 38 : 62. This constancy points out to the thermodynamic stability of the *Z* carbanion (U-shaped) with respect to *E* carbanion (W-shaped). It is only the rate of equilibration that changes with the temperature: at 22 °C the steady-state ratio of isomers is reached within one minute, while at −65 °C it takes *ca.* 60 min for establishing. As regards the reaction **55** + **53c** → 2*E*,4*E*-**57a** + 2*Z*,4*E*-**57a**, under standard conditions the isomer ratio in the product varies with the temperature in the following mode:

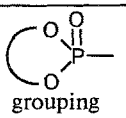
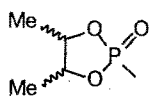
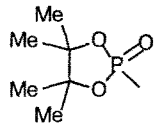
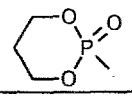
T/°C	−23	2	22	40	80
2*E*,4*E*-**57**:2*Z*,4*E*-**57**	50 : 50	54 : 46	62 : 38	62 : 38	61 : 39

Nonlinearity of these changes, taken together with the constancy of the ratio *E*-**53c** : *Z*-**53c** in the presence of base, characterize the reaction of **55** with **53a** as a system of several equilibria that respond differently to changes of temperature. The reversibility of the steps involving the formation and dissociation of the "aldolate" oxanions is also revealed by the solvent effect.

The part of the 2*E*,4*E*-**57c** in the product formed upon the reaction of aldehyde **55** with phosphonate **53c** increases on passing from hydrocarbons to polar aprotic solvents. This trend becomes even more evident in the presence of 10 mol. % 18-crown-6: in this case in all of the tested solvents the 2*E*,4*E* dienoate predominates in a binary mixture (see Table 6). However, there is no linear correlation between the ratio of 2*E*,4*E*-**57a** to 2*Z*,4*E*-**57a** and any of the polarity criteria (ε, *AN*, *DN*) taken alone.

In the solvents of low polarity (from hexane to CH_2Cl_2), in the absence of the crown ether the reaction is likely to occur on the surface of the solid base. In such a case, neither the dielectric constant (ε) nor the acceptor and donor numbers (*AN*, *DN*) can affect significantly the stereochemical result of the interaction of **55** with **53c**. Therefore, the 2*E*,4*E* : 2*Z*,4*E* ratios observed in these media vary only slightly. In polar aprotic solvents (PhCN, MeCN, DMF, DMSO) the carbanions, formed on the surface of KOH, are readily solvated and thus capable of migrating to the liquid phase. Increasing ε

Table 5. Isomer ratios in the products resulting from the reaction of aldehyde **55** with cyclic phosphonates **53j—l***

Starting phosphonate	 grouping	*E* : *Z* ratio in phosphonate		2*E*,4*E* : 2*Z*,4*E* ratio in **57a**
		initial	steady-state equilibrium	
53j		48 : 52	27 : 73	24 : 76
53k		54 : 46	—	32 : 68
53l		49 : 51	30 : 70	37 : 63

* It is noteworthy that in the case of cyclic phosphonates **53j—l** the newly formed double bond in diene **57a** also has the *E* configuration (*cf.* the footnote on page 1803). Apparently, the enhanced reactivity of the 1,3,2-dioxaphospholane and 1,3,2-dioxaphosphorinane derivatives (**53j—l**) is reflected in a better correlation between the isomer ratio in the product and the respective *E* : *Z* ratio in the steady-state equilibrium of the phosphonates rather than in the appearance of a competing process involving the *erythro*-oxanions.

Table 6. Effect of the solvent and crown ether additive (10 mol.%) on the stereochemistry of the reaction between aldehyde **55** and phosphonate **53c**

Solvent	Polarity parameters			2*E*,4*E* : 2*Z*,4*E* ratio in **57a**	
	ε	*AN**	*DN**	solid KOH	solid KOH—18-K-6
Hexane	1.9	0.0	0.0	41 : 59	66 : 34
Dioxane	2.2	10.8	14.8	46 : 54	58 : 42
Benzene	2.3	8.2	0.0	44 : 56	62 : 38
THF	7.4	8.0	20.0	43 : 57	58 : 42
CH_2Cl_2	8.9	20.4	0.0	40 : 60	71 : 29
Pyridine	12.3	14.2	33.1	49 : 51	62 : 38
PhCN	25.2	15.5	11.9	51 : 49	71 : 29
MeCN	36.0	18.9	14.1	57 : 43	68 : 32
DMF	36.7	16.0	26.6	65 : 35	71 : 29
DMSO	46.7	19.3	29.8	71 : 29	79 : 21

* *AN* and *DN* are empirical, nondimensional parameters characterizing the ability of a solvent to solvate the anions (or the negative poles of molecules) and cations (or the positive poles of molecules), respectively.[68]

Table 7. Dependence of the reaction duration and the ratios between the geometric isomers in phosphonate **53c** and diene **57a** on the nature of the cation in the base

55 + **53c** $\xrightarrow[20\ ^\circ C]{M(Q)OH—PhH}$ **57a**

Cation (M^+or Q^+)	Solvent	Reaction duration* /h	Ratio of isomers		Radius of the cation in aqueus solution r_H/Å
			E : *Z* in **53c**	2*E* : 2*Z* in **57a**	
Series A [M^+]					
Li	Benzene	30	33 : 67	60 : 40	3.82
Na	Benzene	15	35 : 65	46 : 54	3.58
K	Benzene	7	37 : 63	44 : 56	3.31
Li	DMSO	5	40 : 60	78 : 22	
Na	DMSO	3	36 : 64	65 : 35	
K	DMSO	2	38 : 62	71 : 29	
Series B [Q^+]					
Me_4N	Benzene	6	35 : 65	70 : 30	3.67
$BnNMe_3$	Benzene	6	32 : 68	78 : 22	(≥3.67)**
$(Bu^n)_4N$	Benzene	5	32 : 68	86 : 14	4.94

* The ratios given for all runs correspond to 95—100 % conversion of both reactants (according to GLC and ^1H NMR). ** The data are missing.

and *AN* facilitates the dissociation of ionic aggregates and their transformation from the contact ion pairs to the solvent-separated ones.

The existence of a relationship between the solvent polarity parameters (ε, *AN*, *DN*), whose increasing promotes the formation of the solvent-separated ion pairs, and the 2*E*,4*E* stereoselectivity of the reaction under study is supported by the satisfactory correlation coefficient, *r*, found by employing an equation which takes into account the effects of both *AN* and *DN*:

$$\log(\%\ 2E,4E) = 1.573+0.0018(DN)+0.0088(AN) \quad (1)$$

$$(r = 0.908)$$

Numerical values of the coefficient in Equation (1), calculated by applying Sapunov's formula[69] to nine of the ten solven ts presented in Table 6 (with the exception of CH_2Cl_2), imply that the solvent-mediated stabilization of the anions rather than the cations is more important for the stereochemical outcome of the reaction.

Since the *E* : *Z* ratio in the phosphonate **53c** does not practically change in the presence of the base on passing from benzene to DMSO (Table 7), there are good reasons to believe that temperature and solvents affect, first and foremost, the steps involving the formation and dissociation of the oxanion and/or its conversion to the end product *via* a phosphethane-like intermediate (*cf.* Ref. 48).

The effect of the base cation.[57] As the HWE reaction is well known to proceed through the carbanionic intermediates, it is reasonable to expect that the correspond-

ing cations would markedly affect the whole system of reaction equilibria in which they are involved. In particular, the extent of the covalency of the bond between the counterions in carbanionic and oxanionic intermediates may be of great importance for the stereochemistry of the products. This anticipation proved to be conspicuously correct for the reaction of **55** with **53a**. Two series of experiments were carried out: (A) In the presence of two equivalents of solid alkali (MOH) in benzene and DMSO; (B) With equimolar amount of tetraalkilammonium hydroxides (QOH) in benzene. The results are presented in Table 7. In order to assess the effect of a cation on the olefination stereoselectivity the radii of the hydrated Li^+, Na^+ and K^+ ions[70] are also given there as approximation for the radii of the respective cations solvated by benzene or DMSO.

It is well known[71] that in practically all organic solvents studied the effective radii and solvation numbers of these three ions diminish in the same order, as in the case of hydrated ions, *i.e.*, $Li^+ > Na^+ > K^+$. The radii of the weakly solvated (Me_4N^+) or unsolvated ($(Bu^n)_4N^+$) onium ions in aqueous solutions[72] can also be included in this sequence; the radius of the benzyltriethylammonium ion is obviously intermediate between them (see Table 7).

The results in Table 7 imply than an increase in the distance between the centers of opposite charges in ionic intermediates is a factor favorable to the formation of the 2*E*,4*E* stereoisomer in the reaction product. Such an increase in the distance can be achieved either by the solvation of the cations which matches the ratio of the ion charge to its Pauling's (crystallographic) radius (so that the first solvation shell of the Li^+ ion is of the maximum size among the alkali metal ions) or by the elongation of the alkyl groups in the Q^+ cations which occurs on passing from Me_4N^+ to $(Bu^n)_4N^+$ whithin a tight ionic paire and causes thickening of the "separating interlayer" between the centers of positive and negative charges, which simulates a solvent-separated ion pair.

The model plot of the relative content of the 2*E*,4*E* isomer in the reaction product *vs.* the degree of solvation of the cation M^+ or *vs.* the size of the cation Q^+ (the latter values are approximated by the effective ion radii in aqueous solution[70,72] and expressed as the reciprocal value $1/r_H$) indicates that at the $1/r_H$ value of *ca.* 0.167 $Å^{-1}$ the content of the 2*E*,4*E* isomer in diene **57a** would be equal to 100 % (Fig. 3). The corresponding limiting value for the effective radius of a hydrated ion ($r_H \approx 5.9$ Å) approaches the interionic distance in the solvent-separated ion pairs formed by the "delocalized" anions of CH-acids with alkali metal cations in the solvents of low polarity.[73] With allowance made for the radii of the phosphonate *E*- and *Z*-carbanions themselves and of the corresponding oxanions, one should expect the maximum content of the 2*E*,4*E* isomer in the product when the interionic distance in the ionic intermediates is close to 7.5—8 Å. It is not essential whether this effect is due to the separation of counterions by the solvation shell or to the elongation of alkyl groups sorrounding the center of the positive charge in the cation.

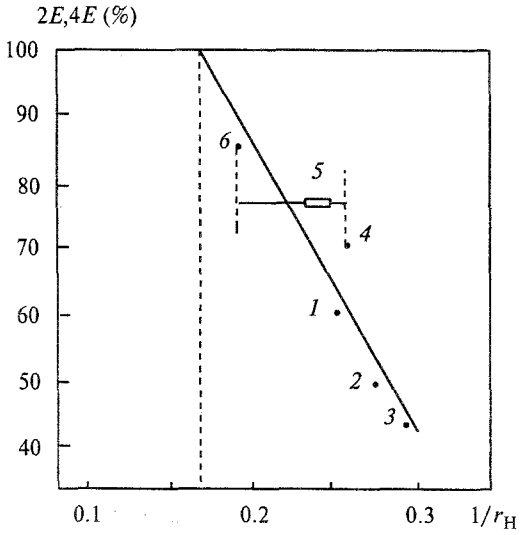


Fig. 3. Dependence of the final content of the 2*E*,4*E* isomer in the reaction product (in PhH, 22 °C) on the radius of the hydrated cation: Li^+ (*1*), Na^+ (*2*), K^+ (*3*), Me_4N^+ (*4*), $BnMe_3N^+$ (*5*), $Bu^n_4N^+$ (*6*). The limiting $1/r_H$ values and the most probable $1/r_H$ value are denoted by the thin and thick horizontal lines, respectively.

The effects of the type of phase transfer catalyst and its concentration.[58,59] In the absence of water in the system solid KOH—benzene—tetrabutylamonium bromide (TBAB), the catalytic effect of TBAB in the reaction **55** + **53c** → **57a** is practically non-existent, that is, neither the 2*E*,4*E* : 2*Z*,4*E* ratio in **57a** nor overall rate of the process are affected. The reaction proceeds efficiently only in the presence of a small amount of water in addition to the equilibrium amount present in wet benzene. The comparison of the data presented in Tables 7 (series B) and 8 shows that in the case of TBAB the reaction takes place predominantly according to the pathway involving the effective formation of $[Bu^n_4N]OH$ from $[Bu^n_4N]Br$ and KOH.

With a view to assessing the optimum amount of TBAB that would provide for a high content of the 2*E*,4*E* isomer in the reaction product a number of runs

Table 8. Effect of the addition of 1 equiv. of QHal on the steady-state *E* : *Z* ratio in phosphonate **53c** and on the final 2*E*,4*E* : 2*Z*,4*E* ratio in diene **75a** in the system solid KOH—wet benzene (22 °C, 0.3—0.5 vol. % of additional water present in the system)

QHal (100 mol.% relative to KOH)	*E*:*Z*-**53c**	2*E*,4*E*:2*Z*,4*E*-**57a**
—	36 : 64	44 : 56
$[BnNEt_3]^+Cl^-$	32 : 68	65 : 35
$[Bu_4N]^+Br$	40 : 60	80 : 20

Table 9. Effect of the TBAB concentration on the duration of the reaction **55**+**53c**→**57a** in the system solid KOH—benzene (22 °C) and on the isomer ratio in the resulting diene

TBAB (mol.% relative to [KOH])	Reaction duration/h	2*E*,4*E*:2*Z*,4*E*-**57a**
0	24	44 : 56
2.5	3	63 : 37
5	2.5	69 : 31
12.5	2.5	72 : 28
25	2.5	75 : 25
50	3	77 : 23
100	3	80 : 20

were carried out in the system solid KOH—benzene at various concentrations of the catalyst.

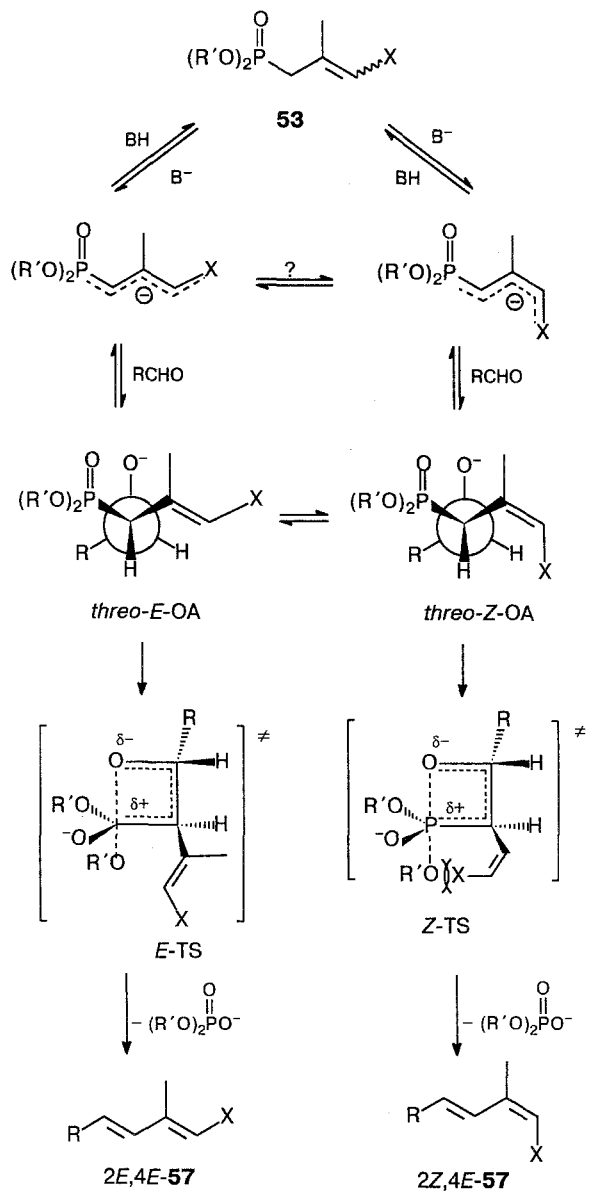
As follows from Table 9, the highest stereoselectivity is only attained at equimolar amounts of KOH and TBAB, *i.e.*, under conditions resembling those for the extraction of ion pairs (for review, see Ref. 74). However, the overall rate of the process, which increases drastically with the introduction of even 2.5 mol. % TBAB to the heterogeneous system, is practically not changed upon its further addition.

The effect of the TBAB concentration on the stereoselectivity of olefination is in contrast to the "saturation effect," which was observed upon the addition of 18-crown-6 to the system solid KOH—benzene.[56] In the latter case an increase in the [18-C-6] from 10 to 100 mol. % does not change the 2*E*,4*E* : 2*Z*,4*E* ratio in **57a**. This is yet another demonstration of the mechanistic difference between the phase transfer processes catalyzed by electroneutral coronands (solubilization of cationic species) and those catalyzed by the quaternary onium salts (ion exchange).

Possible mechanism of the steric control. In the reactions of phosphonates of the type **53** with aldehydes the newly formed double bond (Δ^4) always is in the *E* configuration. Hence, in this particular case, the equilibrium between the *threo* and *erythro* oxanions can be omitted from the system of equilibria postulated for the HWE reaction[41,42,48] as apparently nonexistent. Accordingly, the HWE reaction between phosphonates of type **53** and aldehydes can be summarized as shown below (Scheme 2, only the anionic parts of the intermediates are represented).

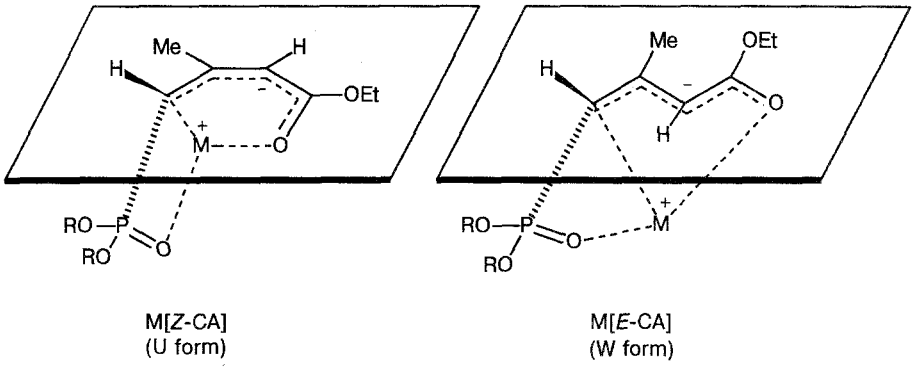
The effects of polar solvents and crown ethers apparently consist in altering the balance of the equilibria involved in the transformation of the phosphonate carbanions (CA) into the "aldolate" oxanions (OA) and the dissociation of *threo*-*E*-OA and *threo*-*Z*-OA. The less covalent the nature of the respective ion pairs is, the higher are their reactivities in both directions. However, since the position of the equilibrium between *E*-CA and *Z*-CA in various systems remains practically unaltered, namely, with the *E* : *Z* ratio in the vicitiny of 36.5 : 63.5

Scheme 2



(which is very close to the respective ratios for other acyclic phosphonates of this type), it can be concluded that both the polar solvent and crown ether accelerate mainly the formation and dissociation of *threo*-*E*-OA and *threo*-*Z*-OA by increasing the population of the solvent-separated ion pairs. The effect of the cation in the base and that of the onium PT catalyst are, obviously, of the same nature.

Consequently, the predominant formation of the 2*E*,4*E* isomers of the dienes **57** upon the reaction of phosphonates **53** with aldehydes can be assumed to result from different stability of the tight ion pairs $M^+[E\text{-CA}]^-$ and $M^+[Z\text{-CA}]^-$ to the attack by the solvent molecules, that is, from the difference in the extent of solvation of the cations M^+ in these two species.



M[*Z*-CA] (U form) M[*E*-CA] (W form)

Fig. 4. Schematic representation of the monomeric, unsolvated molecules of the salts formed by *Z*-**53c** and *E*-**53c** with alkali metals. The P=O bond is represented as a true double bond on the bases of the X-ray crystallographic studies of the chelate magnesium and copper(II) β-ketophosphonates.[75]

For the crystalline chelate salts derived from the dialkyl β-ketophosphonates, it was shown[75] that the metal ions are practically equidistant from the oxygen atoms of the C=O and P=O groupings. On the other hand, molecular orbital calculations and the measuring of the $^1J_{PC}$ and $^3J_{PC}$ constants in the ^{13}C NMR spectra of the lithium salt derived from *P*-allylphosphonic diamide[76] show the *Z* anion to be lower in energy than the *E* anion; in the former case the Li^+ ion is effectively coordinated to both the oxygen atom and C(3) atom in the allyl group. The negative charge in the anion of *P*-allylphosphonic diamide is distributed between the O, C(1), and C(3) atoms, that is, alternated. Taken together, these facts prompt one to assume that in the case of the 3-substituted allylic phosphonates of the type **53** (such as **53c**) the U-shaped *Z*-CA may be regarded as a "strong" bidentate ligand capable of chelating the ion M^+, while the W-shaped *E*-CA would behave as a "weak" monodentate ligand, in which the bonding of M^+ with both C_γ and O atoms is sterically hindered. These two situations are schematically presented in Figure 4.

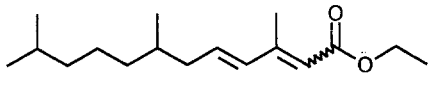
The stable predominance of *Z*-**53c** in its equilibrium with *E*-**53c** established under the action of bases points to the thermodynamic stability of *Z*-CA as compared with *E*-CA. Apparently, the ion pair involving *Z*-CA is lower in energy than $M^+[E\text{-CA}]^-$. The latter, however, is more readily solvated, owing to its relatively low stability, and reacts with electrophiles mainly in the form of a more reactive solvent-separated ionic pair.

Except for the first member in the series, tetraalkylammonium cations (Q^+) are practically not solvated.[71,72] Contact ion pairs $Q^+[Z\text{-CA}]^-$, having a structure similar to that of the contact pairs $M^+[Z\text{-CA}]^-$, probably provide a better coulombic interaction than the pairs $Q^+[E\text{-CA}]^-$. Therefore, the former are more stable and react with electrophiles more slowly than the latter. Recently, structures of a fairly similar type were observed for the tetrabutylammonium salts of such classical CH-acids as dialkyl ethylmalonates and cyanoacetic ester.[77]

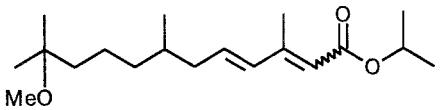
The nature of the ligands at the phosphorus atom seems to affect the configuration of the Δ^2 double bond in the resulting dienoate mainly during the formation of the ionized transition states *E*-TS$^{\neq}$ and *Z*-TS$^{\neq}$ from *threo*-*E*-OA and *threo*-*Z*-OA, respectively (see Scheme 2). It is known[78] that, during the reshaping of the ligand environment which accompanies the transition of the phosphorus from the tetracoordinate to pentacoordinate state, the negatively charged oxygen atom tends to occupy an equatorial position in the emerging trigonal bipyramide. As a result, one of the alkoxy groups is forced to take the apical position, and the transition state *Z*-TS$^{\neq}$ becomes sterically congested due to the spatial interaction between the apical R′O group and the substituent X. In the case of *E*-TS$^{\neq}$ that kind of interaction is topologically impossible, which makes this transition state the favored one.

From these mechanistic considerations the following practical conclusions can be drawn: a) For the preparation of dienes of type **57** with the highest content of the 2*E*,4*E* isomer the most suitable systems were $[Alk_4N]OH$—benzene and the combination of solid KOH and $[Alk_4N]Hal$ (1 : 1) in benzene as its substitute, provided that Alk > Bu^n; b) the highest content of the 2*Z*,4*E* isomer in the product can be obtained by using the system solid KOH—benzene without any phase transfer catalyst. The variation of both the alkoxy groups at the phosphorus atom and the van der Waals volume of the functional group X in the phosphonates **53** under the conditions recommended above provides further tuning of the reaction equilibria, which helps to shift their balance still further toward the required stereoisomer.

Application to the synthesis of biologically active compounds. Characteristic trends in the reactivity of allylic phosphonates of the type **53** were subsequently applied to the stereocontrolled synthesis of certain ecologically benign insecticides[58], namely, of hydroprene (**58**) and methoprene (**59**).



58



59

It is known[79] that among the four possible geometric isomers of **58** and **59** the 2*E*,4*E* isomers possess the highest morphogenetic activity. However, the stereospecific synthesis of these isomers is cumbersome and involves the use of organometallic compounds,[80] and can therefore be employed for preparing only small amounts of standard speciments. The alternative syntheses are β-methylglutaconate[81–83] and phosphonate[84,85] methods, in which the aldehyde C_{10}-component is treated with a complementary (C_6 or C_5) ω-alkoxycabronyl component, afford the products of the non-stereoselective olefination (2*E*,4*E* : 2*Z*,4*E* ~7 : 3), which necessitates subsequent stereochemical enrichment. In industry, this is done in a number of steps, and, as a consequence, the overall yield of the final product containing ~90—92 % of the 2*E*,4*E* isomer, is low.

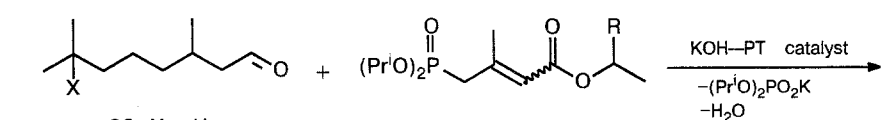
Mechanistic phenomena characterizing the HWE reactions of the phosphonates **53** were employed for enhancing the stereoselectivity of the phosphonate-based approach to the dienes **58** and **59**. The experiments were based on heterogeneous systems comprising solid KOH, an aprotic organic solvent, and a PT catalyst; such systems combine the avaliability of the base and minimum risk of hydrolysis of the resulting diene esters.[58,86]

In the absence of PT catalysts the reactions of 3,7-dimethyloctanal (**60**) and methoxycitronellal (**61**) with phosphonates **53f** and **53g**, respectivelly, in the system KOH(solid)—benzene afforded the binary mixtures of stereoisomers **58a+58b** or **59a+59b**, which yields at best did not exceed 60—61 % while the undesirable 2*Z*,4*E* isomers predominated in both cases.[59] When 18-crown-6 (0.1 equiv.) was added to the same system, the yield of **58** and **59** rose to 80—86 %, and the content of the 2*E*,4*E* isomers in the products thus obtained amounted to 88 and 85 %, respectivelly.[58,86]

On the other hand, the data concerning the effect of the nature of the cation of the base on the stereochemistry of the HWE reaction between the aldehyde **55** and phosphonate **53c** indicated that the application of tetraalkylammonium hydroxides (see Table 7) or equivalent amounts of an alkali metal hydroxide and tetraalkylammonium halide would be promising in the preparation of esters **58** and **59** with a high content of the required 2*E*,4*E* isomer. Actually, when the interaction between **60** and **53f** was carried out in the heterogeneous KOH(solid)—wet benzene—TBAB system, the overall yield of binary mixtures of stereoisomeric dienoates (**58a+58b**) or (**59a+59b**) was considerably higher, and the ratio of the isomers changed sharply in favor of the 2*E*,4*E* isomer. With equimolar amounts of KOH and the PT catalyst ($Q^+ = Bu^n_4N^+$), the fraction of the 2*E*,4*E* isomer of hydroprene (**58**) was 88 % and that of methoprene (**59**) was as high as 93 %.

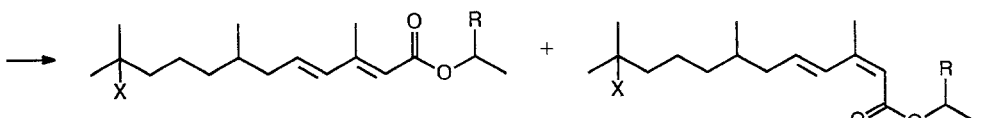
When benzyltriethylammonium chloride (BTEAC) or a commercial mixture of benzyl (*n/s*-alkyl)-dimethylammonium chlorides, alkyl groups ranging from $C_{10}H_{21}$ to $C_{18}H_{37}$ (Catamine AB), was used as the PT catalyst instead of TBAB, the stereoselectivity of the HWE olefination decreased (*cf.* runs *5*, *6*, and *7*, Table 10).

This is in agreement with the previously noted[57] dependence of the 2*E*,4*E*-selectivity of olefination on the effective radius of the cation Q^+ in the ion pair. Although the cations in BTEAC and in Catamine AB contain bulky groups (Bn and C_{10}—C_{18} aklyl), one can suggest that in the deprotonation of phosphonates **53** with QOH, as well as in the formation of ion pairs of Q^+ with *E* and *Z* isomers of the phosphonate carbanion, the partners approach each other from the least hindered side of the quaternary ammonium base. As a consequence, BTEAC and Catamine AB are approximately equivalent to the tetraethylammonium cation. Therefore, the effective radius of the symmetrical $[Bu^n_4N]^+$ ion is greater than those of the cations in BTEAC and Catamine AB, and the **59a** : **59b** ratio is correspondingly higher as well.



60: X = H
61: X = OMe

53f: R = H
53g: R = Me



58a: X = R = H
59a: X = OMe, R = Me

58b: X = R = H
59b: X = OMe, R = Me

Table 10. Effect of the conditions of the reaction of aldehydes **60** and **61** with phosphonates **53f** and **53g** on the yield and the stereoisomeric composition of the resulting hydroprene (**58**) and methoprene (**59**)

Run	X	R	Reaction conditions	Products (overall yield (%))	2*E*,4*E*:2*Z*,4*E* ratio
1	H	H	Solid.KOH (2 equiv.)—PhH	**58a+58b** (60)	45 : 55
2	H	H	Solid.KOH (2 equiv.)—PhH—$[Bu^n_4N]Br$ (2 equiv.)	**58a+58b** (70)	88 : 12
3	H	H	$[Bu^n_4N]OH$ (1 equiv.)—PhH	**58a+58b** (78)	92 : 8
4	MeO	Me	Solid.KOH (2 equiv.)—PhH	**59a+59b** (61)	30 : 70
5	MeO	Me	Solid.KOH (2 equiv.)—PhH—$[Bu^n_4N]Br$ (2 equiv.)	**59a+59b** (85)	93 : 7
6	MeO	Me	Solid.KOH (2 equiv.)—PhH $[BnNEt_3]Cl$ (2 equiv.)	**59a+59b** (71)	80 : 20
7	MeO	Me	Solid.KOH (2 equiv.)—PhH Catamine AB (2 equiv.)	**59a+59b** (83)	80 : 20
8	MeO	Me	$[Bu^n_4N]OH$ (1 equiv.)—PhH	**59a+59b** (96)	93 : 7

The highest preparative yields of **58** and **59** with the best 2*E*,4*E* : 2*Z*,4*E* ratios were achieved when the reactions **60** + **53f** → **58** and **61** + **53g** → **59** were carried out in a seemingly homogeneous (possibly, micellar)[57] system that contained the stoichiometric amount of $[Bu^n_4N]OH$ in dry benzene (see Table 10, runs *3* and *8*).

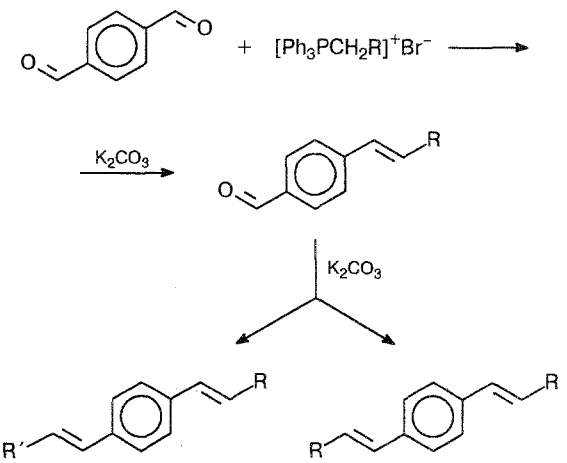
Thus, the use of an equimolar amount of a higher tetraalkylammonium hydroxide in an aprotic organic solvent makes it possible to obtain hydroprene, methoprene and other derivatives of 3-methyl-2,4-alcadienoic acids, such as immunomodulating and antikeratotic substances belonging to the group of retinoic acid, with a high (≥90 %) content of the 2*E*,4*E* stereoisomer by the shortest synthetic path.

Recently, the diene esters of this type were used as the key intermediates in the synthesis of the *Z*-configurated trisubstituted olefins, *e.g.*, the sex pheromones of the dry bean beetle *Callosobruchus maculatus*,[87] white peach scale[88] and Californian red scale.[88]

The Wittig reaction

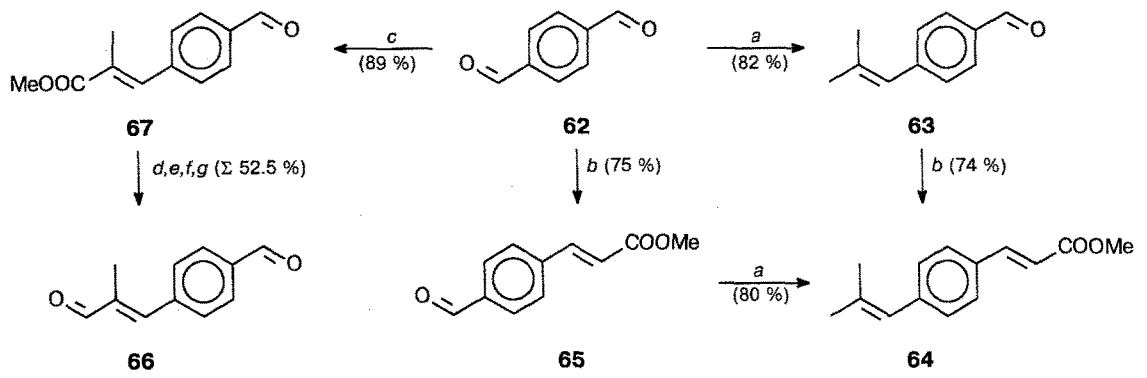
The ability of aromatic,[89,90] heterocyclic,[91] and aliphatic[92,93] dialdehydes to undergo a selective Wittig reaction involving a stabilized phosphorane and one of the aldehyde groups is known enough. Yet another example of the partial olefination of dicarbonyl compounds with phosphoranes presents the addition of $Ph_3P{=}CHCOOAlk$ to either one or the both of the CHO groups of certain arylidenemalonic aldehydes of the general type **46**; both aldehydo groups of the latter are in conjugation with the same double bond and in the geminal position to each other.[94]

On the other hand, the interaction of various dialdehydes with nonstabilized phosphoranes under conventional conditions of the Wittig olefination gives rise only to diolefins.[89,95] The failure of conducting the reaction selectively at one of the aldehyde groups under these conditions can be explained by extremely high reactivity of the nonstabilized phosphorus ylides which are generated in anhydrous homogemeous media. In such cases selective monoolefination can be achieved only when one of the carbonyl groups of the dialdehyde is duly protected.



The recourse to heterophasic reaction media makes it possible to perform first the monoolefination of a dialdehyde[96] and then to employ the second CHO group in a large variety of reactions, *e.g.*, in a second Wittig olefination, for obtaining symmetrical as well as asymmetrically built diolefins.[96]

Scheme 3



Reagents and conditions: *a*. $(Pr^iPPh_3)^+I^-$—K_2CO_3—$(CH_2CH_2O)_2$, 100 °C; *b*. Ph_3P=CHCOOMe, PhH, 80 °C; *c*. $[Ph_3PCH(Me)COOMe]^+I^-$—K_2CO_3—$(CH_2CH_2O)_2$, 100 °C; *d*. $HC(OMe)_3$—$HClO_4$ (cat.); *e*. $LiAlH_4$—Et_2O; *f*. PCC—CH_2Cl_2; *g*. Cationite KU-2-8(H^+).

By applying various modifications of the PTC[2,89,97–99] one can both essentially simplify the procedure of Wittig olefination and obtain uniformly good results even for triphenylphosphonium salts with markedly different reactivity. Thus, it was shown (Scheme 3)[100] that the partial and consecutive interaction of the aldehydo groups of terephthalic aldehyde (**62**) with phosphoranes could be functional substituents in the 1,4 positions of the benzene ring. The reaction of **62** with 1.0 equivalent of isopropyltriphenylphosphonium iodide under the conditions of PTC in the K_2CO_3(solid)—dioxane system afforded 4-(2-methyl-1-propenyl)benzaldehyde (**63**) which was further converted into methyl 4-(2-methyl-1-propenyl)cinnamate (**64**) by a standard procedure.

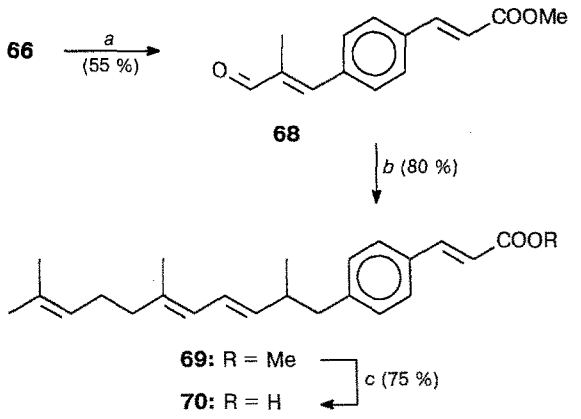
The sequence of the two Wittig reactions is reversible, that is, dialdehyde **62** can be converted initially to methyl 4-formylcinnamate (**65**), and the latter is converted thereafter to ester **64**; the overall yield of **64**, based on **62**, is practically equal (~60 %) in both cases.

The consecutive conversion of the aldehyde groups of **62** by variuos routes makes it possible to synthesize also the 4-substituted cinnamic acids with a longer *nor*-polyprenoid chain.[100] In the same manner one can use the different reactivity is a synthetic equivalent of the synthon **A** (see the "Aldol condensation" section above). In its turn, the dial **66** was obtained in five steps from **62** *via* the aldehydo ester **67**, the latter being obtained from **62** upon partial Wittig olefination under PTC conditions (see Scheme 3) of the two carbonyl groups present in compound **66**, the CHO group attached to the benzene ring enters the Wittig reaction more readily.

Interaction between equimolar amounts of dialdehyde **66** and (methoxycarbonyl)methylidene triphenylphosphorane gave the unsaturated aldehydo ester **68** as the main product with reasonable selectivity (Scheme 4).

The unaffected aldehyde droup in compound **68** is reactive enough towards phosphoranes, which makes it possible to create a second side chain by performing yet another Wittig olefination step. Thus, the reaction of **68** with geranyltriphenylphosphonium bromide (GTPB)

Scheme 4



Reagents and conditions: *a*. Ph_3P=CHCOOMe, PhH, Δ; *b*. $(GerPPh_3)^+Br^-$—K_2CO_3—dioxane, Δ; *c*. KOH—EtOH (aq.), Δ.

under PTC conditions gave in a good yield the polyene ester **69**. The hydrolysis of **69** afforded 4-(2,6,10-trimethyl-1,3,5,9-undecatrienyl)cinnamic acid (**70**), which overall yield over eight steps of the synthesis was 16 % (see Scheme 4).[100] Earlier, compounds **69** and **70** were patented as the medicaments for supressing malignant dermal papillomas.[18]

The olefination of aldehydes **2** (R = COOAlk) with GPTB under PTC conditions was also used as the key step in the two synthetic schemes[5,101] leading to the anti-tumor polyene **5** and hypolipidaemic acid **7** (*cf.* Scheme 1).

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