Recent Synthesis and Transformation of Vinylphosphonates

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Abstract: Vinylphosphonates are an important group of compounds. This review summarizes recent developments in the synthesis and transformations of vinylphosphonates. Owing to the importance of vinylphosphonates, many different synthetic methods have been developed. Especially useful are various organometallic synthetic methods utilizing the chemistry of copper, titanium, zirconium, and lithium, etc. The transformations of vinylphosphonates is also described and include expoxidation, cycloaddition, Suzuki coupling, and Diels-Alder reactions.

1. INTRODUCTION

The knowledge of phosphorus compounds has expanded so rapidly that it constitute now a major branch of chemistry, organic molecules containing phosphorus offer fascinating possibilities for structural, synthetic and mechanistic study [1]. Besides being crucial biomolecules in metabolic processes, as anticancer, antiviral drugs, immuno suppressives, insecticides, antibacterial, and antifungal [2], vinylphosphonates are an exceedingly important group of compounds with important practical applications: e.g. their derivatives are used as copolymers [3], polymer additives [4], flame retardants [5], are important tools in further organic transformations [6], and are useful in many other applications, such as fuel and lubricant additives [7].

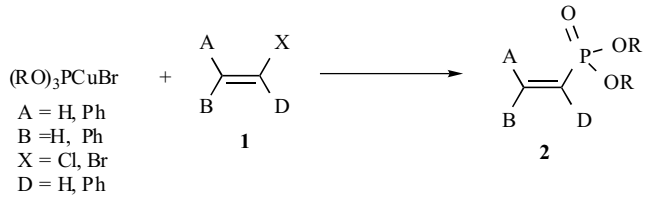
2. PREPARATION OF VINYLPHOSPHONATES

2.1. *Via* Copper Complexes

The chemistry of organocopper(I) reagents has especially received a great deal of attention regarding *cis*-conjugate addition reactions with acetylenic compounds [8]. Addition of the above reagent to acetylenic esters undergo a facile conjugate addition reaction with lithium diorganocuprates with *cis* addition taking place exclusively [9]. 1-Alkynyl sulfoxides and sulfones also undergo *cis*-conjugate addition [10].

In contrast, the reactions of organocopper(I) reagents with a number of 1-alkynyl phosphorus compounds have been observed in a few cases [11].

Reactions of copper(1)halide complexes of trivalent phosphorus with vinylic halides afforded vinylphosphonates **2**. The direct formation of the vinylic carbon to phosphorus bond has been accomplished *via* reaction of vinylic halides **1** with copper(1)halide complexes of trialkyl phosphites. In addition, formation of varying amounts of vinylic chlorides may be observed if the reaction is performed by using vinylic bromides with copper(1)chloride complexes of trialkyl phosphites. This halogen-exchange reaction may be made synthetically useful through the employment of copper(1)chloride complexes of triaryl phosphites or phosphines (Scheme **1**) [12].



Scheme 1.

Recently, stereo- and regioselective synthesis of 1,2,2-trisubstituted vinylphosphonates **3-9** *via* organocopper(I) reagents with good yields (82-97%) had been reported, (Scheme **2**) [13].

Stereoselective syntheses of mono-, di- and trisubstituted diethyl alk-1-enyl-phosphonates (**10-12**) from alkynylphosphonates have been reported (Scheme **3**) [14].

2.2. *Via* Titanium Complexes

A new method of synthesis of 3-amino-1-alkenylphosphonates was described. It involves the addition of imines to the alkynylphosphonate titanium(II) complexes **T2**, which are prepared *in situ* from 1-alkynylphosphonates and Ti(O-*i*-Pr)$_4$ /2 equiv of *i*-PrMgCl. Compounds (**T5 a-i**) were obtained regio- and stereoselectively in high yields [15]. Various types of imines efficiently reacted with the alkynylphosphonate titanium(II)complex **T2**, prepared from 1-alkynylphosphonates, and Ti(O-*i*-Pr)$_4$/2 equiv of *i*-PrMgCl to produce the desired 3-amino-1-alkenylphosphonates in high yields as shown in Table **1**. This one-pot reaction is general and proceeds with aliphatic and aromatic substituents on both the vinylic carbon and the nitrogen atom of the imine, in high yields. Other alkyl-vinylphosphonates **T3**,

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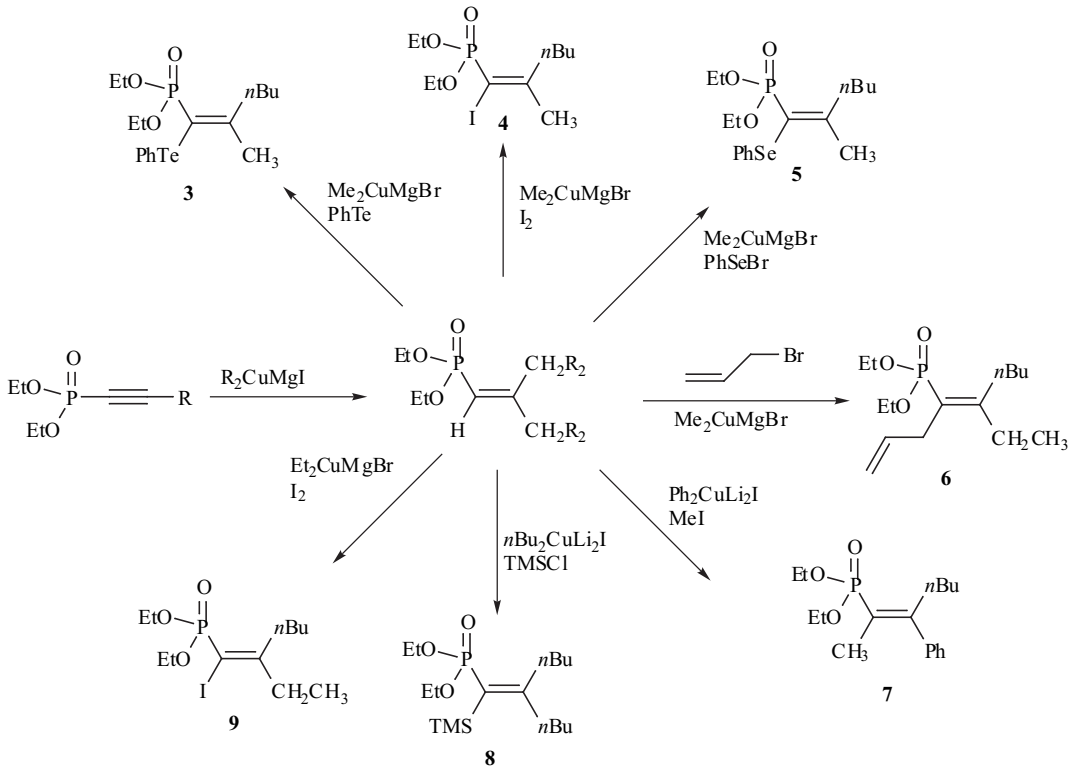
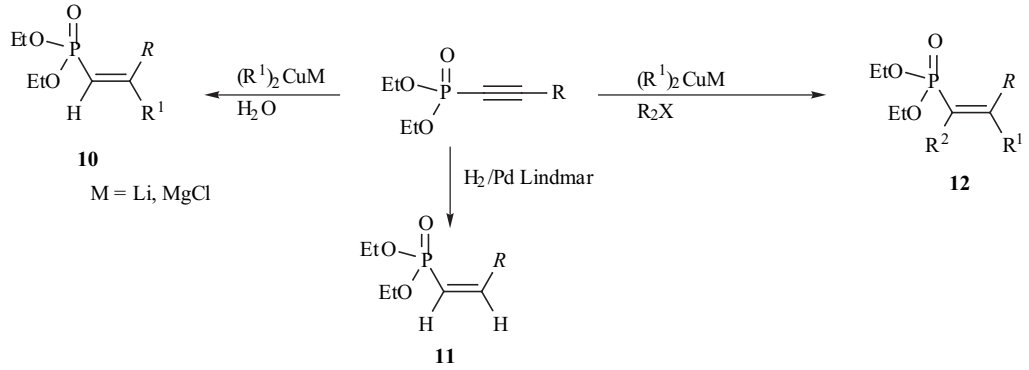


Scheme 2.



Scheme 3.

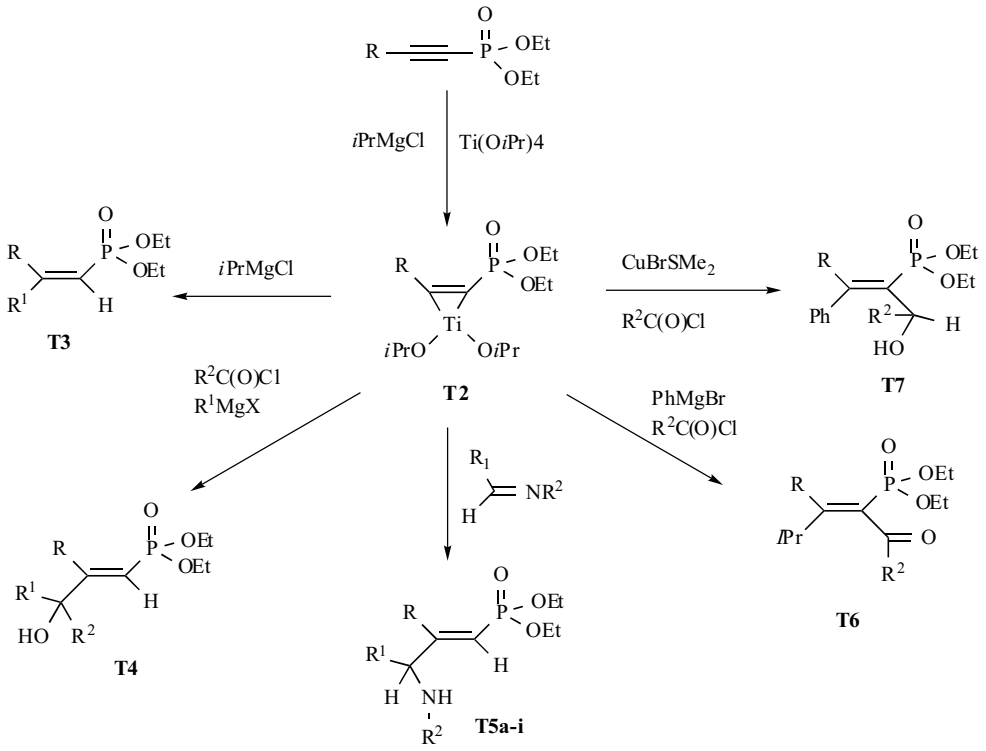
Table 1. 3-Amino-1-Alkenylphosphonates (T5 a-i) Obtained from Addition of Imines to the Alkynylphosphonate Titacycles T2

Entry	R	R1	R2	31P yield	Yield
T5a	Ph	p-tolyl	Me	97%	79%
T5b	Ph	p-MeO-Ph	i-Pr	95%	78%
T5c	n-Bu	Et	Bz	95%	80%
T5d	n-Bu	Ph	Bz	98%	85%
T5e	n-Bu	Ph	Ph	95%	75%
T5f	n-Bu	Ph	i-Pr	98%	79%
T5g	n-Bu	p-MeO-Ph	i-Pr	98%	81%
T5h	1-ClPr	Ph	Ph	95%	70%
T5i	1-ClPr	Ph	Bz	90%	71%

T4, **T6** and **T7** also were obtained by tuning of the Ti(O-*i*-Pr)$_4$/ Grignard reagents (Scheme **4**) [16].

2.3. *Via* Zirconium Complexes

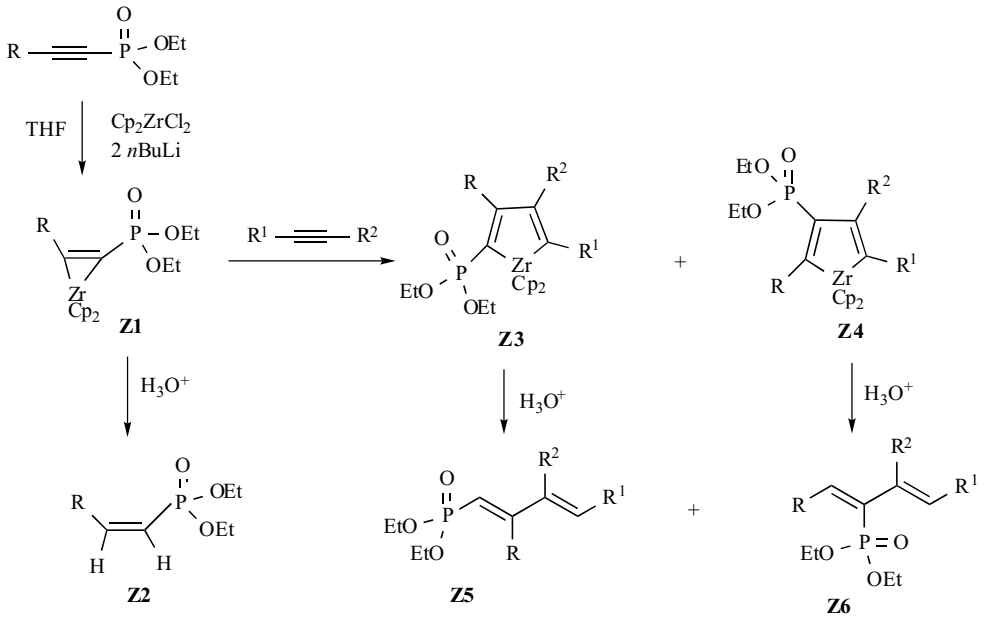
Zirconation of 1-alkynes provides zirconocyles that can be reacted further to give highly functionalized and complex derivatives. Hydrozirconation of alkynes to vinylzirconocenes followed by transmetallation gives access to a host of new organometallic reagents that react with various electrophiles in a highly specific manner [17]. Hydroboration of alkynes followed by Suzuki coupling has been developed over the last ten years into the method of choice for the stereospecific synthesis of highly substituted alkenes [18]. In spite of the great popularity of both these methods, it is surprising that they have never been applied to 1-alkynylphosphonates. 1-Alkynylphosphonates are readily available by lithiation followed by reaction with chlorophosphates. Subsequent conversion of the metallated Vinylphosphonates by electrophiles would be expected to



Scheme 4.

give highly selective and functionalized di- and trisubstituted vinylphosphonates.

Zirconation of 1-alkynylphosphonates followed by reductive cyclization by Negishi's reagent, Cp_2ZrCl_2/2 n-BuLi [19], has been used extensively for the formation of three membered zirconacycle **Z1** in which after simple hydrolysis furnished *cis*-vinylphosphonates **Z2.** Addition of various alkynes to **Z1** produced the five Membered ring zirconacylcles **Z3**, **Z4** in which after hydrolysis afforded



3a R = *n*-Bu, Yield = 79%.
3b R = *n*-Pent, Yield = 76%.
3c R = Cl-Prop, Yield = 63%.
3d R = Ph, Yield = 76%.
3e R = TBDMSiC$_3$H$_6$, Yield = 78%

R^2	R^1	Yield% Z5	Yield% Z6
H	C_4H_9	15	68
H	C_5H_{11}	19	60
H	Ph	11	73
H	C_3H_6Cl	20	57
C_2H_5	C_2H_5	83	<3

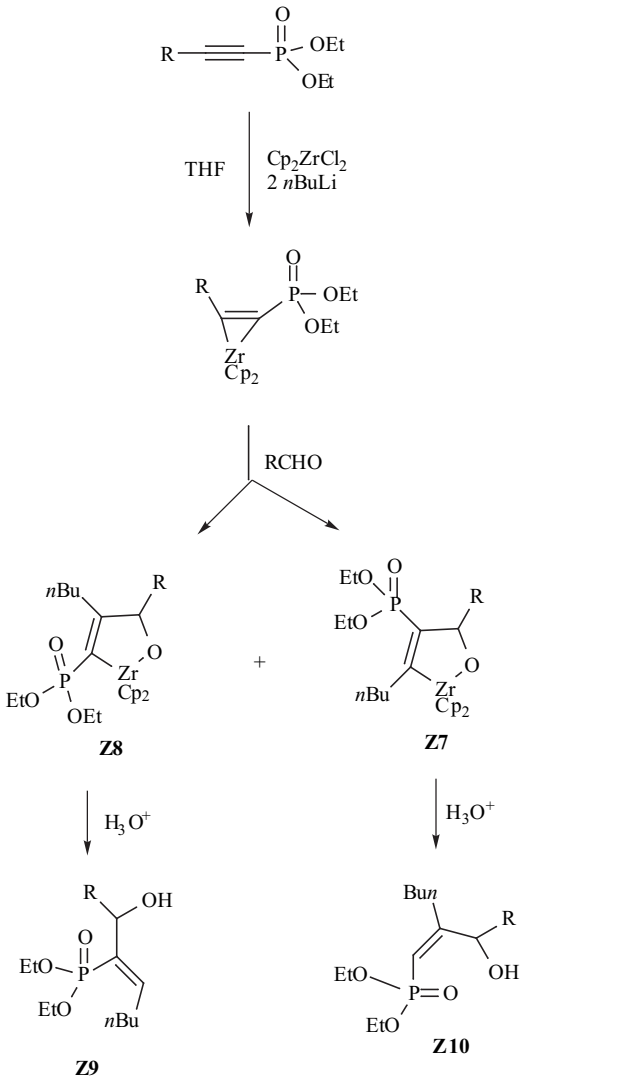
Scheme 5.

compounds **Z5** that have *E,E* configuration of the double bonds, and the *Z,E* compounds **Z6**, (Scheme **5**) [20].

In addition, 1-alkynylphosphonate reacts with Cp_2ZrCl_2 / 2 *n*-BuLi to give a three-membered zirconacycle **Z1** that readily inserts aldehydes. Hydrolysis of the intermediate five-membered zirconacycles **Z7**, **Z8** leads to two products, **Z9** and **Z10**, (Scheme **6**). In the major product, **Z10**, the aldehyde inserted into C2 of the zirconacycle, while in the minor product, **Z9**, the aldehyde inserted into C1.Products **Z10** obtained in 38-75% isolated yields. Products **Z9** are obtained in approximately 1-12%. Essentially, only compounds **Z9** are produced with *ortho*-substituted aldehydes. The regio- and stereochemistry of **Z9** and **Z10** were determined by NMR techniques [21].

Furthermore, the three member ring zirconacycle **Z1**, insert ketones exclusively at C2 to give the five-member ring zirconacycle phosphonates **Z11**, which can be hydrolyzed to give 2-(hydroxymethyl)vinylphosphonates, **Z12**, in excellent yield, (Scheme **7**) [22].

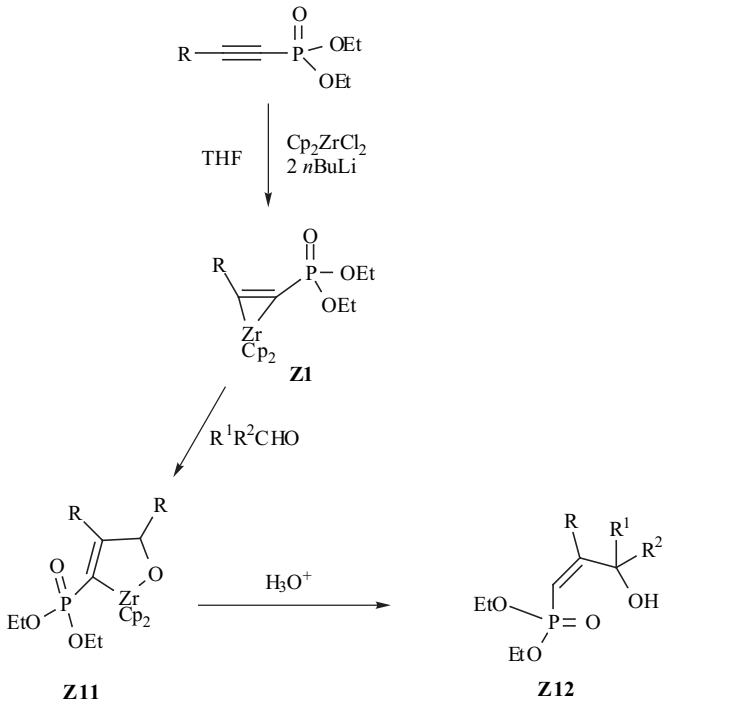
The preparation of l-(hydroxymethyl)vinylphosphonates by the reaction of α-phosphonovinyl carbanions bearing β-alkylthio, β-alkyloxy and β,β-bis(alkylthio) substituents with aldehydes has been reported [23]. It should be noted that α-phosphonovinyl cuprates do not react with oxygen electrophiles. The present reaction, on the other hand, is very general for both dialkyl-, alkylaryl-, and diarylketones. The yields are uniformly high [13,14].



R = Ph, yield, 10%, conversion 98%
R = PhCH=CH, 11%, 98%
R = 1,4-benzodioxane, 9%, 95%
R = *p*-F-Ph, 11%, 75%
R = 1- naphthyl, 12%, 65%
R = *p*-MeO-Ph, 7%, 65%
R = C_6H_{13}, 8%, 95%
R = *O*-MeO-Ph, <1%, 70%
R = 2,4-dichloro-Ph, <1%, 70%

R = Ph, yield, 75%, conversion 98%
R = PhCH=CH, 76%, 98%
R = 1,4-benzodioxane,71%, 95%
R = *p*-F-Ph, 48%, 75%
R = 1- naphthyl, 38%, 65%
R = *p*-MeO-Ph, 38%, 65%
R = C_6H_{13}, 70%, 95%
R = *O*-MeO-Ph, 72, 70%
R = 2,4-dichloro-Ph, 74%, 70%

Scheme 6.

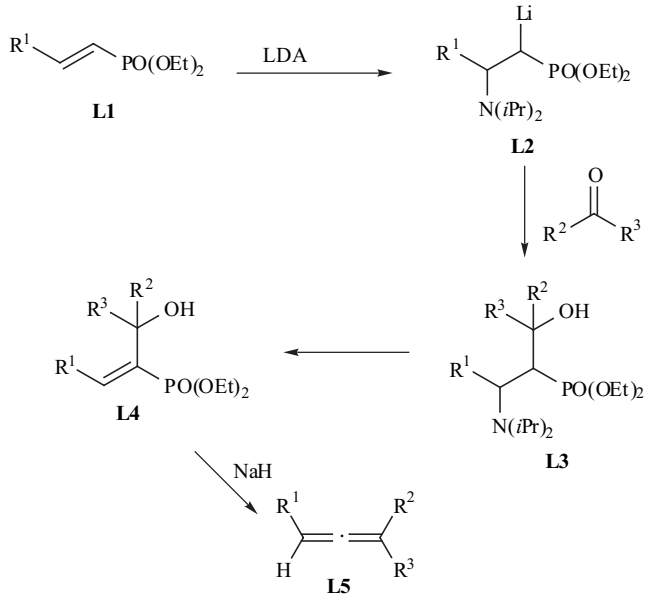


R = *n*Bu, R^1 = Me, R^2 = Ph, conversion 99%
R = *n*Bu, R^1 = R2 = Me, conversion 99%
R = *n*Bu, R^1 = Me, R^2 = *nPent*, conversion 99%
R = *n*Bu, R^1 = *i*Pr, R^2 = Ph, conversion 99%
R = Ph, R^1 = R^2 = Me, conversion 99%
R = ClC_3H_6, R^1 = Me, R^2 = Ph, conversion 95%
R = ClC_3H_6, R^1 = C_5H_{11}, R^2 = Me, conversion 98%
R = ClC_3H_6, R^1 = R^2 = Ph, conversion 95%

Scheme 7.

2.4. *Via* Lithium Salts

A sequence of reactions involving conjugate addition of lithium diisopropylamide (LDA) to alkenylphosphonates **L1** and subsequent aldol-type reaction of the resultant lithiated phosphonates **L2** with aldehydes or ketones produced **L3**. (Scheme **8**). Further elimination products **L4** were produced. It is important to note that **L4** is readily converted to allenes, **L5**, by treatment with a base under Horner-Wadsworth-Emmons conditions. The conversion of **L3** to the 1-(hydroxymethyl)vinylphosphonates, **L4**, proceeded in good to high yields [24].

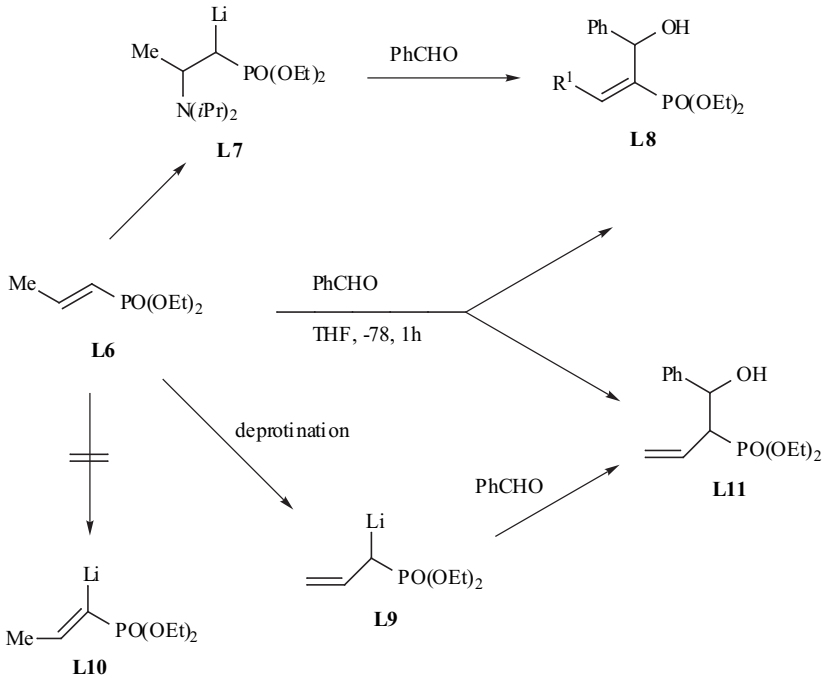


Scheme 8.

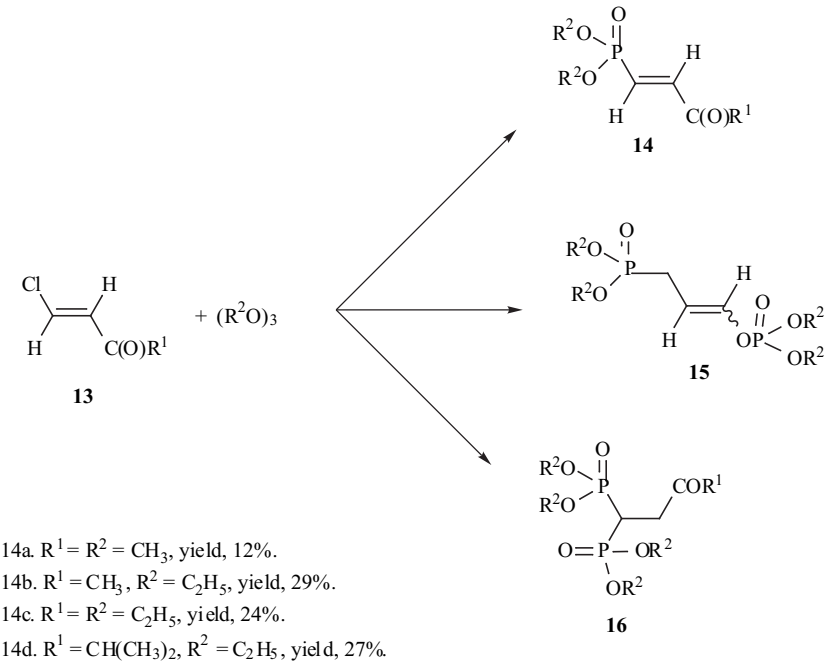
These results imply that conjugate addition of LDA to **L6**, enabled the formation of the kinetic anion, **L7**, which is not stable and is converted to the thermodynamic allylic anion, **L9**, as shown in (Scheme **9**). This suggests that addition of LDA to, **L6**, in the presence of benzaldehyde would increase the yield of **L8**, because the initially formed anion, **L7**, may react rapidly with benzaldehyde before the establishment of the equilibrium with **L9**. Thus, addition of a solution of 1.1 equiv of LDA in THF to a mixture of **L6** and an equivalent of benzaldehyde in THF afforded, after 1 h at -78 °C, the desired product, **L8**, in acceptable 73% yield along with **L11**, in 11% yield [24].

2.5. *Via* Arbusov Reaction

The Michaelis-Arbusov reaction of 2-chlorovinyl ketones with trialkyl phosphates afforded 3-



Scheme 9.



14a. $R^1 = R^2 = CH_3$, yield, 12%.
14b. $R^1 = CH_3$, $R^2 = C_2H_5$, yield, 29%.
14c. $R^1 = R^2 = C_2H_5$, yield, 24%.
14d. $R^1 = CH(CH_3)_2$, $R^2 = C_2H_5$, yield, 27%.
14e. $R^1 = C_6H_5$, $R^2 = CH(CH_3)_2$, yield, 40%.
14f. $R^1 = CH_3$, $R^2 = CH(CH_3)_2$ yield, 47%.
14g. $R^1 = C_6H_5$, $R^2 = CH_3$, yield, 40%.

Scheme 10.

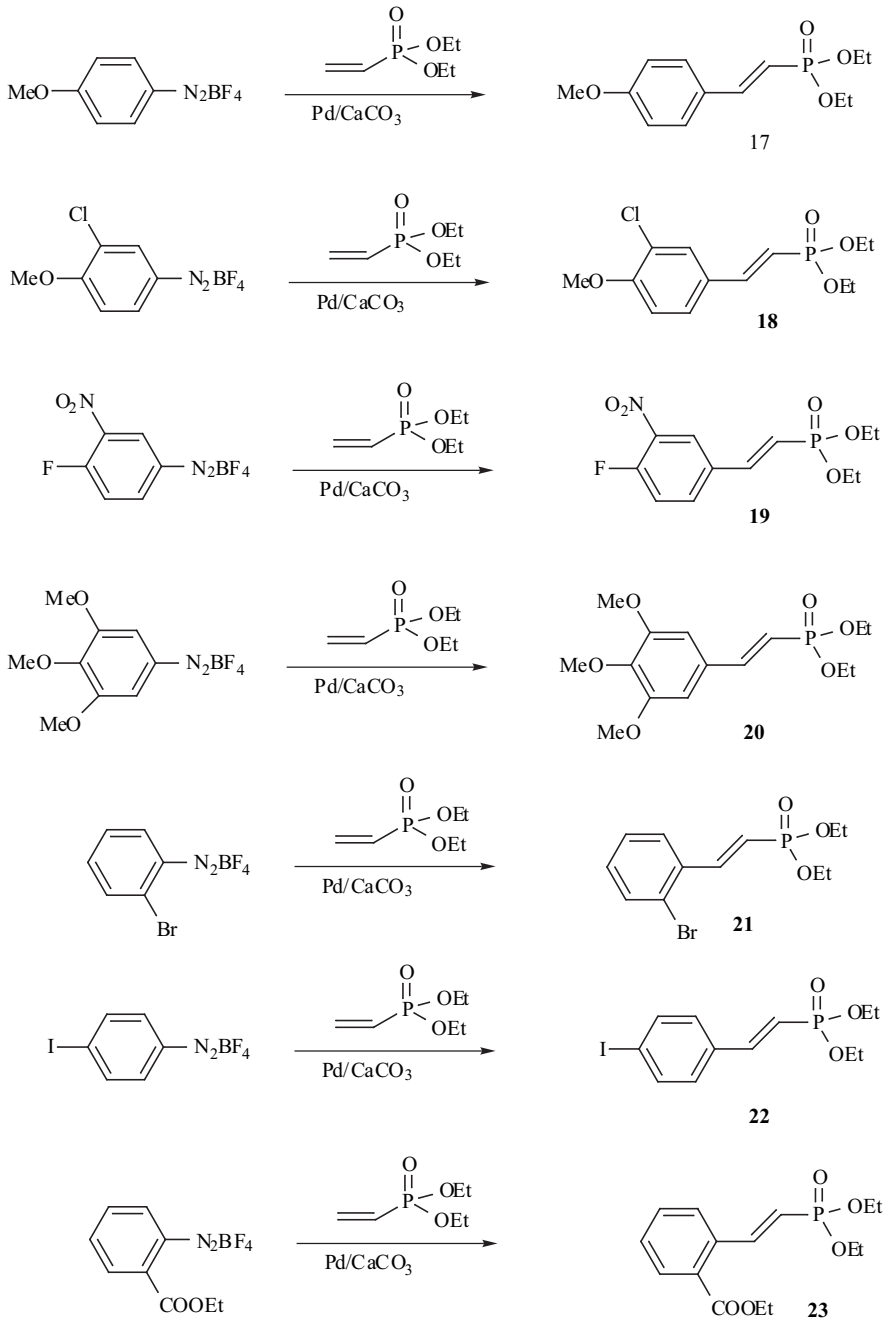
oxovinylphosphonates, **14**, as well as enolphoshonates, **15**, and 3-oxo-1,1-alkanebisphosphonates, **16**, (Scheme **10**) [25].

2.6. *Via* Heck Reaction

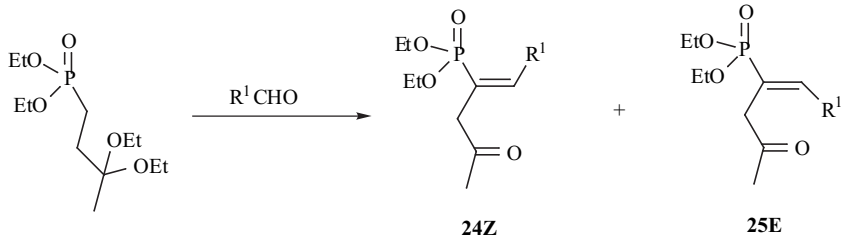
A facile synthesis of aryl vinylphosphonates **17-23** has been reported based on Heck reaction of aryldiazonium salts bearing electron-withdrawing or donating groups with vinylphosphonates. A one-pot procedure consisting of Heck reaction and hydrogenation permits the clean formation of useful Wadsworth-Emmons reagents (Scheme **11**) [26].

2.7. *Via* Olefination Reactions

a) Vinylphosphonates were obtained using Peterson reagent, which is generated *in situ*.[33] Products *Z*, and *E*-1-alkylidene-3-oxobutylphosphonates **24** were obtained in good yields (Scheme **12**) [27].



Scheme 11.

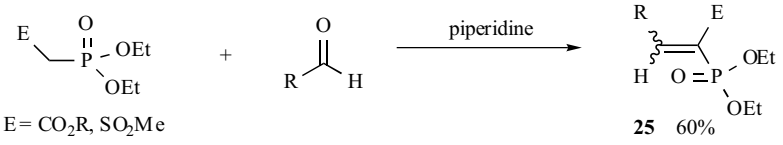


Scheme 12.

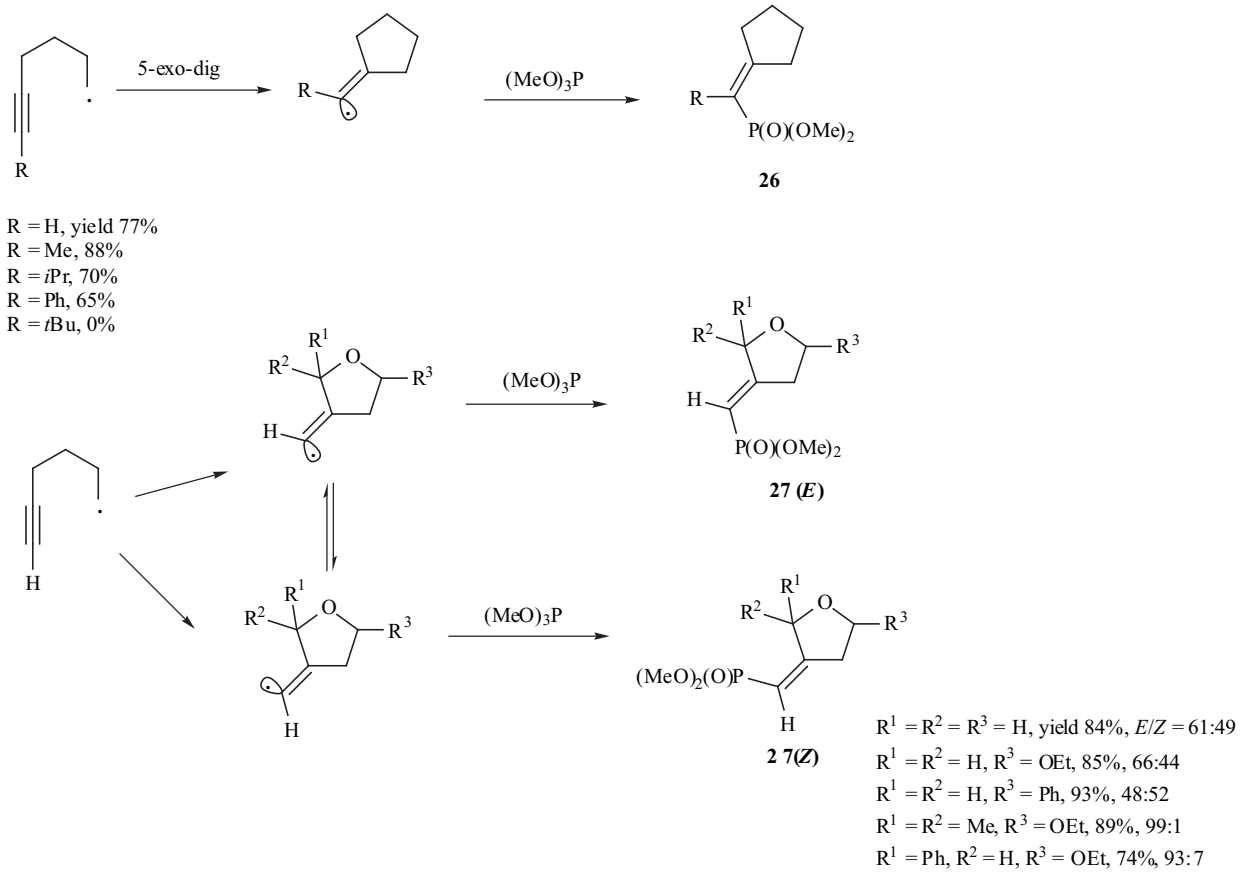
b) Acid or base catalyzed demethoxylation of (2-methoxyethyl)phosphonates produced vinylphosphonates, **25**, in moderate yields (Scheme **13**) [28].

2.8. *Via* Radical Trapping

Vinylphosphonate formation *via* a novel cyclization-vinyl radical trapping sequence has been reported recently, (Scheme **14**). This study provides a novel route to new



Scheme 13.



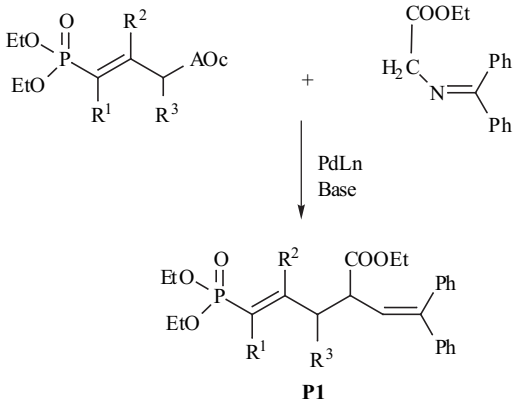
Scheme 14.

vinylphosphonates, **26**, and the biologically active molecules, **27**, (*Z* and *E*) [29].

2.9. *Via* Various Other Catalytic Preparations

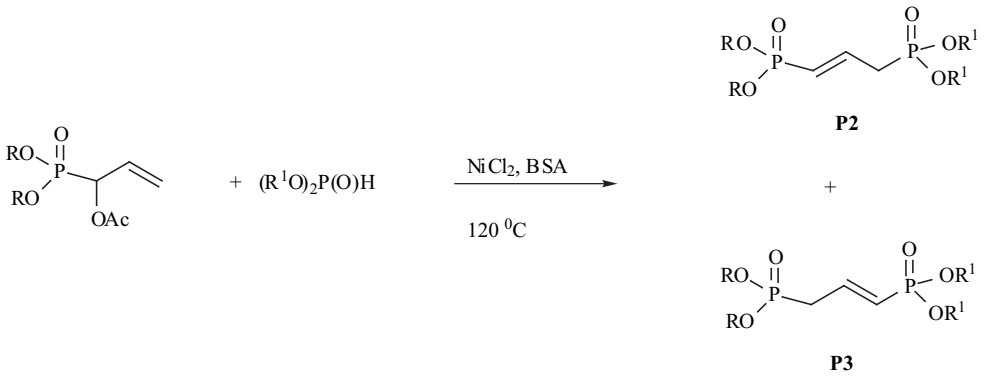
a) The palladium(0)-catalyzed reaction of 3-acetoxy-1-alkenyl phosphonates with ethyl (diphenyl methylene amino acetate) and N,O *bis*(trimethylsilyl) acetamide provided the precursors of the 2-amino-5-phosphonovaleric acid and related compounds, (**P1 a-e**), in high yields (Scheme **15**) [30].

b) The reaction between 1-acetoxyallylphonates or -phosphinates with dialkyl hydrogen phosphites or



P1a. R = Me, $R^1 = R^2 = R^3 = H$, *E*/*Z* 85:15
yield, 77%, *E*/*Z* = 65:35
P1b. R = Et, $R^1 = R^2 = R^3 = H$, *E*/*Z* 90:10
yield, 74%, *E*/*Z* = 77:23
P1c. R = *i*Pr, $R^1 = R^2 = R^3 = H$, *E*/*Z* 93:7
yield, 93%, *E*/*Z* = 87:13
P1d. $R = R^1 = Me$, $R^2 = R^3 = H$, *E*/*Z* 68:32
yield, 90%, *E*/*Z* = 76:24
P1e. R = Pr, $R^1 = R^2 = H$, $R^3 = Me$, *E*/*Z* 90:10
yield, 100%, *E*/*Z* = 100:0

Scheme 15.



Scheme 16.

phenylphosphonous esters in the presence of $NiCl_2$ gave a mixture of the corresponding allyl-and vinylphosphonates **P2**, **P3** (Scheme **16**) [31].

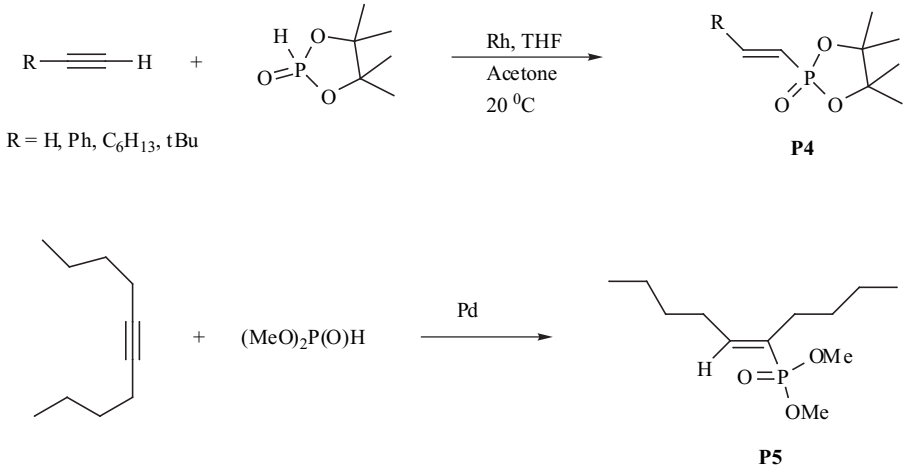
c) Tanaka *et al.* studied reactions of alkynes with the phosphonate (4,4,5,5-tetra-methyl-1,3,21 5 -dioxaphospholane 2-oxide), which is most reactive in the addition to multiple bonds. The reaction catalyzed by Rhodium complexes was shown to be complementary to that catalyzed by palladium to afford the corresponding vinylphosphonates **P4**. As a result, the isomers with *E* configuration of the double bond were obtained at room temperature in high yields (Scheme **17**) [32].

Reactions with internal alkynes are very difficult to occur, they take more than 60 h against 13-22 h for terminal alkynes. However, the products **P5** are formed in high yield in the presence of Pd catalyst, and the process clearly follows the *syn*-addition pattern [33].

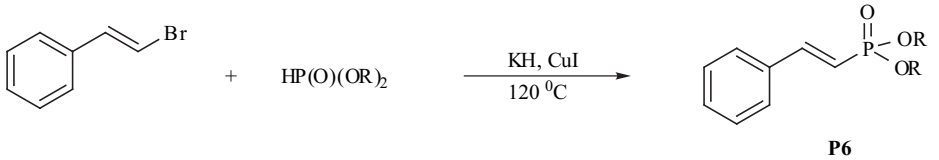
d) The Cu catalyzed reactions of β-bromostyrenes with dialkylphosphites to obtain compounds possessing second harmonic generation (SHG) activity **P6**. Strongly polar solvents, KH as a base, and elevated temperature are necessary (Scheme **18**) [34].

e) Vinylphosphonates **P7** were generated in high yields by the reactions of triethyl phosphite with alkenyl halides having an alkoxy or diethylamino group on α- position in the presence of nickel catalyst, and analogous reactions with β-halovinyl ethers or β-haloenamines occur at higher temperature, but the yields of **P8** are also fairly high (Scheme **19**) [35].

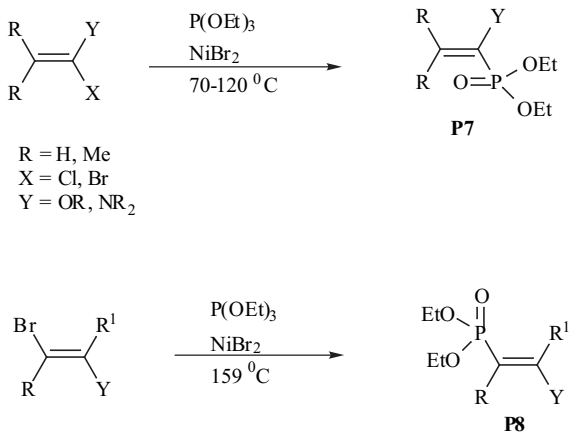
f) (*E*,*E*)-1,3-Diiodobutadiene was converted into bis-1,4-(diethoxyphosphinoyl)-1,3-butadiene, **P9-P11** in high yield (Scheme **20**) [36]. Likewise, mono- and disubstitution products are formed in reactions with 1,3-dienyl halides [37].



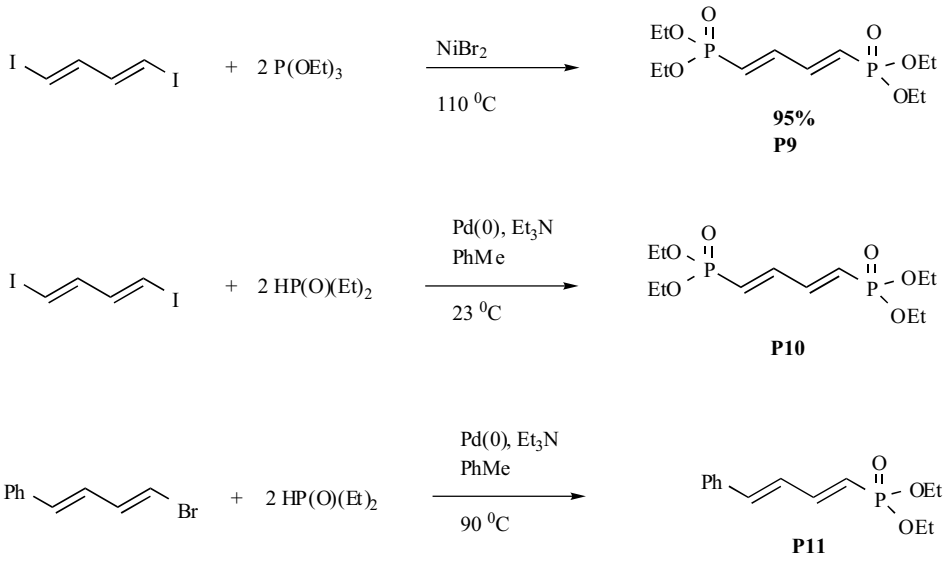
Scheme 17.



Scheme 18.

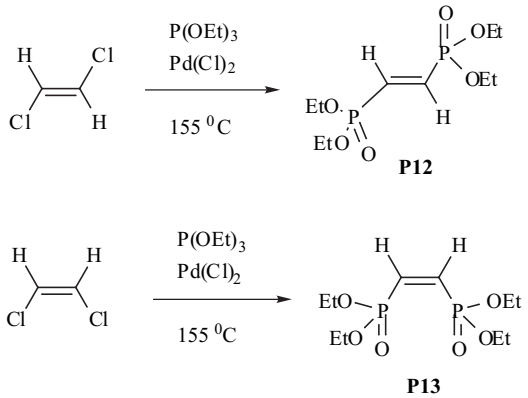


Scheme 19.



Scheme 20.

g) Reactions catalyzed by palladium(II)chloride or acetate also provide almost quantitative yields of the bis-vinylphosphonates products **P12**, **P13**. The process is highly stereospecific: the configuration of the initial alkene is retained in the product. Scheme **21** illustrates the reaction with isomeric 1,2-dichloroethenes as an example [38].

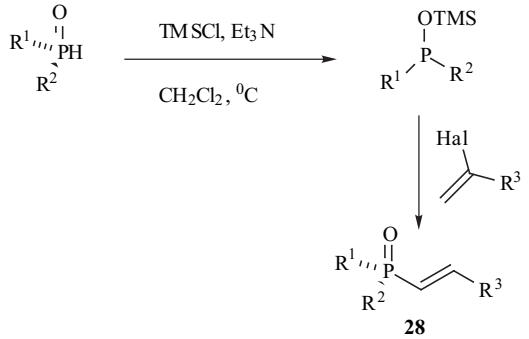


Scheme 21.

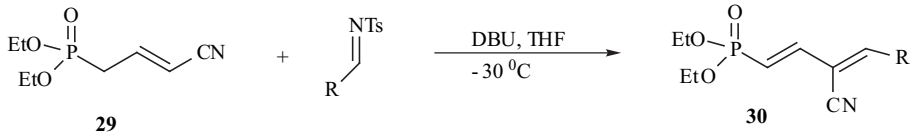
3. OTHER MISCELLANEOUS METHODS FOR THE PREPARATION OF SPECIFIC VINYLPHOSPHONATES

3.1. *Z*- and *E*-di-Substituted Vinylphosphonates

The addition of trimethylsilyloxy phosphorus (III) derivatives, generated *in situ*, to α-haloacrylates and acrylonitriles at room temperature provides a mild, general and stereoselective route to phosphonoacrylates, **28** (Scheme **22**) [39].



Scheme 22.



30a. R = C_6H_5, yield, 72%
30b. R = 4-ClC_6H_4 , 72%
30c. R = 2, 4-$Cl_2C_6H_3$, 75%
30d. R = 4-$(CH_3)_2NC_6H_4$, 83%
30e. R = 4-$C_2H_5C_6H_4$, 81%
30f. R = 4-$CH_3OC_6H_4$, 76%
30g. R = 4-$CH_3C_6H_4$, 80%
30h. R = Naphthyl, 72%

Scheme 23.

Treatment of a catalytic amount of DBU (20 mol%) with a mixture of diethyl 3-cyanoallylphosphonate **29** and *N*-tosylsulfonylimines gave diethyl 3-cyanobuta-1,3-dienylphosphonates **30** in 72-83% yields. All the products (**30a-h**) are assigned 1*E*,3*Z* configurations on the basis of the crystal structure of diethyl (1*E*,3*Z*)-3-cyano-4-naphthylbuta-1,3-dienylphosphonate **46h**, the proton NMR spectra and the proposed reaction mechanism (Scheme **23**) [40].

3.2. Fluorinated Vinylphosphonates

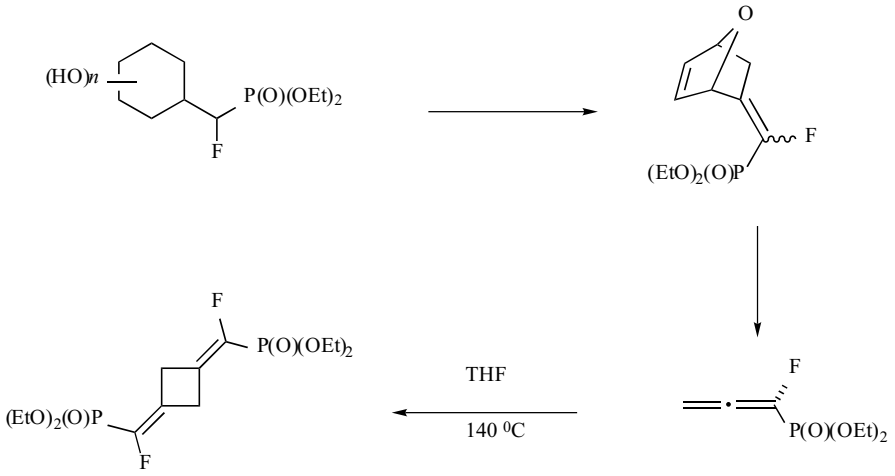
a) Diastereoselective synthesis of cyclic α-fluoromethyldienephosphonates, **32,** using α-fluoroallenephosphonate, **31**, as dienophile was reported, (Scheme **24**) [41]. The dimerization of α-fluoroallenephosphonate and its Diels-Alder reaction with various dienes provide a diastereoselective route to cyclic and bicyclic α-fluorovinylphosphonates, **32** [42].

b) Gross *et al.* [43] reported the palladium-catalyzed stereoselective synthesis of (*E*)-and (*Z*)-α-fluorovinyl-phosphonates **33**, which are analogs of glucose 6-phosphates (Scheme **25**).

c) Fluorinated vinylphosphonates **34** were obtained in one-pot conversion of trifluoro ester to α-fluoro-β-trifluoro-β-alkoxy-vinylphosphonates (Scheme **26**) [44].

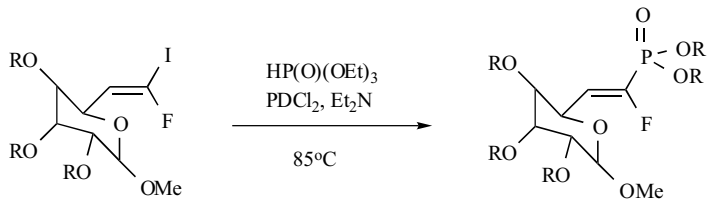
3.3. Chlorinated Vinylphosphonates

New chlorovinylphosphonates **35** bearing a 1,3,2-dioxaphosphorinane ring which are useful for the



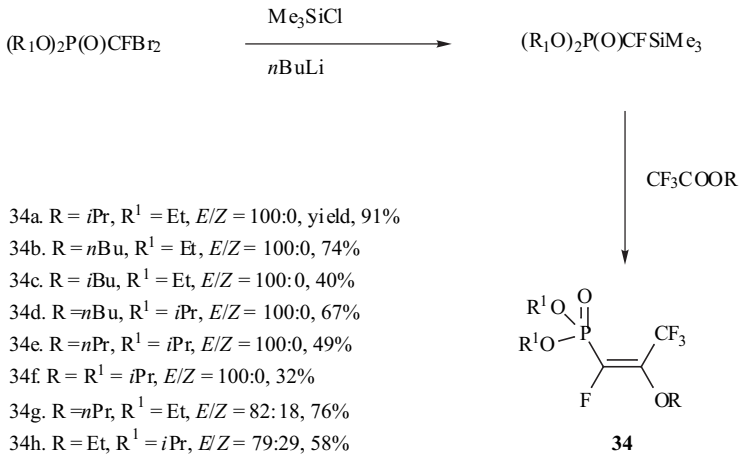
32 73% yield

Scheme 24.

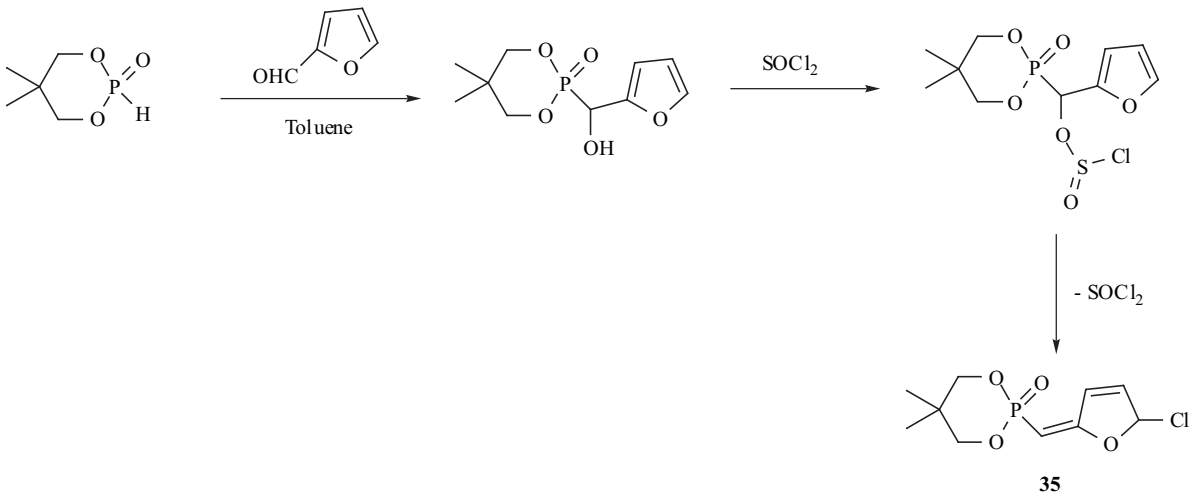


33 31-68% yield

Scheme 25.



Scheme 26.

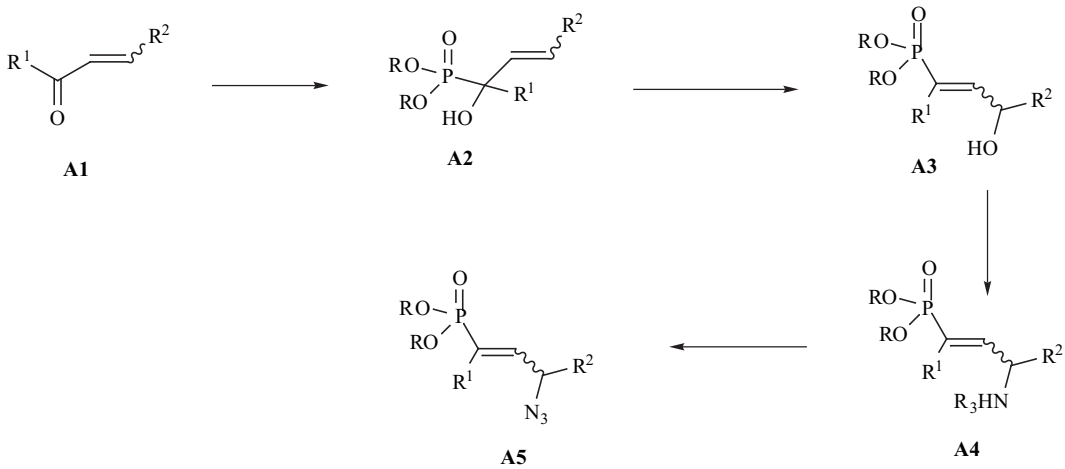


Scheme 27.

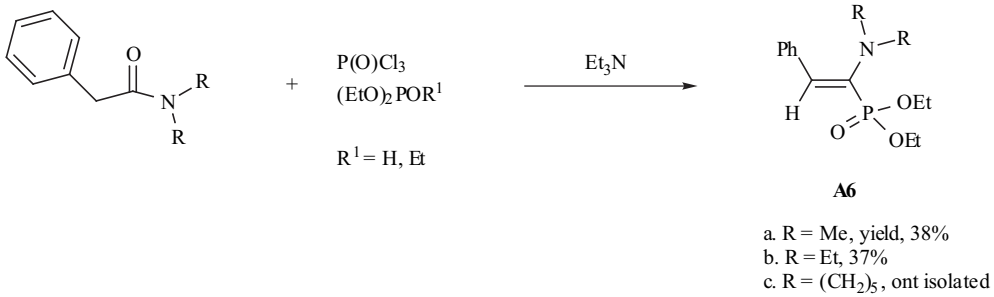
stereospecific synthesis of 5-chlorofurfuryl substituted olefins and chloro-substituted dienes have been obtained by an easy, inexpensive route. The utility of some of these in the synthesis of ferrocenyl- and anthracenyl-substituted unsymmetrical acetylenes has been explored. The structures of these vinylphosphonates was determined by the X-ray (Scheme **27**) [45].

3.4. Amino-Vinylphosphonates

a) Synthesis of (3-amino-1-alkenyl)phosphonic acids from allylic α- and γ-hydroxy-phosphonates has been reported [46]. (3-azido-1-alkenyl)phsophonates **A5** was prepared regioselectivity by reaction of (1-hydroxy-2-alkenyl)phosphonates **A2** and subsequent



Scheme 28.



Scheme 29.

thermal 1,3-rearrangement of the allylic γ-aminophosphonates **A4** (Scheme **28**).

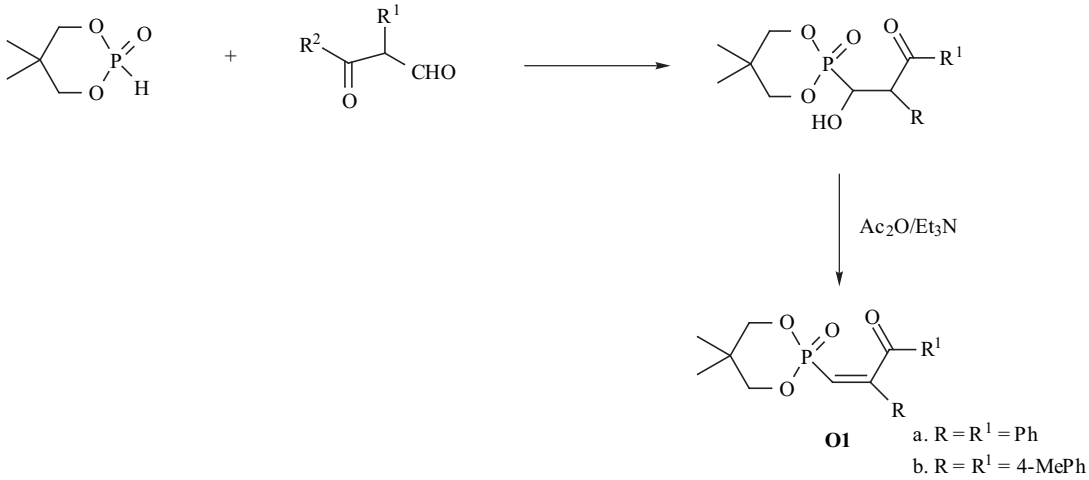
b) The reaction of $PhCH_2C(O)NR_2/P(O)Cl_3$ (R = alkyl) with diethyl or triethyl phosphite afforded E-vinylphosphonates **A6** with high geometrical stereoselectivity and acceptable yields (Scheme **29**) [47].

3.5. Oxo-Vinylphosphonates

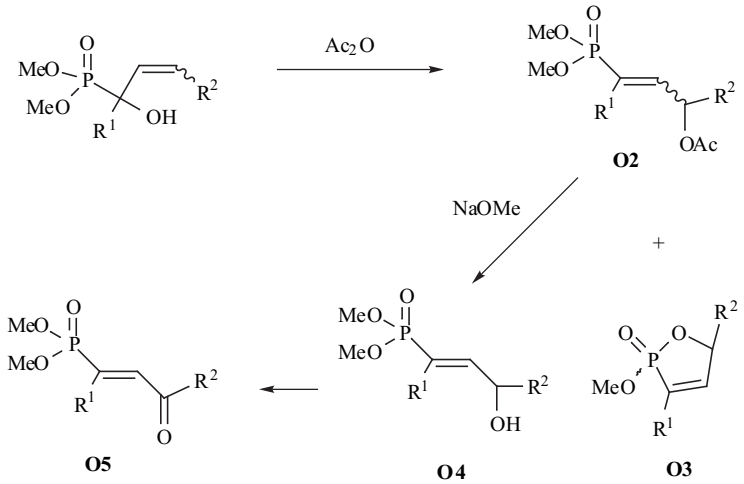
a) Several oxo-phosphonates **O1** were produced by oxidation of α-hydroxyphosphonates, which are prepared by the Pudovik reaction of the cyclic phosphates (Scheme **30**) [48].

b) Different vinylphosphonates, **O2-O5**, including 3-oxo-vinylphosphonates, **O5,** (Scheme **31**), have been synthesized in good yields by $NaOCH_3$-catalyzed regioselective 1,2-addition of dimethyl phosphates to acyclic and cyclic α-enones at -35 °C [49].

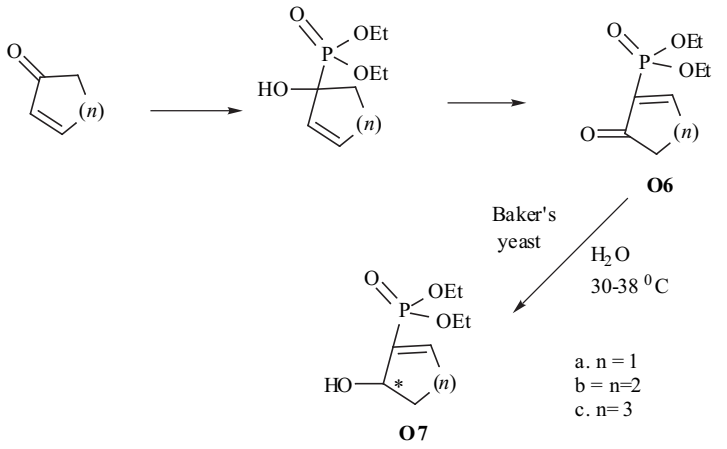
c) Attolini *et al.* studied the reactions transformation of cyclic dialkyl (3-oxo-1-cycloalkenyl) phosphonates **O6**. Baker's yeast-mediated enantioselective reductions afford the corresponding dialkyl (3-



Scheme 30.



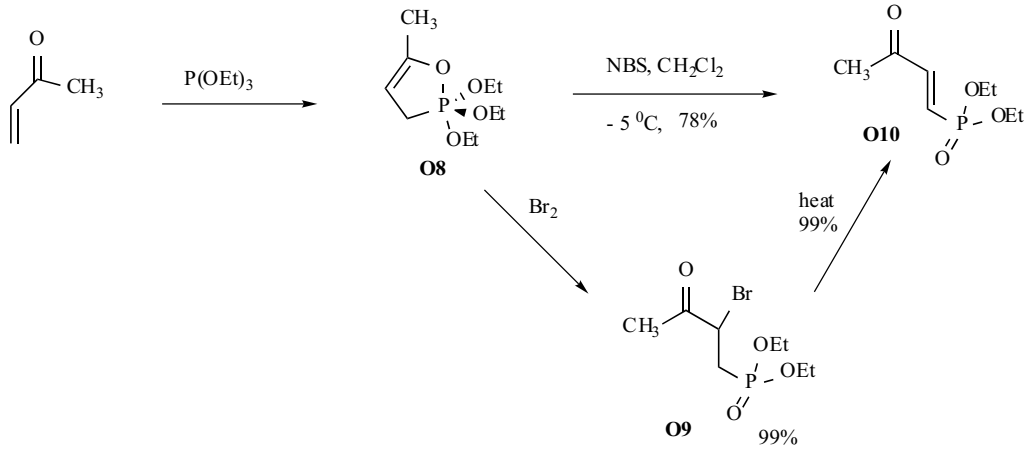
Scheme 31.



O6

O7

Scheme 32.



O8

O9

O10

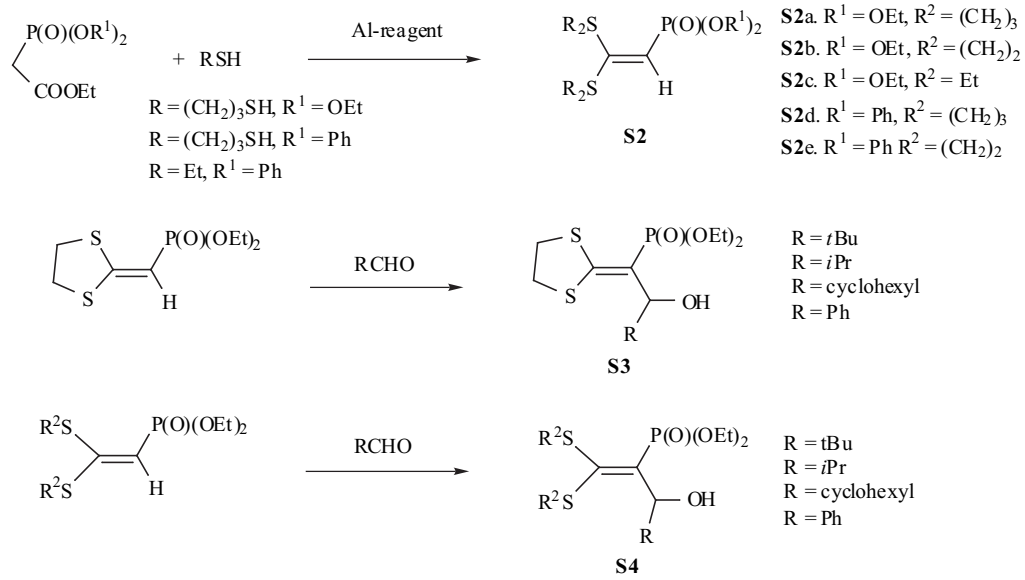
Scheme 33.

hydroxy-1-cycloalkenyl) phosphonates **O7,** (Scheme **32**) [48,50].

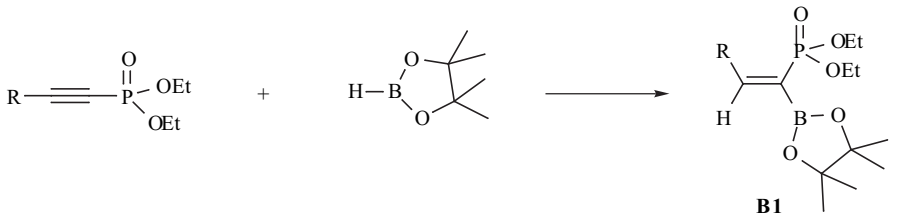
d) 2,2,2-Triethoxy-oxaphospholene **O8** reacts under mild, neutral conditions with bromine to produced 3-oxo-vinylphosphonate **O10** in high yields (Scheme **33**) [51].

3.6. Thio-Vinylphosphonates

Phosphonoketene dithiocetals, (**S2**a-e) were obtained in good yields by the reaction of ethyl phosphonoacetates with thiols in the presence of an alkylaluminium dichloride or dialkylaluminium chloride (Scheme **34**) [52]. Reaction of 2,2-dithio-1-phosphovinyl phosphonates with aldehydes



Scheme 34.



B1

Scheme 35.

afford 1-(hydroxymethyl)thiovinylphosphonates **S3**, **S4** in good to moderate yields.

3.7. Boranated Vinylphosphonates

Hydroboration of alkynylphosphonates with pinacolborane proceeds to give phosphonoboronates **B1** (Scheme **35**). Surprisingly, such compounds have not been reported before [53].

4. REACTIONS, ISOMERIZATIONS AND TRANSFORMATIONS OF VINYLPHOSPHONATES

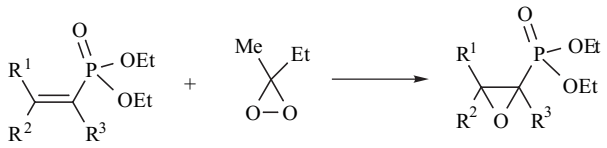
4.1. Allylic Phosphonates from Vinylphosphonates

A facile route to allylic phosphonates *via* base-catalyzed isomerization of the corresponding vinyl phosphonates **K1 a-e** has been reported (Scheme **36**) [54].

4.2. Epoxides from Vinylphosphonates

Epoxyalkylphosphonates are useful intermediates in the synthesis of modified natural and synthetic polymers [55], and also in the preparation of bioactive substances [56].

A new stereoselective route to substituted 1,2-epoxyalkylphosphonates through oxidation of corresponding alk-1-enylphosphonates, **K2**, by '*in situ*' generated ethylmethyldioxirane has been described (Scheme **37**) [57].



37 **K2**

R^1 = alkyl, Ph

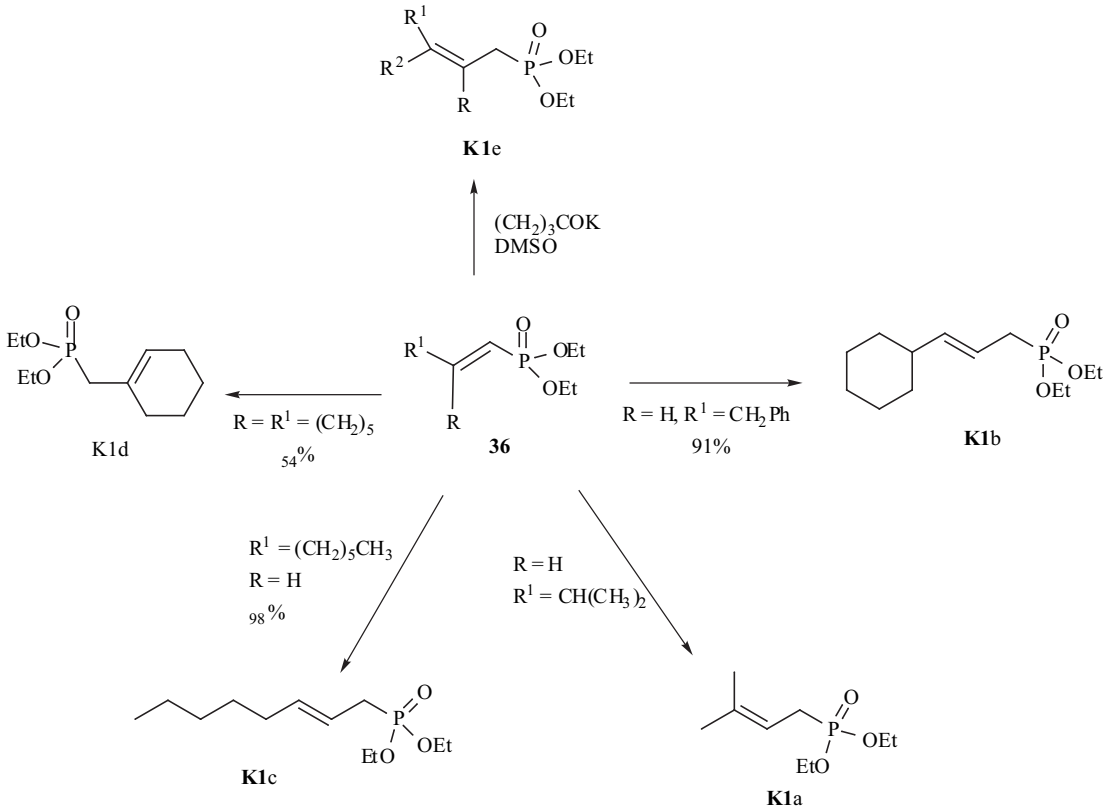
R^1 = alkyl, Ph, H

R^1 = alkyl, H

Scheme 37.

4.3. Hydroxy(methyl) Phosphonates from Vinylphosphonates

Diethyl *trans*-1,2-epoxyphosphonates were synthesized starting from the corresponding diethyl *trans*-vinylphosphonates **38** by the previously described reaction

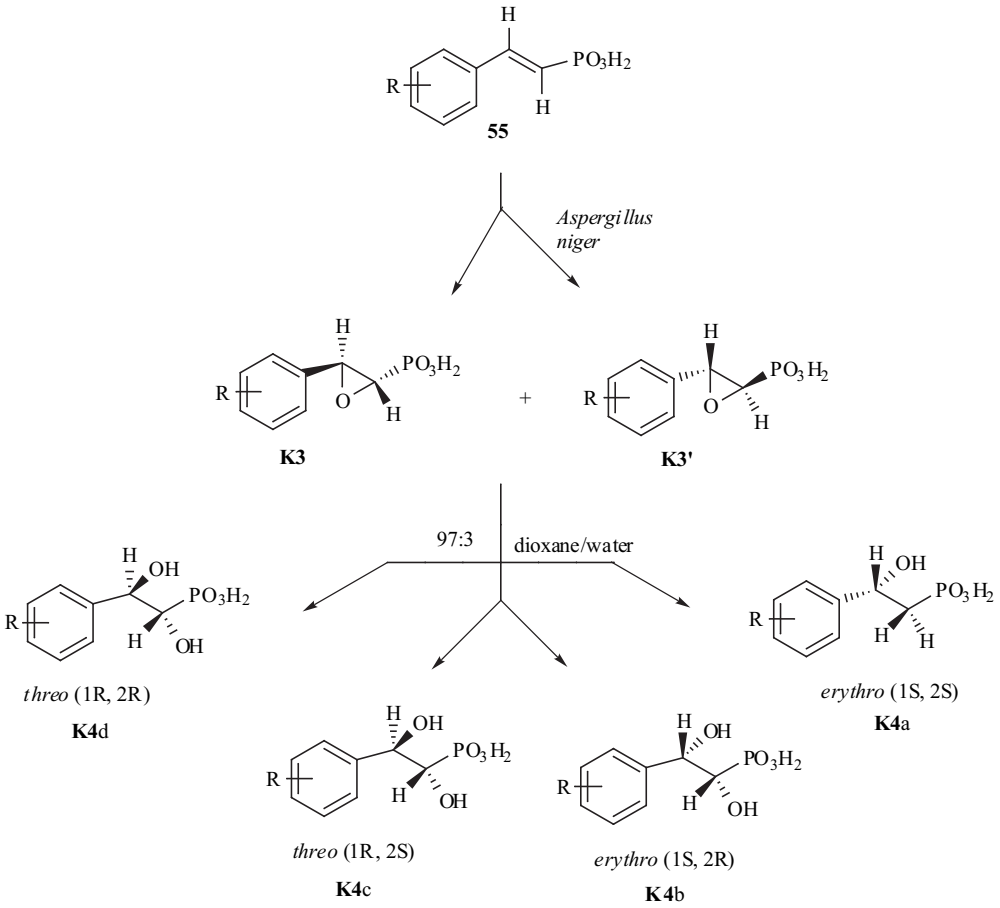


Scheme 36.

with dioxirane [58]. Compounds **38** were prepared by standard Wittig–Horner reaction of tetraethyl methylenebisphosphonate with aromatic aldehydes in aqueous two-phase system [59]. The *threo* isomers **K3a-d** were synthesized independently by the Sharp less approach, using AD-mixes as catalysts for the dihydroxylation of the corresponding *trans*-vinylphosphonates **38**. The use of AD-mix-β gave preferentially the (1*S*,2*S*) isomer. Consequently, the use of AD-mix-α resulted in the preferential formation of the isomer (1*R*,2*R*). Quinine have been used as a chiral selector to determine the course of biocatalytic hydrolysis of *trans*-epoxyethanephosphonates by the action of *Aspergillus niger* and thus verify the usefulness of method for the evaluation of the stereospecifity of this process. Contrary to the chemical hydrolysis, biocatalysis gave preferentially *erythro*-1,2-dihydroxyl-akanephosphonates (with only trace amounts of the *threo* isomers), which were obtained in good yields and with enantioselectivities strongly dependent on the structure of the substrate used. At this moment we are, however, unable to determine, which of the two formed isomers (*1*S,*2*R) or (*1*R,*2*S) is the major one (Scheme **38**) [60].

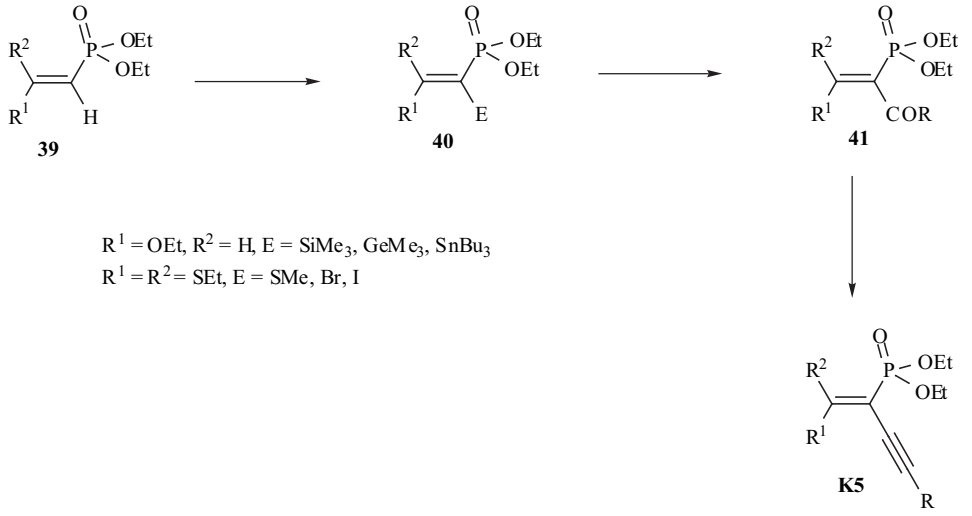
4.4. Alkynyl Vinylphosphonates from Vinylphosphonates

The β-hetero-substituted vinylphosphonates **39a-c** on treatment with LDA or LTMP were readily lithiated at the α-position of the phosphono group, and the resulting α-lithiovinylphosphonates were trapped with various electrophiles to afford the corresponding α-functionalized vinylphosphonates **40** in 55-96%yields. The Friedel-Crafts reaction of α-(silyl)- or α-(germyl)-phosphonoketene dithioacetals, the reaction with acid chlorides gave α-acylated phosphonoketene dithioacetals, **41** in 53-91% yields. The palladium-catalyzed cross-coupling reaction of β-ethoxy-α-(tributylstannyl) vinylphosphonate with a variety of organic halides (R = acyl, allyl, aryl, etc.) provided β-ethoxy-α-substituted vinylphosphonates in good to moderate yields. The palladium-mediated cross-coupling reaction of α-(iodo)vinylphosphonates with terminal acetylenes afforded α-alkynylated vinylphosphonates **K5** in 69-83%yields. Several α-functionalized β-hetero-substituted vinylphosphonates were applied to the synthesis of pyrazoles and an isoxazole possessing a phosphono function (Scheme **39**) [61].



R = H, yield 81%, threo:erythro 64:36
R = *p*-Me, 79%, 85:15
R = *o*-Me, 66%, 79:21
R = *m*-Me, 72%, 70:30
R = *p*-Br, 23%, 60:40
R = *p*-Cl, 73%, 63:37

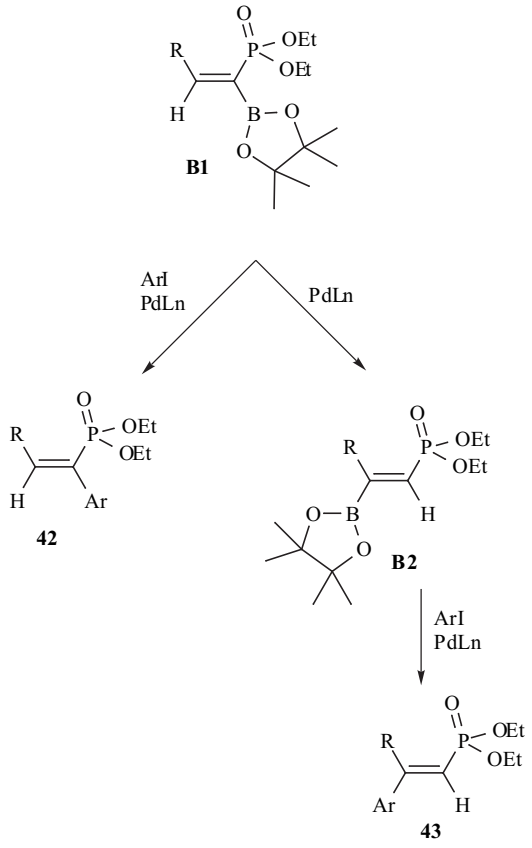
Scheme 38.



Scheme 39.

4.5. Suzuki Coupling of Boranated Vinylphosphonates

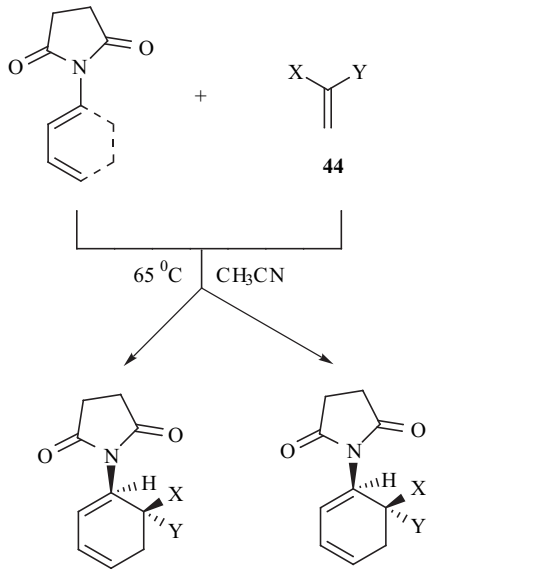
Hydroboration/Suzuki coupling of alkenylphosphonates, **B1**, with PBH, in a one-pot procedure to yield trisubstituted vinylphosphonates **42**, **43** in good overall yields and provides a new synthesis of these compounds (Scheme **40**) [53].



Scheme 40.

4.6. Cycloadducts Formation

Vinyl phosphonates **44** α-substituted with carboxylate, nitrile, sulfone and phosphonate groups reacted with N-buta-1,3-dienylsuccinimide to give [4 + 2] *ortho*-cycloadducts as mixtures of *endo/exo* stereoisomers **K6**, **K7** (Scheme **41**) [62].

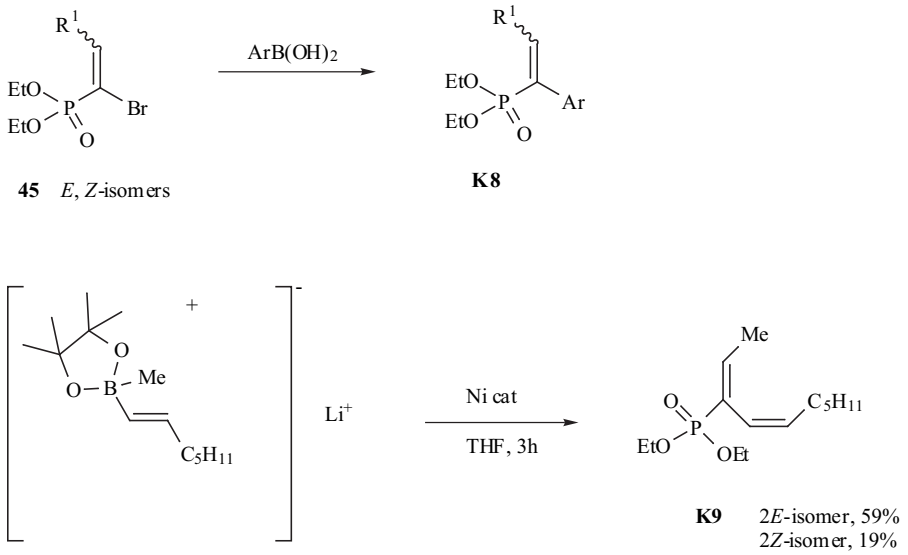


X = P(O)(OMe)$_2$, Y = COOMe, yield, 95% a:b, 65:35
X = P(O)(OEt)$_2$, Y = COOMe, 93% a:b, 55:45
X = P(O)(OEt)$_2$, Y = CN, 80% a:b, 46:54
X = P(O)(OEt)$_2$, Y = COOEt, 93% a:b, 55:45
X = P(O)(OEt)$_2$, Y = SOOMe, 42% a:b, 52:48
X = P(O)(OEt)$_2$, Y = P(O)(OEt)$_2$, 10%
X = P(O)(OEt)$_2$, Y = H, no reaction

Scheme 41.

4.7. Dienes Formation from Vinylphosphonates

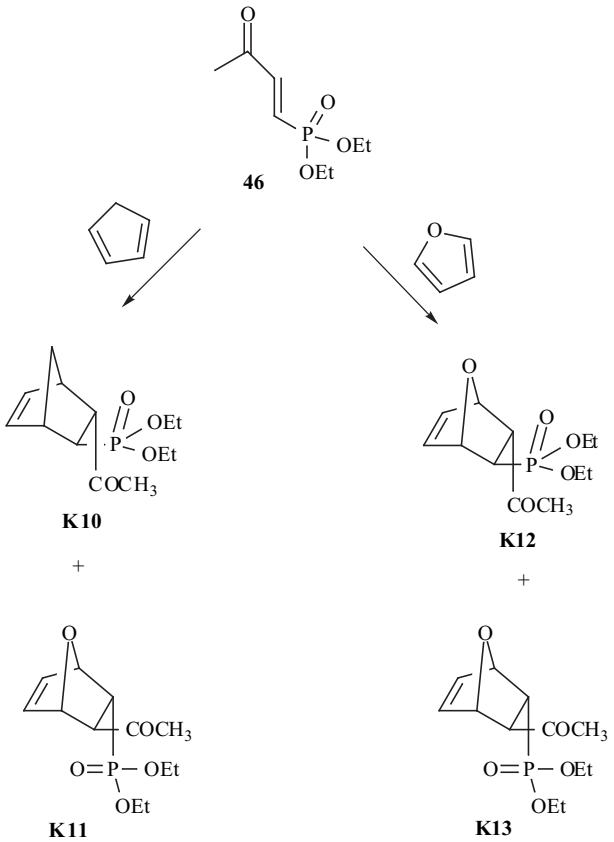
Transition metal-catalyzed arylation and alkenylation of the α-bromovinylphosphonates **45** were investigated with organoboranes and borates. Arylation was successful with the aryl boronic acids and a palladium catalyst, to produce **K8**, while alkenylation was found to proceed with alkenyl borates and a nickel catalyst to afford the diene product **K9** (Scheme **42**) [63].



Scheme 42.

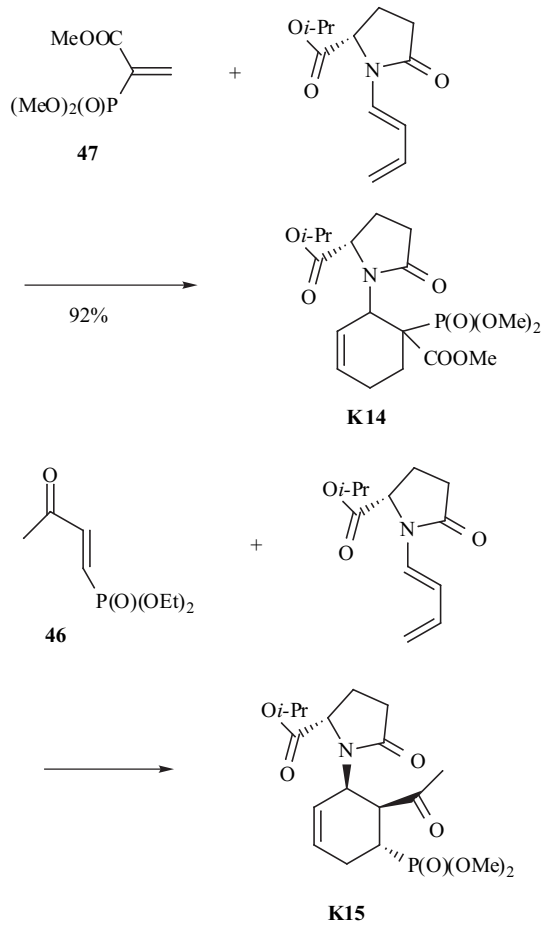
4.8. Diels-Alder Reaction of Vinylphosphonates

The Diels-Adler reactions between diethyl 3-oxo-vinylphosphonate, **46** and cyclopentadiene and furan produced the corresponding diastereomers, **K10**-**K13** (Scheme **43**) [64].



Scheme 43.

Asymmetric synthesis of β-and γ-amidophosphonates, **K14** and **K15** by Diels–Alder reaction between the vinylphosphonate **46**, **47** and chiral aminodiene was reported (Scheme **44**) [65].



Scheme 44.

REFERENCES

[1] (a) Hartly, R. In The Chemistry of Organophosphorus Compounds **1996**, John wiley & sons, New York, USA. (b) Corbridg, D. *In Phosphorus* **1990**, Fourth Edition, Elsevier, New York, USA.

[2] (a) Harnden, R.; Parkin, A.; Parratt, J.; Perkin, R. *J. Med. Chem.* **1993**, *36,* 1343. (b) Smeyers, Y.; Sanchez, F.; Laguna, A.; Ibanez, N.; Ruano, E.; Perez, S. *J. Pharm. Sci.* **1987**, *76,* 753. (c) Megati,

S.; Phadtare, S.; Zemlicka, J. *J.Org. Chem*. **1992**, 57, 2320. (d) Lazrek, H.; Rochdi, A.; Khaider, H.; Barascut, J.; Imbach, J.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clerq, E. *Tetrahedron* **1998,** *54,* 3807. (e) Smith, P.; Chamiec, A.; Chung, G.; Cobley, K.; Duncan, K.; Howes, P.; Whittington, A.; Wood, M. *J. Antibiot. Tokyo* **1995**, *4 8,* 73. (f) Holstein, S.; Cermak, D.; Wiemer, D.; Lewis, K.; Hohl, R. *Bioorg. Med.Chem.* **1998**, *6,* 687. (g) Chance, L.; Moreau, J. *US Patent* 3910886, **1975**.

[3] (a) Jin, J.; Hua, J. *US Patent* 3925506, **1975**. (b) Fujimatsu, M.; Miura, M. *Japanese Patent* 86-250155; *Chem. Abstr.* ***110,*** 9644k.

[4] (a) Spak, A.; Yu, A. *US Patent* 4088710, **1978**. (b) Fuller, B.; Ellis, W.; Rowell, R. *US Patent* 5683820, **1997**.

[5] (a) Shukla, J. *US Patent* 4241125, **1980**. (b) Welch, C; Gonzalez, E; Guthrie, J. *J. Org. Chem.* **1961,** *26,* 3270.

[6] For a review: (a) Minami, T.; Motoyoshiya, J. *Synthesis* **1992,** 333. (b) Thomas, A.; Sharpless, K. *J. Org. Chem.* **1999,** *64,* 8379. (c) Lee, S.; Lee, B.; Lee, C.; Oh, D. *Synth. Commun.* **1999,** *29,* 3621. (d) Telan, L.; Poon, C.; Evans, S. *J. org. Chem.* **1996,** *61,* 7455. (e) Zhao, Y.; Pei, C.; Wong, Z.; Xi, S. *Phosphor Sulfur Silicon* **1992,** *66*, 115. (f) Kim, D.; Rhie, D. *Tetrahedron* **1997,** *53,* 13603. (g) Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998,** *63,* 6428. (h) Defacqz, N; Touillaux, R.; Marchand-Brynaert, J. *J. Chem. Res.-S* **1998,** 512.

[7] For a complete list, *see the IBM patent data base* at: www.delphion.com.

[8] Normant, J. F. *Synthesis* **1972**, *63*. (b) Posner, G.H. *Org.React.* **1972**, *19*, 1. (c) Jukes, A.E. *Adv. Organomet. Chem.* **1975**, *12*, 215. (d) Posner, G.H. *Org. React*. **1978**, *22*, 253. (e) Normant, J.F.; Alexakis, A. *Synthesis* **1981**, 841.

[9] (a) Corey, E.J.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (b) Siddall, J.B.; Biskup, M.; Fried, J.H. *Ibid*. **1969**, *91*, 1853. (c) Klein, J.; Turkel, R.M. *Ibid*. **1969**, *91*, 6189. (d) Klein, J.; Aminadav, N.J. *Chem. Soc.C* **1970**, 1380.

[10] (a) Vermeer, P.; Meijer, J.; Eylander, C. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 240. (b) Truce, W.E.; Lusch, M.J. *J. Org. Chem*. **1974**, *39*, 3174. (c) Truce, W.E.; Lusch, M.J. *Ibid.* **1978**, *43*, 2252. (d) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett*. **1978**, 5131. (e) Meijer, J.; Vermeer, P. *Recl.Trav.Chim.Pays-Bas* **1975**, *94*, 14.

[11] Aguiar, A.M.; Smiley Irelan, J.R .; *J. Org. Chem*. **1969**, *34*, 4030.

[12] Axehad, G.; Laosooksathit, S.; Engel, R.; *J. Org. Chem*. **1981**, *46*, 5200-5204.

[13] Gil, J.M.; Oh, D.Y. *J. Org. Chem.* **1999,** *64,* 2950-2953.

[14] Cristau, H.J.; Xavier Y.; Mbianda, Y.; Beziat, M.B. *J. Organomet. Chem*. **1997**, *52*, 301-311.

[15] Quntar, A.A.; Dembitsky, V.M.; Srebnik, M. *Org. Lett.* **2003**, *5*, 357-359.

[16] Quntar, A.; Srebnik, M. *Chem. Comm*. **2003**, *59*, 58.

[17] (a) Lipshutz, B.J.; Bhandari, A.; Lindsley, C.; Keil, R.; Wood, M.R. *Pure & Appl. Chem.* **1994**, *66,* 1493. (b) Lipshutz, B.H.; *Ace. Chem. Res.* **1997**, *30,* 277.

[18] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95,* 2457.

[19] (a) Negishi, E.; Cederbaum, F.K.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27,* 2829. (b) Buchwald, S.L.; Nielson, R.B.; *Chem. Rev.* **1988**, *88,* 1047. (D) Larock, R.C.; In *Comprehensive Organic Transformations;* VCH Publishers; New York, **1989**. (c) Negishi, E. *Chemica Scripta* **1989**, *29*, 457. (d) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett.* **1995**, 299.

[20] Quntar, A.; Srebnik, M. *Organic Lett.* **2001**, *3*, 1379.

[21] Quntar, A.A.; Srebnik, M. *J. Org. Chem.* **2001,** *66,* 6650-6653.

[22] Quntar, A.; Melman, A.; Srebnik, M. *Synlett* **2002,** *1*, 61.

[23] Kouno, R.; Tsubota, T.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2000,** *65,* 4326- 4332.

[24] Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998,** *63*, 6428-6429.

[25] Hammersvchmitdt, F.; Zbiral, E. *Liebigs Ann.* **1979**, 492-502.

[26] Brunner, H.; Le Cousturier, N.; Pierre J. *Synlett* **2000**, 201-204.

[27] (a) Mohamed-Hachi, A.; About-Jaudet, E.; Combret, J.; Collignon, N. *Synthesis* **1997**, 653-655. (b) Degenhard C.; Burdsall C. *J. Org. Chem*. **1986,** *51*, 3488.

[28] Degenhard, C.; Burdsall, C. *J. Org. Chem*. **1986,** *51*, 3488.

[29] Jiao, X.; Bentrude, W. *J. Amer. Chem. Soc*. **1999**, *121*, 6088-6089.

[30] Attolini, M.; Maffei, M.; Principato, B.; Pfeiffer, G. *Synlett.* **1997**, 384-386.

[31] Lu, X.; Tao, X.; Zhu, J.; Sun, X.; Xu, J. *Synthesis* **1989**, 848.

[32] Zhao, Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.,* **2001**, *40*, 1929.

[33] Han, L.B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571.

[34] Ogawa, T.; Usuki, N.; Ono, N. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 2953.

[35] (a) Kazankova, M.A.; Trostyanskaya, I.G.; Lutsenko, S.V.; Efimova, I.V.; Beletskaya, I.P.; *Russ. J. Org.Chem.,* **1999**, *35*, 428. (b) Kazankova, M.A.; Trostyanskaya, I.G.; Lutsenko, S.V.; Beletskaya, I.P. *Tetrahedron Lett.,* **1999**, *40*, 569.

[36] Trostyanskaya, I.G.; Titskii, D.Yu.; Anufrieva, E.A.; Borisenko, A.A.; Kazankova, M.A.; Beletskaya, I.P. *Izv. Ross. Akad. Nauk, Ser. Khim.,* **2001**, 2003.

[37] Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.,***1980**, *21*, 3595.

[38] (a) German Offen. no.2 *118* 223; *Chem.Abstr.,* **1972**, vol.76, no. 34399w. (b) Honig, M.L.; Martin, D.J. *Phosphorus* **1974**, *4*, 63.

[39] Afarinkia, K.; Evans, M.; Jocelyn, C.; Bueno, J. *Tetrahedron Lett*. **1998,** *39*, 433- 434.

[40] (a) Shen, Y.; Jiang, G.F.; Sun, J.; *J. Chem. Soc*., *Perkin Trans.1*, **1999**, 3495–3498. (b) Yonghong, G.; Takuo, H.; Haimnond, G. *Chem. Commun*. **2000**, 395-396.

[41] Classen, R.; Hagele, G. *Fluorine Chem*. **1996**, *77*, 71-81.

[42] Yonghong, G.; Takuo, H.; Haimnond, G. *Chem. Commun*. **2000**, 395-396.

[43] Gross, R.S.; Mehdi, S.; McCarthy, J.R. *Tetrahedron Lett.* **1993**, *34*, 7197.

[44] Shen, Y.; Zhang, Y. J. *Fluorine Chem*. **2001**, *108*, 69-71.

[45] Muthiah, C.; Praveen Kumar, K.; Aruna Mani, C.; Kumara Swamy, K.C. *J. Org. Chem.* **2000,** *65,* 3733-3737.

[46] Öhler, E.; Kotzinger, S. *Liebigs Ann. Chem*. **1993**, 269-280.

[47] Wang, W.; Xu, G.; Cao, R.; Liu, L. *Heteroatom Chemistry* **2000**, *11*, 512-517.

[48] Kumaraswamy, S.; Senthamizh, R.; Swamy, K. *Synthesis* **1997**, 207-212.

[49] Öhler, E.; Zbiral, E. *Chem. Ber.* **1991**, *124*, 175-184.

[50] Attolini, M.; Bouguir, F.; Iacazio, G.; Peiffer, G.; Maffei, M. *Tetrahedron* **2001**, *57*, 537-543.

[51] McClure, C.; Grote, C.W. *Tetrahedron Lett*. **1991**, *32*, 5313-5316.

[52] Minami, T.; Okauchi, T.; Matsuki, H.; Nakamura, M.; Ichikawa, J.; Ishida, M. *J. Org. Chem.* **1996**, *61*, 8132-8140.

[53] Pergament, I.; Srebnik, M. *Org. Lett*. **2001**, *3*, 217-219.

[54] Kiddle, J.J.; Babler, J.H. *J. Org. Chem.* **1993**, *58*, 3512-3574.

[55] Beck, H.N.; Mac Williams, D.C.; (Dow Chemical Co.); *US Pat*. **4**, 692,355; *Chem. Abs*.**107** 238808x.

[56] (a) Courregelongue, J.; Frehel, D.; Maffrand, J.P.; Paul, R.; Rico, I. *Fr.Pat*. *2*, 596, 393, *Chem.Abs*. **108**, 94780c. (b) Hendlin, D.; Stapley, E.; Jackson, M. *Sciences* **1969**, *166*, 122. (c) Christensen, B.G.; Leanza, W.J.; Beattie, T.R. *Sciences* **1969**, *166*, 123.

[57] Cristau, H.K.; Mbianda, X.Y.; Geze, A.; Beziat, Y.; Marie-Benedicte, G. *J. Organometallic Chem*. **1998**, *57,* 189–193.

[58] Cristau, H.J.; Yangkou-Mbianda, X.; Gaze, A.; Beziat, Y.; Gasc, M.B.J. *Organome*t. *Che*m. **1998**, *57*, 189–193.

[59] Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 396– 398.

[60] Maly, A.; Lejczak, B.; Kafarski, P. *Tetrahedron Asymmetry* **2003**, *14,* 1019–1024.

[61] Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami. T. *J. Org. Chem.* **1998,** *63,* 6239-6246.

[62] Defacqz, N.; Touillaux, R.; Marchand-Brynaert, J. *J. Chem. Res. (S)*, **1998**, 512-513.

[63] Kobayashi, Y.; William, A.D. *Org. Lett*. **2002**, *4*, 4241.

[64] McClure, C.K.; Hansen, K.B. *Tetrahedron Lett*. **1996**, *37*, 2149-2152.

[65] Robiette, R.; Marchand-Brynaert, J. *J. Chem. Soc*., *Perkin Trans.* 2, **2001**, 2155-2158.

Received: 1 February, 2004 **Accepted: 4 March, 2004**