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The Usefulness of Phosphorus Compounds in Alkyne Synthesis

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Abstract: Due to their versatility, β -keto ylides, α -halo ylides, diazomethylphosphonates, halomethylphosphonates and enolphosphates constitute a class of useful phosphorus reagents for the synthesis of alkynes. This review attempts to summarize their applications and focus on the role of each reagent as synthetic intermediates.

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Key words: alkynes, β -keto ylides, thermal decomposition, α -halo ylides, diazomethylphosphonates, halomethylphosphonates, enol phosphates, 1,1- or 1,2-elimination.

1. Introduction

The carbon-carbon triple bond is one of the simplest functional group in organic chemistry but its practical realization often represents major synthetic problems. The subject has been reviewed in several important pioneering books such as *The Chemistry of Acetylene* by Viehe (1969)¹, the *Houben-Weyl-Müller Vol. V/2a* (1977),² the Patai series on *The Chemistry of the Carbon-Carbon Triple Bond* (1978),³ the numerous editions (1971, 1988 and 1992) of the experimental procedures developed or collected by Brandsma in *Preparative Acetylenic Chemistry*,⁴ and more recently the *Modern Acetylene Chemistry* edited by Stang and Diederich (1995).⁵ The purpose of this article is to provide an overview of the contribution of phosphorus reagents which have been designed to perform the synthesis of alkynes, simple or complex, with a terminal or internal triple bond. The main strategy for the production of alkynes using phosphorus reagents, which usually involve two-step operations, proceeds by a one carbon chain elongation of a carbonyl function concomitant with an elimination reaction. In such transformations, the Wittig reaction and its Horner-Wadsworth-Emmons modified version are merely a masked alkynes synthesis, and both of them have been developed so that aldehydes as well as ketones may be easily converted into alkynes. The preparation of specially tailor-made phosphorus reagents coupled with a judicious selection of bases has largely contributed to the intensive development of the method. With the discovery of new bases, the unmasking of the latent triple bond by elimination of hydrogen halide or rearrangement has considerably been facilitated. Each base being effectively adapted to the substrats, each step is effected in a clean manner, minimizing the problems associated with the formation of byproducts and avoiding the partial destruction of the alkynes. The formation of alkynes from enol phosphates, a procedure whose synthetic utility remains undeveloped, has notably benefitted from the discovery of new bases. Today, phosphorus reagents play an important part in alkynes synthesis and more than ten precursors are commercially available. To enhance the practical value of the phosphorus route to alkynes, each section include synthetic protocols for the preparation of the phosphorus precursors and an application of each reagent.

2. Phosponium Ylides Precursors of Acetylenic Compounds

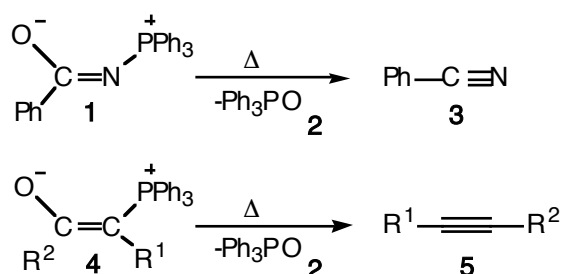
Historically, the phosponium ylides were the first phosphorus reagents to be used in alkynes synthesis. The β -keto ylides are the one category of phosponium ylide that is predictably able to thermal decomposition. Since its discovery in 1959, the reaction has induced a

research which has continued unabated to this day. Because of their satisfying reactivity towards aldehydes, the halomethylenetriphenylphosphoranes are regularly employed as operational precursors of alkynes, although the phosphonates appear to have the greater synthetic utility. Despite everything, the major disadvantage which attends the use of phosphonium ylides remains the tedious formation of triphenylphosphine oxide.

2.1. Thermal Decomposition of Phosphonium Ylides

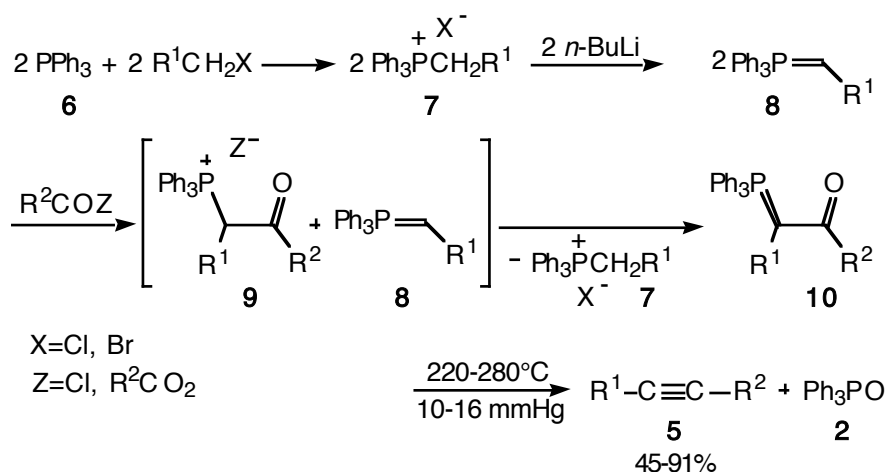
Early reported⁶ preparation of benzonitrile **3** by Staudinger and Hauser in 1921 included a thermal route using the decomposition at 220°C of benzoyliminotriphenylphosphorane **1**. By analogy with this reaction, it was reported in 1959 that "when α -benzoylbenzylidenetriphenyl-phosphorane was heated above its melting point (300°C for 0.5 h), it gave triphenylphosphine oxide and diphenylacetylene quantitatively".⁷

At the same time and independently it was shown by two laboratories^{8,9} that the pyrolysis of β -ketoalkylidenetriphenylphosphorane **4** constituted a general route to alkynes **5** provided that a) neither R¹ nor R² was hydrogen, and that b) R¹ or R² was a phenyl or carbonyl group or an other electron-withdrawing group (Scheme 1).¹⁰ At present, this thermal procedure appears as an important and useful technique for the construction of a variety of alkynes **5** containing an internal triple bond. It is called the "intramolecular Wittig reaction" and, just as in the traditional Wittig reaction, the elimination of triphenylphosphine oxide **2** constitutes probably the driving force of the reaction.¹¹



Scheme 1.

Facing these promising results, the conditions for a full utilization of the thermolysis reaction were investigated. In particular, by using both acyl halides and anhydrides, the α -substituted methylenetriphenylphosphoranes **8** may be converted in fair yields to the necessary starting β -keto ylides **10**. Owing to the suitable selection and arrangement of electron-withdrawing groups R¹ and R², the β -keto ylides **10** were conveniently modified to allow the preparation of an unlimited number of precursors. The generation of alkynes **5** from **10** was accomplished by heating the acylmethylenetriphenylphosphoranes **10** at 220-280°C under vacuum (10-16 mm Hg) with distillation of the alkynes **5** (Scheme 2).



Scheme 2.

This elegant synthetic procedure has been successfully developed with phosphorane precursors **10** containing at least one electron-withdrawing group R¹ (R¹= aryl,^{7,8,12-17} CO₂R,^{8-10,18-35} COSMe,³⁶ CN,³⁷⁻⁴⁵ CHO,⁴⁶ COR,^{20,47,48} SR,^{49,50} SeR,^{51,52} P(O)(OPh)₂⁵³) coupled with either an electron-withdrawing group R² (R²= alkynyl, aryl, substituted aryl, heteroaryl) or a releasing alkyl group; the reported yields are moderate to excellent (45 to 91%). For example, preparation of the ethyl [4-²H₃]but-2-ynoate has been accomplished by this method with 50% yield.⁵⁴

1-Ethoxycarbonyl-2-oxopentylidetriphenylphosphorane.¹⁰ Butyryl chloride (3.1 g, 29.1 mmol) in benzene (10 mL) was added slowly to a stirred solution of ethoxycarbonylmethylenetriphenylphosphorane (10 g, 28.73 mmol) in benzene (100 mL), and the resulting solution set aside at room temperature overnight. The precipitate of ethoxycarbonylmethyltriphenylphosphonium chloride (4.8 g, 12.48 mmol, 43.4%, m.p. 90-91°C) was filtered off and the filtrate evaporated. Crystallisation of the residue from aqueous EtOH gave 1-ethoxycarbonyl-2-oxopentylidetriphenylphosphorane (4.0 g, 9.57 mmol, 33.3%), m.p. 130-131°C.

Pyrolysis of 1-Ethoxycarbonyl-2-oxopentylidetriphenylphosphorane.¹⁰ The phosphorane (3.32 g, 7.94 mmol) was heated for 1 h at 280°C / 10 mmHg in a 50 mL Claisen flask immersed in a Wood's metal bath, the distillate being collected in a receiver cooled in liquid nitrogen. Redistillation gave ethyl hex-2-ynoate (0.87 g, 6.21 mmol, 78%), b.p. 93°C / 24 mmHg.

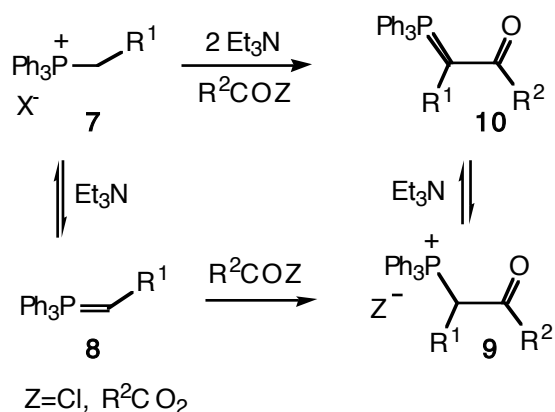
Ethyl 3-(2-Thienyl)propiolate.³² Thiophene-2-carboxylic acid (20 g, 0.16 mol) was treated with SOCl₂ (57 mL) under reflux for 2 h. Evaporation under reduced pressure of the remaining SOCl₂ left the corresponding acyl chloride (20 g, 0.14 mol) which was dissolved in dry benzene (150 mL) and added dropwise to a solution of (ethoxycarbonylmethylidene)triphenylphosphorane (76 g, 0.22 mol) in dry benzene (500 mL). The mixture was refluxed for 12 h. After cooling, the mixture was filtered and the solvent removed under reduced pressure. The betaine, dissolved in CHCl₃, was filtered through SiO₂ and then crystallized twice from EtOAc to give pure betaine (46 g, 0.1 mol). Pyrolysis of the betaine in a bulb-to-bulb apparatus under reduced pressure (10 mmHg) at 240°C gave pure title compound (16 g, 0.09 mol, 64%) as a dense oil.

However, the major disadvantage which attended the full utilization of the thermolysis reaction was the formation, during the preparation of the phosphorane precursors **10**, of a mixture of the desired phosphorane **10** and the starting quaternary phosphonium salts **7** as depicted in Scheme 2. Consequently the production of suitable quantities of alkynes **5** was often handicapped by the rather cumbersome regeneration of the phosphonium salt.

Fortunately, a useful and mild method for the complete consumption of the starting phosphonium salt **7** is available.^{55,56}

Typically, the β -keto ylides **10** are prepared by treatment of α -substituted methylenephosphoranes **8** with acyl chlorides or anhydrides to afford an equimolecular mixture of the desired phosphorane **10** and the starting phosphonium salt **7** (Scheme 2). Acylation of the phosphorane **8** gives the intermediate phosphonium salt **9**, which reacts with the more basic phosphorane **8** *via* a transylidation reaction, to afford the desired phosphorane **10** and the starting phosphonium salt **7**. This 1:1 mixture of components must be separated prior to thermolysis, as appreciable amounts of the undesired phosphonium salt **7** can considerably lower the yield of alkynes **5** in the thermolysis step. At least half of the starting phosphorane **8** is lost by conversion to phosphonium salt **7**. In principle, the presence of a suitable base in the reaction mixture could avoid transylidation.

This disadvantage has been overcome when the acyl halides commonly used in the preparation of the β -keto ylide do not give rise to the formation of ketenes in the presence of bases. Thus, it has been found that the addition of Et₃N (2 eq.) to the phosphonium salt **7**, followed by acyl chloride or anhydride (1 eq.) gives the β -keto ylide **10** in moderate to high yield (Scheme 3).^{55,56}



Scheme 3.

The reaction was general for phosphonium salts with good electron-withdrawing group R¹ (R¹=Ph, SMe, CO₂R, CN) and afforded the highest yields with an ester or nitrile group (52-99%). In this case, the conversion of phosphonium salts **7** to intermediate ylides **8** was nearly complete. Somewhat lower yields were observed when R¹ was a phenyl or thiomethyl substituent. In these cases the equilibrium between **7** and **8** favors the phosphonium salt. Comparison of amine bases showed that DABCO resulted in a comparable yield of β -keto ylide **10** that with Et₃N. This route was particularly attractive for large-scale synthesis of phosphoranes, since all reactions were nearly quantitative and the reagents inexpensive. For example, analytically pure ethyl 4,4,4-trifluorotetrolate has been prepared on large scale (0.5 mol) with 82% yield.^{57,58}

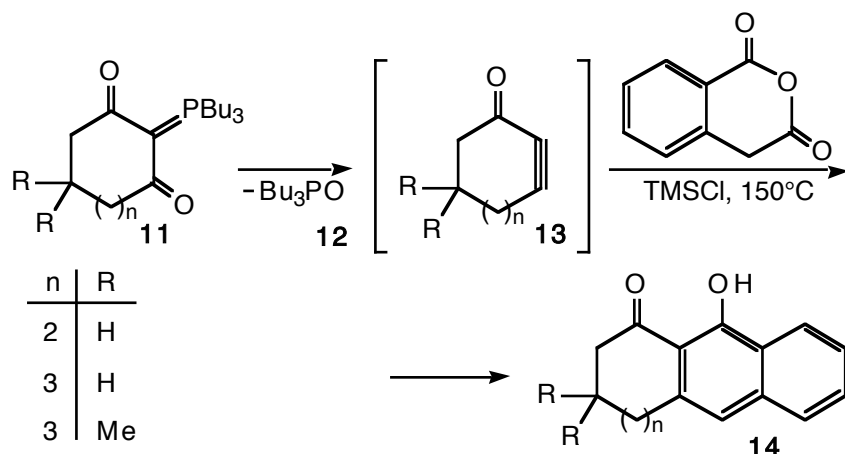
General procedure for the preparation of phosphoranes. 4,4,4-Trifluoro-3-oxo-2-(triphenylphosphoranylidene)butanoic acid, ethyl ester.⁵⁵ A slurry of (carbethoxymethyl)triphenylphosphonium bromide (215 g, 0.5 mol) in 1.1 L of anhydrous THF was cooled in an ice-water bath and treated with Et₃N (150 mL, 1.1 mol). After being stirred for 15 min, the mixture was treated dropwise with trifluoroacetic anhydride (78 mL, 0.55 mol) and allowed to stir for 1 h. The mixture was filtered, the precipitate washed three times with cold THF, and the filtrate concentrated in vacuo to afford a yellow oily residue. Trituration of the residue with 600 mL of water affords a crystalline product, which was collected, washed with water, and dried in vacuo to afford 192 g (86%) of a cream colored solid. A small sample was recrystallized from MeOH-H₂O to afford a white crystalline solid.

An electrolytic method has also been described for the preparation of the bis(β -keto ylide). Thus, electrochemical oxidation of triphenylphosphine **6** in CH₂Cl₂ in the presence of 1,3-dicarbonyl compounds, and 2,6-lutidinium perchlorate resulted in the formation of bis(β -keto ylide) in fair to excellent yields (30 to 100%), in a single step.

Several developments have contributed to extend the scope and synthetic utility of the intramolecular Wittig reaction. For example, the chemistry of triphenylphosphonium 2-[(2-oxo-1,2-diphenylethylidene)hydrazono]propylide has been fruitfully developed on pyrolytic conditions to give various acetylenes such as, 3,4-diphenyl-6-(phenylethynyl)pyridazine, acetylenic azine and pyrazole.⁵⁹⁻⁶¹ The use of the pyrolytic formation method of acetylenic bond was the only successful route to a series of dianthrylacetylenes, diphenanthrylacetylenes, dipyrenylacetylenes and 6,6'-dichrysenylacetylenes.⁶²⁻⁶⁴

Since alkynes of low nucleophilic character play a prominent role as dienophiles in cycloaddition reactions, there has been significant interest in developing efficient methods for their synthesis. For example, the synthesis of fluorinated alkynes, containing perfluoroalkyl or perfluoroaryl groups, by the pyrolysis of the corresponding β -keto ylides was of considerable importance. Thus, a large variety of phosphonium salts containing electron-withdrawing groups R¹ (R¹= CN,^{38,65-68} P(O)(OPh)₂,⁵³ CO₂R,^{69,70} CONR₂,⁷¹ COSMe,³⁶ CHO,⁷² COR,^{73,74} alkenyl,⁷⁵ aryl,^{12-17,76-78} aryloxy,⁷⁹ 2-thienyl⁸⁰) and perfluorinated groups R² were prepared and thermally decomposed to give the corresponding alkynes in moderate to excellent yield.

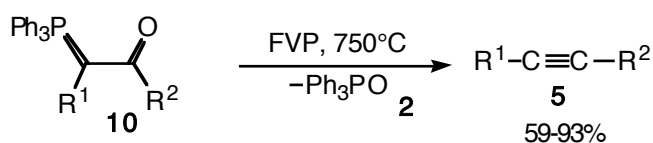
In the Diels-Alder reaction between homophthalic anhydride and the dioxocycloalkylidenetriethylphosphorane **11**, the decisive step consisted in the elimination of triethylphosphine oxide **12** and transient formation of the cycloalkyn-2-ones **13** (Scheme 4).⁸¹ Thus, when a mixture of **11**, homophthalic anhydride and TMSCl in toluene was heated at 150°C for 40 h, the Diels-Alder adducts **14** were obtained in moderate yield. The present results supported the formation of cycloalkyn-2-ones **13** from the phosphoranes **11**.



Scheme 4.

For a long period of time, however, the thermal elimination of triphenylphosphine oxide **2** from β -keto ylides **10**, using standard pyrolysis techniques, was known for only cases in which R^1 was an electron-withdrawing group. All attempts to obtain purely aliphatic or terminal alkynes from the corresponding ylides where R^1 was an alkyl group or H failed completely. In 1983 and 1985 two innovations worthy of merit have been reported. The first one has featured the role of the temperature in the thermal decomposition of β -keto ylides **10**, while the second has featured the use of reducing agents.

It has been reported that when the ylides **10** were subjected to flash vacuum pyrolysis (FVP), they sublimed unchanged at temperature up to 600°C, but at 750°C and 10^{-2} mmHg underwent complete reaction in the desired sense to give triphenylphosphine oxide **2** and the alkynes **5** where R^1 =H or primary alkyl and R^2 =primary, secondary, tertiary, or cycloalkyl, alkenyl or phenyl. The feasibility of using this method to prepare multigram quantities of alkynes **5** by the FVP was currently demonstrated. In each example, the alkynes **5** were collected in pure form and in moderate to excellent yield (59-93%) (Scheme 5).^{82,83}



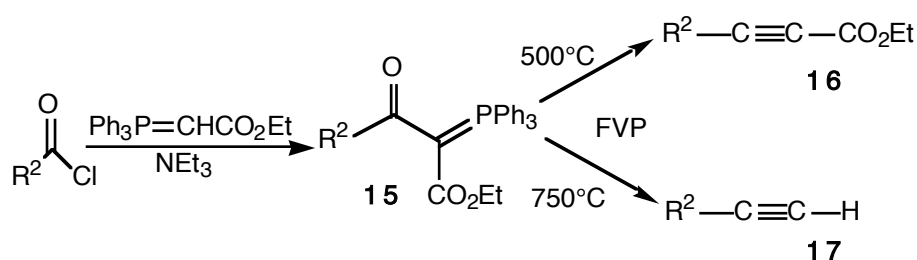
R^1 =H, Me, *n*-Pr, *n*-Bu

R^2 =Et, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, cyclohexyl

Scheme 5.

The clever use of the temperature as a tool is noteworthy and it has been judiciously employed to control the thermal transformation. When the α -ethoxycarbonyl- β -oxo ylides **15** in which R^2 =aryl, substituted aryl or heteroaryl were subjected to FVP at 500°C, triphenylphosphine oxide **2** was again eliminated to afford the acetylenic esters **16**. When working at the higher temperature of 750°C the rearrangement was accompanied by complete

loss of the ethoxycarbonyl group to give the terminal alkynes **17** in moderate yields (16-66%) (Scheme 6).⁸⁴

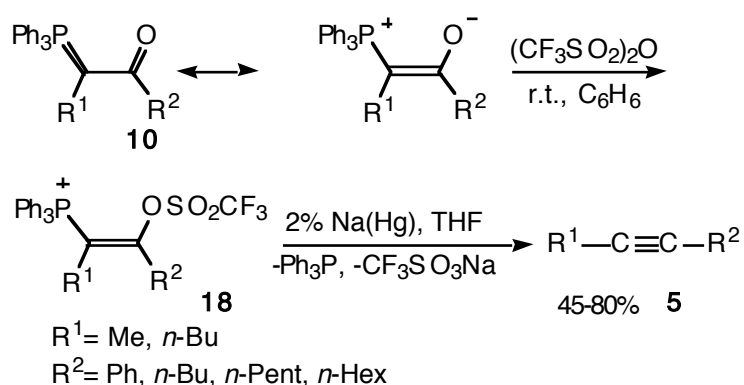


Scheme 6.

With the same technique, a number of functionalized alkynes were prepared in moderate yields including benzofurans *via* the 2-methoxyphenyl alkynes and benzothiophenes *via* 2-methylthiophenyl alkynes,^{85,86} diacylalkynes,^{87,88} terminal 1,3-diyne⁸⁹ and unsymmetrical 1,3-diyne,⁹⁰ 1,3-enynes,⁹¹ pyrroloisindoleones,⁹² styrylalkynes and substituted naphthalenes,^{93,94} protected acetylenic amino acids.⁹⁵ The limit of usefulness of the FVP technique has been reached with the pyrolysis of the tetraoxo ylides and hexaoxo bis(ylides).⁹⁶

Similarly with the pyrolysis of stabilized phosphoranes containing heteroatoms (S, Se) attached to the ylide, the work has been extended to stabilized chloro- or bromophosphoranes. Pyrolysis of the halophosphoranes using a quartz tube heated to 800°C gives the chloro- or bromoalkynes in moderate yields.⁹⁷

A variant to alkynes **5** from β -keto ylides **10** using reducing agents has been described. The ylide was first converted to an enol triflate ester **18** in high yield, then submitted to reduction with sodium amalgam in THF to give the alkyne **5** in moderate to good yield (45-80%) along with triphenylphosphine **6** and sodium triflate (Scheme 7).⁹⁸



Scheme 7.

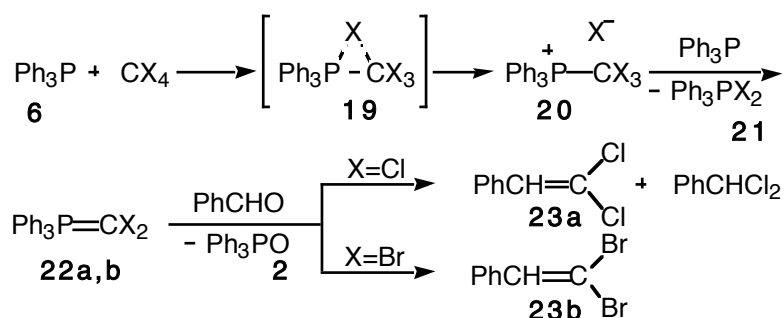
Several examples of allenic derivatives formation, using phosphorus precursors are described in the literature. Generally, these products isomerized to produce the corresponding

thermodynamic acetylenic compounds. The interest of the method is nevertheless limited by the availability of the starting materials.⁹⁹⁻¹⁰⁴

2.2. Dibromomethylenetriphenylphosphorane

In 1962 two laboratories reported independently a route to prepare the dichloro- **22a**¹⁰⁵ and dibromomethylenetriphenylphosphorane **22b**¹⁰⁶ by the reaction of triphenylphosphine **6** with the corresponding carbon tetrahalide^{107,108} and a convenient one-step synthesis for *gem*-dichloro- **23a** and *gem*-dibromoolefins **23b** according to a Wittig reaction. The first reaction was realized between triphenylphosphine **6**, carbon tetrachloride and benzaldehyde on heating at 65°C. It gave after work-up and distillation the *gem*-dichlorostyrene **23a** and the dichlorotoluene in equal quantities (35%). The competing formation of dichlorotoluene demonstrates that the dichlorotriphenylphosphorane **21** (X=Cl) produced in the reaction exchanges with benzaldehyde. The second reaction was realized with carbon tetrabromide and benzaldehyde in CH₂Cl₂ and gave the *gem*-dibromostyrene **23b** in excellent yield (84%) (Scheme 8).

The reaction between triphenylphosphine **6** and carbon tetrahalides is quite complex and can be summarized as it follows. It involves an attack by the triphenylphosphine **6** on "positive halogen", chlorine or bromine, of carbon tetrahalide leading to the intermediate **19**, as depicted in Scheme 8, which evolve towards the trichloro- or tribromomethyltriphenylphosphonium adduct **20** which has been isolated in the chloro case. Reaction of the trichloro- or tribromomethyltriphenylphosphonium **20** with the second molecule of triphenylphosphine **6** generates *in situ* a nucleophile, the stabilized dichloro- **22a** or dibromomethylides **22b**, and an electrophile, the chloro- or bromotriphenylphosphoranes **21**. These results show that under mild conditions and depending on the carbon tetrahalide, considerable control of the product may be obtained (Scheme 8).¹⁰⁶

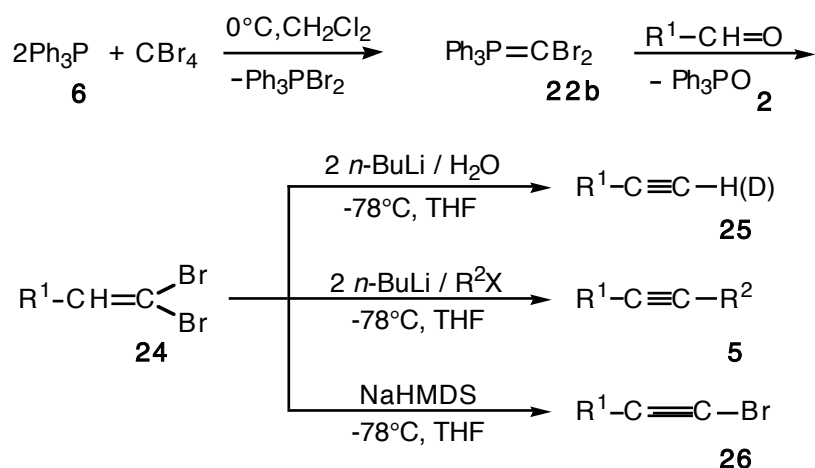


Scheme 8.

The Wittig reaction of the stabilized dichloromethylide **22a** with aldehydes being sluggish, requiring high temperatures, and giving undesirable byproducts, has only a limited synthetic potential. In marked contrast, the stabilized dibromomethylide **22b**, which utilizes carbon tetrabromide as source of positive halogen, has been largely used for the conversion of

aldehydes into *gem*-dibromoolefines **24** (Scheme 9) by one carbon chain elongation (Wittig reaction) and has found a significant synthetic advantage in the synthesis of alkynes **5** (Ramirez-Corey reagent).¹⁰⁹

The procedure is decomposed into two independent steps (Scheme 9). In the first step, the reaction of dibromomethylide **22b** proceeded at 0°C in CH₂Cl₂ with a variety of aldehydes (aliphatic, aromatic, heteroaromatic, α,β -unsaturated) to give the *gem*-dibromoalkenes **24** in good to excellent yields (76 to 100%). In the second step, the *gem*-dibromoalkene **24** was generally treated with *n*-BuLi¹⁰⁹⁻¹¹⁵ (2 eq.) at low temperature in THF and more scarcely with MeLi^{116,117} or *t*-BuLi¹¹⁸ to produce the lithium acetylide, which can be quenched with MeOH, H₂O or D₂O to give the terminal alkyne **25** or trapped with various electrophiles (R²X) to give the corresponding derivatives **5** (Scheme 9 and Table 1).



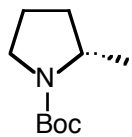
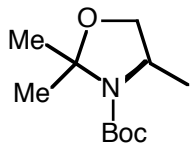
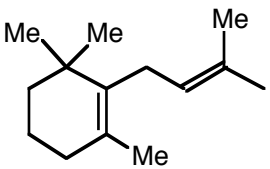
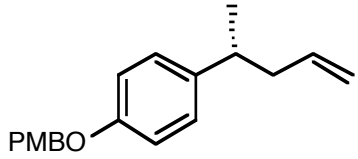
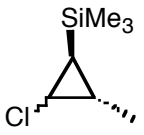
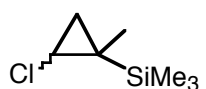
Scheme 9.

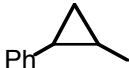
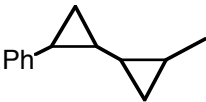
In the case of sensitive molecules the formation of alkynes from *gem* dibromoalkenes can be cumbersome. Since 1,2-elimination then halogen-metal exchange were the more probable steps in the formation of alkynes from *gem* dibromoalkenes and since *trans*-elimination of halogen across a double bond was a favored process, NaHMDS has proved to be the best base to give cleanly and quantitatively the bromoalkynes **26**.^{119,120} Benzyltrimethylammonium hydroxyde in refluxing benzene has also been employed to produce bromoalkynes in the range of 35-80% yield.¹²¹ The bromine of bromoalkyne **26** was next exchanged with *n*-BuLi (1 eq.) to the corresponding lithiated alkyne. This two step sequence can also be performed in one pot.

Although widely used, the dibromoalkenes procedure suffers from serious drawbacks when applied to highly functionalized or sensitive aldehydes. The reaction medium is always contaminated by the dibromotriphenylphosphonium **21** (X=Br) generated *in situ*, which is known to be a strong electrophile as well as a brominating agent and therefore the probable source of side reactions. Consequently, it has been reported that simultaneous addition of the

aldehyde and Et₃N (1 eq.) to the PPh₃-CBr₄ mixture in CH₂Cl₂ at -60°C suppressed side reactions and allowed to prepare sensitive dibromoalkenes **24** in good to excellent yields.¹²⁰ Another drawback results from the formation of triphenylphosphine oxide **2**. The separation of triphenylphosphine oxide **2** from the products is tedious especially when the reaction is realized on large scale. To overcome this difficulty an alternative route to *gem*-dibromoalkene **24** was developed. It is based upon the use of a combination of hexamethylphosphorous triamide (HMPT) and bromotrichloromethane, demonstrating that phosphine attack on bromine was probably involved.¹²² The *gem*-dichloroalkenes are generally obtained in good yields, but the hexamethylphosphoramide (HMPA) generated during the reaction is in turn a byproduct not easy to completely eliminate because of its retention in the final product.

Table 1

5	R¹	R²	Yield (%)	Ref.
a	<i>n</i> -C ₇ H ₁₅	H	95	109
b	<i>n</i> -C ₇ H ₁₅	CO ₂ H	87	109
c	2-thienyl	H	68	110
d	5-methyl-2-thienyl	H	68	110
e	3-methyl-2-thienyl	H	48	110
f	3-thienyl	H	56	110
g		H	70	112
h		H	74	115
i		H	65	113
j		TMS	69	118
k		H	75	116
l		H	69	116

m		D	53	111
n		D	84	111
o	4-MeO-C ₆ H ₄	CO ₂ M	85	114
e				

1,1-Dibromo-2-(4-methoxyphenyl)ethene 24o.¹¹⁴ A solution of CBr₄ (122 g, 368 mmol) in CH₂Cl₂ (500 mL) under N₂ at 0°C was treated with PPh₃ (193 g, 736 mmol) and stirred 1 h at 0°C. The mixture was treated with *p*-anisaldehyde (25 g, 184 mmol) stirred 1 h at 0°C and quenched with H₂O (100 mL). The organics were washed with brine (100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was poured into hexane (3 L) and the supernatant was collected. The residue was redissolved in CH₂Cl₂ (200 mL) and poured into hexane (3 L). The supernatant was collected and this process repeated once more. The combined supernatant were passed through silica gel (150 g) and the eluent was concentrated to afford the title compound; yield: 40 g (80%).

Methyl 3-(4-Methoxyphenyl)propiolate 5o.¹¹⁴ A solution of 1,1-dibromo-2-(4-methoxyphenyl)ethene (30 g, 103 mmol) in anhydrous THF (350 mL) under N₂ at -78°C was treated slowly dropwise with *n*-BuLi (141 mL, 226 mmol, 1.6 M) and stirred 30 min at -78°C and 30 min at 0°C. The mixture was quenched with methyl chloroformate (11.6 mL, 150 mmol) at -78°C and warmed to 0°C for 1 h. The mixture was diluted with 1:1 sat. NaHCO₃/NH₄Cl (124 mL) and the aqueous layer was extracted with Et₂O (125 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo. The oil was chromatographed over silica gel (500 g), eluting with 10% EtOAc/hexane to give 16.7 g (85%) of the title compound.

2-(2,2-Dibromoethenyl)thiophene 24c.¹¹⁰ Triphenylphosphine (100 mmol, 26.2 g) and CBr₄ (50 mmol, 16.6 g) were placed in a well-dried, 500 mL round-bottomed flask equipped with a magnetic stirrer and a gas inlet. Anhydrous CH₂Cl₂ (100 mL) was added under nitrogen, the mixture was stirred at 0°C (ice bath) for 5 min, and 2-thiophenecarboxaldehyde (40 mmol, 4.48 g) was added. After stirring for 1 h at r.t. under nitrogen, the reaction mixture was extracted with pentane (4 vol) according to the original report. Chromatography on silica gel 60-200 mesh (10 g/g; eluent: hexane-CHCl₃, 9:1) yielded 10.3 g (96%) of the title compound.

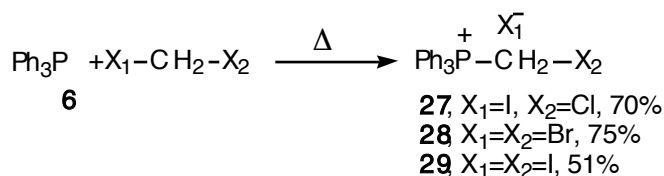
2-Ethynylthiophene 5c.¹¹⁰ A solution of 2-(2,2-Dibromoethenyl)thiophene (30 mmol, 8.04 g) in 300 mL of dry Et₂O was cooled to -78°C under nitrogen, and *n*-BuLi (66 mmol) was added dropwise. After stirring for 1 h at -78°C, the mixture was allowed to warm to r.t., and was stirred for 1 h longer. The mixture was treated as usual and finally distilled to produce 2.2 g (68%) of the title compound.

2.3. Halomethylenetriphenylphosphorane

All of the halomethyltriphenylphosphonium salts are known. Only those containing chlorine, bromine and iodine are used in alkynes synthesis, but the most common and perhaps most generally useful reagents that have been developed for the synthesis of alkynes were the chloro- and bromomethyltriphenylphosphonium salts.

There are a number of synthetic procedures which allow the preparation of halomethyltriphenylphosphonium salts. However, those using chlorocarbene¹²³⁻¹²⁵ or triphenylphosphine **6** in the presence of a controlled amount of water¹²⁶ are somewhat complicated. Perhaps the most convenient transformation for the synthesis of these precursors involves the quaternarisation reaction of triphenylphosphine **6** with methylene dihalides (Scheme 10). For example, using chloriodomethane as electrophile, the

chloromethyltriphenylphosphonium iodide **27** was obtained upon its reaction with triphenylphosphine **6** and isolated in 70% yield. The reaction has been studied in several solvents and at different temperatures (Table 2).¹²⁷ When the reaction was carried out in THF, the salt **27** began to precipitate as white solid in the course of the initial 0.5 h heating at reflux. The phosphonium salt **27** amounted to a 60% isolated yield after a 8 h reaction, and to a 70% yield after 20 h.



Scheme 10.

Table 2¹²⁷

Ph ₃ P (mmol)	ICH ₂ Cl (mmol)	Solvent	Solvent (mL)	Temp (°C)	Time (h)	Yield (%)
10	12	Et ₂ O	20	20-25	20	8
10	11	THF	10	50	20	34
120	150	THF	150	67	8	60
120	150	THF	150	67	20	70
50	70	<i>t</i> -BuOH	50	83	6	72
100	110	DMF	120	100	8	0

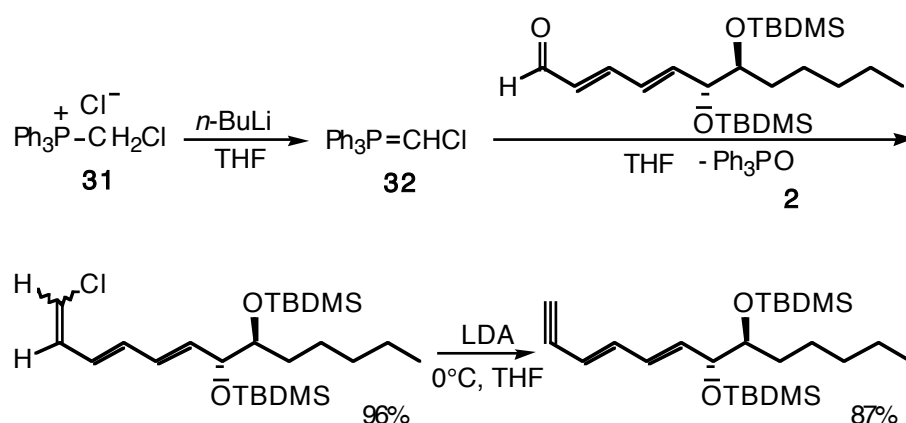
The same quaternarization reaction has been applied to the preparation of bromomethyltriphenylphosphonium bromide¹²⁸ **28** and iodomethyltriphenylphosphonium iodide¹²⁹ **29** with 75 and 51% yield respectively, by reaction between triphenylphosphine **6** and the corresponding methylene dihalides.

Preparation of chloromethyltriphenylphosphonium iodide 27.¹²⁷ Triphenylphosphine (120 mmol) was dissolved in 150 mL of THF in a 500 mL round-bottomed flask equipped with a magnetic stirrer, a pressure-equilibrating dropping funnel, a thermometer, and a Widmer reflux condenser topped with a nitrogen inlet tube. The mixture was stirred rapidly while chloriodomethane (150 mmol) was added. The flask was immersed in an oil bath and the mixture was heated at reflux for ca. 20 h. The resulting white precipitate was filtered, and the solids were washed thoroughly with 5 x 50 mL of THF in a nitrogen atmosphere. The phosphonium salt was dried in vacuo at 50-60°C for several hours; it was stored in a Schlenk tube under nitrogen. The dried product weighed 37 g (70% yield based on triphenylphosphine).

Preparation of bromomethyltriphenylphosphonium bromide 28.¹²⁸ A solution of 60.0 g (0.228 mole) of triphenylphosphine and 89.2 g (0.460 mole) of methylene bromide in 500 mL of dry toluene was refluxed for 24 h. The mixture was cooled to 0°C and the salt crystals were collected by filtration and washed with toluene. The filtrate was refluxed for another 24 h, and a second crop of crystals was collected. The combined solids were dried in vacuo and weighed 77.4 g. (75%).

Preparation of iodomethyltriphenylphosphonium iodide 29.¹²⁹ A solution of 0.115 mole of triphenylphosphine and 0.15 mole of methylene iodide in 30 mL of benzene in a flask equipped with a reflux

chloromethylenetriphenylphosphorane **32** leading to a mixture of *E*- and *Z*-isomers generally in good to excellent yields (79-96%). The dehydrohalogenation of the chloroolefins was next effected by treatment *in situ* with an excess of base or in a separate operation. Several procedures have been developed which include the use of either the same base, PhLi in Et₂O,¹⁴⁰⁻¹⁴⁵ *n*-BuLi at -78°C,¹⁴⁶⁻¹⁴⁸ or two different bases, *n*-BuLi / MeLi at room temperature,^{149,150} *n*-BuLi / LDA at -70°C¹⁵¹ or 0°C¹⁵² (Scheme 12), *n*-BuLi-THF / *t*-BuOK-DMSO,³¹⁵ lithium piperidine¹⁵³ and NaNH₂ / NH₃ at low temperature,¹⁵³ NaHMDS / *n*-BuLi in THF¹³⁸ or *t*-BuOK in *t*-BuOH at room temperature.^{127,139,154} The alkynes were isolated in excellent yields (86-95%).

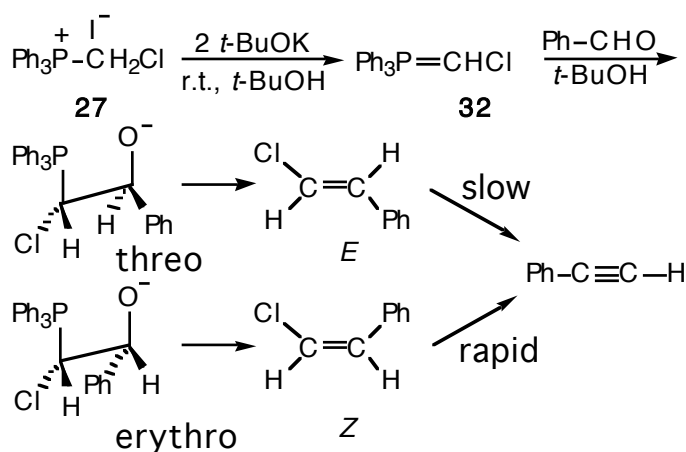


Scheme 12.

***cis*-1-cyclohexyl-2-trimethylsilylethynylethylene.**¹⁴⁹ To a cooled (-78°C) suspension of chloromethyltriphenylphosphonium chloride (1.30 g, 3.78 mmol) in 10 mL of THF was added *n*-BuLi (3.70 mmol) in hexane. After 0.75 h at -78°C, the *cis*-aldehyde (167 mg, 1.21 mmol) was added in 1 mL of THF. The cooling bath was removed and replaced by ice water. After 3 h the product was isolated by pentane extraction. Filtration through a short column of acidic alumina and evaporation distillation (b.p.100°C (bath) and 0.7 mm) afforded 173 mg (83% overall) of the chlorodiene.

To a cooled (0°C) solution of chlorodiene (60 mg, 0.35 mmol) in 10 mL of dry THF was added 3 mL of 1.6 M methylolithium. The cooling bath was removed, and the solution was stirred at room temperature for 12 h. Addition of TMSCl (0.5 mL) and isolation of the product by pentane extraction afforded after evaporative distillation (130°C (bath) at 0.7 mm) 53 mg of the desired *cis*-enyne.

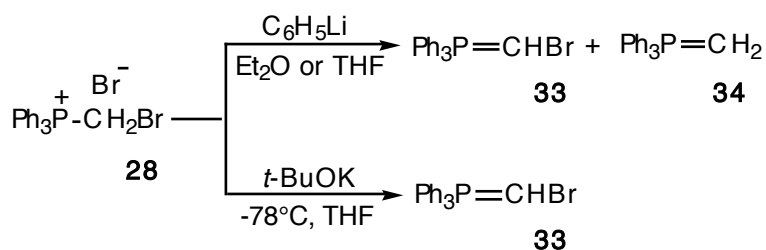
The chloromethyltriphenylphosphonium halides are well suited to the one-pot conversion of aldehydes into homologous alkynes, especially when *t*-BuOK in *t*-BuOH was used. Formation from **27** of the chloromethylenetriphenylphosphorane **32** was detected by the appearance at room temperature of a characteristic orange-red slurry. Addition of an aldehyde leads to conversion into the corresponding chloroolefins as a mixture of *E*- and *Z*- isomers in reasonable yields (45-81%). According to the amount of base and the reaction time the course of the reaction can be modified to give either the chloroolefins or the alkynes. Thus, in the presence of an excess of *t*-BuOK (2.5 eq.) in refluxing *t*-BuOH, both isomers issued of aromatic aldehydes are dehydrochlorinated to give phenylacetylene (Scheme 13).¹²⁷



Scheme 13.

The chloromethylenetriphenylphosphorane **32** has also been reacted with α,β -unsaturated ketones to give the corresponding chloroolefines. On treatment with *n*-BuLi, the chloroolefines gave carbenoids, stable at low temperature, which underwent on warming the Fritsch-Buttenberg-Wiechell rearrangement to give the isomeric enyne.¹⁵⁵

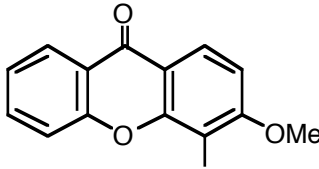
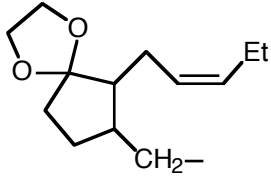
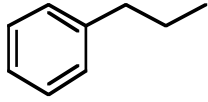
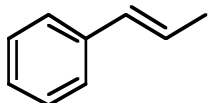
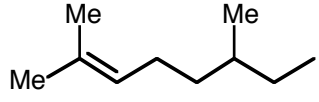
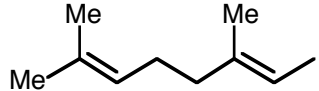
Formation of the bromomethylenetriphenylphosphorane **33** from bromomethyltriphenylphosphonium bromide **28** was of peculiar interest because it was directly involved in the one-pot conversion of aldehydes into the homologous alkynes without the isolation of intermediates. However, there arises the critical issue of regioselectivity of attack to the α -proton or α -halogen by the base. Thus, when PhLi was employed to generate the ylide, not only was benzene recovered, but a large amount of bromobenzene was produced.¹²⁹ With either *p*-tolyllithium or *p*-chlorophenyllithium appreciable quantities of *p*-bromotoluene and *p*-bromochlorobenzene were respectively obtained.¹²⁸ These observations demonstrate that initial bromine abstraction by the base competes favorably with proton abstraction to give a mixture of methylene- **34** and bromomethylene- **33** triphenylphosphorane. The use of Grignard reagents, sodium hydride or sodium methoxide generally gave little or no ylide, and lithium piperidide,^{136,137} which has been claimed to circumvent the problem of bromine exchange, did not improve the yields (Scheme 14). The use of NaH in DME containing a little DMSO has been reported in the conversion of nickel *meso*-formyloctaethylporphyrin into *meso*-ethynyl compound.^{156,157}



Scheme 14.

The preferred base for the one-pot synthesis of alkynes from aldehydes using **28** was found to be *t*-BuOK in THF.¹⁵⁸⁻¹⁶³ The use of *t*-BuOK in THF at low temperature increases regioselectivity, reaction rate and yield. Thus, when a suspension of the bromomethyltriphenylphosphonium bromide **28** in dry THF was treated with an excess of *t*-BuOK at low temperature, the yellow colored ylide **33** was formed then allowed to react with aldehydes (aliphatic, aromatic and α,β -unsaturated) to produce directly the desired alkynes **25** in moderate to excellent yields (36-100%) (Table 3). Unfortunately, the alkynes **25** were contaminated with the bromoolefins which are entirely *E*-isomers. In agreement with the Wittig reaction using nonstabilized ylides, the olefination reactions with aldehydes are not highly stereoselective, and mixtures of *Z*- and *E*-isomers are regularly obtained with a *Z*-dominance. In the formation of alkynes *via* dehydrobromination of the bromoolefins with a base, the *Z*-isomer reacting much faster than the *E*-counterpart is more rapidly consumed than the *E*-isomer which frequently contaminates the alkyne. The presence of unreacted bromoolefins being the major drawback, it is crucial to maintain the reaction mixture for an extended period of time to improve the yields of alkynes **25**.¹⁵⁸⁻¹⁶³

Table 3

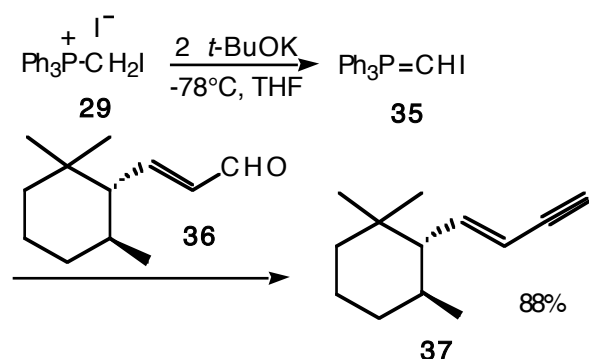
25	R¹	Yield (%)	Ref.
a	Phenyl	58	158
b	2-MeO-C ₆ H ₄	65	160
c	3-MeO-C ₆ H ₄	54	158
d	4-MeO-C ₆ H ₄	79	158
e	4-Cl-C ₆ H ₄	39	158
f	4-THPO-C ₆ H ₄	74	162
g	4-allylO-C ₆ H ₄	60	161
h	3,4-(OCH ₂ O)-C ₆ H ₄	38	158
i	4-MeO-C ₆ H ₄	80	158
j	1-naphthyl	77	158
k		100	158
l		65	159
m		40	158
n		45	158
o		36	158
p		62	158

4-Tetrahydropyranloxyphenacylacetylene 25f.¹⁶² To a suspension of bromomethyltriphenyl-phosphonium bromide (21.3 g, 48.8 mmol) in anhydrous THF (200 mL) cooled to -78°C was added *t*-BuOK (10.9 g, 97.6 mmol) portionwise. The mixture was stirred at that temperature for 30 min. To this ylide solution was added a solution of 4-tetrahydropyranloxybenzaldehyde (3.35 g, 16.3 mmol) in anhydrous THF (80 mL) over a period of 20 min. The resulting mixture was stirred at -78°C for 2 h, and then warmed up to room temperature, being stirred for 2 h at room temperature. After dilution with H₂O (200 mL), the product was extracted with Et₂O. The combined ethereal extracts were washed with water and brine, successively, dried over MgSO₄, and concentrated in vacuo. Column chromatography on silica gel (YMC gel, 300 g, CH₂Cl₂/*n*-hexane 2/3) afforded the desired crystalline phenylacetylene (2.42 g, 74% yield).

General procedure for the synthesis of phenolic acetylenes 25g.¹⁶¹ Potassium *t*-butoxide (1 g, 25.6 mmol) was suspended in dry THF and the bromomethyltriphenyl-phosphonium bromide (5.45 g, 12.5 mmol) added to

it at -78°C under N_2 . The creamy mixture was stirred for 1 h before the aldehyde (10 mmol) was slowly added to it. After 4 h at -78°C , the mixture was stirred at 25°C for 16 h and quenched with saturated NH_4Cl . After acidification with 2 M HCl and extraction with Et_2O , the Ph_3PO , which precipitated on concentrating the Et_2O , was filtered off. The residue afforded pure acetylene after column chromatography.

The iodomethylenetriphenylphosphorane **35** is the most recently prepared of the halomethylides. It has been effectively obtained from the iodomethyltriphenylphosphonium iodide **29** using NaHMDS as base.^{164,165} The possibility of making this phosphorane has been examined using a variety of solvents and bases (*t*-BuOK, LDA, LiHMDS , NaHMDS , lithium piperidide) and it has been found that the iodomethylenetriphenylphosphorane can be made readily by the use of NaHMDS in THF at room temperature.¹⁶⁴ Effectively, the iodomethyltriphenylphosphonium salts undergo halogen-metal exchange as well as proton abstraction by the alkyl- or aryllithiums, and the former mode of attack is greatly favored in that case.¹²⁹ It is especially gratifying that the reaction of this phosphorane **35** with a variety of aldehydes leads stereoselectively to the *Z*-isomers. The stereoselectivity of the iodoolefins depending on the reaction temperature, the ratio of *Z/E*-isomer increases markedly at low temperature. In a multi-step synthesis of 9-demethyl-5,6-dihydroretinol, an application from the area of vitamin A synthesis, the iodomethylenation of aldehyde **36** in the presence of *t*-BuOK in excess in THF at low temperature has been reported to afford the homologous alkyne **37** with 88% yield (Scheme 15).¹⁶⁶



Scheme 15.

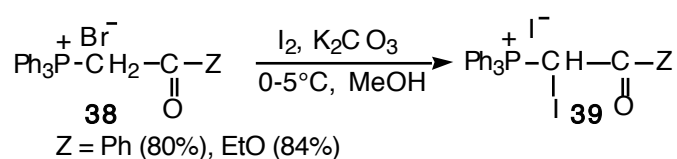
(2*S*,3*S*)-2-[(*E*)-But-1'-en-3'-yn-1'-yl]-1,1,3-trimethylcyclohexane **37.**¹⁶⁶ *t*-BuOK (1.06 g, 9.45 mmol) was added to a suspension of iodomethyltriphenylphosphonium iodide (2.51 g, 4.74 mmol) in THF (90 mL) at r.t. The resulting solution was cooled to -78°C , and then a solution of aldehyde **36** (0.85 g, 4.74 mmol) in THF (10 mL) was added. After stirring at -78°C for 2 h, the solution was allowed to reach room temperature, diluted with hexane and washed with brine and water. The organic layer was dried over MgSO_4 and the solvent was removed under vacuum. Chromatography (SiO_2 , 90/10 hexane/ether) afforded 0.73 g (88%) of the title compound.

Owing to all these investigations a number of factors which may affect the regioselectivity of the attack by bases have been recognized. Especially it has been found that attack at bromine was more likely than at chlorine, and that halogen attack was more likely using bases in the order $t\text{-BuLi} > n\text{-BuLi} > \text{PhLi} >$ lithium piperidide. The difficulties which attend the preparation of alkynes involving α -halo ylides being closely related to the choice of the

precursor and deprotonating agent, these observations have significantly extended the knowledge on the role of bases and the scope of these reagents.

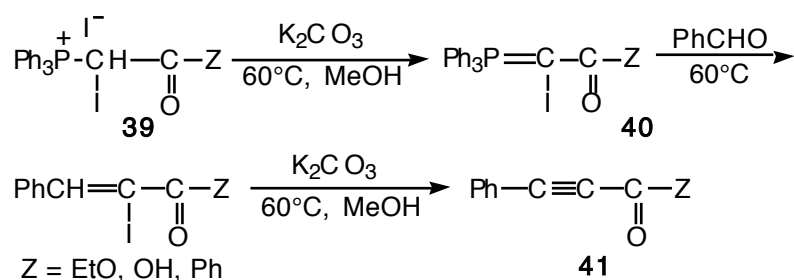
2.4. Iodomethyltriphenylphosphoniumphenacylide

Phosphonium ylides have been shown to react with a variety of halogenating agents, providing direct access to α -halo ylides. However, halogenations have essentially been investigated with stabilized ylides, usually β -keto or β -carbalkoxy ylides. Generally, reaction of carboalkoxymethylenetriphenylphosphorane with chlorine, bromine or iodine leads to mixtures of desired halo ylides and the conjugate acid of the starting ylide.¹⁶⁷⁻¹⁶⁹ This resulted of a deprotonation or transylation of the generated halo ylide by the more basic starting ylide. Thus, there is loss of one-half of the starting ylide. For example, bromination of stabilized phosphonium ylides proceeds as described to give a 77% yield of one-half equivalent of α -bromo ylide.^{167,169,170} However, the (ethoxycarbonyliodomethyl)triphenylphosphonium iodide **39** was obtained in high yield, 80%, from commercial (ethoxycarbonylmethyl)triphenylphosphonium bromide **38** by direct iodination in MeOH in the presence of potassium carbonate (Scheme 16).¹⁷¹ An interesting variation using treatment of the α -bromo ylide with methanolic potassium iodide for the direct preparation of the α -iodo ylide in high yield (80-84%) has also been reported.¹⁶⁷



Scheme 16.

Together with its innovations, the α -iodo ylides **40** appear as useful reagents for the two carbon chain elongation of aromatic aldehydes to propiolic esters, acids and benzoylalkynes **41** (Scheme 17).^{171,172} The process is divided into two independent steps, iodination of the ylide in the first one, and Wittig reaction to a vinyl iodide followed by elimination of HI in the second one. The reaction works well with aromatic and α,β -unsaturated aldehydes, but no reaction was observed with aliphatic aldehydes.^{171,172} Halogenation of ylides has also been realized with reagents such as phenyliodide dichloride.^{167,173,174}



Scheme 17.

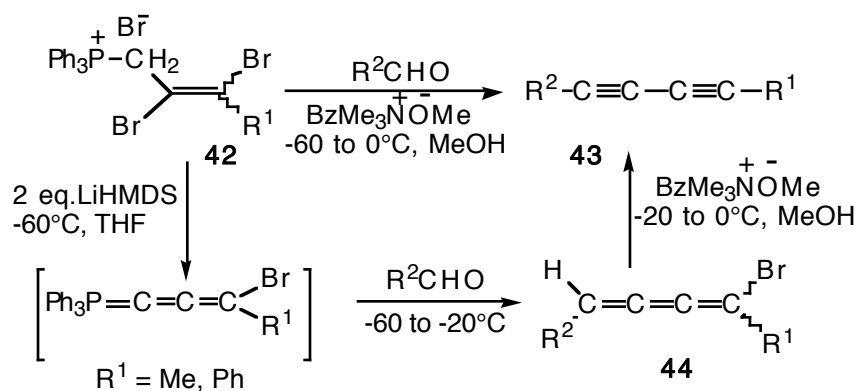
This halogenation reaction appears effective for the preparation of synthetically useful ylides, but full utilization of these reagents as precursors of alkynes remains handicapped by the loss of one half of the ylide during transylidation reaction.

(Ethoxycarbonyliodomethyl)triphenylphosphonium iodide 39 (Z=OEt).¹⁷¹ A solution of iodine (8.89 g, 0.035 mol) in MeOH (35 mL) is added dropwise at 0–5°C to a well-stirred, two-phase system consisting of solid potassium carbonate (4.83 g, 0.035 mol) and (ethoxycarbonylmethyl)triphenylphosphonium bromide (15.0 g, 0.035 mol) in MeOH solution (35 mL). The temperature is then maintained between 0 and 5°C during 4 h. A lemon-yellow precipitate appears. After the reaction mixture has warmed to room temperature, the precipitate is collected by filtration and washed with cold MeOH (100 mL). The crude product is stirred in water (2 x 200 mL) until the water remains neutral. The product is stored at 0°C in the dark; yield: 17 g (80%).

Synthesis of β -substituted propiolic acids 41.¹⁷¹ A solution of aldehyde (0.0175 mol) in MeOH (25 mL) is added dropwise to a well stirred suspension of (ethoxycarbonyliodomethyl)triphenylphosphonium iodide **39** (10.5 g, 0.0175 mol) in a two-phase system consisting of MeOH (25 mL) and K₂CO₃ (2.415 g, 0.0175 mol). The mixture is heated during 4 h at 60°C (until discoloration occurs). After return to room temperature, the reaction mixture is filtrated and the filtrate evaporated under reduced pressure. The solid residue obtained can be worked up as follows. To the residue, water (50 mL) and 50% NaOH solution (20 mL) are added, and steam is injected until 500 mL of water is condensed into a distillation receiver. After the reaction mixture is cooled in an ice-bath, Ph₃PO is filtered off. The aqueous phase is extracted with C₆H₆ (2 x 100 mL) to eliminate unreacted aldehyde and traces of Ph₃PO. Acidification of the aqueous layer by concentrated HCl gives the title compound. The precipitate is collected by filtration and dried under reduced pressure. The solid is recrystallized from water or CHCl₃/ligroin (52–70% yield).

2.5. Dibromoallyltriphenylphosphonium bromide

Phosphacumulenes ylides are established precursors in the preparation of aryl and halogen-substituted [3] cumulenes. Though they are generally unstable, the halo [3] cumulenes can be handled without difficulty and they have been used in the preparation of 1,4-disubstituted 1,3-diyne **43**. The entire formation of 1,3-diyne was performed in one reaction vessel and involved the 1,4-elimination of HBr from 1-bromo-1,2,3-butadienes **44** resulting of a Wittig reaction between an aldehyde, aliphatic or aromatic, and the (*trans*-2,3-dibromo-3-phenyl-2-propen-1-yl)triphenylphosphonium bromide **42** (Scheme 18).¹⁷⁵ The *E*-isomer of the phosphonium salt was prepared with 88% yield by treatment of the *E*-isomer of the 1,2,3-tribromo-3-phenylprop-2-ene with triphenylphosphine **6** in toluene for 36h at room temperature.¹⁷⁵



Scheme 18.

In a typical reaction excess benzyltrimethylammonium methoxide was slowly added to a methanolic solution of the triphenylphosphonium bromide and the aldehyde at -60°C . Product diynes are obtained on warming the reaction mixture to 20°C followed by standard workup and purification. The overall yields of the pure diynes **43** are in the range of 43-91%. They are presumably formed *via* the reaction sequence shown in Scheme 18. The choice of LiHMDS in THF at -70°C used when $\text{R}^1 = \text{Ph}$ facilitates the isolation of the unstable 1-bromo-1,4-diphenylbutatriene **44** ($\text{R}^1 = \text{R}^2 = \text{Ph}$) which was the only product as a mixture of *E*- and *Z*- isomers. Subsequent treatment with excess benzyltrimethylammonium methoxide in MeOH at -30°C resulted in an extremely facile 1,4-dehydrobromination of both *E* and *Z* components to give diphenylbutadiyne with 47% yield.¹⁷⁵

3. Phosphonates Precursors of Acetylenic Compounds

Phosphonates being considerably more nucleophilic than their phosphorane counterparts play an important part in modern alkynes synthesis. They are present in the field with about ten readily available reagents among which some are commercially available. The synthetic approach to alkynes is based on a two-step combination of a Horner-Wadsworth-Emmons carbonyl olefination and a 1,2- or 1,1-elimination reaction. By using the more nucleophilic anions of phosphonate reagents, both aldehydes and ketones are successfully converted to alkenes in generally good to excellent yields, and the subsequent formation of alkynes *via* the alkenes thus produced is frequently achieved in mild conditions. The phosphonate reagents appear to be well fitted to deliver common alkynes in high yields and in large scale or to introduce a triple bond in a complex molecular architecture.

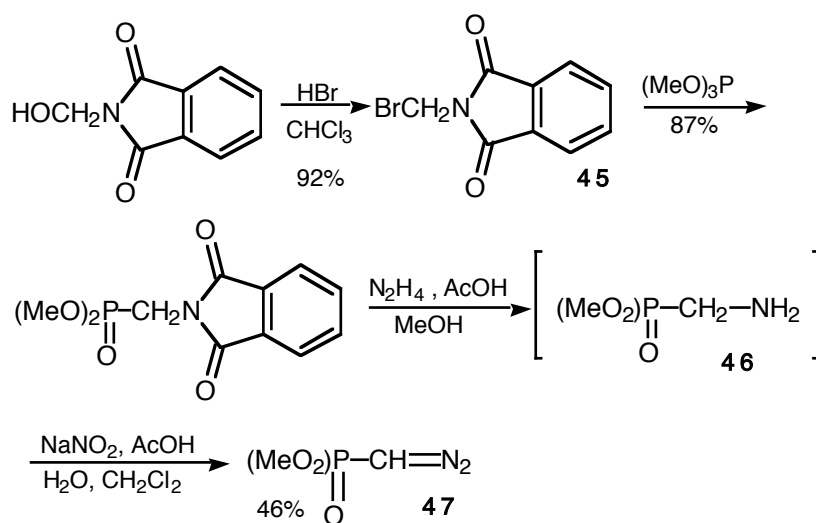
3.1. The 1-Diazomethylphosphonates

Two types of phosphonate reagents containing a diazomethyl group are known, the dimethyl¹⁷⁶ **47** and diethyl 1-diazomethylphosphonates¹⁷⁷ **50** and the dimethyl 1-diazo-2-oxopropylphosphonate¹⁷⁸ **53**. Both can be regarded as reagents containing a latent alkyne function. Their metallated derivatives on reaction with the carbonyl group of aldehydes or

ketones undergo olefination reaction followed by subsequent unmasking of the alkyne by an alkylidencarbene rearrangement. In this regard, the transformation which allows the introduction of a triple bond in one sequence at the carbonyl carbon of the starting aldehyde or ketone is precious and of great importance.

3.1.1. Dimethyl and Diethyl 1-Diazomethylphosphonates

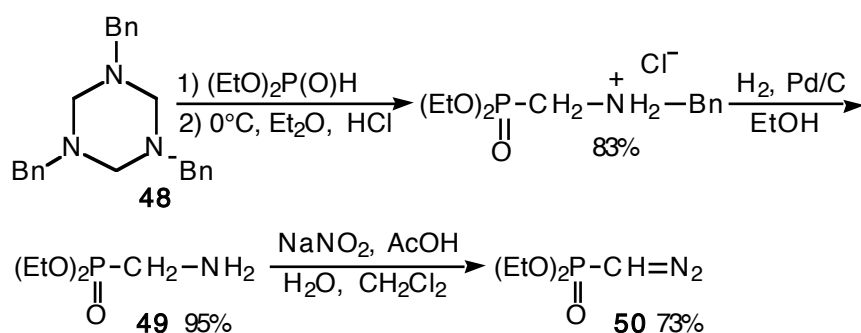
Possibly the most frequently used and most widely known phosphorus reagent for efficient, one-carbon homologation of aldehydes and ketones to terminal or internal alkynes, is the dimethyl diazomethylphosphonate **47** (Seyferth-Colvin-Gilbert reagent).¹⁷⁶ Early reported preparation of **47** includes the diazotation of the unisolated dimethyl aminomethylphosphonate **46** prepared on protected form by a Michaelis-Arbuzov reaction between the trimethylphosphite and the bromomethylphthalimide **45** (Scheme 19). Dimethyl diazomethylphosphonate **47** was isolated in 46% yield as a distillable yellow liquid which was stable indefinitely when stored in a refrigerator.¹⁷⁶ To minimise the chance of explosive decomposition on distillation it was recommended to filter an ethereal solution of the crude product through a short column of alumina prior to distillation.¹⁷⁹



Scheme 19.

Dimethyl diazomethylphosphonate 47.¹⁷⁶ A solution of 53.8 g (0.20 mol) of dimethyl phthalimidomethylphosphonate and 95% anhydrous hydrazine (0.21 mol) in 400 mL of MeOH was stirred at r.t. under nitrogen for 45 h. Then 20 mL of AcOH was added and the mixture was stirred 5 min longer and filtered. The precipitated phthalhydrazide was dried, 29.7 g (92%). The filtrate was evaporated at reduced pressure and the residue was dissolved in 50 mL of AcOH. A solution of sodium nitrite (21.7 g, 0.30 mol, in 50 mL of H₂O) was added dropwise over 5 min while the flask was being swirled in an ice bath. The flask was kept in the ice bath, with occasional swirling for another 5 min, and then 53 g of sodium carbonate was added slowly in portions, followed by 200 mL of ice water. The reaction mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were extracted with 100 mL of a saturated NaHCO₃ solution, dried (Na₂SO₄), and concentrated at reduce pressure. The orange liquid residue was short-path distilled to give 13.77 g (46%) of the diazo compound, b.p. 59°C (0.42 mm), as a yellow liquid.

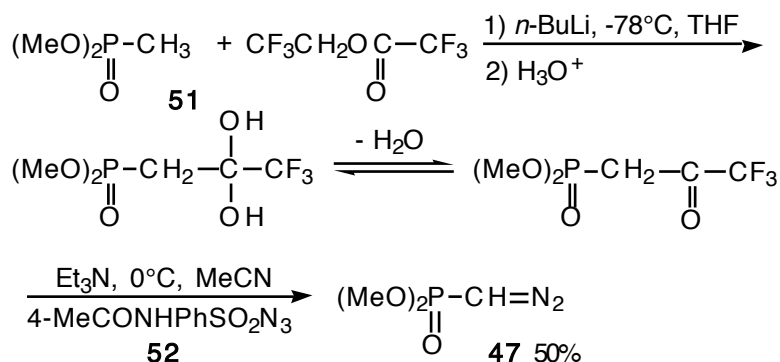
Although most workers have opted for the original route (Scheme 19), an alternative procedure for the preparation of the aminomethylphosphonate has been described. It involves the hydrogenolytic debenzoylation of the phosphonate obtained by reaction of the 1,3,5-tribenzyl-hexahydro-1,3,5-triazine **48** with a dialkylphosphite. This method, offering the advantages of easy deprotection and high yields, has been applied to the preparation of the stable and distillable diethyl aminomethylphosphonate **49** with 95% yield (Scheme 20). After diazotization of the amine the diethyl diazomethylphosphonate **50** was obtained with 73% yield as a stable (at 4°C) compound.¹⁷⁷



Scheme 20.

Diethyl diazomethylphosphonate 50.¹⁷⁷ To a solution of diethyl aminomethylphosphonate **49** (39.0 g, 232 mmol), in CH_2Cl_2 (217 mL) at -5°C was added with stirring aqueous sodium nitrite (19.33 g, 280 mmol, 108 mL H_2O), followed by glacial AcOH (28 g, 462 mmol) dropwise over 10 min. On stirring at 0°C for 4 h the CH_2Cl_2 layer became bright yellow. The mixture was transferred to a chilled separating funnel, and the CH_2Cl_2 layer run into cold aqueous potassium carbonate (75 g in 100 mL of H_2O). The aqueous layer was extracted once with CH_2Cl_2 , and the combined organic phases shaken with potassium carbonate until well neutralized. The layers were separated, and the organic phase dried (K_2CO_3), filtered through a short pad of neutral alumina, and the solvent stripped at reduced pressure below 40°C . Distillation of the residual oil afforded diethyl diazomethylphosphonate **50** as a bright yellow liquid (30.5 g, 73%), stable at 4°C under an argon atmosphere. b.p. $86\text{-}88^\circ\text{C}/0.2$ torr.

The two previous preparations included an aminomethylphosphonate intermediate. A recently reported procedure offers a shorter, more convenient route to **47** from the readily available dimethyl methylphosphonate **51** and a diazo transfer reagent **52** (Scheme 21).¹⁸⁰ The synthesis was based upon a diazo transfer reaction coupled with a deacylation step. The keto form was certainly the reactive species in the diazo transfer and deacylation steps. However, the overall yield (50%)¹⁸⁰ was quite identical to that reported previously (46%) (Scheme 19).¹⁷⁶



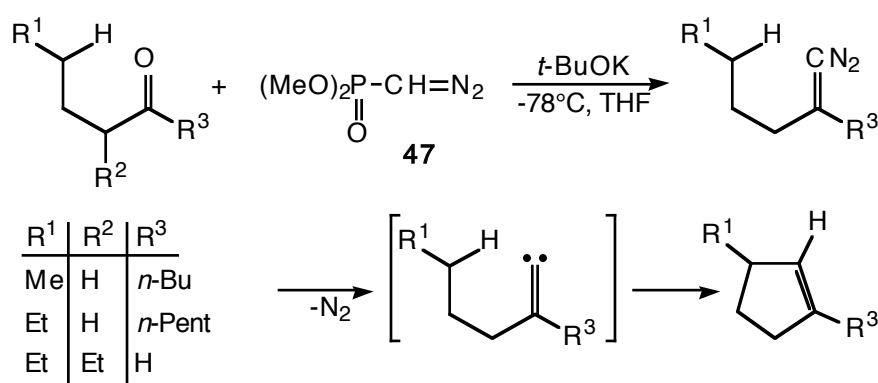
Scheme 21.

As part of a general study on the synthetic utility of trimethylsilyldiazomethane and dimethyl diazomethylphosphonate **47**, it was reported in 1973 that the base-induced reaction of these reagents with carbonyl compounds, mainly diaryl ketones and electrophilic aryl aldehydes, leads directly to the corresponding homologous alkynes.^{179,181} Although these results were unexpected, they did promise considerable interest. The phosphorus diazomethanes were found to be rather more stable and more easy to handle than diazomethyltrimethylsilane. Surprisingly, the corresponding anions were found much less stable and had to be generated at -78°C ; in THF they merely converted benzophenone into diphenylacetylene in higher yield (94% using *n*-BuLi and 77% using *t*-BuOK) than the silicon-based reagent (80% using *n*-BuLi and 50% using *t*-BuOK). Quickly, the dimethyl diazomethylphosphonate **47** was recognized as a highly versatile synthetic intermediate and simple innovations have significantly enhanced the breadth and efficiency of this type of transformation.^{179,181}

Potassium *tert*-butoxide was selected as base instead of *n*-BuLi in order to make the counterion of **53** larger, to enhance the rate of decomposition of betaines and also to avoid undesired side reactions. Moreover, one of the difficulties which was encountered in this reaction being the slow conversion of carbonyl groups, the maintenance of the reaction mixture at low temperature for an extended period of time (16-20 h) has allowed complete consumption of the anion of **47** by reaction with a large variety of carbonyl compounds. These modifications were successful since even carbonyl groups issued of enolizable aldehydes and ketones and aryl aldehydes of low electrophilicity were homologated to alkynes (Table 4). In addition, it was possible to prove by low-temperature NMR analyses that the alkynes **5** are forming at -78°C .^{182,183}

Owing to the synthetic importance of alkynes, the sequence that allows the one-carbon chain homologation of aldehydes ($R^2=H$) into terminal alkynes is especially useful and for that reason dimethyl diazomethylphosphonate **47** is frequently involved in the synthesis of natural products possessing complex molecular architecture. For example, **47** was employed in several multi-step syntheses of active compounds including modified forskolin,¹⁸⁴ immunosuppressive agents,¹⁸⁵⁻¹⁸⁹ vitamin D3 metabolites,¹⁹⁰⁻¹⁹⁵ alkaloids of various activity,¹⁹⁶⁻¹⁹⁹ antibiotics,²⁰⁰⁻²⁰² natural toxins,²⁰³ selective inhibitors of GABA transaminase,²⁰⁴ cytotoxic agents²⁰⁵⁻²¹² and others.²¹³⁻²¹⁷

In complement with the rearrangement of diazoalkenes **54** that produces terminal alkynes, dimethyl diazomethylphosphonate **47** has also been used in intramolecular C-H insertion²¹⁸⁻²²³ that leads to cyclopentenes formation (Scheme 23),²¹⁹ and intermolecular O-H insertion with an alcohol that gives an enol ether.²²⁴



Scheme 23.

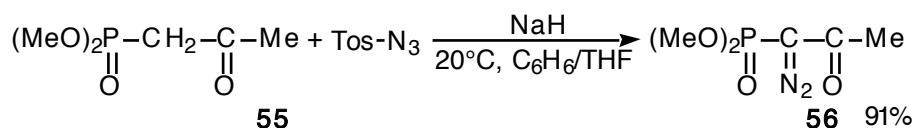
General procedure for the preparation of cyclopentenes.²¹⁹ Potassium *tert*-butoxide (1.12 g, 10 mmol) was dissolved in 30 mL of anhydrous THF contained in a 50 mL round-bottomed flask equipped with a magnetic stirring bar. The flask was purged with nitrogen, sealed with a rubber septum, and cooled to -78°C (dry ice / 2-propanol). A solution of dimethyl diazomethylphosphonate **47** (1.50 g, 10 mmol) in 3 mL of THF was added *via* syringe over a 5 min period. After this mixture had been stirred for an additional 5 min, a solution of a ketone (5.0 mmol) in 3 mL of THF was added during the course of 5 min. Stirring was continued at -78°C for 18 h, with occasional venting to relieve internal pressure.

The solution was allowed to warm to r.t., and 50 mL of pentane was added. The resulting mixture was washed with water (5 x 100 mL) and dried (Na_2SO_4), and the solvent was removed by either rotary evaporation or simple distillation. The crude reaction mixture was chromatographed on neutral silica gel (pentane), all of the material eluting before the starting ketone being collected.

3.1.2. Dimethyl 1-Diazo-2-Oxopropylphosphonate

An ingenious and elegant improvement in the standard synthetic procedure for the preparation of alkynes **5** using dimethyl diazomethylphosphonate¹⁷⁶ **47** has featured the use of dimethyl 1-diazo-2-oxopropylphosphonate **56** (Ohira reagent)¹⁷⁸ in the presence of basic MeOH. The design of reagent **56** is based upon the structural analogy with the 2-diazo-1,2-dicarbonyl compounds. The dimethyl 1-diazo-2-oxopropylphosphonate **56** was obtained in a single step with 83% yield by reaction of the α -metallated derivative of the readily available dimethyl 2-oxopropylphosphonate **55** with tosylazide (Scheme 24).²²⁵ It has been observed

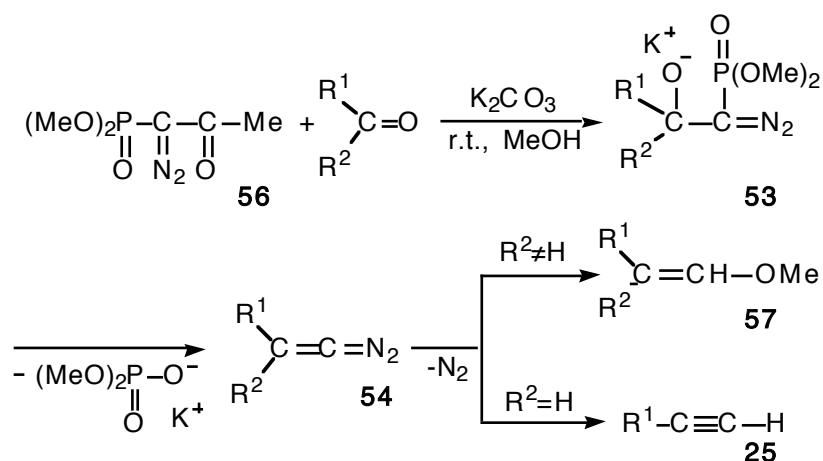
that the sodium enolate prepared in NaH/THF/C₆H₆ solution gives superior results (80-96% yields) to *t*-BuOK/THF/C₆H₆ (20-50% yields) or Et₃N / MeCN (30-60% yields).²²⁵



Scheme 24.

General procedure for synthesis of dimethyl 1-diazo-2-oxoalkylphosphonates 56.²²⁵ To a cold (0-5°C) suspension of NaH (25.2 mg, 1.05 mmol) in C₆H₆ (3 mL) and THF (0.5 mL) is added a dimethyl 2-oxoalkylphosphonate **55** (1.0 mmol) in C₆H₆ (1 mL). After stirring for 1 h, TosN₃ (207 mg, 1.05 mmol) in C₆H₆ (0.5 mL) is added and the reaction mixture is allowed to warm to 20°C. After 2 h the mixture is filtered on a celite pad, concentrated in vacuo and chromatographed on silica gel (AcOEt / hexane, 1 / 1) affording dimethyl 1-diazo-2-oxoalkylphosphonates (80-91%).

Facile hydrolysis of 2-diazo-1,3-dicarbonyl compounds to the corresponding deacetylated compounds, under mild basic conditions has long been known and employed in the preparation of diazocarbonyl compounds. The same protocol was applied to dimethyl 1-diazo-2-oxopropylphosphonate **56** which was cleanly transformed in almost quantitative yield into the anion of **56** by acyl cleavage with excess K₂CO₃ in MeOH at 0°C. The *in situ* generated anion undergoes reactions with both aldehydes (R²=H) and ketones (R²≠H) to give the alkynes **25** or the enol ethers **57** (Scheme 25). The use of potassium carbonate in MeOH was crucial to the success of the reaction to exclude a too great concentration of the reactive potassium anion and thus preventing its decomposition. In marked contrast, no product or only trace of **47** was obtained when using NaOH in aqueous MeCN probably because of the decomposition of the corresponding unstable anion formed in high concentration.¹⁷⁸



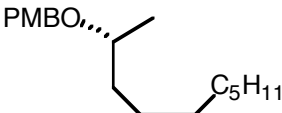
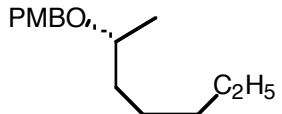
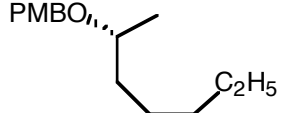
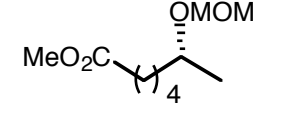
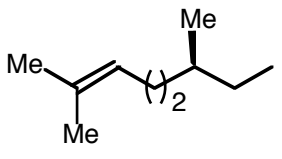
Scheme 25.

A clear illustration of the advantages of this novel synthetic procedure was provided by the one-pot conversion of decyl aldehyde to 1-undecyne with 62% yield and of cyclohexanone

into the corresponding methyl enol ether with 63% yield.¹⁷⁸ Several recent results have significantly extended the scope and synthetic utility of this advantageous one-pot procedure. Testing a variety of different aldehydes, the desired alkynes were obtained in good to excellent yields and in analytically pure form after simple aqueous work-up (Table 5).²²⁶ The reaction works with aryl- and alkylsubstituted aldehydes as well as with hindered substrates. For example, dialdehydes give rise to diynes and the transformation of chiral aldehydes occurred without racemisation. A variety of functional groups such as ethers, methyl esters, acetals and non-conjugated double-bond are tolerated. This method avoids the use of strong bases, low temperature and inert gas techniques.²²⁶

Typical experimental procedure.²²⁶ To a solution of 290 mg (1.00 mmol) of aldehyde and 276 mg (2.00 mmol) of K_2CO_3 in 15 mL of dry MeOH are added 230 mg (1.20 mmol) of dimethyl 1-diazo-2-oxopropylphosphonate **56** and stirring is continued until the reaction is complete as indicated by TLC (4 h). The reaction mixture is diluted with Et_2O (23 mL), washed with an aqueous solution of $NaHCO_3$ (5%) and dried over $MgSO_4$. Evaporation of the solvent yields 217 mg (76%) of alkynes as a slightly yellow oil in analytically pure form.

Table 5²²⁶

25	R¹	Yield (%)
a		76
b		77
c		80
d		83
e	C_6H_5	73
f	4-MeO- C_6H_4	78
g	4-Cl- C_6H_4	97
h	1,3- C_6H_4	74
i	2-thienyl	80
j	$n-C_{11}H_{23}$	96
k		96
l	$MeO_2C-(CH_2)_7-$	82
m	$C_6H_5-CH(Me)-$	72

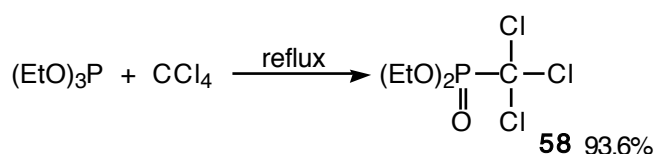
Starting from easily available reagents, this simple procedure described by Ohira can be effected at ambient temperature, is not sensitive to stoichiometry and constitutes an expeditious route for the synthesis of alkynes by one carbon chain elongation from aldehydes.²²⁷⁻²³²

3.2. The α -Halogenated Methylphosphonates

Several dialkyl α -halogenated methylphosphonates containing one, two or three halogen atoms, essentially chlorine, bromine and iodine are known.²³³ They owe their synthetic utility to their use in preparation of mono- or dihaloalkenes which are masked alkynes. The facile formation of a carbanion in the α -position to the phosphoryl group coupled to a geminal disubstitution operation of the carbonyl group (Horner-Wadsworth-Emmons reaction) results in production of mono- or dihaloalkenes able to provide access to internal or terminal alkynes by 1,2-, or 1,1-elimination reactions. The carbanions are usually obtained by proton-metal exchange reaction with primary alkylolithiums and lithium amides, or by halogen-metal exchange reaction with primary alkylolithiums.

3.2.1. Diethyl Trichloromethylphosphonate

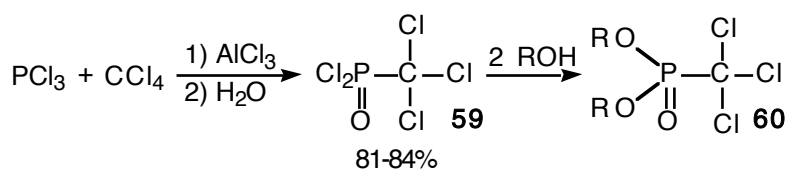
The diethyl trichloromethylphosphonate²³⁴ **58** is obtained in pure form with almost quantitative yield (93.6%) by simply refluxing triethylphosphite with dry tetrachloride in large excess (Scheme 26). The reaction is realized without difficulty on molar scale.



Scheme 26.

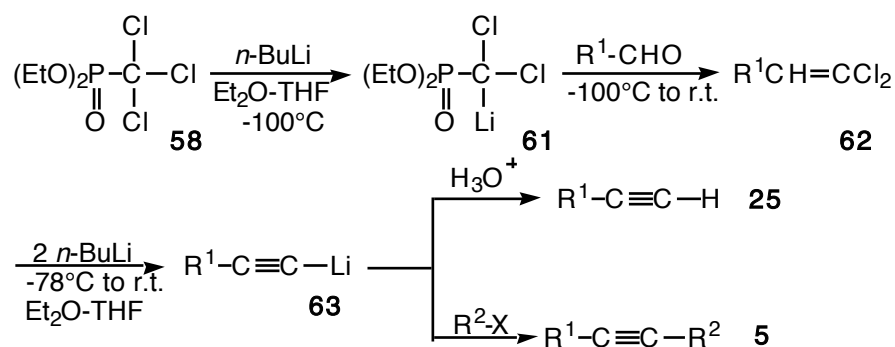
Diethyl trichloromethylphosphonate 58.²³⁴ Triethylphosphite (50 g) was refluxed overnight with 250 mL (large excess) of dry carbon tetrachloride. The colourless solution was distilled under reduce pressure to yield 72 g (93.6%) of diethyl trichloromethylphosphonate, as a colourless mobile liquid, bp, 135-137°C at 16 mm Hg, 127-128°C at 13 mm Hg.

Another route to trichloromethylphosphonyl derivatives which has been occasionally employed involves the trichloromethylphosphonyl dichloride **59** obtained by a Kinnear-Perren reaction.²³⁵ It offers the advantage over the previously reported procedure to leave the investigators free to choose the two phosphorus appendages. Alcoholysis²³⁶⁻²⁴² of **59** in anhydrous conditions yields the desired trichloromethylphosphonates **60** (Scheme 27).



Scheme 27.

From the diethyl trichloromethylphosphonate **58**, a relatively general procedure for the conversion of large amounts of carbonyl compounds to higher terminal alkynes *via* the *gem*-dichloroalkenes has been developed. This sequence (Scheme 28)²⁴³ is initiated by the addition of the diethyl 1,1-dichloro-1-lithiomethylphosphonate **61**, generated at -100°C by halogen-metal exchange reaction between **58** and *n*-BuLi, to an aldehyde to give on warming the *gem*-dichloroalkenes **62** in good to excellent yields (75-97%). Further treatment of these *gem*-dichloroalkenes **62** with an alkyllithium (ethyl or butyl) in Et₂O or THF at a suitable temperature (-10°C or -70°C) affords the corresponding lithium alkynides **63** which can be hydrolysed or directly alkylated (Scheme 28).^{243,244} Table 6 shows that a wide variety of acetylenic compounds such as enynes or thioenynes are readily available; moreover the *Z/E* stereochemistry of the starting 2-alkenals is preserved. Alkylation of metallated terminal acetylenes is restricted mainly to primary alkylating agents, the introduction of α -branched chains or vinylic moieties being more difficult.



Scheme 28.

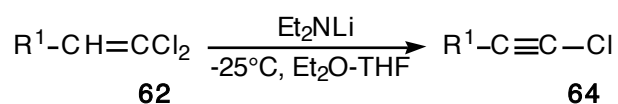
Table 6

5 or 25	R ¹	R ²	Yield(%)	Ref.
a	C ₉ H ₁₉	H	94	243
b	(C ₂ H ₅) ₂ CH	H	83	243
c	<i>c</i> -C ₆ H ₁₁	MeOCH ₂	88	243
d	<i>c</i> -C ₆ H ₉	MeOCH ₂	88	243
e	CH ₃ -CH=CH	MeOCH ₂	76	243
f	C ₆ H ₅ -CH=CH	H	57	243
g	2-MeO-C ₆ H ₄	H	91	243
h	4-MeO-C ₆ H ₄	H	86	243
i	2-Cl-C ₆ H ₄	H	73	243
j	4-Cl-C ₆ H ₄	H	83	243
k	(C ₂ H ₅)(CH ₃)CH	H	68	245

4-Methoxyphenylethyne (typical experimental procedure) 25g:²⁴³ In the absence of moisture and under a nitrogen atmosphere *n*-BuLi (80 mL of 1.44 M solution in Et₂O, 0.11 mol) is added to a mixture of Et₂O (70 mL) and THF (70 mL) at -40°C. 1,1-Dichloro-2-(4'-methoxyphenyl)ethene (10.15 g, 0.05 mol) is introduced at -70°C and the reaction mixture is allowed to warm to room temperature. It is then hydrolysed with aqueous 1 M sulfuric acid. The alkyne is extracted with pentane, the extracts washed with water, and dried with MgSO₄. The solvent is removed and the product **25g** distilled at reduced pressure; yield 5.7 g (86%); b.p. 95°/12 torr.

1-Cyclohexyl-2-(methoxymethyl)ethyne (typical experimental procedure) 5c:²⁴³ The procedure is the same as that described previously. Before hydrolysis, chlorodimethyl ether (4 g, 0.05 mol) are added to the lithium acetylenide at -70°C with stirring for 10 min. After the same work-up as above the product **5c** is distilled; yield 6.7 g (88%); b.p. 90°/13 torr.

1,1-Dichloro-2-alkenes **62**, when treated with lithium amides, for example Et₂NLi, give 1-chloro-1-alkynes **64** in high yields (Scheme 29 and Table 7).²⁴³



Scheme 29.

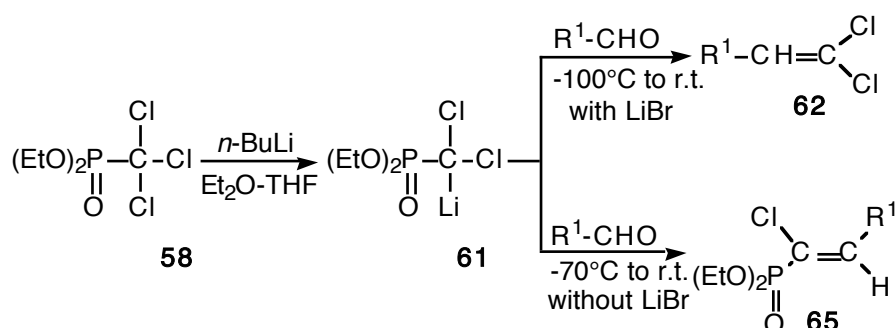
Table 7²⁴³

64	R¹	Yield (%)
a	C ₉ H ₁₉	90
b	(C ₂ H ₅) ₂ CH	75
c	<i>c</i> -C ₆ H ₁₁	80
d	<i>c</i> -C ₆ H ₉	87
e	C ₆ H ₅ CH=CH	78
f	2-MeO-C ₆ H ₄	67
g	4-MeO-C ₆ H ₄	73
h	2-Cl-C ₆ H ₄	66
i	4-Cl-C ₆ H ₄	87

An illustration of the advantages of this synthetic procedure is provided by the preparation of optically active 1-alkynes from chiral aldehydes,²⁴⁵ substituted butenyne,^{246,247} sesquiterpenes^{248,249} and annulenes.^{250,251}

The synthesis of 1-alkynes **25** proceeds generally well with aldehydes according to Scheme 28 but subsequent experiments indicated that the course of the reaction depends both on the temperature and especially on the presence of LiBr in the reaction medium. In fact, using commercial or purified *n*-BuLi in hexane without salts, the resulting carbanion **61** gives essentially the diethyl α-chlorovinylphosphonate **65** instead of the desired *gem*-dichloroalkenes^{245,252} **62**. By contrast, using LiBr-containing *n*-BuLi prepared in Et₂O, and operating in the previously described conditions, the *gem*-dichloroalkenes **62** are produced in

good yields without contamination by the vinylphosphonate **65**. Thus, the use of commercial *n*-BuLi (the only deviation from the experimental conditions originally described) in the reaction sequence seems not compatible with the formation of *gem*-dichloroalkenes **62** which may be attended by considerable amounts of undesired side products (Scheme 30).^{245,252}

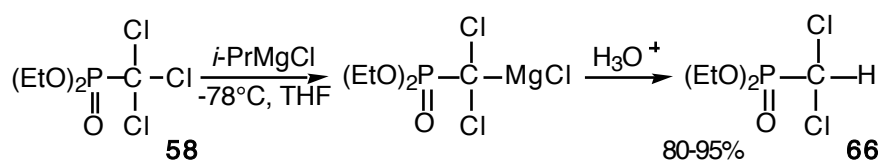


Scheme 30.

In the optimum situation, each of the steps of this reaction sequence may be conveniently executed in one pot without isolation of the intermediates.

3.2.2. Diethyl Dichloromethylphosphonate

The diethyl dichloromethylphosphonate **66** is obtained either by monodechlorination of the diethyl trichloromethylphosphonate²⁵³⁻²⁶⁰ **58** or by chlorination of the diethyl chloromethylphosphonate **68**. The first route has been envisaged by many authors who attempted optimization of the synthesis of **66** from the readily available diethyl trichloromethylphosphonate **58**. Various approaches have been tried, for instance abstraction or exchange of one chlorine atom with a base or reductive procedures (Table 8). Thus, the reactions of **58** with covalent organic bases (such as $(\text{EtO})_3\text{P}$ ²⁵³ and $(\text{Me}_2\text{N})_3\text{P}$ ²⁵⁴), charged organic bases (such as *n*-BuLi^{243,255-257} and *s*-BuLi), with Bu_3SnH , $\text{Cl}_3\text{SiH}/\text{Et}_3\text{N}$ ²⁵⁸ or molecular hydrogen have been studied. In each of these cases the reaction gave the required product **66**, often in reasonable yield, but always contaminated by undesirable side products. Finally, it has been found that magnesium-chlorine exchange reaction by means of isopropylmagnesium chloride in THF at low temperature results in the formation of pure **66** (Scheme 31).^{259,260} The use of the Grignard reagent favours the metal-halogen exchange reaction and avoids problems such as attack at phosphorus and carbene formation because of the increased thermal stability of the dichloroanion. The desired product **66** being easily purified by means of a simple distillation is obtained in excellent yield (80-94%).^{259,260}



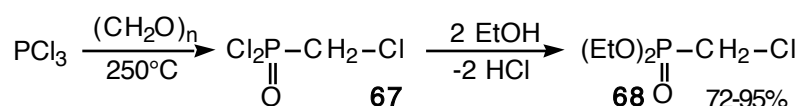
Scheme 31.

Diethyl dichloromethylphosphonate 66.²⁵⁹ To a stirred mixture of previously standardised 1.9 M solution of isopropylmagnesium chloride (83 mL, 158 mmol) and THF (400 mL) cooled to -78°C, was added dropwise a solution of diethyl trichloromethylphosphonate **58** (38.3 g, 150 mmol) in THF (50 mL) over a period of 15 min. The resulting mixture was stirred at -78°C for further 15 min and then a solution of absolute EtOH (12 g, 260 mmol) in THF (15 mL) was added dropwise to the mixture. After 5 min the mixture was allowed to warm to -40°C and was then poured into a beaker containing a mixture of 3M HCl (70 mL), an equal volume of crushed ice, and CH₂Cl₂. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 60 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated to yield a yellow oil which when distilled gave the title compound as a colourless oil. (32 g, 94%; bp 133°C at 10 mm Hg).

Table 8²⁵⁹

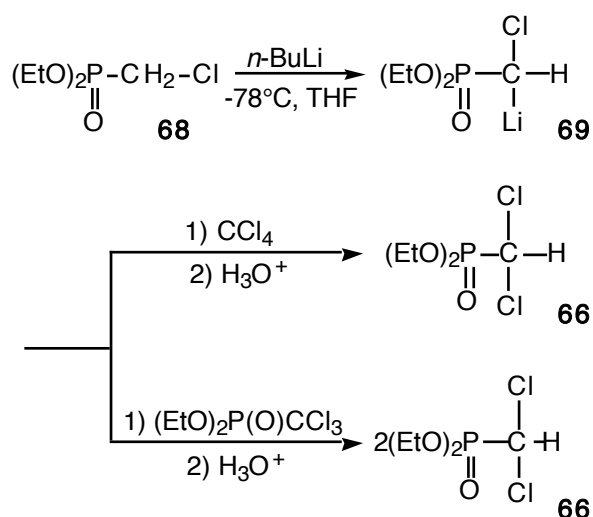
Base used	Conditions	Yield (%)
<i>n</i> -BuLi	-78°C, THF, 3M HCl quench	85
<i>n</i> -BuLi	LiCl/LiBr, 3M HCl quench	85
<i>s</i> -BuLi	-78°C, THF, EtOH, 3M HCl quench	80
<i>s</i> -BuLi	LiCl/LiBr, 3M HCl quench	80
(EtO) ₃ P	Hexanol reflux	65
(Me ₂ N) ₃ P	r.t., THF, EtOH, 4M HCl quench	92
<i>i</i> -PrMgCl	-78°C, THF, 3M HCl quench	94

The second route to diethyl dichloromethylphosphonate **66** uses the diethyl chloromethylphosphonate **68** as precursor. This route involves the intermediacy of the chloromethylphosphonyl dichloride **67** prepared in up to 67% yield by reaction between phosphorus trichloride and formaldehyde at 250°C.^{233,261-266} Further treatment of **67** with anhydrous ethanol produces diethyl chloromethylphosphonate **68** (Scheme 32).²³³



Scheme 32.

When the diethyl 1-chloro-1-lithiomethylphosphonate **69** is generated from **68** using *n*-BuLi at low temperature, it reacts smoothly with a variety of chlorinating agents, CCl₄ or **58** (Scheme 33) to produce the diethyl dichloromethylphosphonate **66** in large scale and with good yields.^{267,268} It has been demonstrated that the use of lithium salts, LiCl and LiBr, increases stability of the lithium carbenoid **69** and thus **66** can be isolated in yields up to 60-90%.²⁶⁷

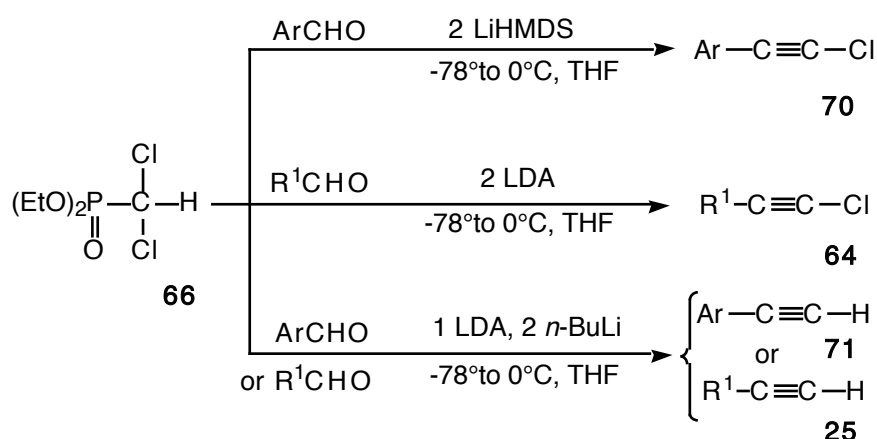


Scheme 33.

From diethyl dichloromethylphosphonate **66**, a variety of alkynes, chloroalkynes **64** and symmetrical or unsymmetrical diarylalkynes **5** (Table 9) were synthesized. The initial step is the olefination of the carbonyl group into *gem*-dichloroalkenes **62** by a Horner-Wadsworth-Emmons reaction between the diethyl 1,1-dichloro-1-lithiomethylphosphonate **64** and aldehydes, aliphatic and aromatic, or ketones. The second step, which takes place on warming, is a 1,1- or a 1,2-*trans* elimination. The former occurs in the case of ketones whereas the latter occurs with aldehydes.²⁵⁹

LiHMDS (2 eq.) appears as a well suited base for the one carbon chain extension of aromatic aldehydes to aromatic chloroalkynes **70**. However, LiHMDS was insufficiently strong enough to effect the *trans* elimination when aliphatic aldehydes were used as starting materials. Thus, aliphatic chloroalkynes **64** were obtained from dichloromethylphosphonate **66** and aliphatic aldehydes in the presence of LDA (2 eq.)²⁵⁹

Reaction of a mixture of **66** and an aldehyde, aliphatic or aromatic, in internal quench conditions with LDA (1 eq.) in THF at -78°C followed by addition of *n*-BuLi (2.1 eq.) affords terminal alkynes **25** in high yields and high degree of purity. LDA, reformed from the second equivalent of *n*-BuLi, effects the elimination on the intermediate dichloroalkenes while *n*-BuLi effects the chlorine-lithium exchange reaction to lead to the lithiated alkynes hydrolyzed into alkynes **25** after acidic work-up (Scheme 34).²⁵⁹

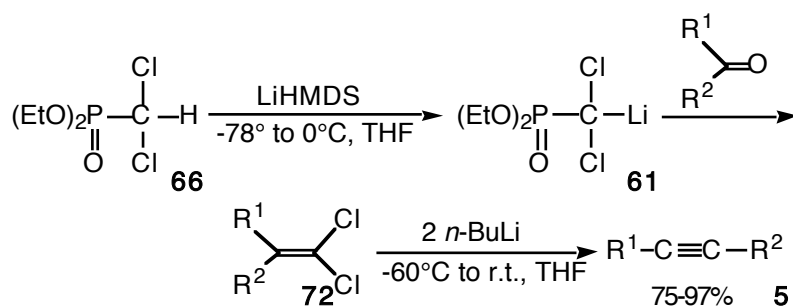


Scheme 34.

General Procedure for the Preparation of 1-Alkyl- or 1-aryl-2-chloroalkynes 64 or 70.²⁵⁹ To a stirred mixture of a previously standardised 1.38 M solution of *n*-BuLi (37 mL, 50 mmol) and THF (40 mL) at -78°C was added a solution of HMDS (8.96 g, 56 mmol, with aromatic aldehydes), or a solution of diisopropylamine (5.66 g, 56 mmol, with aliphatic aldehydes) in THF (20 mL) dropwise over several min. The mixture was stirred at -78°C for 15 min and the a mixture of diethyl 1,1-dichloromethylphosphonate (4.42 g, 20 mmol) and the aldehyde (20 mmol) in THF (10 mL) was added dropwise maintaining the temperature at -78°C . After stirring for 15 min the temperature was allowed to rise to 0°C and the mixture was stirred for 2 h at this temperature. Water (20 mL) was then added dropwise, the phases separated and the aqueous phase washed with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried (MgSO_4), filtered and evaporated on a rotary evaporator. The crude residue was then passed through a silica plug with hexane as eluent to obtain the title compounds as mobile oils.

General Procedure for the Preparation of Arylalkynes 71.²⁵⁹ To a 1.5 M solution of *n*-BuLi (14 mL, 21 mmol) cooled to -20°C was added a solution of diisopropylamine (2.23 g, 22 mmol) in THF (30 mL) dropwise with stirring over 15 min. The resulting clear solution was then cooled to -78°C and a solution of diethyl dichloromethylphosphonate (4.42 g, 20 mmol) and the aldehyde (20 mmol) in THF (30 mL) was added dropwise over a 30 min interval. The resulting red solution was then stirred at -78°C for a further 30 min and then allowed to slowly warm to 0°C . The now brown mixture was then cooled to -78°C and a 1.5 M solution of *n*-BuLi (28 mL, 42 mmol) was added dropwise over 30 min. The solution was once again allowed to warm to 0°C and is then quenched by the dropwise addition of 3 M HCl (30 mL) until the solution was pH 5-6. The phase were separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were then washed with H_2O (10 mL) and dried (MgSO_4) and then filtered and evaporated. The crude alkynes were then distilled to give the title compounds as pure colourless oils.

Simultaneous addition of diethyl dichloromethylphosphonate **66** and a ketone to LiHMDS (1 eq.) in THF at low temperature affords on warming the non-isolated 1,1-dichloro-2,2-diarylethenes **72**. This one on treatment with *n*-BuLi (2 eq.) at -60°C undergo halogen-metal exchange to give a carbenoid^{269,270} which rearranges to produce the required symmetrical or unsymmetrical diarylalkynes **5** (Fritsch-Buttenberg-Wiechell rearrangement). The reaction which has been investigated with a variety of symmetrical and unsymmetrical diaryl ketones on preparative scale produces the desired diarylalkynes **5** in good to excellent overall yields (75-97%) (Scheme 35 and Table 9).²⁷¹



Scheme 35.

Table 9²⁷¹

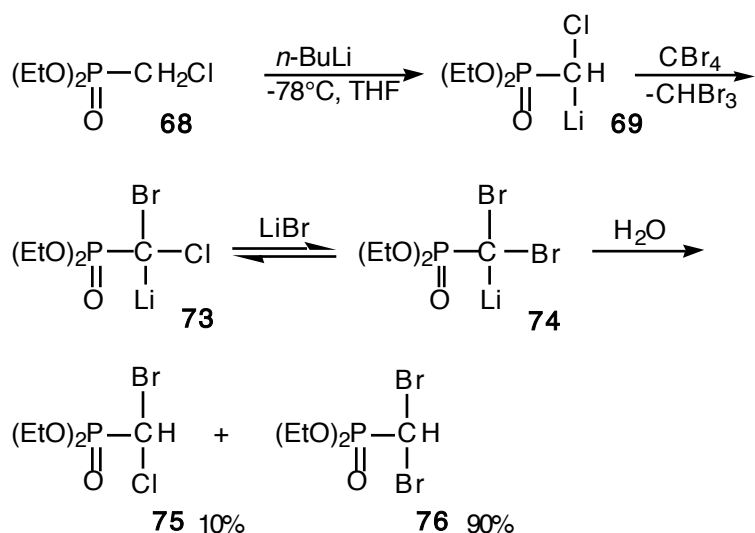
5	R¹	R²	Yield (%)
a	C ₆ H ₅	C ₆ H ₅	95
b	2-Me-C ₆ H ₄	2-Me-C ₆ H ₄	75
c	2-Cl-C ₆ H ₄	C ₆ H ₅	92
d	2-Me-C ₆ H ₄	C ₆ H ₅	89
e	3-Me-C ₆ H ₄	C ₆ H ₅	91
f	4-Me-C ₆ H ₄	C ₆ H ₅	93
g	4-MeO-C ₆ H ₄	C ₆ H ₅	88
h	4-CF ₃ -C ₆ H ₄	4-MeO-C ₆ H ₄	97
i	4-MeO-C ₆ H ₄	4-MeO-C ₆ H ₄	86
j	4-F-C ₆ H ₄	4-F-C ₆ H ₄	89
k	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	86
l	4-Me ₂ N-C ₆ H ₄	4-Me ₂ N-C ₆ H ₄	87
m	2-thienyl	2-thienyl	95

Synthesis of diarylalkynes 5.²⁷¹ 1.6 M *n*-BuLi in hexane (14 mL, 22 mmol) was added to THF (20 mL) and cooled to -78°C. A solution of HMDS (3.90 g, 24 mmol) in THF (20 mL) was then slowly added at this temperature via a dropping funnel. The mixture was then allowed to slowly warm to 0°C before once again cooling to -78°C. A mixture of diethyl dichloromethylphosphonate (4.42 g, 22 mmol) and the diaryl ketone (20 mmol) in THF (50 mL) was then slowly added to the mixture maintaining the temperature at -78°C. Stirring was continued at this temperature for 10 min and then the reaction was allowed to warm to 0°C over a period of 30 min. The mixture was cooled to -60°C and *n*-BuLi (29 mL, 46 mmol) was added. The brownish mixture was then left to warm to 0°C over a period of 30 min. H₂O (20 mL) was then added to the mixture with rapid stirring and the mixture was extracted with Et₂O (3 x 30 mL) and the ethereal extracts washed with H₂O (2 x 20 mL) then with 2 M HCl (3 x 5 mL) before drying (MgSO₄), filtration and evaporation to yield the crude compounds. These can be purified further by filtration through a silica gel plug using hexane as eluent or trituration with anhydrous hexane or column chromatography.

Depending upon the reaction conditions, the diethyl dichloromethylphosphonate **66** appears as an attractive synthetic reagent for the direct and selective transformation of carbonyl compounds to higher acetylenic derivatives by 1,1- or 1,2-elimination.

3.2.3. Diethyl Dibromomethylphosphonate

The diethyl dibromomethylphosphonate **76** was prepared from the diethyl chloromethylphosphonate **68**.²⁷² The lithium carbenoid **69**, generated by adding *n*-BuLi to **68** at -75°C , was treated at the same temperature with tetrabromomethane in the presence of lithium bromide for 40 min to give the 1-bromo-1-chloro-1-lithiomethylphosphonate **73**. At -70°C , due to metal-assisted ionization, **73** behaves as an electrophile and as such it reacts with LiBr to give mainly the 1,1-dibromo-1-lithiomethylphosphonate **74**. Upon quenching with water the procedure leaves a crude mixture of **75** (90%) and **76** (10%) in 80-90% yield (Scheme 36). The olefination reaction for the synthesis of *gem*-dibromoalkenes from **76** has been applied to a variety of substrates including aldehydes and ketones.²⁷² These *gem*-dibromoalkenes **24** and **77** have mainly been used as source of alkylidene carbenes themselves generators of alkynes **5** by 1,2-migration.²⁷³⁻²⁷⁵

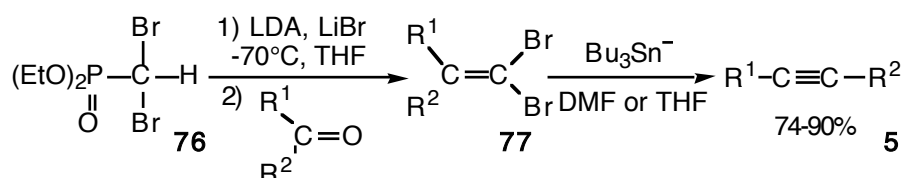


Scheme 36.

Diethyl dibromomethylphosphonate 76.²⁷² Anhydrous LiBr (3.5 g, 0.04 mol) is dissolved under nitrogen in THF (100 mL), *n*-BuLi (0.02 mol + 10%) in Et₂O is added at -10°C , the mixture is cooled to -75°C , and diethyl chloromethylphosphonate **68** (3.7 g, 0.02 mol) in THF (20 mL) is added dropwise with stirring. After 8 min stirring at -75°C , tetrabromomethane (6.6 g, 0.02 mol) in THF (30 mL) is added at -70°C (sometimes the solution acquires a darkish colour). The stirring is continued for 40 min and water (40 mL) is added. The resultant mixture is extracted with CH₂Cl₂ (2 x 50 mL). The organic layers are dried with anhydrous MgSO₄ and the solvent and tribromomethane formed are removed under vacuum to leave a crude mixture of **75** + **76**; yield: 80-90%.

The crude mixture of **75** and **76** is treated in THF at -70°C with LDA in the presence of LiBr. The lithiated reagents thus obtained react with carbonyl compounds at -70°C but not as readily as the corresponding dichloro compound **61**. Reaction with sterically hindered ketones affords the corresponding 1,1-dibromoalkenes **77** in good yields (45 to 70%).²⁷² The 1,1-dibromoalkenes **77** are generators of alkylidene carbenes, which are very reactive intermediates in organic synthesis. If the substituent R² on the alkene of alkylidene carbene is a hydrogen or phenyl group, 1,2-migration occurs to give alkyne **5** (Scheme 37).²⁷⁴ Thus, when DMF solutions of dibromoalkenes **77** (R²= H or Ph) were treated with the stannyl anion

Bu₃Sn⁻, generated from Me₃SiSnBu₃ (3 eq.) in the presence of TASF [(Et₂N)₃S⁺SiMe₃F₂⁻] (3 eq.) at room temperature for 3 h, the desired alkynes **5** were obtained. When CsF was used instead of TASF, the yield of **5** decreased markedly. The reactions were carried out under several different conditions and THF can also be used as solvent. Various dibromoalkenes **77** were used for this reaction, and alkynes **5** were obtained in high yields (Table 10).²⁷⁵



Scheme 37.

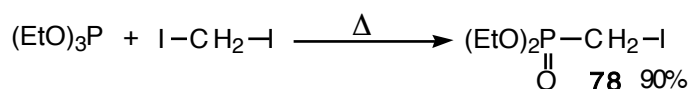
Table 10²⁷⁵

5	R¹	R²	Yield (%)
a	(CH ₃) ₃ CCO ₂ (CH ₂) ₅	C ₆ H ₅	74
b	C ₈ H ₁₇	C ₆ H ₅	90
c	CH ₃ (CH ₂) ₃	4-Me-C ₆ H ₄	76
d	BzO(CH ₂) ₃	H	76

General procedure for the synthesis of alkynes 5:²⁷⁵ To a solution of Me₃SiSnBu₃ (3 equiv.) and 1,1-dibromoalkene **77** (1 equiv.) in THF or DME (ca 0.25 M solution) was added TASF (3 equiv.) at 0°C and the solution was stirred at the same temperature for an appropriate hour. To this solution AcOEt was added and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to give the desired alkyne.

3.2.4. Diethyl Diiodomethylphosphonate

The diethyl diiodomethylphosphonate **79**, reported in 1993, is the most recently described halomethylphosphonate. It is prepared from readily available diethyl iodomethyl-phosphonate **78**, itself being obtained with 90% yield by a Michaelis-Arbusov reaction (Scheme 38) between triethyl phosphite and diiodomethane.²⁷⁶

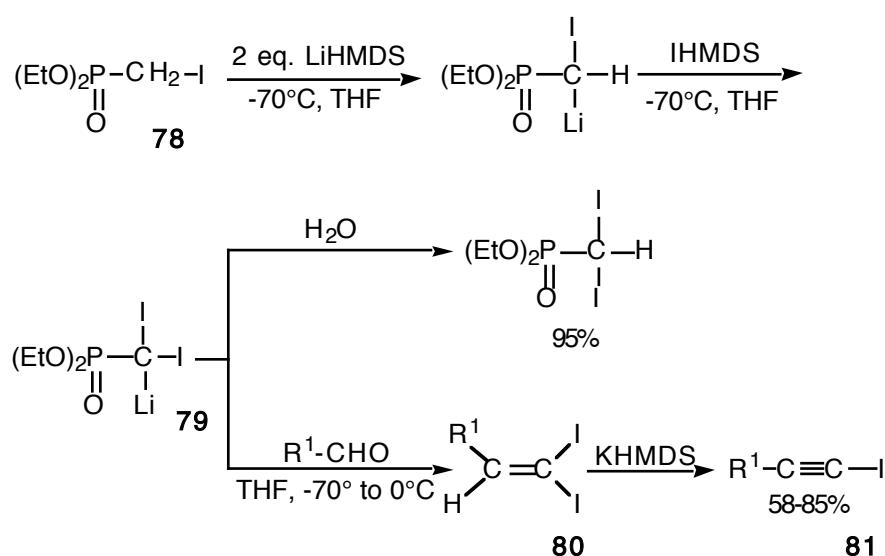


Scheme 38.

Diethyl iodomethylphosphonate 78.²⁷⁶ Triethylphosphite (83 g, 1 mol) was added to CH₂I₂ (200 g, 1.5 mol) at 185°C which was refluxing half-way up a column (10") containing glass helices and a condenser set for distillation. The rate of addition was adjusted so that distillation (70-110°C) occurred steadily and the temperature increased, finally to 220°C. Heating was continued for a further 10 min. The products were ethyl iodide (74 g, 95%), CH₂I₂ (68 g, 34%), and diethyl iodomethylphosphonate **78** (120 g, 90%).

Addition of diethyl iodomethylphosphonate **78** to a mixture of LiHMDS and IHMDS, prepared *in situ* from LiHMDS and iodine in THF at -70°C, gave access to diethyl 1,1-diiodo-

1-lithiomethylphosphonate **79** which was hydrolyzed to give diethyl diiodomethylphosphonate in 95% yield or which could be directly transformed into diiodoolefines **80** by reaction with carbonyl compounds. The *in situ* formation of diiodoolefines **80** gives successful results starting from aldehydes as well as from aliphatic, aromatic and functionalized ketones. It is also worth noting that starting from aldehydes and using this method in the presence of an excess of base (LiHMDS or KHMDS), leads to *in situ* dehydrohalogenation of diiodoalkenes **80**, thus yielding iodoacetylenes **81** in good yields (58-85%) (Scheme 39).²⁷⁷



Scheme 39.

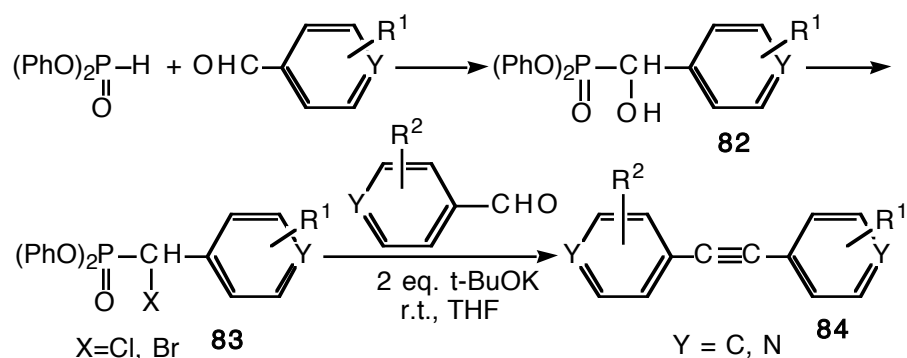
1,1-Diiodoalkenes **80:**²⁷⁷ *n*-BuLi (0.90 mL of a 2.5 M solution in hexane, 2.23 mmol), freshly titrated, was added at 0°C to a solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.36 g, 2.23 mmol) in THF (6 ml). The solution was stirred 30 min at 0°C, then cooled to -70°C. A solution of I₂ (0.26 g, 1.02 mmol) in THF (2 mL) was added, then after 5 min, a solution of diethyl iodomethylphosphonate **78** (0.28 g, 1.02 mmol) in THF (2 mL) was added. After 90 min at -70°C, the carbonyl compound (1.02 mmol) in THF (1 mL) was added. The mixture was stirred 5 min at -70°C, then warmed 1 h at 0°C and 2 h at r.t. After addition of water (2 mL), the aqueous solution was extracted with Et₂O (5 x 35 mL). The combined organic layers were dried (MgSO₄) and evaporated. The diiodoalkenes were chromatographed over silica gel [light petroleum (b.p. 50-55°C)/Et₂O, 3/1].

3.3. The Dialkyl α -Halobenzylphosphonates

Among the classical phosphorus reagents that have been frequently reported as precursors of internal acetylenes are metallated halobenzylphosphonates. For example, the α -chlorostilbenes formed upon reaction of aldehydes with α -metallated chlorobenzylphosphonate by a Horner-Wadsworth-Emmons reaction are readily converted under very mild conditions into internal alkynes **84** by 1,2-elimination reaction (Scheme 40).^{278,279} This approach permits sensitive functional groups to be part of the acetylenes. Since some difficulties may be encountered in the two first steps of this sequence, formation of α -hydroxyphosphonates **82** and α -halophosphonates **83**, they have been investigated in depth.²⁸⁰

Numerous significant synthetic efforts have been devoted to the investigation of methods for the generation of α -hydroxyphosphonates **82** from dialkylphosphites and aldehydes (aryl, substituted aryl and heteroaryl) by the Pudovik reaction. The more common procedure involved the addition of a small amount of alcoholic alkoxide ion to the reaction mixture. An alternative to the use of anionic bases is the use of neutral amines, the most commonly employed amine being triethylamine. It is apparent that amine bases will only catalyse adduct formation if the resulting adduct can be induced to precipitate from solution by suitable choice of solvent. For that reason, another innovation which has been developed in recent years is the use of a solid phase material as a basic catalyst. The advantage of such an approach is the simplicity of product isolation.²⁸⁰

The nucleophilic halogenation of **82** has been realized in moderate to good yield with a variety of halogenating reagents : POCl₃,^{278,281,282} PPh₃ / CCl₄,²⁸³ SOCl₂²⁸⁴ for chlorination, and PPh₃ / CBr₄,²⁸⁵ PPh₃Br₂ / Py,²⁸⁵ CH₂=CHCH₂Br / CDI,²⁸⁶ SOBr₂²⁸⁴ for bromination, to produce the corresponding α -halophosphonates **83** (X=Cl, Br).



Scheme 40.

Owing to the facile olefination of the carbonyl group of aromatic or heteroaromatic aldehydes under the usual conditions of the Horner-Wadsworth-Emmons reaction, NaH or *t*-BuOK in THF (or DMSO) at room temperature are currently used as bases for the formation of α -metallated chlorobenzylphosphonates. By using an excess of bases (2 eq.) the resulting α -chlorostibenes are converted to internal alkynes **84**. According to the sensitivity of the alkynes, the yields are good to excellent (Table 11). A number of compounds containing an additional triple bond and bearing electron-withdrawing and -donating groups in 4, 4' positions of the aromatic ring have recently been prepared with success by employing this method.^{278,279,281,282,287}

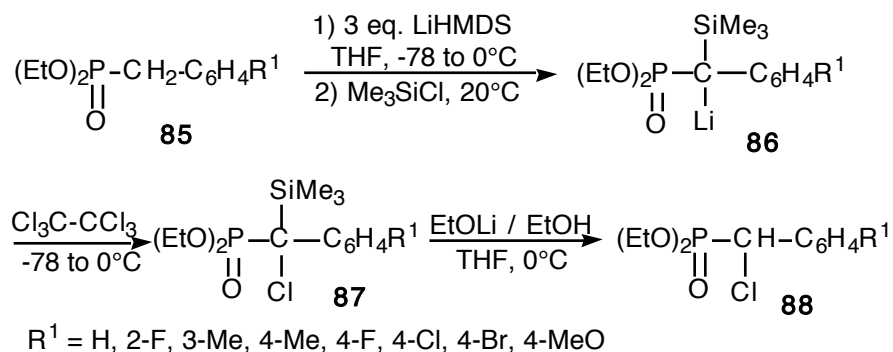
Table 11

84			Yield (%)	Ref.
a	4-O ₂ N-C ₆ H ₄	4-O ₂ N-C ₆ H ₄	67	278

b	4-O ₂ N-C ₆ H ₄	4-NC-C ₆ H ₄	80	278
c	4-O ₂ N-C ₆ H ₄	4-Pyridyl	22	278
d	4-O ₂ N-C ₆ H ₄	(ClCH ₂ CH ₂) ₂ N-C ₆ H ₄	60	278
e	4-O ₂ N-C ₆ H ₄	4-MeO-C ₆ H ₄	58	288
f	4-O ₂ N-C ₆ H ₄	4-Me ₂ N-C ₆ H ₄	40	281
g	4-Pyridyl	4-MeO-C ₆ H ₄	81	282
h	4-Pyridyl	4-Cl-C ₆ H ₄	79	282
i	4-Pyridyl	4-Br-C ₆ H ₄	76	282
k	4-Pyridyl	4-I-C ₆ H ₄	22	282
l	4-Pyridyl	4-Pyridyl	60	282
m	4-Cl-C ₆ H ₄	4-Me ₂ N-C ₆ H ₄	32	288
n	4-Br-C ₆ H ₄	4-MeO-C ₆ H ₄	26	288
o	4-NC-C ₆ H ₄	4-C ₅ H ₁₁ O-C ₆ H ₄	34	288

4-Iodophenyl-4-pyridylacetylene 84f.²⁸¹ Diphenyl 1-Chloro-1-(4-pyridyl)methanephosphonate (1.4 g, 3.9 mmol) and 4-iodobenzaldehyde (1 g, 4.3 mmol) were treated with *t*-BuOK (0.92 g, 8.2 mmol) in THF (20 mL) for 3 h at room temperature. After evaporation, water (20 mL) was added to the residue, which was extracted with CH₂Cl₂ and dried over MgSO₄. The organic layer was removed and recrystallized from EtOH-CHCl₃ (1:1) to give the product in 22% yield, m.p. 196°C.

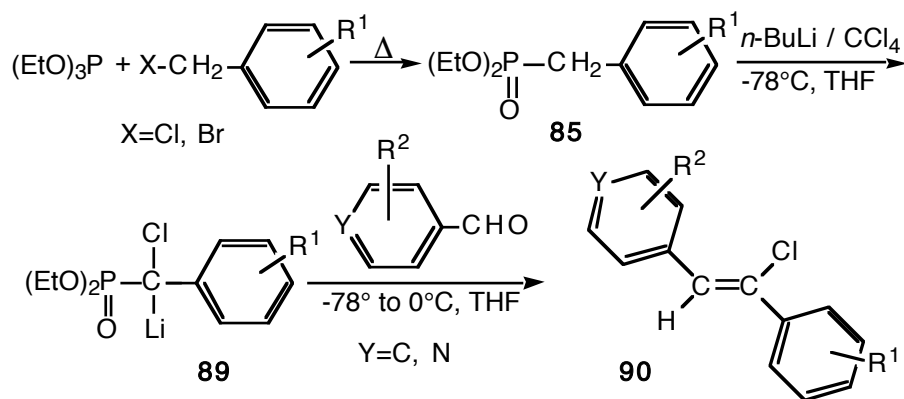
However, full utilization of this mild method for the synthesis of substituted diphenyl acetylenes is often handicapped by the availability of the two intermediates α -hydroxy- **82** and α -chlorophosphonates **83** (Scheme 40) which are obtained in modest yields and often contaminated with by-products. These disadvantages are overcome when the key intermediates, the diethyl α -chlorobenzylphosphonates **88**, are prepared from the readily available diethyl benzylphosphonates **85** via an electrophilic chlorination of the diethyl 1-lithio-1-(trimethylsilyl)benzylphosphonates **86** with hexachloroethane.^{289,290} The TMSCl protecting group, which ensures a clean and complete chlorination in benzylic position, is easily removed from **87** to liberate the parent α -chlorobenzylphosphonates **88** in analytically pure form and high yields (90-95%).^{289,290} This recently reported one-pot procedure offers a shorter, more efficient route to α -chlorobenzylphosphonates **88** (Scheme 41) than the previously described.



Scheme 41.

General procedure for the synthesis of diethyl α -chlorobenzylphosphonates **88.**²⁹⁰ A freshly titrated solution of *n*-BuLi (18.75 mL of a 1.6 M solution in hexane; 30 mmol) was added to THF (20 mL) cooled to -78°C. A mixture of HMDS (5.15 g, 32 mmol) and diethyl benzylphosphonate **85** (10 mmol) in THF (20 mL) was slowly added at this temperature *via* a dropping funnel. Few minutes later, the reaction mixture was allowed to warm slowly to 20°C and TMSCl (1.3 g, 12 mmol) in THF (10 mL) was rapidly added. After 15 min, the reaction mixture was cooled to -78°C and the hexachloroethane (11 mmol) in THF (20 mL) was slowly added. After 15 min, the reaction mixture was allowed to warm-up to 0°C and then treated with an excess of EtOLi in EtOH. After 15 min, the reaction mixture was poured with stirring into a mixture of 3M HCl (20 mL), CH₂Cl₂ (20mL) and ice (10 g) and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts are dried over MgSO₄ and evaporated under reduce pressure to afford the desired product as a pale-yellow oil. The isolated products were pure enough to make further purification useless. The chloro derivatives can be distilled under reduce pressure with a bulb-to-bulb apparatus or chromatographed on a silica column (70-230 mesh) and eluted with hexane/AcOEt (70/30).

Another useful technique for the olefination of the carbonyl group of aldehydes into chlorostilbene derivatives is based upon the electrophilic chlorination of metallated diethyl benzylphosphonates with CCl₄. For example, treatment of diethyl benzylphosphonates **85** with *n*-BuLi in THF at low temperature followed by addition of CCl₄ gave the diethyl chlorobenzylphosphonate **88** which is slowly deprotonated by the trichloromethyl lithium produced in the reaction medium to generate the diethyl 1-chloro-1-lithiobenzylphosphonates **86**. When **89** were allowed to react at low temperature with aldehydes, chlorostilbenes **90** were obtained in 69-87% yields (Scheme 42).²⁹¹



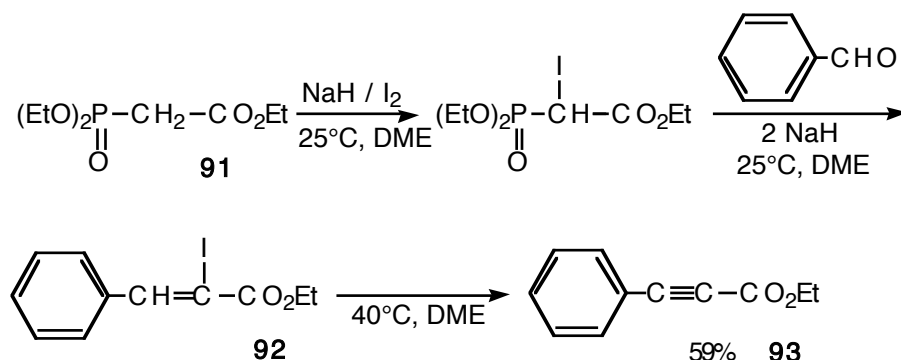
Scheme 42.

A more recent procedure for the synthesis of substituted diphenyl acetylenes involves the participation of α -bromobenzylphosphonates. A one-pot procedure for the high yielding synthesis of pure diethyl α -bromobenzylphosphonates has also been described. It involves the sequential electrophilic bromination of the diethyl 1-lithio-1-(trimethylsilyl)benzylphosphonates **86** with dibromotetrachloro- or dibromotetrafluoroethane to form the diethyl α -bromo(trimethylsilyl)benzylphosphonate, from which the parent diethyl α -bromobenzylphosphonates can be liberated in analytically pure form and high yields (85-95%) (Scheme 41) by removal of the TMS group with an ethanolic solution of EtOLi.²⁹⁰

Similarly, acetylenic sulfones can be prepared by reaction of diethyl chloro-(phenylsulfonyl)methylphosphonate with aromatic aldehydes in the presence of *t*-BuOK in excess.²⁹²

3.4. Triethyl α -Iodophosphonoacetate and Dialkyl 1-Chloro-2-Oxoalkyl-phosphonates

The same approach for effecting a geminal halogenation-functionalization at a carbonyl group *via* an olefination reaction associated with an 1,2-elimination has also been reported from phosphonoacetate and β -ketophosphonate for the synthesis of terminal functional acetylenes. For example, a one-pot procedure for the transformation of the carbonyl group of aldehydes into propiolate has been described (Scheme 43).²⁹³⁻²⁹⁶ The reaction involves α -iodination in DME at room temperature of the sodium phosphonate anion of triethyl phosphonoacetate **91** followed by olefination of benzaldehyde at room temperature to give the 1-iodo-1-(carboxyethyl)-2-phenylethylene **92** which was converted in the presence of NaH in excess at 40°C into ethyl phenylpropiolate **93** with 59% yield.²⁹³ Thus, a one-pot synthesis of substituted acetylenes is possible using halophosphonates directly or halophosphonates prepared *in situ* without the isolation of intermediate vinyl halides.

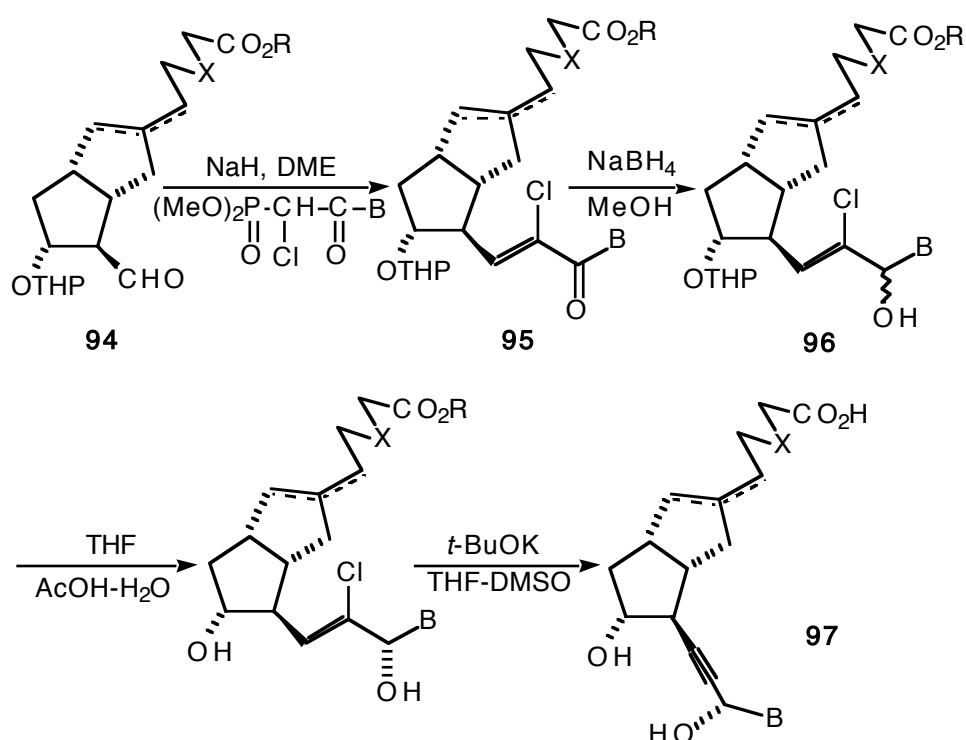


Scheme 43.

Ethyl β -phenylpropiolate **93.**²⁹³ Triethyl phosphonoacetate **91** (11.2 g, 0.05 mol) was added at 25°C dropwise to a slurry of 50% NaH (2.4 g, 0.05 mol) in 100 mL of dry DME. The solution was stirred for 1 h until hydrogen gas evolution ceased. To the homogeneous solution was added dropwise iodine (12.7 g, 0.05 mol) dissolved in a minimum of solvent. After the addition, the solution was stirred at r.t. for 1 h and cooled to 10°C; 50% NaH (4.8 g, 0.10 mol) was added to the chilled solution all at once. The mixture was allowed to come to r.t. gradually during which time rapid gas evolution took place. Benzaldehyde (5.3 g, 0.05 mol) was added dropwise keeping the temperature at 25°C. After the addition the solution was heated slowly to 40°C at which temperature rapid gas evolution took place. After gas evolution had ceased, the solution was cooled and a large excess of water added. The aqueous solution was extracted with Et₂O (2 x 100 mL), and the ether extract dried over MgSO₄ and evaporated. The residue now was distilled giving 5.1 g. (59%) of distillate, b.p. 78-80°C (0.1 mm).

Due to the inherent instability of natural prostacyclin toward hydrolytic conditions, many efforts have been made to develop chemically stable prostacyclin analogues by introducing several structural modifications and especially a triple bond in the lower side chain. The grafting of ω -chains was achieved by Horner-Wadsworth-Emmons reaction with the appropriate halogenated β -ketophosphonates.²⁹⁷⁻²⁹⁹ Thus, the chlorinated or brominated β -

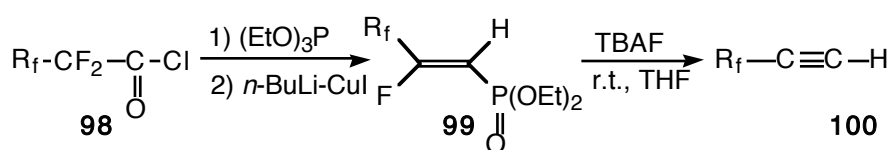
ketophosphonates were prepared in about 50% yield by reaction of β -ketophosphonates anion (NaH, DME, 0°C) with *N*-chloro-²⁹⁹ or *N*-bromosuccinimide.^{297,298} Then the aldehydes **94** were condensed with sodium salt of β -ketophosphonate to give a mixture of *E* and *Z*- α -chloro- or bromoenones **95**, whose reduction with NaBH₄ in MeOH at -40°C produced a mixture of the allylic alcohols **96**. Dehydrochlorination with *t*-BuOK in THF-DMSO at room temperature or dehydrobromination with 50% aqueous NaOH in toluene, catalytic NBU₄/HSO₄ at room temperature, converted the 1,3,4-double bond into the desired triple bond **97** (Scheme 44).²⁹⁹



Scheme 44.

3.5. The Diethyl 2-Perfluoroalkenylphosphonate

Extremely restricted methods are known for synthesizing perfluoroalkylsubstituted terminal acetylenes **100**. An efficient method has been reported by dephosphorylation of **99** at the sp²-hybridized carbon atom catalyzed by fluoride ion, which provides a method for the synthesis of perfluoroalkylacetylenes **100** from perfluoroalkanoyl chlorides **98** (Scheme 45).³⁰⁰⁻³⁰²



Scheme 45.

The perfluoroalkanoyl chlorides **98** were converted to *Z*-1*H-F*-1-alkene-1-phosphonates **99** by reaction with triethylphosphite followed by the reduction with *n*-BuLi/CuI reagent. When phosphonates **99** thus prepared were treated with catalytic amount of TBAF at 0°C in THF, the corresponding perfluoroacetylenes **100** were produced in good yields (74-89%) (Table 12), together with a quantitative amount of (toxic) diethyl fluorophosphate.

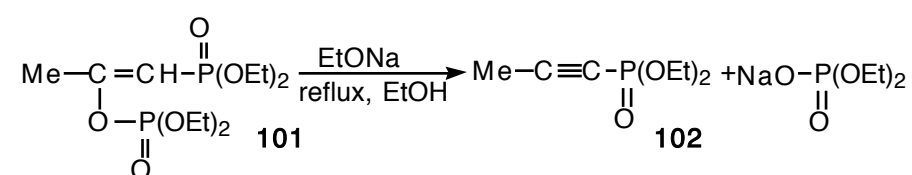
Table 12³⁰⁰

100	R_f	Yield (%)
a	CF ₃ CF ₂	89
b	CF ₃ (CF ₂) ₅	85
c	CF ₃ (CF ₂) ₇	74
d	CHF ₂ (CF ₂) ₈	75

General procedure.³⁰⁰ To a solution of (*Z*)-1*H-F*-1-alkene-1-phosphonate **95** (3 mmol) in anhydrous THF (8 mL) was gradually added a solution of TBAF (1 M in THF, 0.3 mL) under a nitrogen atmosphere at 0°C. After being stirred at room temperature for 2 h, the reaction mixture was poured onto ice-water followed by extraction (Et₂O), drying (Na₂SO₄), and evaporation. Silica gel chromatography or distillation of the crude product gave pure fluoroalkylacetylene **96**. In the case of R_f=C₂F₅, fluoroethylacetylene was collected at -70°C from the reaction mixture (TG used as a solvent) under reduced pressure.

4. Enol Phosphates Precursors of Acetylenic Compounds

The first transformation of an enol phosphate into an acetylene was recorded in 1957. It was reported the formation of diethyl 1-propynylphosphonate **102** in 69% yield by the action of sodium ethoxide in refluxing ethanol on 2-(diethoxyphosphoryl)-1-methylvinylphosphate **101** (Scheme 46).³⁰³⁻³⁰⁵ This transformation into terminal acetylene was achieved with conservation of the carbon chain. However, owing to the constraints introduced by the structural requirement, and the difficulties frequently encountered in the choice of the base and elimination conditions, for a long period of time this method has not been developed.³⁰⁶



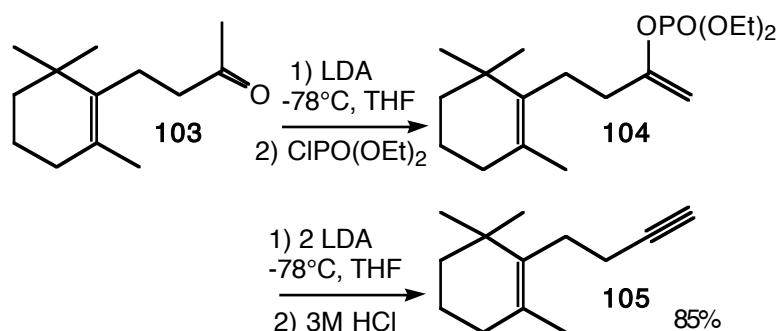
Scheme 46.

Starting vinyl phosphates may be obtained from enolizable ketones by reaction of the sodium enolate with a chlorophosphate; the reaction affords the *trans* isomers exclusively. With ketones that enolize little or not at all the interaction of the α -chloroketone with triethylphosphite by the Perkow reaction yields predominantly the *cis*-enol phosphate. The Perkow reaction may also be used to obtain *cis*-enol phosphate from enolizable ketones. Finally, methyl ketones are transformed, through their chloromethyl derivatives, into vinyl phosphates containing a terminal methylene group. In all cases the yields of vinyl phosphates

are good to excellent. A number of enol phosphates were prepared and their base-catalyzed elimination was examined under a variety of conditions.³⁰⁶

Many efforts have been done to discover a base which might cause elimination of the phosphate from the enol without also bringing about isomerization or hydrolysis. Thus, taking the *trans*-enol phosphate of ethyl benzoylacetate as model, it has been shown that the experimental conditions are crucial, and that successful elimination of phosphate with aqueous base at room temperature requires the presence of activating groups on both sides of the carbon system. For example, aqueous sodium hydroxide in aqueous dioxane or aqueous ethanol at room temperature gave only acetophenone and sodamide in liquid ammonia at -70°C gave phenylpropionamide in 72% yield while at -33°C phenylacetylene was the sole product.³⁰⁶

Fortunately, in 1980 several innovations have significantly extended the synthetic utility of the formation of alkynes by elimination of a phosphate anion. In search of a practical and efficient method to convert dihydro- β -ionone **103** into the required acetylenic intermediate **105**, several highly basic and sterically hindered amides (LDA, LTMP) were tested in order to form cleanly the "kinetic" enol phosphate **104** which on basic treatment eliminate regioselectively the phosphate anion (Scheme 47).^{307,308}



Scheme 47.

It was found that sequential but one-pot treatment of dihydro- β -ionone **103** with LDA (1.05 eq.) at low temperature in THF, then with diethyl chlorophosphate (1.1 eq.) between -78 and 25°C and again LDA (2.25 eq.) at low temperature, produces the acetylde intermediate which upon acidification and usual workup affords the desired alkyne **105** in 85% isolated yield. β -Ionone itself was cleanly converted into the corresponding terminal acetylene in 72-85% yield.³⁰⁷ This procedure was quite satisfactory in a few other cases where no isomer formation was possible. However, when it was applied to 2-octanone and 6-methyl-5-hepten-2-one, both of which gave the desired acetylenes in only 20-25% yields. Since both ketones are cleanly and regioselectively converted into the corresponding enol phosphates, the difficulty must lie in the β -elimination step.³⁰⁷ Later, the method has been applied with success in the conversion of geranylacetone into geranylacetylene in 67% yield,

using LTMP as base (3.15 eq.), in the synthesis of silasqualene,³⁰⁹ and in the multi-step synthesis of manoalide³¹⁰ and aphidicolin^{311,312} in the terpene field. On the basis of the enol phosphate route, several fluorophenylproparginols having hebicidal activity have been prepared from ketones.³¹³ A thermal variant has also been reported, but the conversion was not complete. Thus, heating the diethyl 3-(fluoren-9-ylidene)-1,3-diphenylpropen-1-yl phosphate at 120°C for 100 h gave the 3-(fluoren-9-ylidene)-1,3-diphenylpropyne in modest yield (10.1%).³¹⁴

1-(3-Butynyl)-2,6,6-trimethyl-1-cyclohexene.³⁰⁷ The following is representative of the LDA procedure for the conversion of methyl ketones into terminal acetylenes. To a solution of LDA prepared at 0°C from diisopropylamine (10.6 g, 105 mmol) and *n*-BuLi in hexane (2.3 M, 45.6 mL, 105 mmol) in 200 mL of dry THF is added dropwise dihydro- β -ionone (19.4 g, 100 mmol) in 20 mL of THF at -78°C. After the solution was stirred for 1 h, diethyl chlorophosphate (19.0 g, 15.9 mL, 110 mmol) was added at this temperature. After the reaction mixture was gradually warmed to room temperature it was added dropwise to a solution of LDA in THF (225 mmol) prepared at -78°C as described above. The resultant mixture was warmed to room temperature over 3 h and quenched with water. The organic compounds were extracted with pentane, washed with 1 N HCl, water, and aqueous NaHCO₃, dried over MgSO₄, and distilled to give 15.0 g (85%) of the title compound.

5. Conclusion

Undoubtedly, the preparation of terminal or internal alkynes from carbonyl compounds using phosphoranes or phosphonates by a two-step procedure, including a Wittig or a Horner-Wadsworth-Emmons reaction and an elimination reaction, is a valuable and fairly general synthetic method. They may each be employed as reagents to produce in large scale common alkynes with good purity or to introduce the triple bond in complex polyfunctional molecules. Therefore, the procedure involving the formation of the carbon-carbon double bond prior to unmasking the alkynes, the more reactive phosphonate reagents appear to have the greater synthetic utility. Not only a number of phosphonate reagents are now available, but the more recent innovations have been accomplished in this field. They may be used for the preparation in mild conditions either of terminal or internal alkynes, and in addition the elimination of diethylphosphate salt in water simplifies considerably the purification of the alkynes. Finally the formation of alkynes by the enol phosphates route, instead of ponctual utility, should merit an exhaustive study. Henceforth, it appears that the phosphorus reagents are versatile precursors and there will be of increasing importance in preparative chemistry of alkynes.

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