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Conversion of carbonyl compounds to alkynes: general overview and recent developments

Damien Habrant, Vesa Rauhala and Ari M. P. Koskinen*

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The preparation of alkynes from carbonyl compounds *via* a one-carbon homologation has become a very useful pathway for the synthesis of acetylenic compounds, both internal and terminal. This *tutorial review* provides an overview of the different methods available for this transformation, including their scope and limitations, recent developments and applications in total syntheses.

1. Introduction

Carbon-carbon triple bonds are long-known and well studied functional groups. In his 2009 total synthesis of Soraphen A, Trost takes advantage of the versatility of the alkyne functionality to reach the natural product, the paper being entitled "a flexible alkyne strategy".[1] Indeed, as highlighted by the authors, alkynes are very interesting because they can be used both as nucleophiles (after deprotonation in the case of a terminal alkyne) or as electrophiles (after activation with a suitable transition metal).[2] Recent developments in organic chemistry, such as the Sonogashira cross-coupling reaction,[3] the Grubbs olefin metathesis[4] or the "click-chemistry",[5] to name a few, have enhanced the synthetic utility of alkynes. Terminal alkynes are the most interesting ones since they can be used as key precursors to convey molecular complexity. One widely used way of accessing alkynes is the one-carbon homologation of aldehydes or ketones. Following Corey's pioneering work in this area,[6] several methods have appeared in the literature. Phosphorous-based reagents are commonly used and their application in alkyne synthesis has been reviewed by Savignac *et al.* in 2000 with great emphasis placed on the preparation of the phosphorous reagent.[7] This tutorial review will describe the general methods used for the transformation of carbonyl compounds to alkynes, focusing mainly on recent developments and substrate scope and limitations of each method. We hope that this review will provide helpful information to the synthetic chemist looking for the adequate method to perform this transformation.

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2. The Corey–Fuchs procedure

2.1 Original procedure

In 1972, Corey and Fuchs presented a simple and expeditious method for the transformation of aldehydes to acetylenes.[6] This one-carbon homologation proceeds in 2 steps (Scheme 1). The first step is the conversion of aldehyde **1** to the homologated dibromoolefin **2**, reaction known as the Ramirez olefination.[8] The yields observed for the production of **2** generally range between 80 and 90%. Two alternative procedures were described:

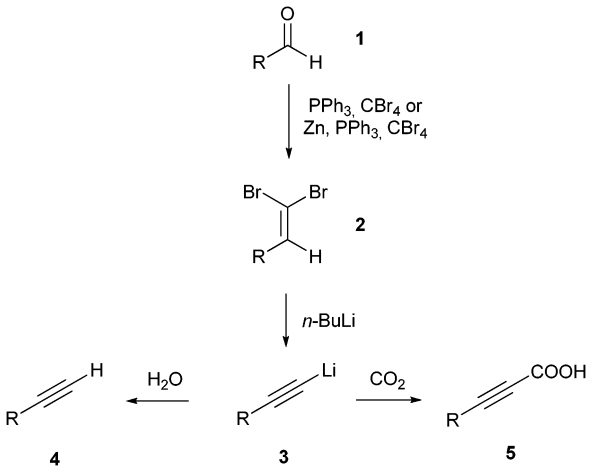
(a) addition of the aldehyde (100 mol%) to a mixture of PPh_3 (400 mol%) and CBr_4 (200 mol%) in CH_2Cl_2 at 0 °C for 5 min,[8]

Damien Habrant

Damien Habrant studied chemistry at the universities of Nantes and Strasbourg. He carried out his PhD under the supervision of the late Dr Charles Mioskowski in Strasbourg, working on the development of a new class of antioxidants and the use of arsonium derivatives for the synthesis of 1,3-dienes. Since 2008, he joined the group of Prof Ari M. P. Koskinen at the Helsinki University of Technology, Finland, working on the total synthesis of Calyculin C.

Vesa Rauhala

Vesa Rauhala received his MSc degree in chemistry from University of Oulu in 1998 under the guidance of Professor Ari M. P. Koskinen. From 2000 to 2004 he did PhD studies in the Laboratory of Organic Chemistry, Helsinki University of Technology in the group of Professor Ari M. P. Koskinen. In 2007, he obtained his PhD degree in chemistry from the studies of spirocycle fragment of Calyculins.



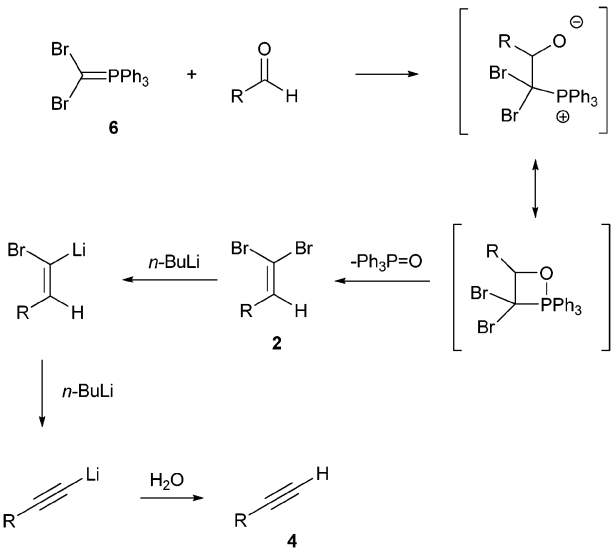
Scheme 1 The Corey–Fuchs procedure.

(b) addition of the aldehyde (100 mol%) to the reagent prepared from the reaction between Zn dust (200 mol%), PPh_3 (200 mol%) and CBr_4 (200 mol%) in CH_2Cl_2 at rt for 24–30 h.

Procedure (b) is generally preferred because it uses less phosphine, the isolation of the dibromoolefin is easier and the yields tend to be somewhat higher than using procedure (a).

The second step involves the treatment of **2** with *n*-BuLi (200 mol%) at −78 °C. A lithium-halogen exchange first takes place with the first equivalent of *n*-BuLi, after which the second equivalent is used for the elimination process. Lithium acetylide **3** is then formed, whose hydrolysis furnishes the terminal acetylene **4**. Compound **3** can also be treated with a variety of electrophiles, such as alkyl halides, aldehydes, epoxides or CO_2 to afford for instance the corresponding propargylic acid **5**, as described in the original procedure.

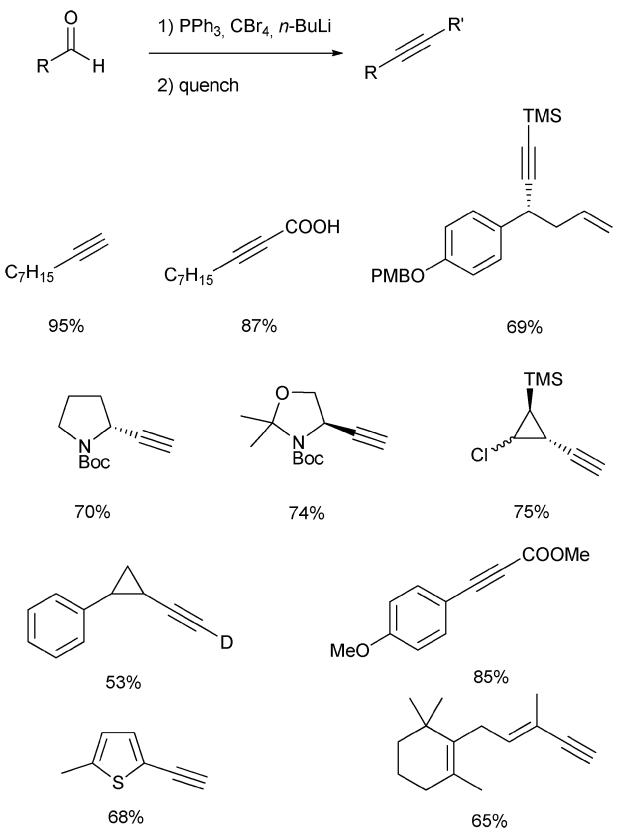
From a mechanistic point of view, the reaction of the phosphorous ylide **6** (formed by the reaction of PPh_3 and CBr_4) with the aldehyde can be regarded as an analog of the Wittig olefin synthesis since mechanisms involved are quite similar (formation of a betaine followed by elimination and formation of triphenylphosphine oxide, Scheme 2).



Scheme 2 Mechanism of the Corey–Fuchs alkynylation.

2.2 Scope and limitations

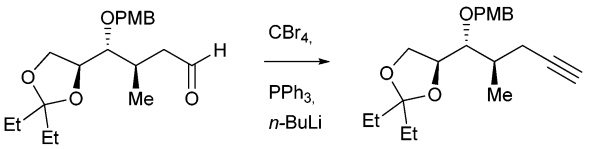
This methodology has been used for the preparation of variously substituted alkynes; some examples are depicted in Scheme 3.[7] A wide range of aldehydes are homologated, including linear, cyclic, aromatic, heteroaromatic or α,β-unsaturated ones.



Scheme 3 Examples of alkynes prepared by the Corey–Fuchs method.

Ari M. P. Koskinen

Professor Ari M.P.Koskinen studied at the Helsinki University of Technology, Finland, receiving a MSc. (Chem. Eng.) in 1979 and a Doctor of Technology in 1983. After postdoctoral studies at the University of California, Berkeley he worked as a Project Leader in New Drug Development at Orion Corporation–Fermion, Finland (1985–1987). Returning to academia, he joined the University of Surrey, England, as a lecturer in 1989. He was then appointed as Professor of Chemistry at the University of Oulu, Finland in 1992, and transferred to his current position at the Helsinki University of Technology in August, 1999 as Professor of Organic Chemistry.



Scheme 4 Use of the Corey–Fuchs procedure by Roush.

Different electrophiles can be used, giving access to propargylic acid, TMS, deuterium or ester derivatives.

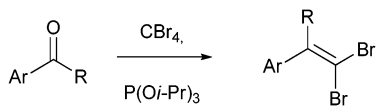
This pioneering method is still widely used nowadays. For example, it was applied for the preparation of a highly functionalised alkyne in 98% yield, in the Roush total synthesis of Amphidinolide E (Scheme 4).[9]

2.3 Recent improvements

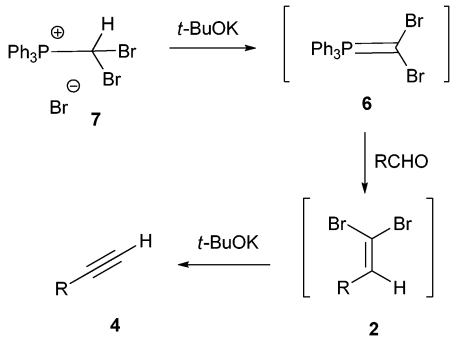
Many methods derived from the original Corey–Fuchs protocol have appeared in the literature since 1972; these methods are nicely presented in Savignac's review,[7] and therefore, only the latest improvements will be presented here.

2.3.1 Modification of the Ramirez olefination. In 2008, Lautens presented a Horner-Wadworth-Emmons (HWE) modification of the Ramirez dibromoolefination (Scheme 5).[10] Replacing PPh_3 with $P(Oi\text{-}Pr)_3$ gives similar results with aldehydes, but shows better reactivities towards ketones and greatly facilitates the purification step.

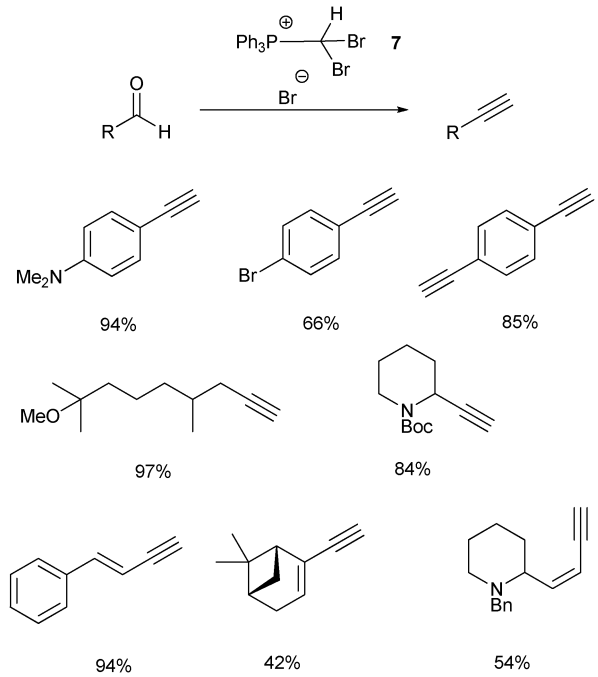
2.3.2 *In situ* formation of dibromoolefin 2. In 1999, a modified procedure using dibromomethyl-triphenylphosphonium bromide **7** was described, which allows a *one-pot* conversion of aldehydes to alkynes (Scheme 6).[11] Ylide **6** is generated by reaction of *t*-BuOK (190 mol%) on **7** (200 mol%). After a few minutes, the aldehyde (100 mol%) is added to the yellow-brown mixture. After less than 5 min, the dibromoolefin **2** is quantitatively formed (TLC) and a second addition of *t*-BuOK (500 mol%) occurs either at −78 °C (for most of the aromatic aldehydes) or at rt (for the aliphatic ones). Hydrolysis of the lithium acetylide is preferentially done using brine for ease of work-up.



Scheme 5 Lautens modification of Ramirez reaction.



Scheme 6 Modification of the Corey–Fuchs alkyne synthesis.

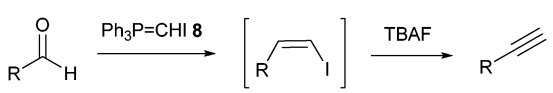


Scheme 7 Preparation of alkynes using **7**.

Compared to the original procedure, this *one-pot* method avoids the intermediate isolation of the dibromoolefin **2** and the whole reaction can be effected at rt in some cases. Substrate scope for this alternative method is shown in Scheme 7. This procedure appears to be quite efficient since aromatic, aliphatic and α,β-unsaturated aldehydes are converted to the homologated terminal alkynes in moderate to excellent yields.

2.3.3 Synthesis of alkynes *via* (*Z*)-iodoalkenes. Thadani presented in 2008 a derived method where terminal alkynes are obtained from aldehydes *via* dehydrohalogenation of (*Z*)-1-iodo-1-alkenes with TBAF.[12] Reaction of aldehydes (100 mol%) with phosphorane **8** (110 mol%) at −78 °C provides the corresponding (*Z*)-1-iodo-1-alkenes (the (*Z*) selectivity is essential for the dehydrohalogenation). TBAF (250 mol%) is then added and the mixture is heated at 60 °C for 6 h for aromatic substrates or at 80 °C for 12 h for aliphatic ones. Aldehydes are obtained in good yields and this method using the mild base TBAF proves to be efficient with a wide range of substrates (Table 1).

Table 1 Synthesis of alkynes by Thadani



R	Yield (%)	*R*	Yield (%)
2-MeO–C_6H_4	81	1-Naphthyl	80
2-NO_2–C_6H_4	80	1-Pyridyl	74
4-Ac–C_6H_4	83	3-Thienyl	75
3,5-$(CF_3)_2$–C_6H_3	77	$PhCH_2CH_2$	73
4-CN–C_6H_4	80	$CH_3(CH_2)_3CH(OTBS)$	78

3. The Colvin rearrangement

3.1 Original procedure

As part of general studies of the synthetic utility of organosilicon and organophosphorus compounds, Colvin reported that the reaction of trimethylsilyldiazomethane **9** or dimethyldiazomethylphosphonate **10** (DAMP) with carbonyl compounds leads to the homologous acetylenes (Scheme 8).[13,14] The case of DAMP will be discussed in the next paragraph.

The mechanism involves an initial attack of $TMSC(Li)N_2$ at the carbonyl function to provide α-diazoalkoxide **11** which undergoes elimination of TMSOLi to give diazoalkene **12**. Wolff rearrangement of **12** with expulsion of N_2 affords the homologous alkyne (Scheme 9).

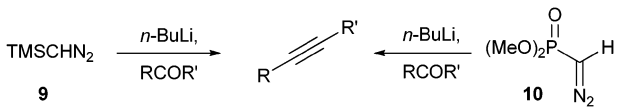
Until 1994, only three successful examples of this procedure had been reported. In the original paper, Colvin described the preparation of diphenylacetylene in 80% yield and diphenylpropynone in 58%, starting from benzophenone and benzil, respectively. Later, Ohira published an isolated example of the conversion of decanal to 1-undecyne in 61% yield using slightly modified conditions.[15]

3.2 Broadening the scope of the reaction

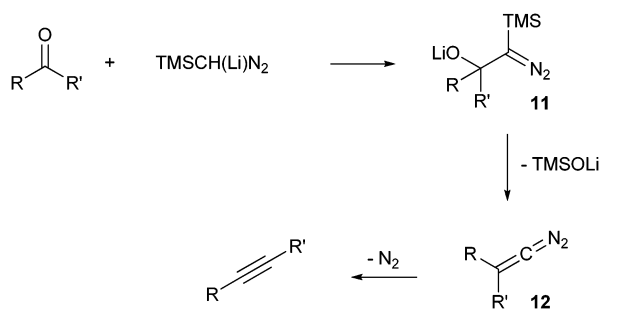
In 1994, Shioiri decided to reinvestigate this reaction and found general conditions for the reaction of aldehydes and aryl alkyl ketones with $TMSC(Li)N_2$ (Table 2).[16] In a representative experiment, $TMSCHN_2$ (120 mol%) is added to a solution of LDA (120 mol%) in THF at −78 °C. After 30 min, a solution of the carbonyl compound (100 mol%) is added at −78 °C, and after 1 h the mixture is heated to reflux for 3 h.

This reaction appears to be general for both alkyl aryl ketones and aldehydes. For ketones, the reaction conditions are tolerant to electron donating and electron withdrawing groups. The nature of the alkyl part does not appreciably affect the yield. Heteroaromatic ketones react in a similar way while conjugated ketones give lower yields. Concerning the aldehydes, the reaction is applicable to aromatic and aliphatic substrates with complete retention of stereochemistry in the case of chiral compounds. Interestingly, α,β-unsaturated aldehyde can be homologated to the corresponding enyne.

This procedure has found its place in some recent total syntheses (see Scheme 10 for examples using lactols as substrates). In Myers' synthesis of the Kedarcidin core structure, this method is used to convert lactol **13** to acetylene **14** in 81% yield.[17] In Furstner's approach to Hikizimycin, mannofuranose **15** is submitted to the Colvin rearrangement and yields 57% of terminal alkyne **16** and 12% of its C-silylated analogue. The latter is easily desilylated to furnish alkyne **16** in 65% yield overall.[18]

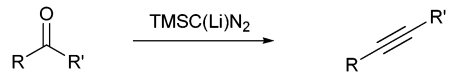


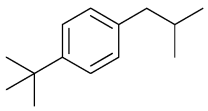
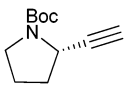
Scheme 8 Synthesis of alkynes by Colvin.

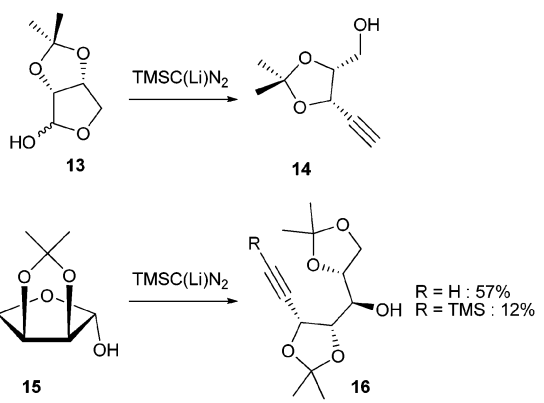


Scheme 9 The Colvin rearrangement.

Table 2 Synthesis of alkynes *via* Colvin rearrangement



R	R′	Yield (%)
C_6H_5	Me	52
4-MeO–C_6H_4	Me	82
4-Cl–C_6H_4	Me	78
C_6H_5	Et	62
C_6H_5	*i*-Pr	50
C_6H_5	*n*-Bu	65
2-Naphthyl	Et	84
2-Thienyl	Me	61
2-Pyridyl	Me	60
(*E*)-Styryl	Me	34
4-MeO–C_6H_4	H	86
$C_6H_5CH_2CH_2$	H	70
	H	90
	H	92
(*E*)-Styryl	H	71



Scheme 10 Examples of application of the Colvin rearrangement in total synthesis.

4. The Seyferth-Gilbert homologation

4.1 Original procedure

As previously mentioned, Colvin discovered that treatment of a carbonyl compound with the salt of DAMP leads to the formation of the homologous alkyne (Scheme 8).[13,14] DAMP was originally discovered by Seyferth.[19–21]

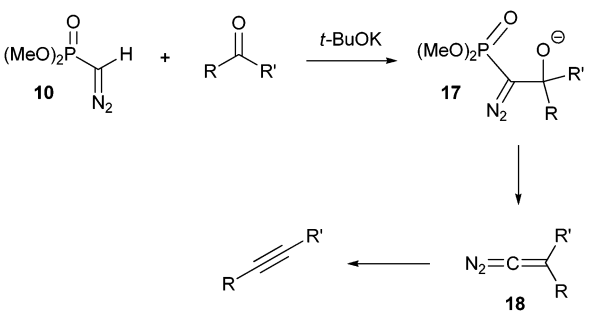
In the original procedure, a solution of DAMP (220 mol%) in THF is treated at −78 °C with *n*-BuLi or *t*-BuOK (220 mol%). Then just after addition of the carbonyl compound (100 mol%), the reaction mixture is warmed to rt and reaches completion after 16 h. DAMP proves to be more stable and easier to handle than $TMSCHN_2$ and gives higher yields (using benzophenone, diphenylacetylene is obtained in 80% yield for $TMSCHN_2$ and 94% yield for DAMP).

Unfortunately, this method is only effective for diaryl ketones (a range of benzophenones are converted to the corresponding alkynes in 38–97% yield) and highly electrophilic aryl aldehydes (only 4-nitrobenzaldehyde can be homologated, 86% yield). Attempts to extend the reaction to ketones and aldehydes containing enolizable protons or α,β-unsaturation have not been satisfactory and give only low yields of the alkyne (0–30%). However, the fact that by-products are water soluble makes this technique attractive since the product alkyne can be isolated after a simple aqueous work-up.

4.2 Extending the scope of the reaction

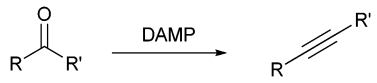
With these results in hand, Gilbert studied this reaction in order to increase the substrates scope.[22,23] He found that using *t*-BuOK instead of *n*-BuLi and keeping the reaction mixture at −78 °C after addition of the carbonyl compound for 12–20 h dramatically enhances the breadth and efficiency of this transformation. The mechanism of this transformation was also studied (Scheme 11).

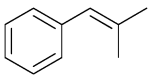
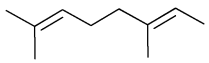
Changing the base from *n*-BuLi to *t*-BuOK was guided by the fact that *t*-BuOK would make the counterion of **17** larger and therefore enhanced its rate of decomposition.[24] Keeping the reaction mixture at −78 °C for a longer period of time was thought to avoid side-reactions (such as enolization of the carbonyl compound and derived reactions) and thermal decomposition of the anion of DAMP. From a mechanistic point of view, it is assumed that the attack of the DAMP anion on the carbonyl partner is reversible and a relatively slow process leading to adduct **17** (in a similar manner as in the HWE olefination). After elimination of potassium dimethylphosphate, the thermally unstable diazoalkene **18** is obtained. Loss of N_2 from **18** leads to an alkylidenecarbene which undergoes 1,2-shift to give rise to the desired alkyne.

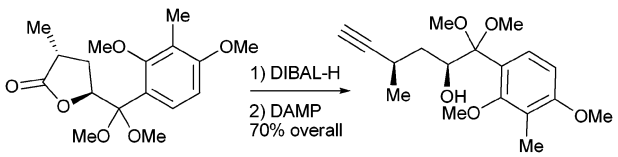


Scheme 11 Mechanism of Gilbert's procedure.

Table 3 Preparation of alkynes by Gilbert



R	R′	Yield (%)
$C_6H_5CH_2$	H	80
$CH_3(CH_2)_3CH(C_2H_5)$	H	79
2-Furan	H	50
4-MeO–C_6H_4	H	88
4-NO_2–C_6H_4	H	84
	H	40
	H	27
C_6H_5	Me	67
4-NO_2–C_6H_4	Me	55
C_6H_5	C_6H_5	92



Scheme 12 Example of utilisation of DAMP in total synthesis.

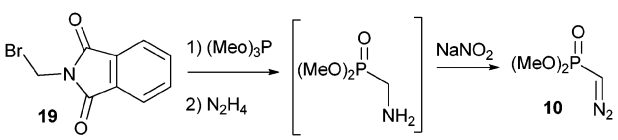
Gilbert's modifications dramatically enhances the scope of substrates compatible with this transformation since enolizable aldehydes and ketones as well as aryl aldehydes of relatively low electrophilicity are converted to the corresponding alkynes in good yields (Table 3). Unfortunately, α,β-unsaturated aldehydes give lower yields and dialkylketones are unreactive.

This reagent has also been used for the transformation of a lactol to the corresponding homologated alkyne, for instance in Rawal's total synthesis of Elisapterosin B (Scheme 12).[25]

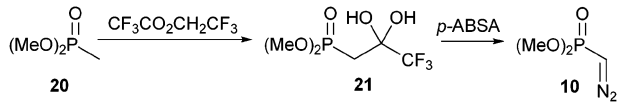
4.3 Preparation of the reagent 10

DAMP is not commercially available, and therefore needs to be prepared. The original synthesis from 1971 involves a Michaelis–Arbuzov reaction between trimethylphosphite and *N*-bromomethylphthalimide **19**.[21] Amination and diazotization of **19** gives DAMP in an overall yield of 37% (Scheme 13).

An improved procedure for the preparation of DAMP was published in 1996 using a diazo transfer technique



Scheme 13 Original preparation of DAMP.



Scheme 14 Improved synthesis of DAMP.

(Scheme 14).[26] Commercially available dimethyl methylphosphonate **20** is temporarily trifluoroacetylated to furnish intermediate **21** which exists as the ketone hydrate. Diazotization of **21** using 4-acetamidobenzenesulfonyl azide (*p*-ABSA) yields DAMP, after spontaneous detrifluoroacetylation. This method allows the preparation of DAMP in 50% overall yield and avoids purification of any intermediate.

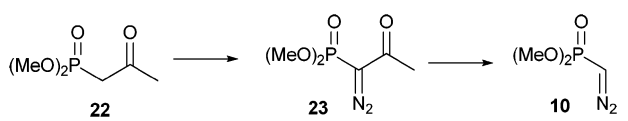
5. The Ohira-Bestmann modification[27]

5.1 Original procedure

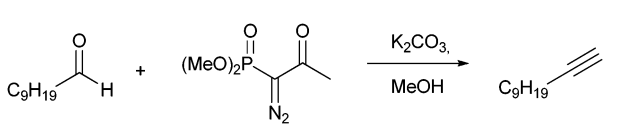
During his studies to find a convenient way to prepare DAMP, Ohira prepared dimethyl-1-diazo-2-oxopropylphosphonate **23** by diazotization of commercially available dimethyl 2-oxopropylphosphonate **22**.[28] He noticed that treatment of **23** (100 mol%) with K_2CO_3 (20 mol%) in methanol at 0 °C produced DAMP in 90% yield.[29] The methoxide anion attacks the carbonyl group of the starting material **23** faster than the hydrogen of **10** (Scheme 15). The low concentration of methoxide anion also prevents **10** from decomposing.

Phosphonate **10** is therefore produced *in situ* from **23** and it is used for the synthesis of alkynes under Gilbert's conditions with similar results as with isolated **10**. Only one example for the formation of an alkyne from an aldehyde is described in this original procedure, using decanal. Treatment of decanal (100 mol%) with phosphonate **23** (150 mol%) and K_2CO_3 (200 mol%) in methanol at 0 °C for 5 h affords 1-undecyne in 62% isolated yield (Scheme 16). In the case of ketones, the internal alkynes can not be obtained, but instead enol ethers of the homologated aldehydes, as described by Gilbert for the reaction of DAMP with ketones in the presence of alcohol.[30]

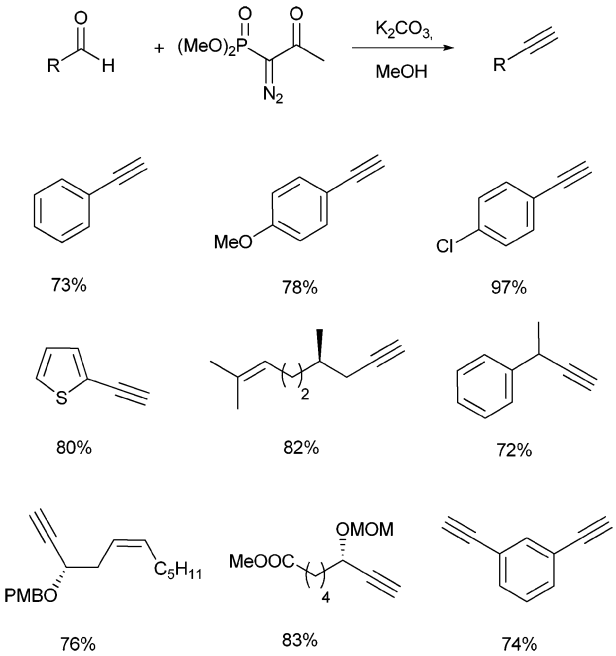
Following this single example, Bestmann decided to examine this reaction in more detail and studied its scope and limitations (see Scheme 17 for representative examples).[31] K_2CO_3 (200 mol%) and **23** (120 mol%) are successively added on a variety of aldehydes (100 mol%) in dry methanol at rt. After completion (4–16 h of stirring, depending on the nature of the aldehyde), the corresponding alkynes can be obtained in good to excellent yields (73–97%) and in analytically pure from after simple work-up. This method avoids the use of



Scheme 15 Preparation of DAMP by Ohira.



Scheme 16 First example of the use of **23** in the synthesis of alkyne.



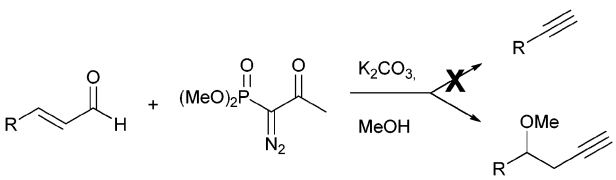
Scheme 17 Synthesis of alkynes by Bestmann.

strong bases, low temperatures and inert gas techniques. The scope of the reaction moreover appears to be general. Aromatic, heteroaromatic and alkyl aldehydes are efficiently converted to alkynes. The reaction works as well for hindered aldehydes. The transformation of α-alkoxyaldehydes occurs without racemisation. Finally, dialdehydes give rise to diynes (in that case, 240 mol% of **23** were used).

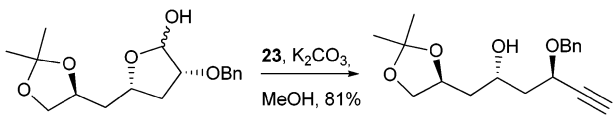
This method appears to be very general and functional groups such as ethers, methyl esters, acetals or non-conjugated double bonds are tolerated. Unfortunately, in the case of α,β-unsaturated aldehydes, the expected ynones can not be obtained (Scheme 18). In theses cases, initial conjugate addition of methanol and subsequent transformation to the alkyne yield the corresponding homopropargylic methyl ethers.

Similar to the Seyferth-Gilbert reagent, phosphonate **23** has also been used to homologate lactols (selected example represented in Scheme 19).[32]

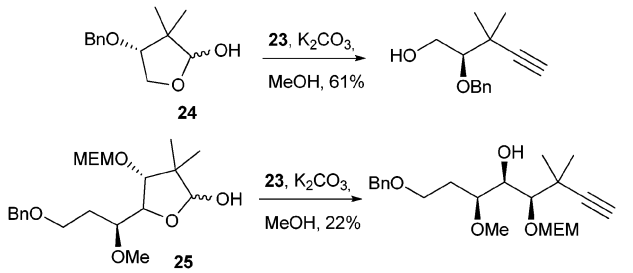
In the case of lactols, the reaction conditions might need to be forced to ensure good conversion of the starting material as shown in Scheme 19 (higher temperature, prolonged reaction



Scheme 18 Reaction of **23** with α,β-unsaturated aldehydes.



Scheme 19 Reaction of **23** with a lactol.



Scheme 20 Influence of the lactol-aldehyde equilibrium.

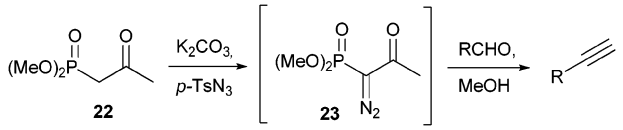
time). Moreover, in the course of our total synthesis of Calyculin C, we have experienced that the transformation of the lactol to the corresponding homologated alkyne can be substrate-dependent and probably relies on the lactol-aldehyde equilibrium (Scheme 20). Indeed, in the case of model compound **24**, homologation occurs in an acceptable yield of 61% after exposure of the substrate to a large excess of **23** and K_2CO_3 (400 mol% each), longer reaction time (5 days) and higher temperature (36 °C).[33] Applying the same conditions to the substrate **25**, which is suitable for the synthesis of the natural product, gives only poor conversion and a low yield of 22% of the corresponding aldehyde is obtained (41% yield based on the recovery of the lactol).[34]

5.2 *In situ* formation of phosphonate 23

A few years later, Bestmann described further improvements of this technique.[35] Highlighting the fact that **23** not being commercially available is a remaining problem for an extended use of this reagent, he presented an improved procedure where commercially available dimethyl-2-oxopropylphosphonate **22** can be used directly as a reagent for this transformation (Scheme 21). Diazo transfer between **22** (120 mol%) and *p*-TsN_3 (120 mol%) in the presence of K_2CO_3 (300 mol%) in acetonitrile produces **23**, as described by Koskinen for the diazo transfer on 1,3-dicarbonyl compounds.[36] After 2 h, the aldehyde (100 mol%) in MeOH is added and the reaction is stirred at rt for 8 h. Purification involves either simple aqueous work up and several extractions with pentane or column chromatography for products insoluble in pentane, in order to separate the alkyne from the *p*-toluenesulfonamide formed in the diazotization step.

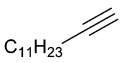
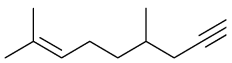
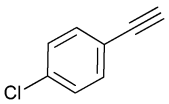
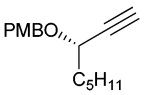
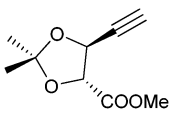
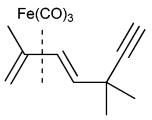
The authors compared the efficiency of this *one-pot* procedure to the original one (Table 4).

The scope and limitations are similar for both methods. Alkyl and aryl aldehydes are homologated in good yields. Compounds containing enolizable protons react in good yields; if a stereogenic center is present at the α-position of the aldehyde, no epimerisation is observed. This reaction is also tolerant with the presence of metal complexes. Only



Scheme 21 *In situ* formation of **23**.

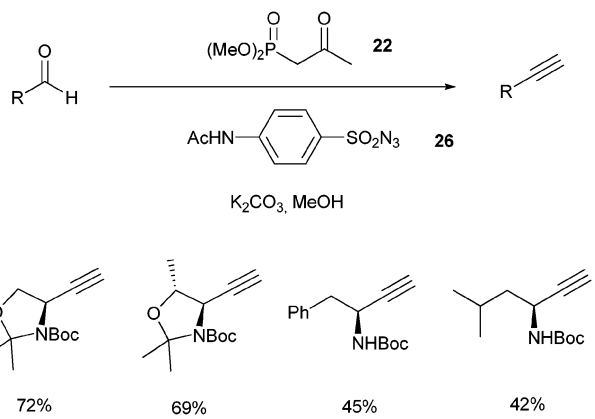
Table 4 Comparison of the *one-pot* and sequential procedures

Alkyne	Yield (%)	
	One-pot	Sequential
	89	96
	72	96
	83	97
	73	80
	65	73
	68	70

highly electron rich aldehydes like azulene-1-carbaldehyde do not react using both methods, even under forcing conditions. However, other electron rich aldehydes have been homologated using the classical sequential procedure.[37]

The yields of the *one-pot* procedure are in all cases lower than the original sequential one (from 2 to 24% less), but the transformation occurs in acceptable yields in general. The authors recommend the new *one-pot* sequence for its simplicity, but in the case where the yields are critical (in the course of total syntheses for instance), they would rather advice the use of the two-step procedure.

Meffre *et al.* presented their version of the *in situ* method to prepare alkynes from protected amino aldehydes (Scheme 22).[38] This method involves a similar type of formation of **23** as the original procedure, but it uses 4-acetamidobenzene



Scheme 22 Meffre's modification.

sulfonyl azide **26** as the aza source. They also changed the solvent from methanol to chloroform to decrease the possible side reactions of the formed sulfonamide with the aldehyde. The diazo transfer from **26** to **22** appears to be slower than using *p*-TsN_3, but **26** is preferred for ease of preparation, purification and manipulation. The homologation itself is slower (24 h at 0–10 °C), but if performing the reaction at higher temperatures (40–50 °C) diminishes the reaction time, it also leads to a loss of enantiopurity.

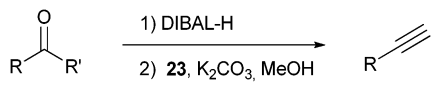
In a typical experiment, **26** (340 mol%) and K_2CO_3 (350 mol%) are added at 0 °C on a solution of **22** (340 mol%) in $CHCl_3$. After 48 h in an ice-bath, a second portion of K_2CO_3 (160 mol%) is added, followed by a solution of the aldehyde (100 mol%) in MeOH and the reaction is stirred at the same temperature for 24 h.

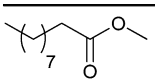
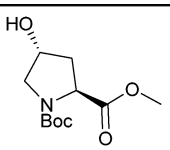
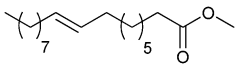
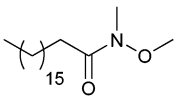
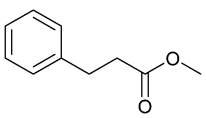
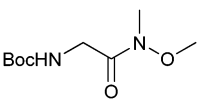
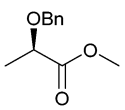
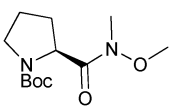
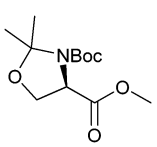
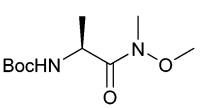
This procedure has been applied on Garner's aldehyde and the threonine derivative. Both substrates are converted to the corresponding ethynyloxazolidines in good yields. Extension to α-aminoaldehydes derived from naturally occurring phenylalanine and leucine leads to the homologated alkynes in good enantiomeric purity (92%), albeit in lower yields. However, control experiments using isolated diazophosphonate **23** give similar results.

5.3 Tandem processes using Ohira-Bestmann reagent

5.3.1 From esters or Weinreb amides. An elegant *one-pot* procedure for the conversion of esters and Weinreb amides into the corresponding terminal alkynes, *via in situ* production of the aldehyde, was published by Hinkle in 2004.[39] The starting esters or Weinreb amides (100 mol%) are dissolved in CH_2Cl_2 and treated at −78 °C with DIBAL-H (120 mol%). After full conversion of the starting material, excess DIBAL-H is quenched by adding MeOH. The aldehyde solution is then allowed to warm up to 0 °C, treated with K_2CO_3 (200 mol%) and **23** (120 mol%) in MeOH and stirred overnight. Good to excellent yields are obtained for the preparation of terminal alkynes, starting both from methyl esters and Weinreb amides (Table 5). As observed previously for the transformation of aldehydes to alkynes, this procedure is tolerant to a wide range of functional groups such as non-conjugated double bonds, ethers or carbamates. Chiral compounds completely retain their stereochemistry. The alkynylation takes place in the presence of a free alcohol (one extra equivalent of DIBAL-H is required). In that case, it is also noteworthy to point out that this reaction has been carried out efficiently on a 0.11 mol scale of the starting ester (27 g).

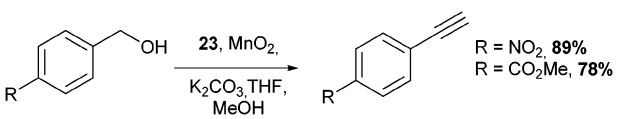
Table 5 Preparation of alkynes from esters or Weinreb amides



Substrate	Yield (%)	Substrate	Yield (%)
	88		75
	76		85
	84		78
	72		83
	71		77

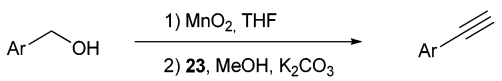
5.3.2 From activated alcohols. During the course of his programme to develop new *one-pot* manganese dioxide-mediated oxidation processes (TOP), leading from activated primary alcohols to a range of synthetically useful functionalities *via in situ* trapping of the intermediate aldehydes, Taylor described the conversion of activated alcohols into terminal alkynes using Ohira-Bestmann reagent.[40,41]

Initial attempts for this transformation, where all the reagents are mixed together, are described in Scheme 23. The alcohol (100 mol%), MnO_2 (500 mol%), phosphonate **23** (120 mol%) and K_2CO_3 (200 mol%) in a THF–MeOH (1/1) mixture furnish the expected alkyne after 18 h at rt. Unfortunately, this procedure appears to be limited to highly electron deficient benzyl alcohols and only the two substrates shown in Scheme 23 give good yields. The presence of methanol in the reaction reduces the activity of MnO_2, but attempts to replace methanol by other alcohols failed.



Scheme 23 *One pot* preparation of alkynes from activated alcohols.

Table 6 Sequential *one pot* conversion of activated alcohols



Ar	Yield (%)	Ar	Yield (%)
4-NO_2–C_6H_4	99	4-OMe–C_6H_4	56
4-COOMe–C_6H_4	97	1-Naphthyl	89
4-Br–C_6H_4	85	4-Diphenyl	92
2-Br–C_6H_4	94	3-Pyridyl	68
C_6H_5	87	C_6H_5—≡	59

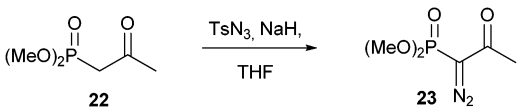
With these observations, the authors decided to investigate a sequential *one-pot* procedure. The oxidation of the alcohol (100 mol%) is therefore performed using MnO_2 (500 mol%) in THF at rt for 3–24 h. After full conversion of the alcohol, MeOH, K_2CO_3 (200 mol%) and **23** (120 mol%) are added. After stirring overnight, the terminal alkynes are obtained in good to excellent yields (Table 6). This modified procedure appears to be more efficient and more general than the previous one. The yields obtained for the two substrates described with the first method are higher using the two-step sequence (89% *vs.* 99% for the nitro compound and 78% *vs.* 97% for the ester), and the products were analytically pure after simple work-up. Substrates containing electron withdrawing groups furnish the highest yields of the corresponding alkynes, but good results are also obtained with benzyl alcohol itself and derivatives bearing an electron donating group as well as with bicyclic compound, diaromatic derivative, heteroaromatic and less activated alcohol. The limitation of this procedure to activated alcohols and the difference in yields and reaction time observed most likely depend on the oxidation step and not on the homologation step itself.

5.4 Preparation of phosphonate reagent 23

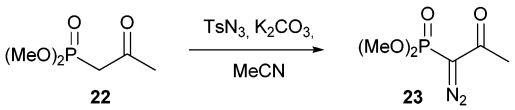
Phosphonate **23** is an air and moisture stable yellow liquid. It was initially prepared in 83% yield by diazotization of dimethyl 2-oxopropylphosphonate **22** using TsN_3, as presented earlier (Scheme 24).[28]

A recent modification of this procedure was published by Taylor (Scheme 25).[41] This improved procedure uses the milder base K_2CO_3 and allows the preparation of **23** with 97% yield.

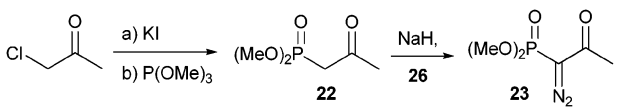
Phosphonate **22** being a somewhat expensive starting material, Pietruszka described an alternative scalable synthesis of **23** starting from inexpensive chloroacetone (Scheme 26).[42] Treatment of chloroacetone with KI followed by reaction with trimethyl phosphite furnishes **22**. Deprotonation of **22** using sodium hydride followed by treatment with 4-acetamidobenzene sulfonyl azide **26** produces the Ohira-Bestmann



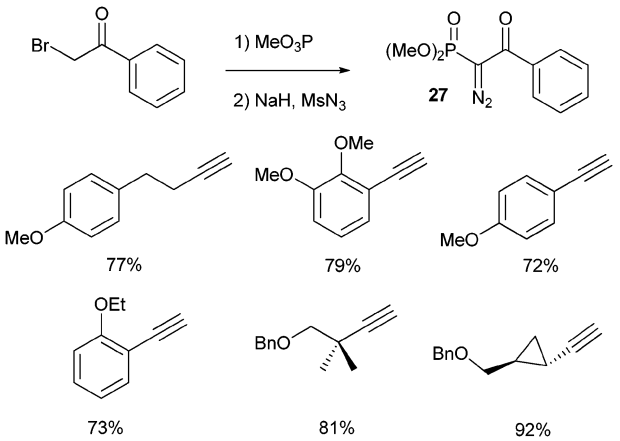
Scheme 24 Original preparation of **23**.



Scheme 25 Improved preparation of **23**.



Scheme 26 Preparation of **23** from chloroacetone.



Scheme 27 Preparation and use of **27** in alkyne synthesis.

reagent. This method allows the preparation of **23** in an up to 50 g scale.

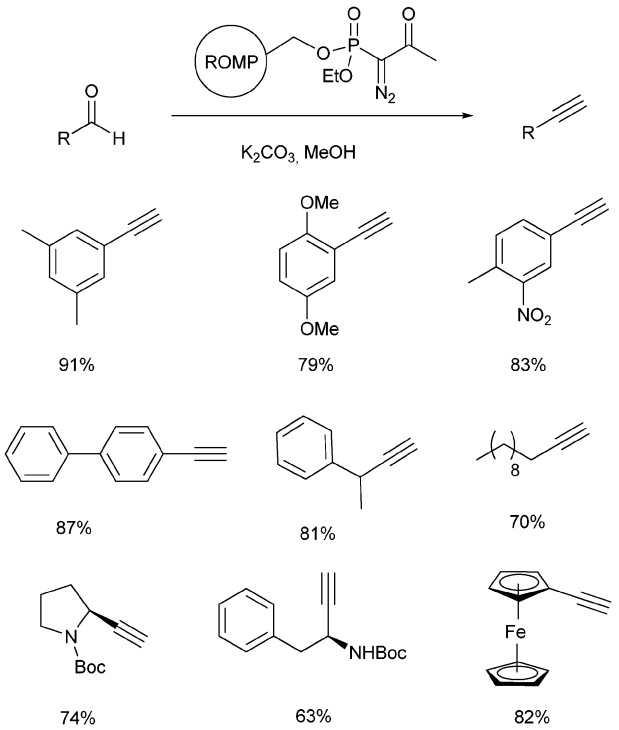
5.5 Alternative phosphonate

The high price of phosphonate **22** combined with the fact that the acyl group is lost during the formation of **10** from **23** were highlighted when Taber published a new phosphonate reagent that can efficiently be used in the homologation of aldehydes to alkynes.[43] Phosphonate **27**, where the methyl group of **23** is replaced by a phenyl ring, has been prepared in 2 steps from inexpensive 2-bromoacetophenone and shown to react with aldehydes in the presence of K_2CO_3 in MeOH to give the corresponding alkynes in good yields (Scheme 27). **27** proves to be an efficient reagent for this transformation and therefore represents a promising and inexpensive alternative to **23**.

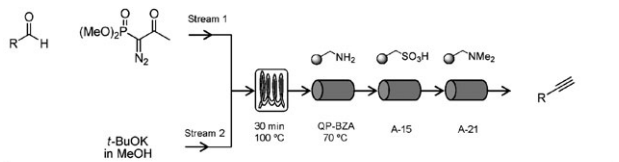
5.6 Supported and continuous flow versions

5.6.1 Gel-supported phosphonate. In 2004, Barrett described a supported version of the Ohira-Bestmann reagent and its application for the preparation of alkynes.[44] ROMP-gels are a general class of high-loading polymer supported reagents derived from the ring-opening metathesis polymerization (ROMPolymerization) of norbornene or 7-oxanorbornene monomers. Studies were carried out to examine the influence of the cross-link structure, co-monomers and polymer structure on reaction efficiency. These optimization procedures led to the preparation of a three-component ROMP-gel that efficiently transforms aldehydes into the homologated alkynes in good yield (63 to 91%) and purity (87 to >95%) (Scheme 28).

As observed for the non-supported procedure, the homologation of aldehydes to alkynes using ROMP-gel is effective for aryl and alkyl derivatives. Moreover, no racemization is observed for chiral compounds and the method is compatible with the presence of metal complexes. The scope of this reagent therefore appears to be the same as the soluble classical Ohira-Bestmann reagent **23**. The main advantage of this new method is that no aqueous work-up is required to isolate the alkyne. However, the ROMP-gel technique requires



Scheme 28 Preparation of alkynes using supported phosphonate.



R	Yield (%)	R[a]	Yield (%)
4-Cl-3-OMe-C_6H_3	81		71
2-NO_2-C_6H_4	77		
2-Br-C_6H_4	79		
4-diphenyl	82		
4-CN-C_6H_4	72		64
4-Br-C_6H_4	84		
2-anthracyl	73		
	65		78

Scheme 29 Flow synthesis of alkynes. [a]Substitution of A-15 by alumina.

extended reaction times (from 30 h to 5 days) compared to the original procedure.

5.6.2 Continuous flow. In 2009, Ley's group described the application of the homologation of aldehydes to terminal acetylenes in the presence of phosphonate **23** using continuous flow based equipment.[45] The flow conditions use commercially available pumping systems and heated flow coils in combination with packed glass tubes containing suitable scavenger in order to obtain pure material in the exit (Scheme 29).

The aldehyde (130 mol%) and **23** (100 mol%) in methanol are injected through an injection loop as stream 1 while *t*-BuOK (120 mol%) in MeOH is injected as stream 2. Both streams are mixed through a T-piece and the mixture is then heated at 100 °C through a convection-flow coil (CFC, residence time: about 30 min). On exiting the CFC, the flow is directed through 3 consecutive scavenger columns:

- QP-BZA: a tube packed with a Quadrapure-benzylamine resin operating at 70 °C that eliminates any excess aldehyde,
- A-15: Amberlyst-15 sulfonic acid cartridge which removes the base and protonates any phosphoric residue,
- A-21: Amberlyst-21 dimethyl amine that cleans up and removes any remaining acid material.

At the end of these scavengers, a pure acetylene product flow is obtained. This method allows the preparation of various aromatic acetylenes. The reaction conditions are compatible with the presence of halides, nitro, cyano, acetal or ester groups. When *N*-methyl-2-formylindole is used as starting material, the corresponding methyl ketone is obtained instead of the acetylenic compound. This result is rationalized by the fact that the polar acetylene can undergo further hydrolysis using residual water catalyzed by the A-15 (this kind of resins are known to be hygroscopic). This problem is solved by substituting the A-15 cartridge by an alumina-filled one. With this modification, polar aldehydes are cleanly and efficiently converted to the corresponding alkynes.

6. Comparison of the methods

From a general point of view, the Corey–Fuchs procedure and derived methods suffer from drawbacks when applied to sensitive aldehydes. First, the use of a strong base in excess can be problematic for highly functionalized substrates. Moreover, the reaction media is contaminated with by-products, such as triphenylphosphine oxide, which can make the isolation of the alkyne tedious, and dibromotriphenylphosphorane Ph_3PCBr_2, which is known to be a strong electrophile and a brominating agent (the probable side reactions can however be suppressed by simultaneously adding Et_3N with the aldehyde on the PPh_3/CBr_4 mixture[46]). The advantage of this method compared to the others is that a wide range of electrophiles can be used to react with the lithium acetylide formed in the course of the reaction, giving access to variously substituted alkynes. Moreover, in the case of α,β-unsaturated aldehydes, the homologation takes place; enynes can therefore be obtained using this procedure without any isomerisation of the double bond.

Compared to the other methods, the Colvin rearrangement offers the advantage of using commercially available $TMSCHN_2$ as the carbon source for the homologation. Drawbacks of this method are the necessary use of a strong base, the cold temperatures needed to perform the reaction and the highly nucleophilic nature of the reagent which makes this method incompatible with substrates containing electrophilic functional groups.

Concerning the Seyferth-Gilbert protocol, the disadvantages of this method rely on the fact that strong bases are still required and long reaction times combined with low temperatures are not experimentally friendly. The main drawback is that reagent **10** is not commercially available and its preparation still requires multi-step synthesis.

The Ohira-Bestmann procedure, where the Seyferth-Gilbert reagent **10** is produced *in situ*, has become the most popular

way of transforming an aldehyde into the corresponding alkyne, and the most recent developments include modifications or improvements of this method. The extremely mild reaction conditions make this reaction compatible with a wide range of substrates and the ease of purification is a valuable advantage for the synthetic chemist. However, using this method, enyne can not be obtained from α,β-unsaturated aldehydes and ketones do not lead to the formation of internal alkynes. Finally, phosphonate **23** is not commercially available and needs to be prepared. However, major improvements for the preparation of **23** have been described, and it can now be prepared efficiently in a single step or even *in situ* from **22**.

7. Conclusions

The transformation of carbonyl compounds to the corresponding acetylenic derivatives has become a very popular way of producing internal and terminal alkynes. This review has highlighted the main methods described for this homologation reaction.

The Ohira-Bestmann protocol using phosphonate **23** has become the most widely used method for this transformation. The other methods described here, namely the Corey–Fuchs procedure, Seyferth-Gilbert homologation and Colvin rearrangement should, however, be considered more than just alternatives to the Ohira-Bestmann method. Each of them have found applications in recent total syntheses and represent efficient ways of accessing alkynes.

However, in the quest of more environmentally friendly procedures, these methods can still be optimized considering the nature of hazardous reagents they are based on. Recent efforts using supported reagents or continuous flow reactions are pointing in that direction, but the doors for ''greener'' procedures are still open.

To summarize, the preparation of acetylenic compounds from carbonyl compounds is a popular and well-studied procedure. The scopes of the different methods cover the vast majority of functional groups and we believe that this review can be a useful tool to the synthetic chemist looking for appropriate conditions applicable to a specific substrate.

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