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Synthesis, synthetic interests, and biological activities of β -substituted vinylphosphonates

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ABSTRACT

β -Substituted vinylphosphonates constitute an original class of organophosphorus reagents of which several compounds exhibit attractive biological properties. The review exemplifies and discusses the different synthetic methods described for their synthesis, which involve well known reactions, but also more specifically designed methods. In addition, the uses as synthetic intermediates as well as the therapeutic uses of the title compounds are also summarized.

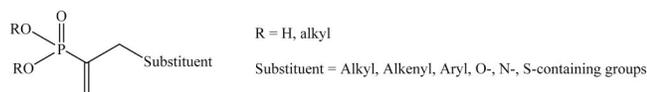
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KEYWORDS

Functionalized vinylphosphonates; β -substituted vinylphosphonates; biologically active phosphonates; aminovinylphosphonates

GRAPHICAL ABSTRACT



1. Introduction

Vinylphosphonates have been known for more than sixty years.^[1–3] Among this class of compounds, β -substituted vinylphosphonates and their related acids (Figure 1) are frequently found as significant biologically active compounds. Therefore, numerous methods for their synthesis have been implemented.

The purpose of this article is to exemplify the different synthetic methods described for the synthesis of these compounds and to review their synthetic potential. Furthermore, their biological activities and their use for the synthesis of biologically active compounds is also addressed.

2. Synthetic methods

The different methodologies listed below appear mainly following the chronology of the corresponding reports.

2.1. Use of α -halogenomethylvinylphosphonates 1 and 2 as starting reagents

These compounds, namely dimethyl α -(bromomethyl)vinylphosphonate **1** and diethyl α -(bromomethyl)vinylphosphonate **2**, have been used repeatedly for the synthesis of β -substituted vinylphosphonates and may react as nucleophiles as well as electrophilic reagents depending on the strategy used.

They can be easily obtained through simple reactions (Scheme 1), i.e. the bromination of dimethyl α -methylvinylphosphonate **3** with *N*-bromosuccinimide (NBS), as described by Collard and Benezra^[4] leads to **1** with moderate yield, whereas **2** is prepared through bromination of

diethyl α -(hydroxymethyl)vinylphosphonate **4**,^[5] which in turn is obtained from tetraethyl methylenebisphosphonate using Villieras' method.^[6]

On the other hand, dimethyl α -(chloromethyl)vinylphosphonate **6** can be obtained in moderate yield in a two steps procedure,^[7] *via* **5**, starting with chlorophosphorylation of allyl chloride (Scheme 2).

2.1.1 α -Halogenomethylvinylphosphonates as nucleophiles

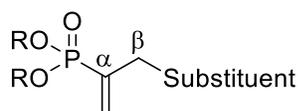
Collard and Benezra^[4] in 1982 reported an original synthesis of phosphorus heterocycles, namely α -methylenephosphonates (by analogy with α -methylene lactones). This entails a Reformatsky reaction between dimethyl bromomethylvinylphosphonate **1** and ketones or aldehydes and involves an organozinc substituted vinylphosphonate **8** (Scheme 3).

However, these α -methylenephosphonates were shown to possess very low biological activities.

Knochel and Normant^[8] later showed that the above organozinc reagents could add readily to alkynes, leading to phosphonyl substituted dienes **9** (Scheme 4).

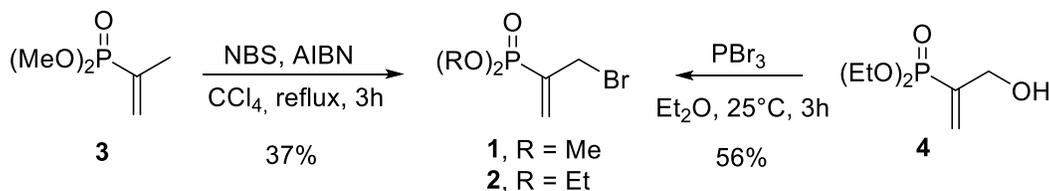
It was further shown that the reaction of these same organozinc reagents can be used for the synthesis of phosphonate-containing carbohydrates **10** (Scheme 5).^[9] In this case, the zinc reagent was prepared from a zinc-silver alloy deposited on graphite.

A similar indium related reagent was involved in a useful and short synthesis of phosphoryl substituted sialic acid analogues,^[10,11] (Scheme 6), which could even be carried out in aqueous solvent due to the stability of the organoindium phosphonate reagent.

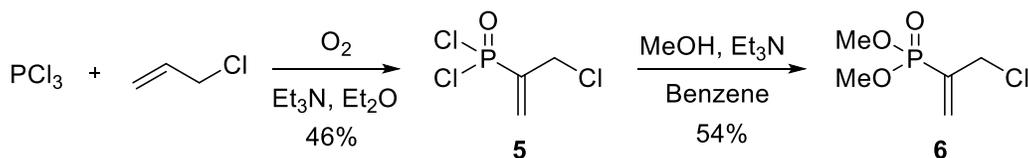


Substituent = alkyl, alkenyl, aryl,
O-,N-,S-containing groups

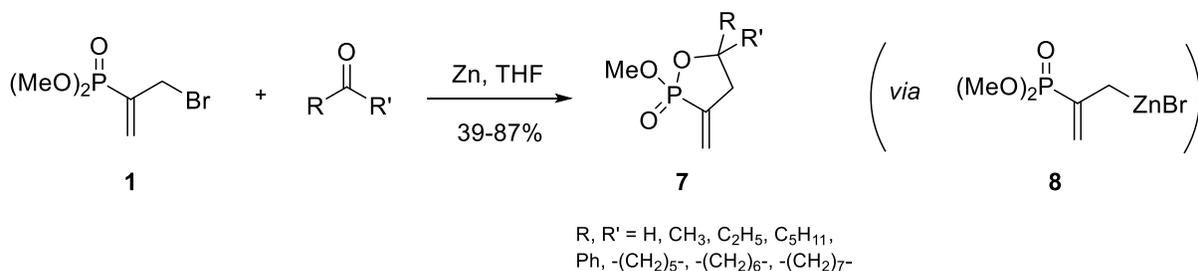
Figure 1. General structure for β -substituted vinylphosphonates.



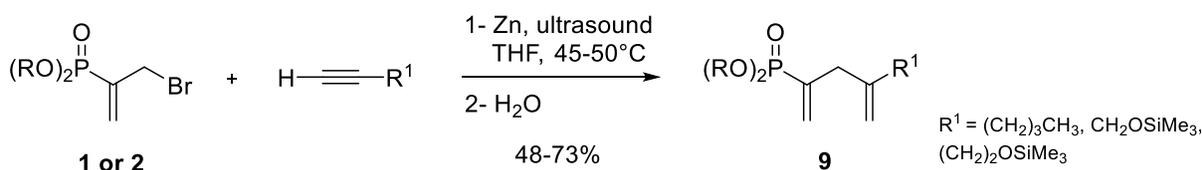
Scheme 1. Syntheses of dimethyl α -(bromomethyl)vinylphosphonate 1 and diethyl α -(bromomethyl)vinylphosphonate 2.



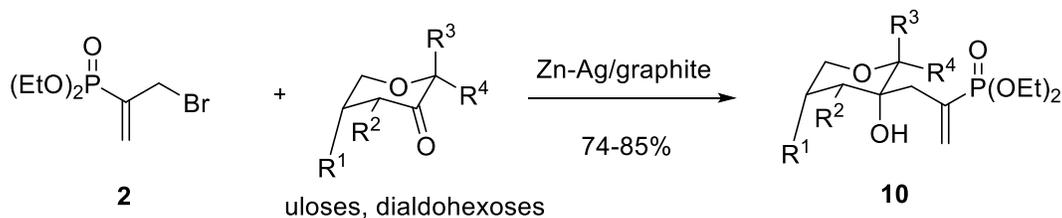
Scheme 2. Synthesis of dimethyl α -(chloromethyl)vinylphosphonate 6.



Scheme 3. General synthesis of α -methylene phosphonates from 1.



Scheme 4. Addition of phosphonyl-containing organozinc reagents to alkynes.



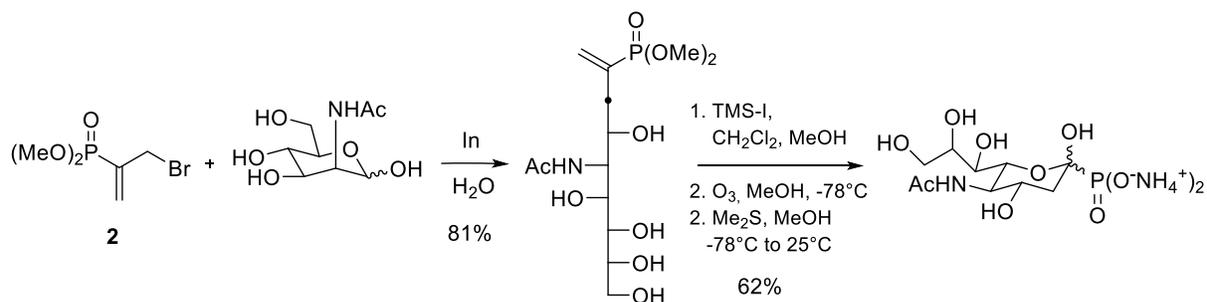
Scheme 5. Synthesis of phosphonate-containing carbohydrates 10 from 2.

2.1.2 α -Halogenomethylvinylphosphonates as electrophiles

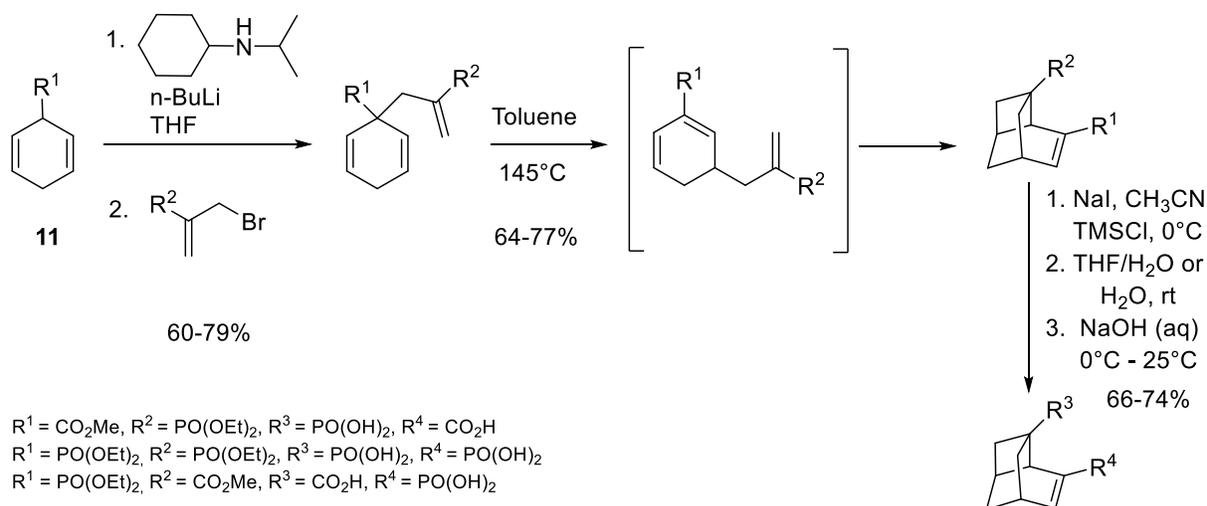
The electrophilic character of these reagents stems from the presence of the electron-withdrawing phosphonate group bound to the double bond as well as the leaving group at the allylic position. Therefore, a number of studies involve their reactions with different nucleophiles.

The first example was described by Ganem *et al.*^[12] in their elegant synthesis of phosphonate analogues of

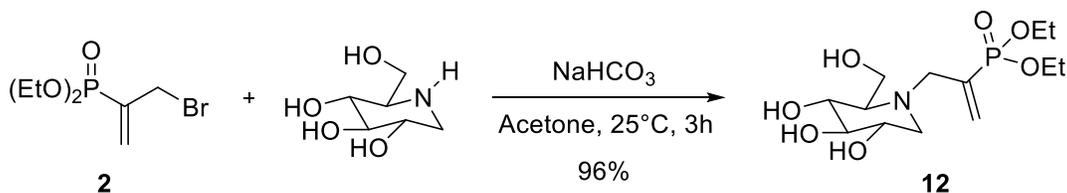
chorismic acid¹. Thus, alkylation of 2 with the cyclohexadienyl ester 11 led to the intermediate vinylphosphonate which upon heating gave a Cope rearrangement followed by an intramolecular Diels-Alder reaction to yield the tricyclic derivative (Scheme 7). Final hydrolysis yielded the corresponding phosphonic acid which was shown to display interesting inhibitory activities toward the enzyme.



Scheme 6. Synthesis of phosphoryl substituted sialic acid analogues from **2**.



Scheme 7. Synthesis of phosphonate analogues of chorismic acid from **2**.



Scheme 8. Synthesis of deoxynojirimycin derivatives **12** from **2**.

Fuchs^[13] reacted this same reagent with amines to prepare deoxynojirimycin derivatives **12**, for evaluation as potential agents in anti-retroviral studies (Scheme 8).

More recently, Alexakis^[14] reported the alkylation of **2** with zinc enolates under copper catalysis. The presence of chiral organophosphorus ligands allowed an efficient control of the enantioselectivity, leading to up to 99% enantiomeric excess for **13** (Scheme 9).

However, these very good results are hampered by the low yields encountered due to the side reaction between **2** and the zinc enolate, which transfers the R group instead of the enolate moiety, thus leading to the by-product **14**.

Finally, the reactivity of dimethyl α -(chloromethyl)vinylphosphonate **6** with several carbon, nitrogen and oxygen based nucleophiles was extensively studied by Tebby *et al.*,^[7,15] (Scheme 10). The different products obtained in each example may be considered as useful starting material for the synthesis of more functionalized vinylphosphonates.

2.2. Mannich reaction starting from diethylphosphorylacetic acid

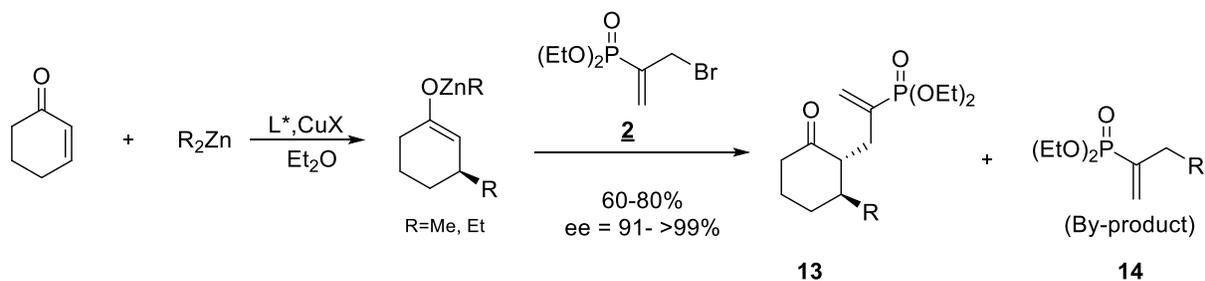
This title compound which was easily obtained by saponification of triethyl phosphonoacetate **15**, reacted with formaldehyde and a dialkyl amine to lead to the expected Mannich products **16**, namely β -aminovinylphosphonates^[16] (Scheme 11).

The mechanism involves a Mannich reaction between **15** and two equivalents of formaldehyde, and an amine, followed by amine elimination and decarboxylation.

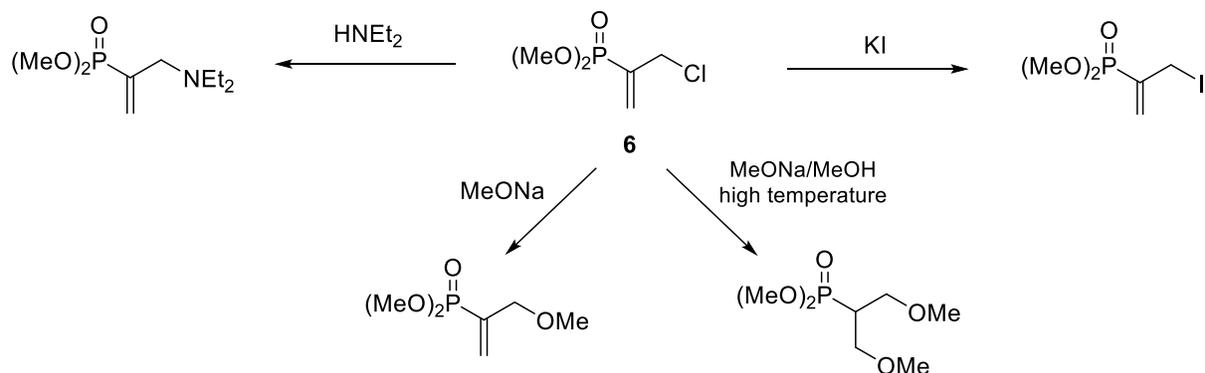
The reaction was further extended^[17] to the synthesis of β -alkoxyvinylphosphonates **17** by replacing the amine with an alcohol (Scheme 12), and in the presence of catalytic amounts of piperidine.

2.3. From *N*-tosylvinylsulfoximines

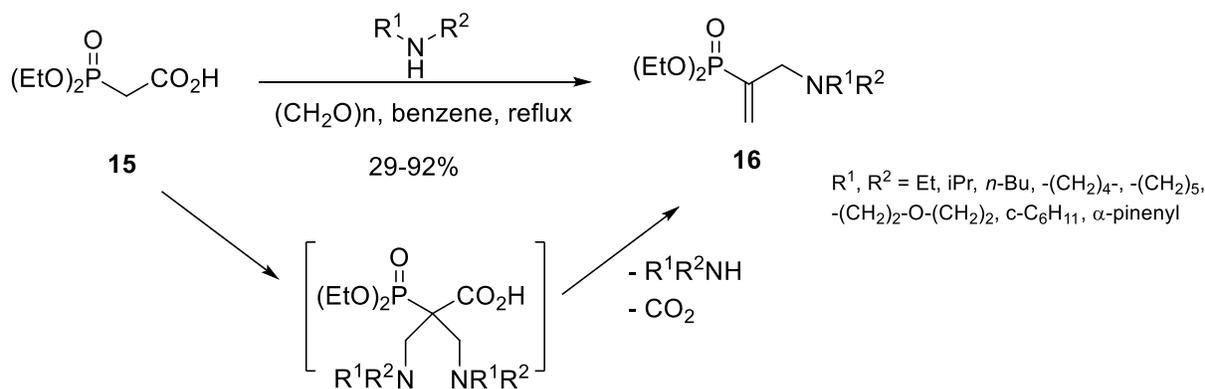
Because of the presence of the strong electron withdrawing *N*-tosylsulfonyl group, the title compounds are known as



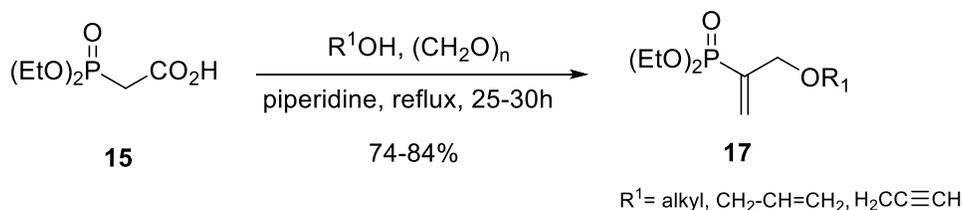
Scheme 9. Copper-catalyzed alkylation of **2** with zinc enolates.



Scheme 10. Several carbon, nitrogen and oxygen -substituted vinylphosphonates obtained from **6**.



Scheme 11. β -aminovinylphosphonates from diethylphosphorylacetic acid using a Mannich reaction.



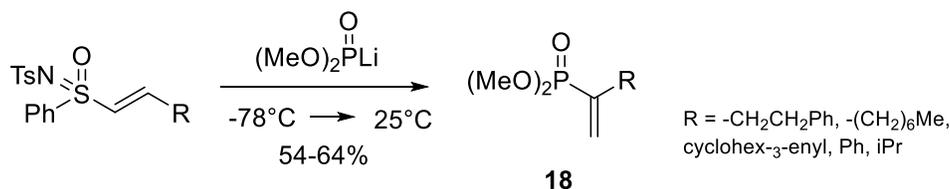
Scheme 12. β -alkoxyvinylphosphonates from diethylphosphorylacetic acid using a Mannich reaction.

valuable acceptors in the Michael addition. Jackson *et al.*^[18] described their reaction with lithium dimethyl phosphonate as nucleophile (Scheme 13), leading to α -alkylvinylphosphonates **18**.

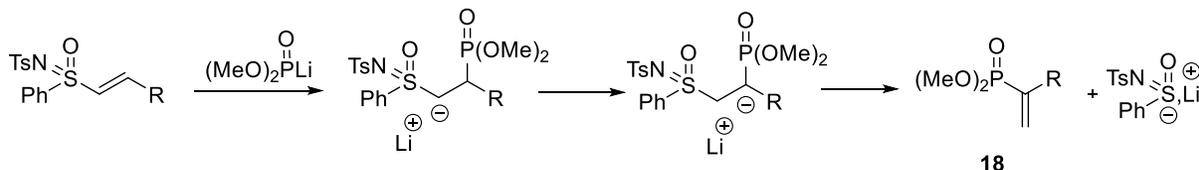
The reaction involves an addition/elimination mechanism since the incoming phosphonate group is also an electron withdrawing one, able to stabilize the negative charge created, thus inducing the loss of the sulfoxy group (Scheme 14).

2.4. Acid catalyzed rearrangement of phosphonate substituted aziridines

This methodology, reported in 2001 by Tardella,^[19] involves several steps starting from tetraethyl methylenebisphosphonate. Alkylation with iodomethyl trimethylsilyl silane, followed by Wadsworth-Emmons reaction with aldehydes, leads to the silyl substituted vinylphosphonate **19** which upon treatment with ethyl nosyloxycarbamate yields the



Scheme 13. Synthesis of α -alkylvinylphosphonates from N-tosylvinylsulfoximines.



Scheme 14. Proposed mechanism for the synthesis of α -alkylvinylphosphonates from N-tosylvinylsulfoximines.

aziridine **20**. Acidic treatment finally produces the expected aminovinylphosphonates **21** (Scheme 15).

2.5. Use of α -vinylphosphonate radicals

Minami *et al.*^[20] described the direct generation of synthetically useful α -phosphonovinyl radicals by treatment of α -phosphonovinyl halides **22** with a tributyltin radical in the presence of AIBN, followed by trapping with electron-rich olefins (Scheme 16). This gave access to highly functionalized vinylphosphonates **23**.

2.6. Baylis-Hillman reaction

This reaction consists in a carbon-carbon bond formation between the α -position of an activated alkene and an aldehyde, catalyzed by a nucleophilic species such as a secondary or a tertiary amine or a phosphine. Thus, the reaction of diethyl vinylphosphonate as starting activated alkene, in the presence diazabicyclooctane (DABCO) as catalyst,^[21] allowed the synthesis of β -substituted products **24** (Scheme 17) by use of different aldehydes. The reactions were found to occur with good yields, but with slow rates (completion occurs usually after 7 days to one month). The use of formaldehyde did not give access to the simplest homologue of the series, *i.e.* **4** (R = H).

Later, a Baylis-Hillman type reaction was developed by Tomioka,^[22] relying on the addition of Lithium diisopropylamide (LDA) on a vinylphosphonate, and subsequent aldol-type reaction of the resultant lithiated phosphonate with aldehydes or ketones, giving the elimination products **25** (Scheme 18). Thus, the overall transformation results formally in a Baylis-Hillman reaction.

2.7. By means of a claisen rearrangement

Diethyl 3-hydroxypropen-2-ylphosphonate **4**, which can be obtained only by the Villieras method,^[6] can enter a transesterification reaction with triethyl orthoacetate or dimethoxy-2,2-propane in the presence of propionic acid as catalyst and simultaneous removal of ethanol to produce intermediate **26**, which immediately enters a [3,3] sigmatropic

transposition (Scheme 19). This led to 1-alkenylphosphonates **27** in which the substituent β to the phosphonate group contains either a ketone or an ester function, respectively.^[23]

2.8. Using the Michaelis-Arbuzov reaction

This reaction is the most useful method for the preparation of dialkyl alkylphosphonates, in which an organic halide reacts with a trialkyl phosphite (Scheme 20).^[24]

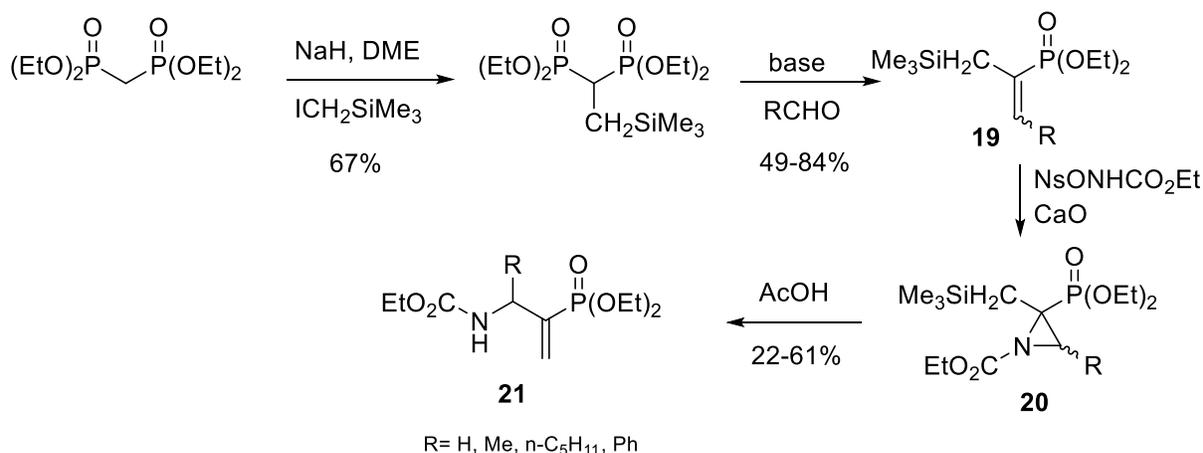
For the synthesis of the title compounds, Inokawa *et al.*^[25,26] reported a two steps procedure involving the Michaelis-Arbuzov reaction of trialkyl phosphites **28** with acyl chlorides, known to yield 1-oxo alkyl phosphonates (58–80% yield). Further Wittig olefination with methylene-triphenylphosphorane generated *in situ* led to α -alkylalkenylphosphonates **29**, with good to moderate overall yields (Scheme 21).

Another method consists in performing the Michaelis-Arbuzov reaction from a vinylic halide. However, it is known that these reagents are inert in this reaction, but the presence of NiCl₂ or NiBr₂ as catalysts may promote the reaction. Fadel *et al.*^[27] employed this methodology for the synthesis of β -aminopyrrolidenevinylphosphonates **32**, as outlined in Scheme 22.

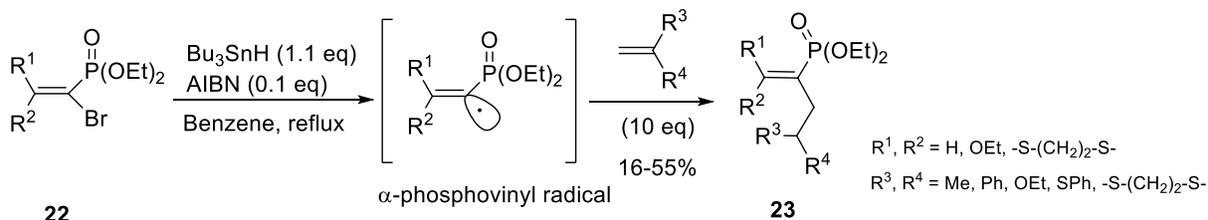
Thus, the S_N2 displacement of the allylic bromide **30** by oxazolidinones or tosylamide in the presence of a base (Cs₂CO₃ or NaH) constitutes the first step of the synthesis, and the vinylic bromide **31** thus obtained was further reacted with triethyl phosphite at 150 °C in the presence of a catalytic amount of nickel bromide. The resulting vinylphosphonates **32** were obtained in good yields.

2.9. Metal-catalyzed additions of dialkyl phosphites to alkynes: hydrophosphorylation

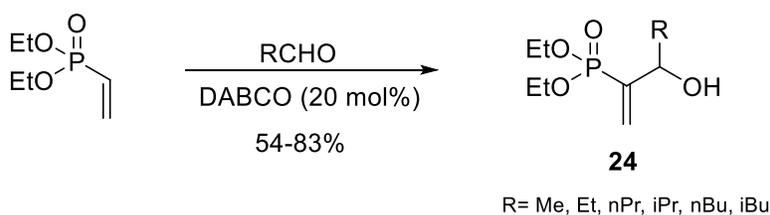
This reaction results formally in the addition of a dialkyl phosphite onto the triple bond of an alkyne. It can be carried out under palladium- or nickel-catalysis.



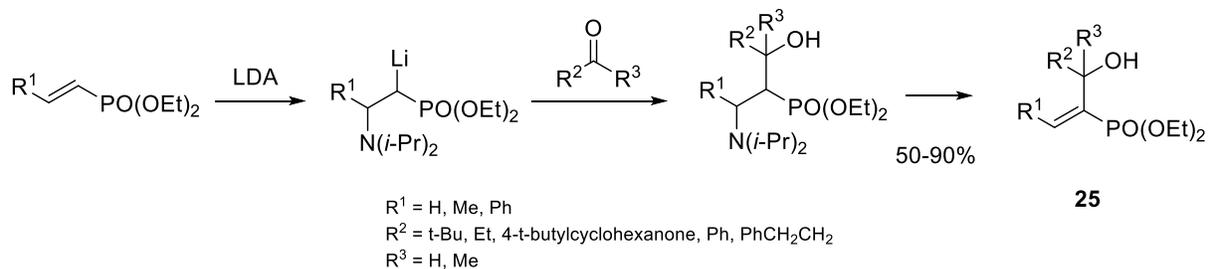
Scheme 15. Acid-catalyzed rearrangement of phosphonate-substituted aziridines.



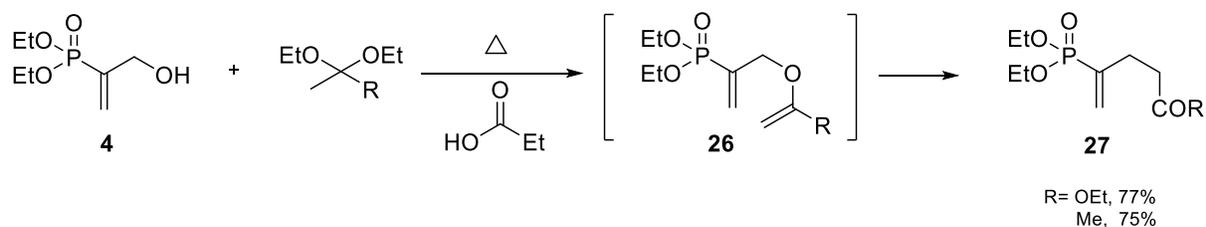
Scheme 16. Synthesis of β -substituted vinylphosphonates using α -phosphonovinyl radicals.



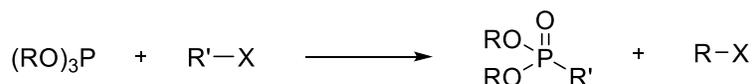
Scheme 17. Synthesis of β -hydroxy substituted vinylphosphonates through Baylis Hillman reaction.



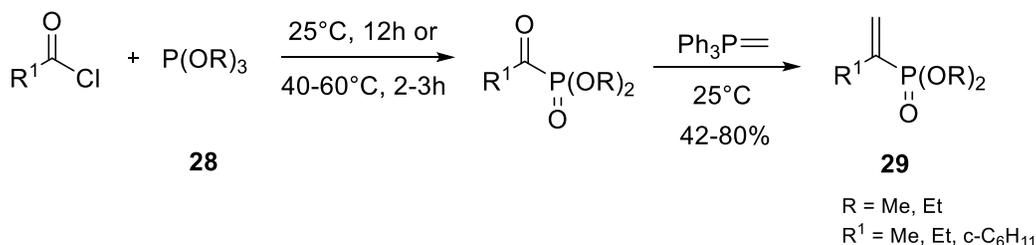
Scheme 18. Baylis-Hillman like reaction starting from vinylphosphonates.



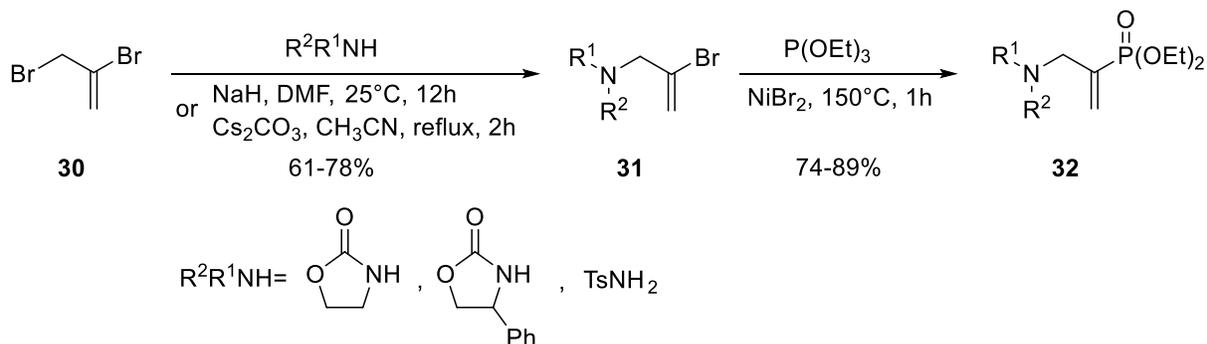
Scheme 19. Synthesis of β -substituted vinylphosphonates using a Claisen rearrangement.



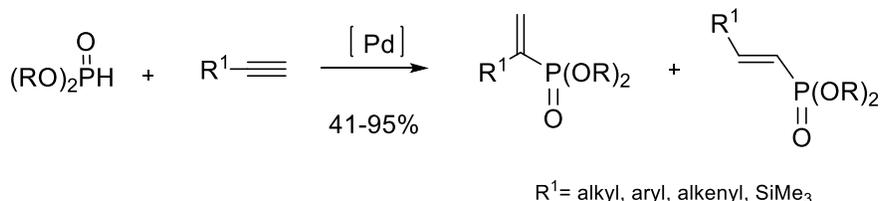
Scheme 20. General scheme for the Michaelis-Arbuzov reaction.



Scheme 21. Michaelis-Arbuzov reaction of trialkyl phosphites with acyl chlorides, followed by Wittig olefination.



Scheme 22. Synthesis of β -aminopyrrolidinevinylphosphonates using the Michaelis-Arbuzov reaction.



Scheme 23. Palladium-catalyzed hydrophosphorylation of alkynes.

2.9.1 Palladium-catalyzed hydrophosphorylation of alkynes

The first example for this reaction was reported in 1996 by Tanaka,^[28] in which dialkyl phosphites add readily to alkynes in the presence of a catalytic amount of palladium catalysts (Scheme 23).

Among the different catalysts assessed, those possessing weakly basic ligands were found to be the most effective ones. The mechanism involves an oxidative addition of the dialkyl phosphite onto palladium to produce species **A**, which then inserts on the triple bond of the alkyne to give **B** and **B'**. Final reductive elimination of the metal leads to the product **33** or **34** (Scheme 24).

The reaction was found to produce two regioisomers among which the Markovnikov product **33** was the major one. However, more sterically hindered alkynes (e.g. trimethylsilyl acetylene $\text{R}^1=\text{SiMe}_3$) led to the anti-Markovnikov product **34** as the major product. Interestingly, enynes give rise to a chemoselective reaction in which the triple bond reacts solely.

A similarly based reaction, named selenophosphorylation of alkynes^[29] was further described, allowing the simultaneous introduction of a phosphonate and a phenylselenide groups, starting from an alkyne and diphenyl phenylselenylphosphonate **35**, with complete regio- and stereoselectivity (Scheme 25), leading to products **36**.

Thiophosphorylation of alkynes^[30] occurred essentially under similar conditions, also with complete regio- and stereoselectivity, except in the case of aromatic alkynes, for

which mixtures of stereoisomers were obtained (Scheme 26). The corresponding products **37** were obtained with satisfactory to very good yields.

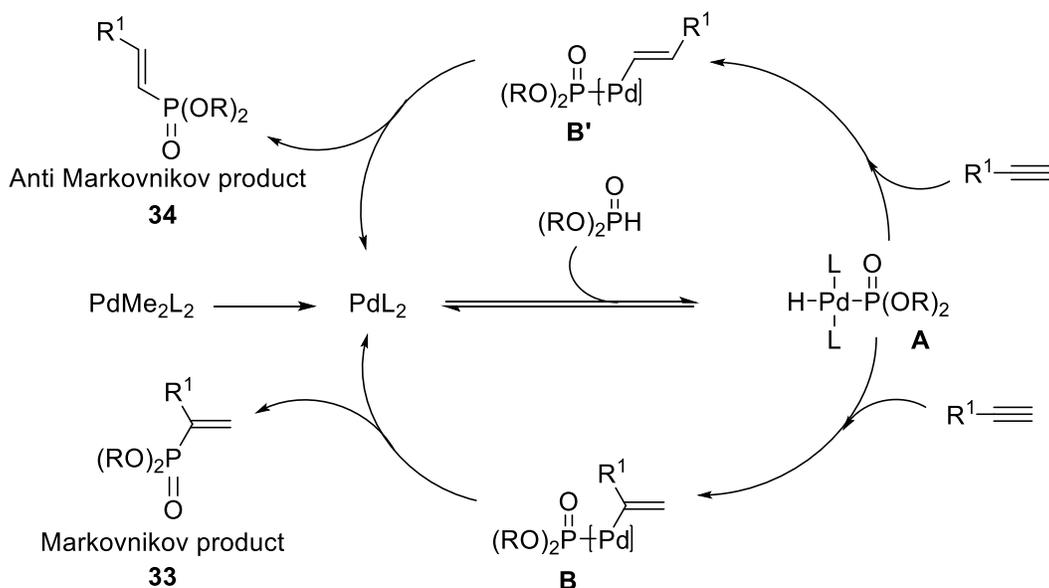
Finally, a more recent study by Beletskaya et al.^[31] describes their efforts to set up a novel catalytic system to accomplish the hydrophosphorylation of terminal and internal alkynes with high isolated yields (up to 96%) and excellent regio- and stereoselectivity (>99:1) in favor of the Markovnikov product. The key factor was to apply a low-ligated palladium/triphenylphosphane (1:2) catalytic system in the presence of a catalytic amount of trifluoroacetic acid (Scheme 27).

2.9.2 Nickel-catalyzed hydrophosphorylation of alkynes

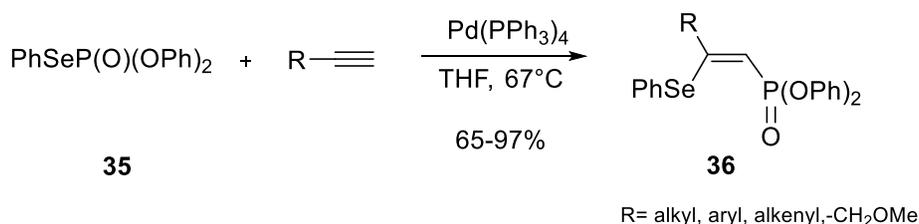
The replacement of noble metals by cheaper ones is highly desirable since it can directly lead to a large cost reduction for the preparation of the products, which is crucial for an industrial process. In this area, Han^[32] developed an alternative synthesis based on a similar reaction as the previous one, but using nickel complexes as catalysts (Scheme 28).

Here again, the mechanism involves an oxidative addition of the dialkyl phosphite on the metal, giving rise to the intermediate **C** which was evidenced by NMR and crystallographic data. Further insertion of the alkyne leads to a nickel intermediate, which undergoes reductive elimination to yield the final product (Scheme 29).

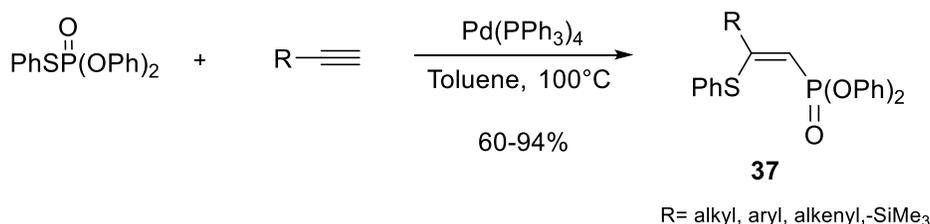
Although a mixture of regioisomers (Markovnikov and anti-Markovnikov products) was obtained from the above



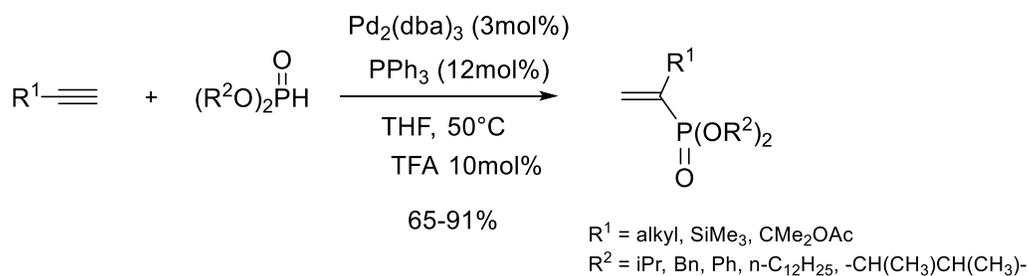
Scheme 24. Proposed mechanism for the palladium-catalyzed hydrophosphorylation of alkynes.



Scheme 25. Selenophosphorylation of alkynes.



Scheme 26. Thiophosphorylation of alkynes.

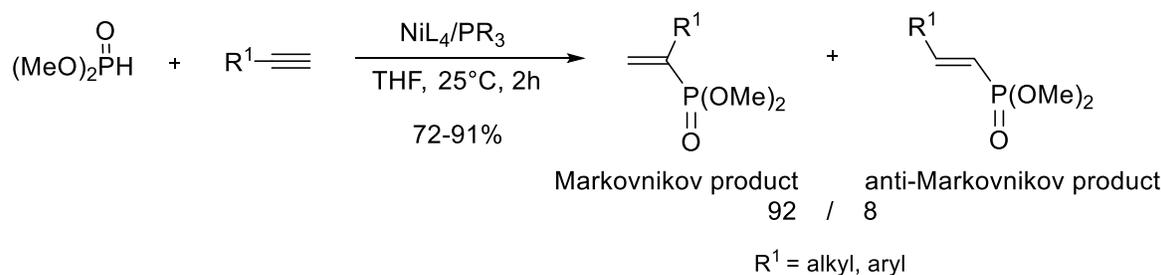


Scheme 27. Palladium-catalyzed hydrophosphorylation of alkynes leading to the Markovnikov product.

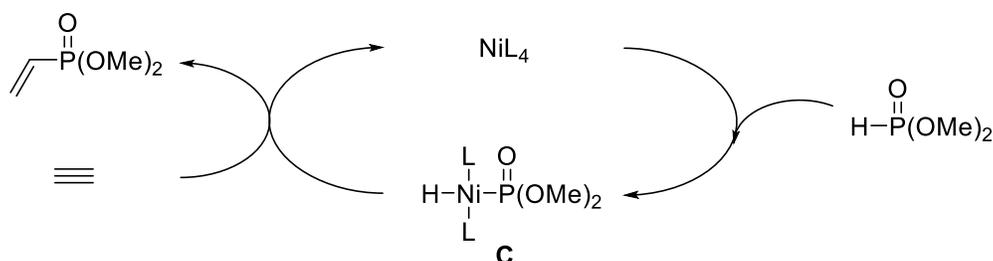
reactions, the authors found that, interestingly, selective generation of the Markovnikov product could be achieved *via* this single nickel-catalyzed reaction by slightly tuning the reaction conditions, *i.e.* by changing the nature of the phosphorus ligand in the nickel catalyst, or using diphenylphosphinic acid as additive (**Scheme 30**). The Markovnikov/anti-Markovnikov ratio was up to 94:6.

Additionally, a similar addition reaction of dialkyl phosphites onto dialkyl acetylenedicarboxylates was reported by Keglevich *et al.*^[33] to yield mixtures of mono- and bis adducts **38** and **39**, respectively (**Scheme 31**).

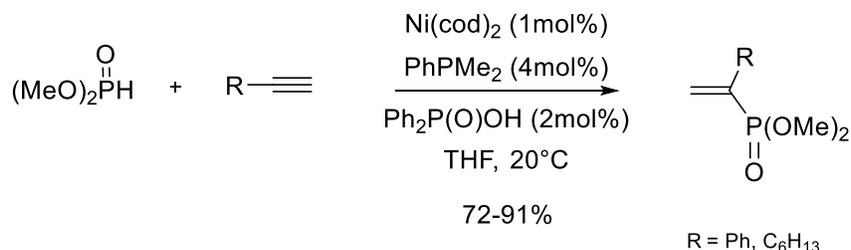
Due to the activated character of the alkyne, the reaction could be performed under solvent-free and microwave conditions, without the need of a catalyst.



Scheme 28. Nickel-catalyzed hydrophosphorylation of alkynes.



Scheme 29. Proposed mechanism for the Nickel-catalyzed hydrophosphorylation of alkynes.



Scheme 30. Nickel-catalyzed hydrophosphorylation of alkynes leading to the Markovnikov product.

2.10. Organocatalytic reactions

Organocatalysis is a valuable alternative method to transition metal catalytic substitution reactions since it prevents the eventual presence of metal residue in the final product and avoids the use of expensive catalysts. Furthermore, the organocatalyst (usually a phosphine or an amine) is easily removed by simple aqueous washing or by chromatography. This methodology was used for the synthesis of numerous vinylphosphonates.

2.10.1 Organocatalytic cyclization of allenylphosphonates

The cyclization of allenylphosphonates **40** with imines, α,β -unsaturated esters, and enones promoted by tributyl- or triphenylphosphine afforded pyrrolines, tetrahydropyridines **41** and cyclopentenes bearing phosphoryl functions^[34] (Scheme 32).

It was also shown that the use of a chiral phosphine as catalyst provided an enantioselective variant of these cyclization reactions, and afforded enantiomeric excesses of up to 90%.

2.10.2 Organocatalytic displacement reactions

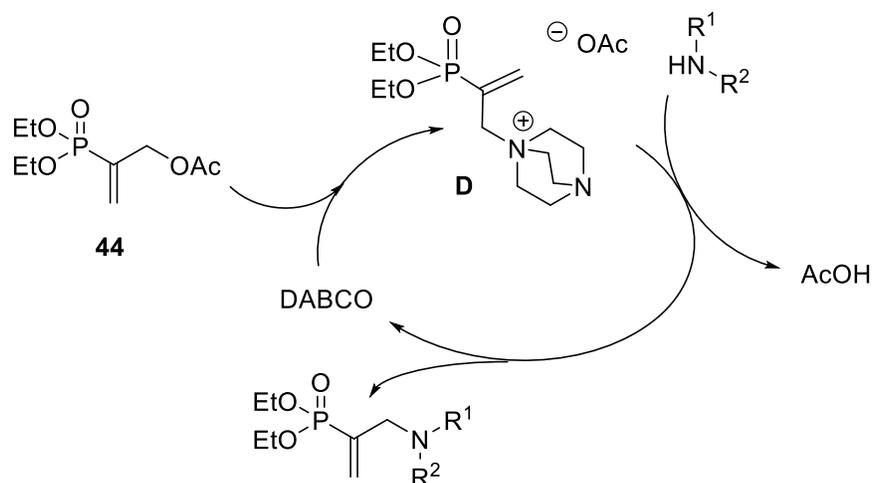
In this area, we and others have shown that acetoxyvinylphosphonates can enter organocatalytic substitution to yield

aminovinylphosphonates. Thus, Krische^[35] reported the triphenylphosphine-catalyzed substitution of acetoxy group in 2-(diethylphosphonyl)-substituted allylic acetates **42** by 4,5-dichlorophthalimide to afford (4,5-dichlorophthalimido)-phosphonic acid esters **43** (Scheme 33). Several analogues were obtained but the reactions needed somewhat harsh conditions (refluxing toluene, two equivalents of nucleophile).

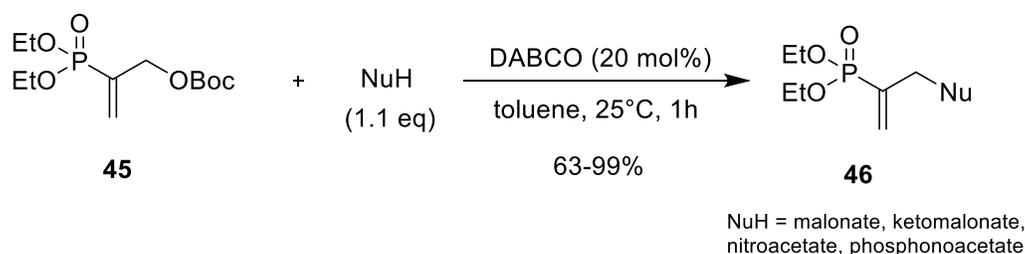
On the other hand, starting from acetoxyvinylphosphonate **44**, easily obtained from hydroxyphosphonate **4**, we were able^[36] to obtain several aminovinylphosphonates, using DABCO as organocatalyst. The reactions are easily performed at room temperature (Scheme 34).

It was also shown that the use of the organocatalyst was not necessary when using strongly nucleophilic amines. The reaction presumably proceeds *via* displacement of the acetoxy group in **44** by DABCO to generate intermediate **D**, whose further attack by the nucleophilic amine leads to the expected aminovinylphosphonate, together with organocatalyst regeneration and formation of acetic acid (Scheme 35).

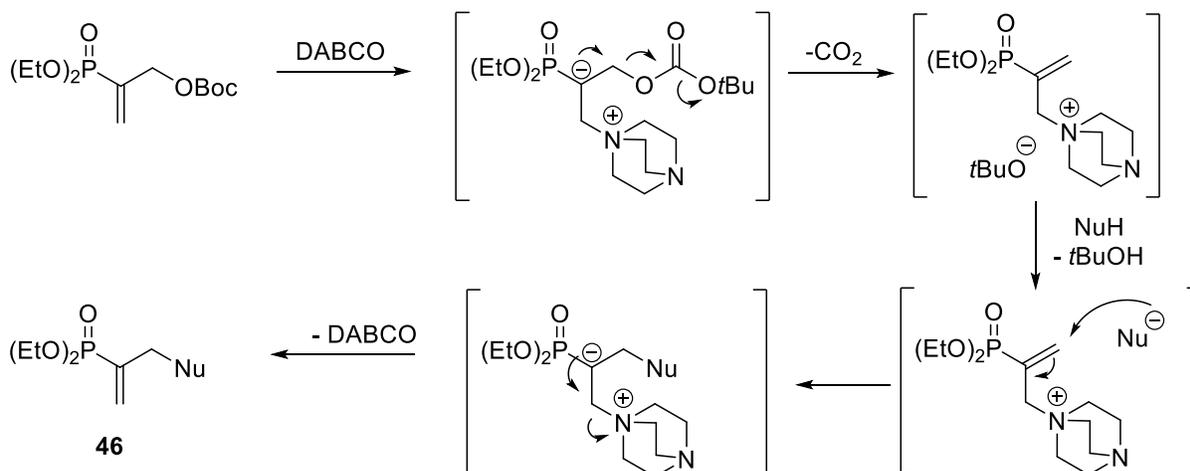
However, the reaction cannot be extended to the use of less nucleophilic reagents, typically soft carbon nucleophiles (e.g. malonate derivatives), which may be rather considered as pronucleophiles, and therefore need activation before they can act as nucleophiles. This problem was resolved through the use of another reagent diethyl 3-*tert*-



Scheme 35. Proposed mechanism for the organocatalyzed synthesis from acetoxyvinylphosphonate **44**.



Scheme 36. Organocatalyzed synthesis of β -substituted vinylphosphonates from diethyl 3-*tert*-butoxycarbonylpropen-2-ylphosphonate **45**.



Scheme 37. Proposed mechanism for the organocatalyzed synthesis of β -substituted vinylphosphonates from **45**.

reaction (section 2.8), organocatalytic reactions (section 2.10), and ring closing metathesis (section 2.11).

Additionally, Krawczyk^[39] reported the synthesis of the simplest aminovinylphosphonic acid **49** *via* a three steps procedure, starting from easily available reagents (Scheme 39).

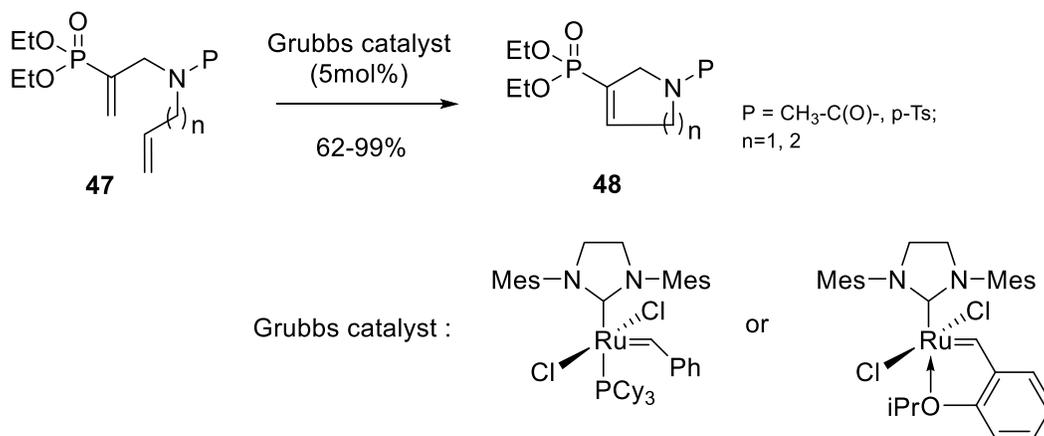
In 2002, Tardella^[19] described a two steps synthesis of α -hydroxy- β -amino-phosphonates **50** from aminovinylphosphonates (Scheme 40). Thus, ozonolysis of the double bond in **51**, followed by borohydride reduction led to the expected products with good yields.

The structure of the obtained products can be found in several known compounds exhibiting biological activities

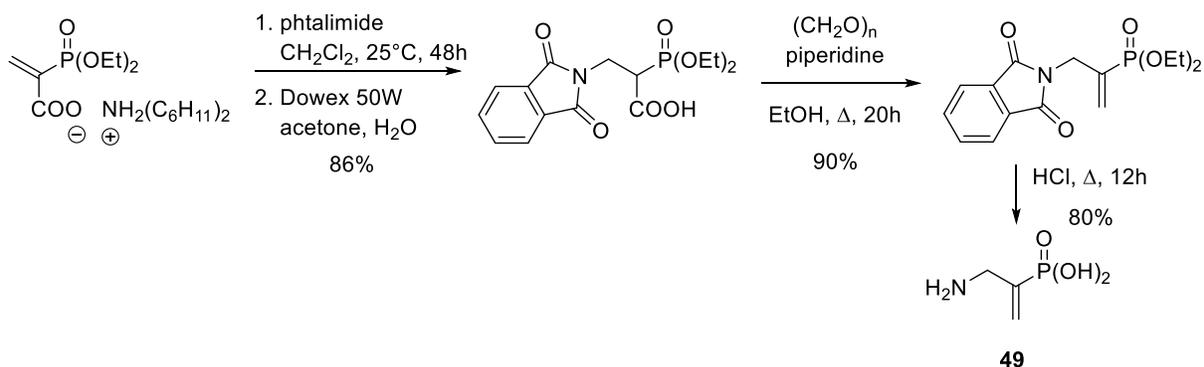
(*i.e.* Calpain I inhibitors,^[40] HIV protease transition state inhibitors,^[41] herbicide,^[42] human renin inhibitor,^[43]) (Figure 2), which might be synthesized *via* this method.

4. β -substituted vinylphosphonates as glutamate metabotropic receptors

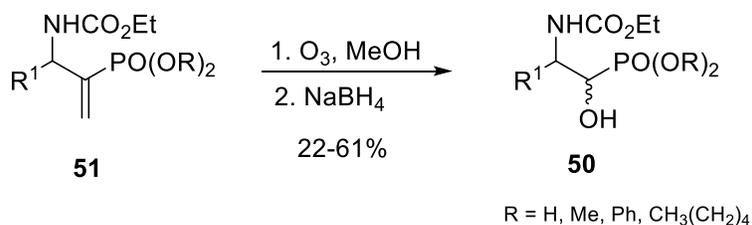
Glutamic acid is the most important neurotransmitter in the central nervous system. However, high concentrations of this amino acid may promote neurone degeneration. 2-Amino-4-phosphonobutanoic acid (AP4) isosteres are known to be efficient activators of glutamic acid receptors,



Scheme 38. Synthesis of azaheterocyclic vinylphosphonates by ring closing metathesis.



Scheme 39. Synthesis of aminovinylphosphonic acid 49.



Scheme 40. Synthesis of α -hydroxy- β -amino-phosphonates 50 from aminovinylphosphonates.

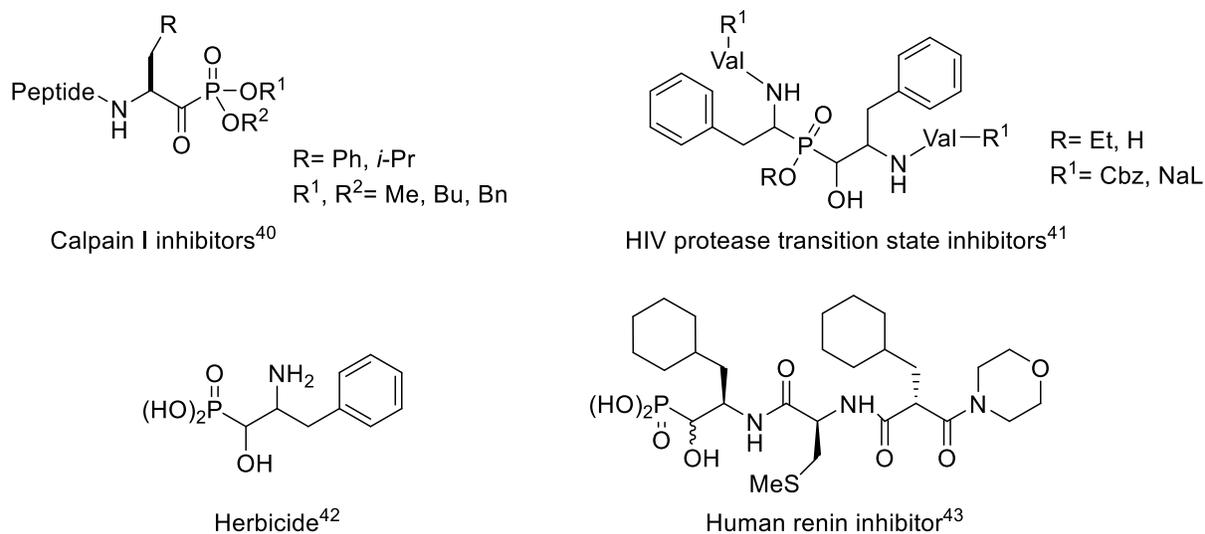
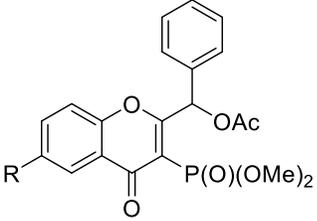
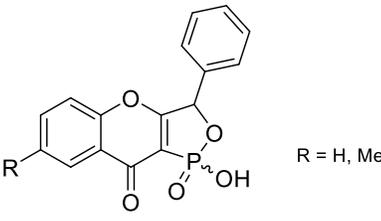
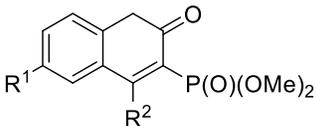
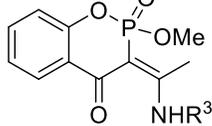
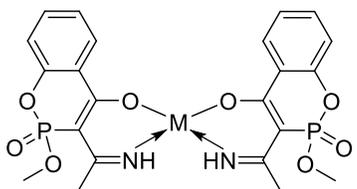
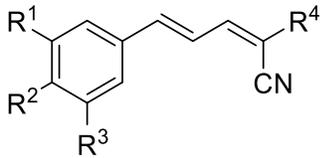
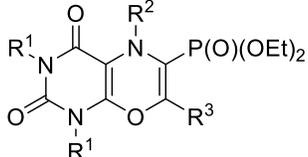
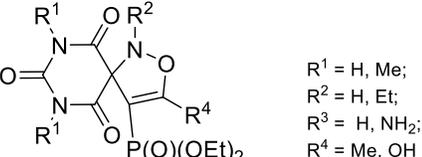
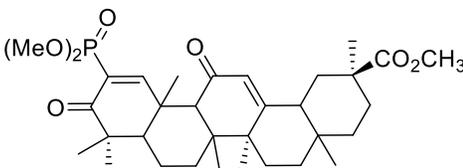
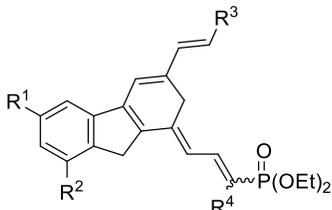
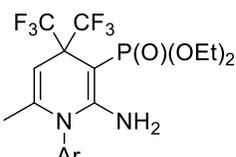
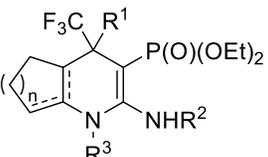


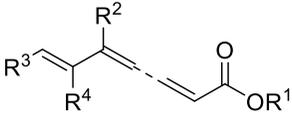
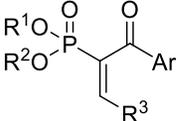
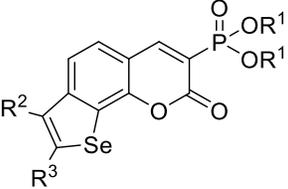
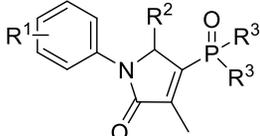
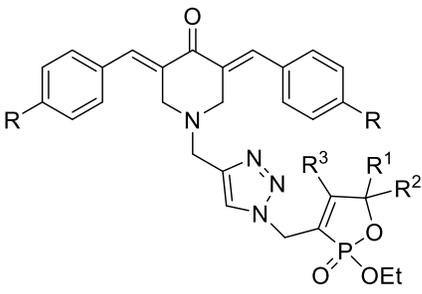
Figure 2. Several known hydroxy phosphonates exhibiting biological activities, which could be obtained from β -substituted vinylphosphonates.

Table 1. Continued.

Structure	Activity	Reference
  <p>R = H, Me</p>	<i>In vitro</i> alkylating and <i>in vivo</i> antitumor activity	[50]
  <p>R¹ = CH₃, H; R² = CH₃, Ph, (CH₂)₂P</p> <p>R³ = CH₃, (CH₂)₂OH, Bn</p>	Cytotoxic effects, alkylating properties	[51]
 <p>M = Pd, Pt</p>	Cytotoxic effects	[52]
 <p>R¹, R² = H, OH, alkoxy,...; R³ = H, NH₂, SH,...; R⁴ = NH₂, NH-alkyl, P(O)(OH)₂,...</p>	Modulator of cell proliferation	[53]
  <p>R¹ = H, Me; R² = H, Et; R³ = H, NH₂; R⁴ = Me, OH</p>	Antitumor activity	[54]
	Inhibition of bladder and pancreatic cancer cell growth	[55]
 <p>R¹ = H, Br; R² = H, OMe; R³ = C₆H₅, CH=CHC₆H₅; R⁴ = H, p-ClC₆H₄, COOEt, COOMe, CN, COOH, P(O)(OEt)₂</p>	Anti-osteoclastic bone resorption activity	[56]
  <p>R¹ = CF₃, CO₂Et; R², R³ = H, Ar; n = 1, 2</p>	Cytotoxic activity	[57]

(continued)

Table 1. Continued.

Structure	Activity	Reference
	Tak1 kinase inhibitors	[58]
	DNA intercalating properties and antitumor activity	[59,60]
	Antiproliferative agents	[61]
	Antiproliferative Agents	[62]
	Antitumor activity	[63]

and may be active against this degenerative process. Their diastereoselective synthesis was described by Ojea *et al.*^[44] (Scheme 41).

Thus, Michael addition of a lithium azaenolate onto trimethylsilylvinylphosphonate **52** leads to a phosphorus-stabilized carbanion **E** which reacts with benzaldehyde in a Wadsworth-Emmons condensation to yield a mixture of two diastereomeric precursors **53a** and **53b**, which, after separation and hydrolysis, lead to enantiomerically pure AP4 homologues **54a** and **54b**.

5. Miscellaneous known compounds

Table 1 gathers the β -substituted vinylphosphonates reported for their biological properties. Thus, their structures, and the corresponding literature reference are listed.

6. Conclusions

Vinylphosphonates possessing diverse substituents at the β -position of the alkene structure have been shown to exhibit several biological properties. These might be related to the nature of these substituents, *e.g.* amino, keto, ester,

functions, as well as their peculiar phosphonate structure. Therefore, numerous synthetic methods involving well known organic reactions were designed for their synthesis, but also more specific reactions from the field of synthetic organophosphorus chemistry (*e.g.* Michaelis-Arbuzov or Mannich reactions) were also assessed. The considered compounds often possess stereogenic centers whose structures may influence their biological behavior. However, only few enantioselective syntheses have been reported. This might presumably become a future goal for this class of organophosphorus compounds through, for example, the use of enantioselective catalytic or organocatalytic based syntheses.

Note

1. Chorismic acid is the starting point for the biosynthesis of aromatic aminoacids *via* enzymatic catalysis by chorismate mutase. Therefore, inhibition of this enzyme is of interest for the design of new antibacterial agents.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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