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Reactions of 1-alkynylphosphonates with group (IV) complexes

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Abstract

This article describes our recent methods for the synthesis of substituted vinylphosphonates by reacting 1-alkynylphosphnates with group (IV) complexes. *cis*-Vinylphosphonates, 1,3-butadienylphosphonates, 1-(hydroxymethyl)vinylphosphonates, 2-(hydroxymethyl)vinylphosphonates, (*E*) 3-oxo-1-alkenylphosphonates were produced as a result of the reactions between zirconium complexes and 1-alkynylphosphonates. On the other hand, titanium complexes afford 3-aminovinylphoshonates, 1,4-bis-phosphonates, and various other di- and tri-substituted vinylphosphonates. An evaluation of access of these recently synthesized vinylphosphonates as MMP-2 inhibitors has shown that certain compounds are very potent and promising.

Keywords: Vinylphosphonates; Gr(IV) complexes

1. Introduction

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

The preparation of vinylphosphonates is varied [8–13]. Carbocupration reactions of 1-alkynylphosphonates is an attractive approach to the synthesis of highly substituted vinylphosphonates [14]. We have recently developed new selective methods for the synthesis of various vinylphosphonates by the reaction of 1-alkynylphosphonates with group (IV) metals followed by addition of various functional groups.

2. Reactions of 1-alkenylphosphonates zirconium complexes with alkynes

Initially, *cis*-vinylphosphonates **3**, were synthesized stereoselectively by treatment of 1-alkynylphosphonates with Negishi's reagent, Cp_2Zr_2/2*n*-BuLi [15], followed by hydrolysis. Addition of various alkynes to the three-membered ring zirconacycle intermediate produced 1,3-butadienylphosphonates after hydrolysis of the five-membered ring zirconacycles **4**, **5** [16].

Compounds **6** have *E*,*E* configuration of the double bonds, and *Z*,*E* configuration for compounds **7** (Scheme 1) [20].

When terminal alkynes were added, **7** was the major isomer in all cases, apparently due to steric reasons.

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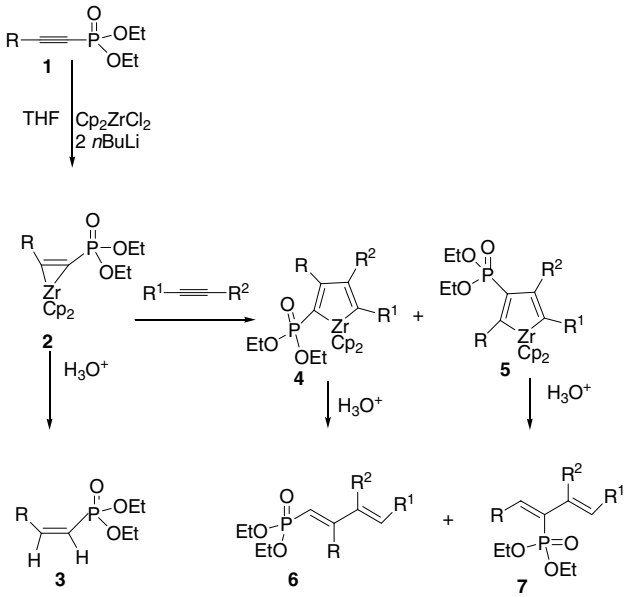


Scheme 1.

With an internal alkyne (Table 1, entry e), compound **6e** was essentially the only product isolated, **7e** being obtained in less than 3%. The regio- and the stereochemistry of compounds **3**, **6**, **7** were determined based on the values of coupling constants obtained from the NMR data.

These dienes undergo a variety of reactions including 1,3-dipolar additions,[17] cycloaddition with CH_2N_2 [18], and [2 + 2] cycloadditions [19]. In addition, these compounds possess biological activities by themselves [20].Synthesis of these compounds are few in number.

Table 1
Synthesis and isolated yields of **6** and **7**

Entry	R^2	R^1	Yield[a] (%)	
			6	**7**
a	H	C_4H_9	15	68
b	H	C_5H_{11}	19	60
c	H	Ph	11	73
d	H	C_3H_6Cl	20	57
e	C_2H_5	C_2H_5	83	<3[b]

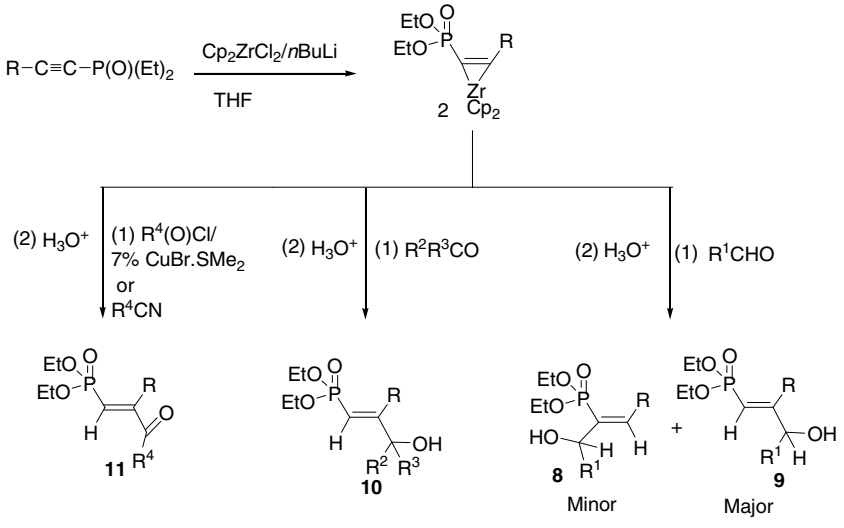
[a] Isolated yields GC–MS conversion for combined **6** and **7** was ~99% based on the starting materials.
[b] Not isolated.

In the literature there is no general method for their preparation. They have been prepared by isomerization of 1-alkynylphosphonates in the presence of palladium salts [21], Knoevenagel reaction [15], by reaction of unsaturated cyanophosphonates with *N*-tosylsulfonylimines [22].

3. Reactions of 1-alkenylphosphonates zirconium complexes with aldehydes, ketones, nitriles, and acyl chlorides

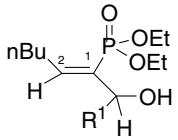
Another very useful reaction is the insertion of aldehydes into three-membered zirconacycles **2**, two five-membered zirconacycles were obtained, which upon hydrolysis gave **8** and **9** (Scheme 2) [23].

The reaction was followed by ^{31}P NMR of products **8** and **9** which absorbed in the 18–19.5 ppm range. The major product **9** (Table 3) occurs by insertion of the aldehydes into C2 of the zirconacycle, apparently due to steric factors. Evidence for this is the very low yields of **8** obtained with *o*-anisaldehyde (Table 2, entry h) and 2,4-dichlorobenzaldehyde (Table 2, entry i). In each case



Scheme 2.

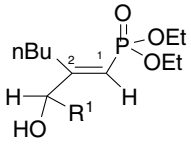
Table 2
Selected NMR data and yields of **8**



Entry	R^1	Equivalent of aldehyde	Conversion[a] (%)	Isolated yield (%)	$^3J_{PH}$ (Hz)	$^2J_{PC2}$ (Hz)	$^3J_{PC3}$ (Hz)
a	Phenyl	1.2	98	10	47	9.7	6.8
b	PhCH=CH	1.2	98	11	47	7.8	6.6
c	1,4-Benzodioxane	1.2	95	9	48	9.4	6.8
d	*p*-F-C_6H_4	2	75	11	47	9.2	6.7
e	1-Naphthyl	2	65	12	47	9.4	6.6
f	*p*-MeO-C_6H_4	2	65	7	47	9.4	6.6
g	C_6H_{13}	2	95	8	48	9.4	6.8
h	*o*-MeO-C_6H_4	2	96	<1	[b]	[b]	[b]
i	2,4-Dichloro-C_6H_3	2	70	<1	[b]	[b]	[b]

[a] The total conversion of **2** was determined by ^{31}P NMR of the crude reaction mixture.
[b] Not isolated.

Table 3
Selected NMR data and yields of **9**



Entry	R^1	Equivalent of aldehyde	Conversion[a] (%)	Isolated yield (%)	$^3J_{PC3}$ (Hz)	$^3J_{PC3'}$ (Hz)
a	Phenyl	1.2	98	75	6.8	22.2
b	PhCH=CH	1.2	98	76	6.8	21.4
c	1,4-Benzodioxane	1.2	95	71	6.8	21.5
d	*p*-F-C_6H_4	2	75	48	6.6	21.6
e	1-Naphthyl	2	65	38	6.8	21.2
f	*p*-MeO-C_6H_4	2	65	38	6.8	21.1
g	C_6H_{13}	2	95	70	7.1	21.4
h	*o*-MeO-C_6H_4	2	96	72	6.9	21.7
i	2,4-Dichloro-C_6H_3	2	70	47	6.7	22.1

[a] The total conversion was determined by ^{31}P NMR of the crude reaction mixture in the presence of a standard reference.

less than 1% of compound **8** was detected by ^{31}P of the crude reaction mixture and was not isolated. The reaction proceeds both for aromatic and aliphatic aldehydes.

Also, the regio- and the stereochemistry of the two isomers was determined by NMR analysis of the coupling constants.

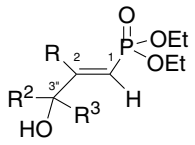
The products, **8**, are equivalent of Baylis–Hillman type carbon–carbon bond formation of alkenylphosphonates [24]. Compounds like **8** are readily converted to allenes by treatment with base under Horner–Wadsworth–Emmons conditions [25].

On the other hand, insertion of ketones into the phosphonate zirconacycles proceeds both with complete stereo- and regiospecificity, into C2 of the zirconacycle to provide after hydrolysis 2-(hydroxymethyl)vinylphosphonates, **10** (Scheme 2) [26].

Compounds, **9**, **10**, are not known in the literature, there is no method reported in the literature for the preparation of 2-(hydroxymethyl)vinylphosphonates. In addition, this straightforward, one-pot method is very general for both dialkyl-, alkylaryl-, and diarylketones. It is also suitable with cyclic and unsaturated ketones (Table 4). The reaction also proceeds very well for cyclic ketones such as cyclohexanone (Table 4, entry e) and cyclopentanone (Table 4, entry d). In addition, 2-cyclohexenone gave the doubly allylic alcohol (Table 4, entry g).

In competitive experiments, we reacted alkynes, aldehydes and ketones, with zirconacycles. We found that aldehydes and ketones insert much faster than alkynes, whereas the reaction of ketones and aldehydes occurs at about the same rate to give 1:1 mixture of products.

Table 4
2-(Hydroxymethyl)vinylphosphonates, **10**, from 1-alkynylphosphonates[a]

Entry	$RC{\equiv}CP(O)(OEt)_2$	Ketone		$^3J_{PC3,\text{(allylic carbon of R)}}$ (Hz)	$^3J_{PC3''}$ (Hz)	Yield[b] (%) ( )[c] **10**
a	R = *n*-Bu	Acetophenone	R = Bu, R^2 = Me, R^3 = Ph	8.1	21.8	85 (99)
b	R = *n*-Bu	Acetone	R = Bu, $R^2 = R^3$ = Me	8.0	21.2	87 (99)
c	R = *n*-Bu	2-Hexanone	R = Bu, R^2 = Me, $R^3 = C_2H_4$	9.4	20.9	80 (99)
d	R = *n*-Bu	Cyclopentanone	R = Bu, cyclopentyl	6.8	21.2	82 (95)
e	R = *n*-Bu	Cyclohexanone	R = Bu, R^2/R^3 = cyclohexyl	5.7	20.9	79 (96)
f	R = *n*-Bu	Tetralone	R = Bu, R^2/R^3 = tetrahydronaphtyl	5.7	24.9	81 (96)
g	R = *n*-Bu	Cyclohexenone	R = Bu, R^2/R^3 = cyclohexenyl	7.1	22.7	78 (94)
h	R = Ph	2-Hexanone	R = Ph, R^2 = Me, $R^3 = C_4H_9$	8.3	18.6	80 (99)
i	R = Ph	Acetophenone	R = Ph, R^2 = Me, R^3 = Ph	8.0	19.2	80 (99)
j	R = Ph	Acetone	R = Ph, $R^2 = R^3$ = Me	8.3	19.2	81 (99)
k	$R = Cl(CH_2)_3$	*p*-Anisylbenzyl ketone	$R = Cl(CH_2)_3$, R^2 = Bnz, R^3 = *p*-MeOPh	8.1	21.2	75 (95)
l	$R = Cl(CH_2)_3$	Acetone	$R = Cl(CH_2)_3$, $R^2 = R^3$ = Me	7.1	21.2	79 (98)
m	$R = Cl(CH_2)_3$	Cyclopropyl benzyl ketone	$R = Cl(CH_2)_3$, R^2 = Ph, R^3 = c-Pr	7.4	21.2	80 (98)
n	$R = Cl(CH_2)_3$	Benzophenone	$R = Cl(CH_2)_3$, $R^2 = R^3$ = Ph	8.6	23.3	81 (96)

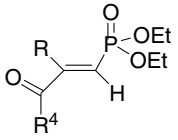
[a] The reaction was conducted in anaerobic conditions.
[b] Isolated yield.
[c] Yield determined by ^{31}P NMR.

In a further study, we discovered that the zirconacycles **2**, can easily insert either acyl chlorides or nitriles to provide after acidic workup, (*E*) 3-oxo-1-alkenylphosphonates, **11**, (Scheme 2), in isolated yields of 55–83% (see Table 5). Insertion produces only one regio- and stereoisomer [27]. The reaction is quite general and proceeds well with both aliphatic and aromatic acyl chlorides. Acetonitrile and *p*-methoxybenzonitrile also inserted efficiently. Insertion of isobutyl chloroformate was particularly interesting which produced the vinylphosphonocarboxylate, **11c**, the first representative of this class of compounds.

Unlike the acyl chlorides reactions in which 7 mole% of $CuBr \cdot SMe_2$ was necessary for the reactions to proceed, the reaction with nitriles proceeded smoothly in the absence of a catalyst.

This one-pot, direct and selective synthesis of compounds **11** is superior to other methods. Firstly, the other methods have not been shown to be general and the yields are variable, generally low and accompanied

Table 5
(*E*) 3-oxo-1-alkenylphosphonates obtained by insertion of acyl chlorides and nitriles into zirconacycles



Entry	R	R^4	Yield (%) isolated (^{31}P NMR)[c]
a	*n*-Bu	Et[a]	78 (95)
b	*n*-Bu	*t*-Bu[a]	81 (97)
c	*n*-Bu	*i*-BuO[a]	83 (97)
d	*n*-Bu	Ph[a]	65 (91)
e	*n*-Bu	2-F-C_6H_4[a]	60 (85)
f	*n*-Bu	$C_6H_5CH{=}CH$[a]	60 (87)
g	*n*-Bu	Np[a]	55 (85)
h	*n*-Bu	4-MeO-C_6H_4[b]	70 (94)
i	Ph	CH_3[a]	65 (91)
j	Ph	CH_3[b]	68 (93)

[a] Obtained from the acyl chloride.
[b] Obtained from the nitrile.
[c] Conversion to **11**% determined by ^{31}P NMR of the reaction mixture.

by many side products. Secondly, the reaction works equally well with either acyl chlorides or nitriles, with the use of one or the other depending on which is more readily available, making available novel ketones and esters.

Compounds **11** are potentially very attractive synthetic intermediates. For instance they readily undergo Diels–Alder reactions [28]. They have been used in the synthesis of thiazolehydroxyphosphonates and other heterocycles [29–32]. Enantioselective reduction of **11** by baker's yeast provided 3-hydroxy-1-alkenylphosphonates with up to 95% ee [33]. The latter compounds have been found useful in the synthesis of biologically active compounds [34,35]. However, the preparation of **11** is restricted to several procedures that provide access to a limited number of structures. Compounds **11** were initially prepared as mixtures in low yield by Michaelis–Arbusov or Michaelis–Becker reactions of 2-chlorovinylketones [36]. McClure prepared one derivative of **11** ($R = CH_3$, $R^1 = H$) by reacting NBS with 2,2,2-triethoxy1,2-oxaphospholene [37]. Maffei and co-workers [34], prepared cyclic dialkyl(3-oxo-1-alkenylphosphonates) by oxidation of the corresponding hydroxyl derivatives according to Ölher's method [31]. Thus, though proven to be useful, no general synthesis of substituted **11** has been reported to date.

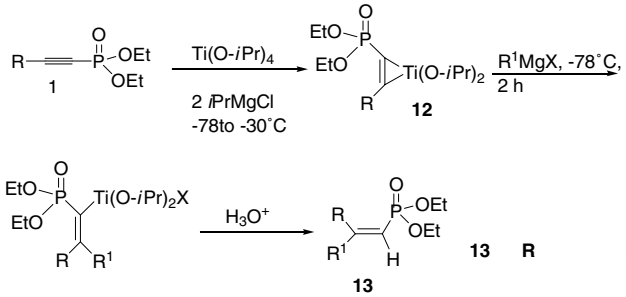
4. Reactions of 1-alkynylphosphonates with titanium complexes

4.1. Synthesis of various di- and tri-substituted vinylphosphonates

The potentially enhanced reactivity of titanacycle isopropoxides tempted our curiosity, so we decided to study the chemistry of the titanium(II) complexes [38], in order to expand the usefulness of this reagent and provide compounds not attainable with zirconacycles, **2**, thus complementing the reactions we have developed with the latter. Its preparation from relatively inexpensive starting materials makes it an attractive alternative to divalent titanacene compounds.

Many interesting new reactions involving divalent titanium isopropoxides have been developed. When the intermediate titanacycle prepared from 1-alkynylphosphonate **1**, and Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl, was reacted with an additional equivalent of R^1MgCl, followed by aqueous workup, the vinylphosphonates, **13**, were isolated (Scheme 3). This intrigued us. We assumed that two equivalent of *i*-PrMgCl went into formation of the titanacycle. The other Grignard then attacked and inserted into the Ti–C bond. The reaction did not proceed when the Grignard reagents were replaced by *n*-BuLi. Since the diisopropoxytitanacycle is a stable species at low temperature, it was reasonable to expect that replacement of the third equivalent of isopropylmagensium chloride by another Grignard would give the corresponding 1,4-addition product. This indeed proved to be the case. When phenyl- or ethylmagnesium bromide were used in step two (Scheme 3), aqueous workup provided the corresponding disubstituted vinyl phosphonates **13** [39].

Reacting an alkynylphosphonate (1 mmol), Ti(O-*i*-Pr)$_4$ (2 mmol), *i*-PrMgCl (5 mmol) followed by an acyl chloride (1 mmol) overnight with warming to room temperature provided in good yields compounds **14a–c** (Scheme 4). A possible mechanism involves the in situ formation of a ketone that then reacts with the titanacycle to form the allylic alcohol. As the previous case (Scheme 3), another Grignard may be substituted for isopropyl Grignard. Compounds **14a–c** were prepared with *i*-PrMgCl and the appropriate acyl chloride, while **14d** was prepared from BnzMgCl and **14e** from



13	R	R^1	%Isolated Yield
a	*n*Bu	*i*Pr	85%
b	Ph	*i*Pr	75%
c	$Cl(CH_2)_3$	*i*Pr	63%
d	*n*Bu	Et	83%
e	Ph	Et	77%
f	*n*Bu	Ph	84%
g	$Cl(CH_2)_3$	Et	68%

Scheme 3.

PhMgCl. The ability to select different Grignards and acylchlorides makes it possible to synthesize a very large number of compounds.

Interesting C–C bond formations occurred when the initially formed titanacycle was allowed to react with stoichiometric amounts of PhMgCl and an acid chloride (Scheme 5). Products **15** were obtained in good yields. A possible mechanism involves attack by the Grignard on an intermediate cyclopropene oxide. The sequence is equivalent to *syn* addition of a Grignard followed by an aldehyde [23,26,27].

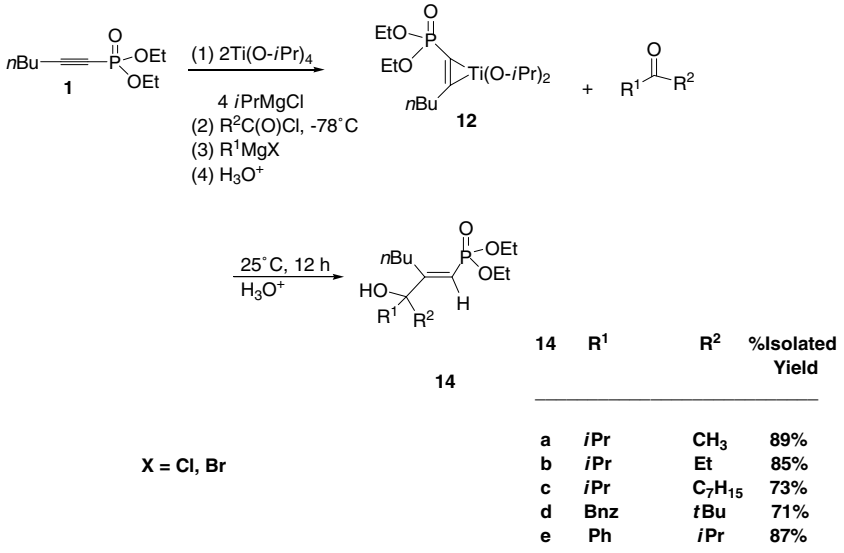
The reaction takes a somewhat different course when a Cu(I) catalyst (10 mol%) is added, followed by an acyl chloride. Under these conditions, double insertion with C–C bond formation occurred to give **16** (Scheme 6).

The reactions described here between titanacycles derived from 1-alkynylphosphonates, **1**, Grignards and electrophiles are novel and provide access to new vinylphosphonates that can be summarized the Scheme 7.

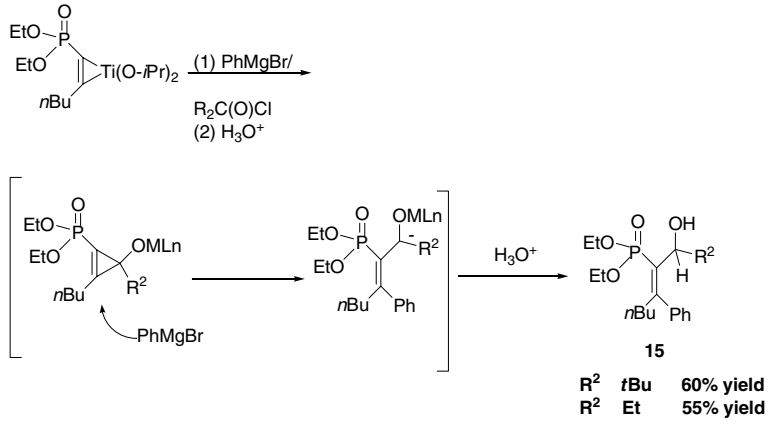
4.2. Synthesis of 3-aminovinylphosphoantes

Another advantage of the titanium(II) complex over the zirconium(II) complex was our successful preparation of 3-amino-1-alkenylphosphonates by addition of imine to the alkynylphosphonate titanium(II) (Scheme 8) [40].

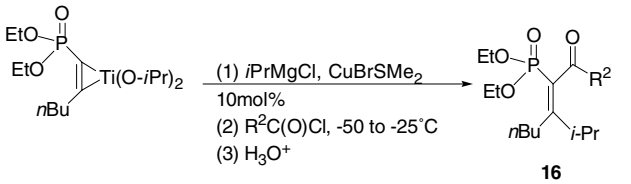
Various types of imines efficiently reacted with the alkynylphosphonate titanium(II) complex **12**, prepared from 1-alkynylphosphonates, and $Ti(O\text{-}i\text{-}Pr)_4/2$ *i*-PrMgCl to produce the desired 3-amino-1-alkenylphosphonates in high yields as shown in Table 6 (**11**). This one-pot reaction is general and proceeds with aliphatic and aromatic substituents on both the



Scheme 4.



Scheme 5.



16

16	R^2	%Yield
a	*t*Bu	78%
b	Ph	30%
c	Et	35%

Scheme 6.

vinylic carbon and the nitrogen atom of the imine, in high yields.

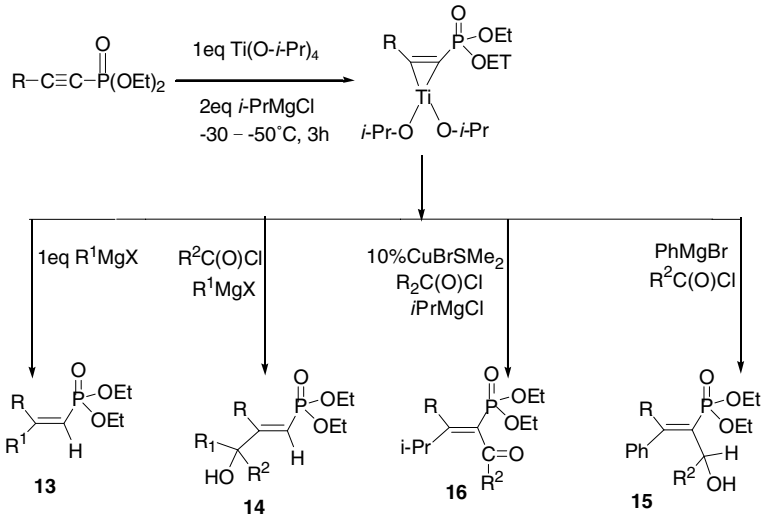
Only one isomer of the 3-aminovinylphosphonate was produced, in which carbon-carbon bond formation occured on C2 of the titanacycle. This regioselectivity seems to be controlled by steric factors.

4.3. Synthesis of 1,4-bis-phosphonates

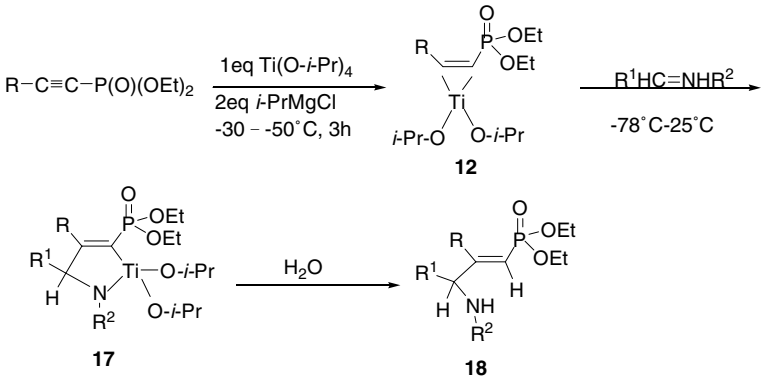
When the diethyl 1-hexynylphosphonate was reacted with two equivalent of the Ti(O-*i*Pr)$_4$/2 *i* PrMgCl reagent [41], allowed to warm to 25 °C and hydrolyzed, an unexpected compound was formed. Dimerization had occurred not to give the expected 1,3-butadienylphosphonate but rather the 1,4-bisallylphosphonate **21** [2-butyl-3-(diethoxy-phosphorylmethyl)-hept-2-enyl]-phosphonic acid diethyl ester which was isolated as the only product in about 75% yield (Table 7).

Four deuterium atoms were incorporated to **22** which can be explained by four C–Ti bonds in **20**. This means that two Ti atoms were incorporated into the intermediate precursor leading to **21** or **22**. A possible structure accounting for deuterium incorporation would be a 5,6-titanio-bicyclo[2.1.1]hexane **20.** Binuclear complex **20** could be generated from the initially formed cyclization product, **19,** by the presence of an additional equivalent of the Ti(O-*i*Pr)$_4$ (Scheme 9).

When bromine and iodine were added to the intermediate **20**, compounds **23** were obtained. This can be



Scheme 7.



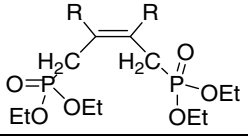
Scheme 8.

Table 6
3-Amino-1-alkenylphosphonates **18a–i** obtained from addition of imines to the alkynylphosphonate titanacycles

Entry	R	R^1	R^2	^{31}P yield[a] (%)	Isolated yield (%)
a	Ph	*p*-Tolyl	Me	97	79
b	Ph	*p*-MeO-Ph	*i*-Pr	95	78
c	*n*-Bu	Et	Bz	95	80
d	*n*-Bu	Ph	Bz	98	85
e	*n*-Bu	Ph	Ph	95	75
f	*n*-Bu	Ph	*i*-Pr	98	79
g	*n*-Bu	*p*-MeO-Ph	*i*-Pr	98	81
h	1-ClPr	Ph	Ph	95	70
i	1-ClPr	Ph	Bz	90	71

[a] Determined by ^{31}P NMR of the reaction mixture.

Table 7
Yields and selected NMR data of **21**



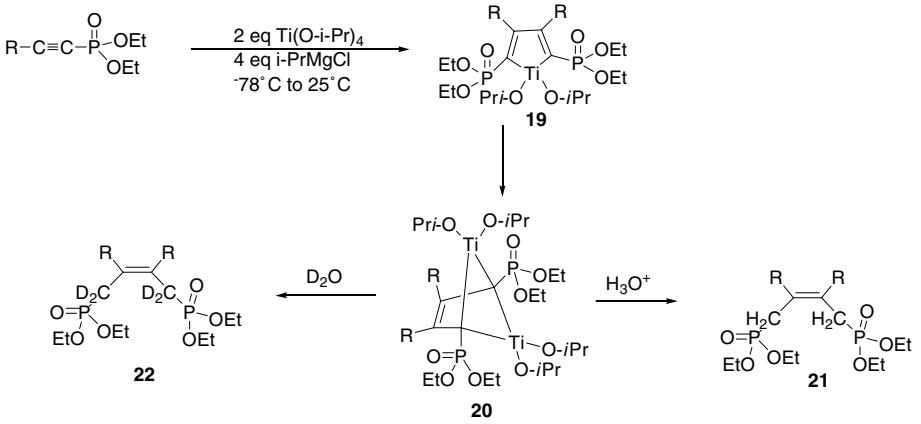
1	R	δ ^{31}P NMR	$^2J_{PH}$	Yield (%) NMR (isolated)
a	*n*-Pentyl	29.06	19.2	95 (76)
b	*n*-Bu	28.97	20.2	93 (75)
c	Ph	27.65	18.9	85 (71)
d	Cl-$CH_2CH_2CH_2$	28.39	19.2	85 (72)
e	*m*-F_3CPh	26.44	19.5	80 (63)

explained by initial complexation of the halogen with one of the titanium atoms of **20**, followed by oxidative elimination to **19** and $X_2Ti(O\text{-}iPr)_2$. The latter then is halogenated in the usual manner (Scheme 10).

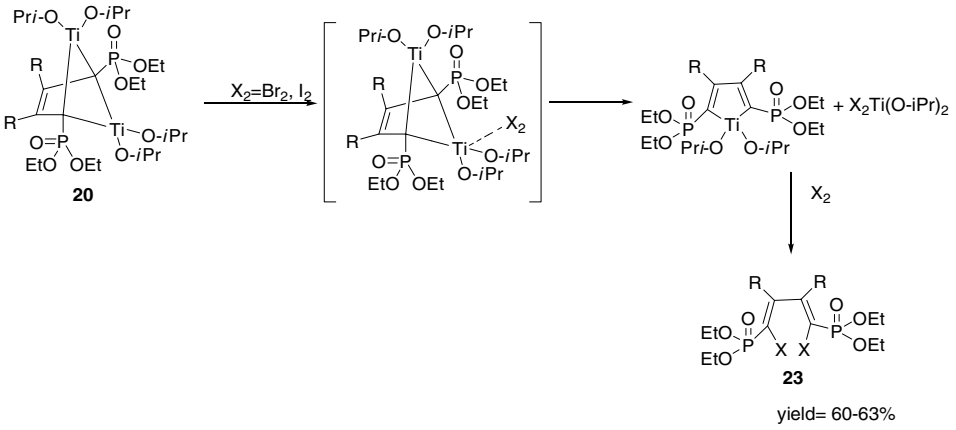
5. A comparison between zirconium and titanium complexes reactivity with 1-alkynylphosphonates

Although zirconium and titanium belong to the same group in the transition elements (group IV), many differences in reactivity between Zr (II) and Ti (II) complexes were observed, which can be summarized as follows:

(a) Unlike the addition of imines to the 1-alkynylphosphonate Ti(II) complexes which produced 3-aminovinylphosphonates in good yields, all attempts to add imines to the 1-alkenylphosphonate zirconacylces failed.
(b) New types of reactions and compounds have been obtained by tuning of $Ti(O\text{-}i\text{-}Pr)_4/i$-PrMgCl, including Grignards addition and the tri-substituted



Scheme 9.



Scheme 10.

vinylphosphonates. These reactions and compounds could not be obtained using "Cp_2Zr" intermediates.

(c) The reactions of the 1-alkenylphosphonate zirconacycles with various nucleophiles took place at room temperature. On the other hand, nucleophiles added to 1-alkenylphosphonate Ti(II) complexes at low temperature (from −30 to −50 °C). In addition, longer time was required for the reactions of zirconacycles compared to the Ti(II) complexes reactions.

(d) Both 1-alkenylphosphonate zirconacycles and 1-alkenylphosphonates Ti(II) complexes failed to insert either *n*-BuLi or chloro-diethylphosphite.

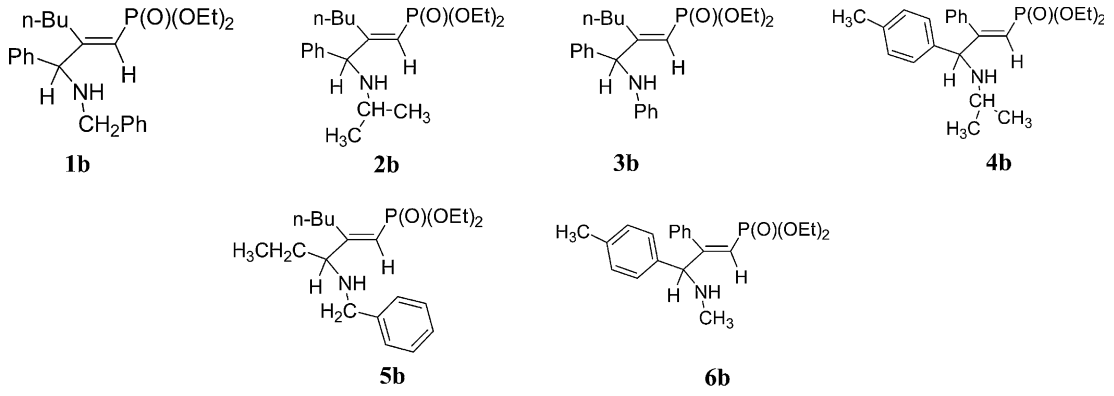
(e) Warming the reactions of 1-alkenylphosphonate zirconacycles to room temperature, produced *cis*-vinylphosphonate after hydrolysis. On the other hand, warming 1-alkenylphosphonate Ti(II) complexes above −30 °C, produced unidentified products, which is indicative that the Ti(II) complexes are not stable at temperature above −30 °C. Addition of two equivalents of Ti(O-*i*-Pr)$_4$, and four equivalents of *i*-PrMgCl to 1-alkynylphosphonates produced 1,4-bisphosphonates.

(f) An advantage of Zr(II) complexes over Ti(II) complexes was that cleaner reactions were obtained by Zr(II), apparently, due to the steric cyclopentyl ligand on zirconium, compared to *i*-propoxide ligands on titanium.

6. Biological evaluation as MMP-2 inhibitors

Various new types of vinylphosphonates and vinylphosphonic acids compounds recently prepared in our lab were tested in vitro for inhibition of matrix metallo-proteinase (MMP-2) which are a family of structurally related zinc dependent enzymes. MMPs, mainly MMP-2 which is a type IV collagenase (gelatinase) play an important role in the degradation of extracellular matrix proteins that constitute cellular connective tissue and are strongly involved in both normal and pathological tissue remodeling [42–46]. The degradative activity of MMPs is tightly controlled both by the latency of the secreted enzymes as well as by the presence of naturally occurring inhibitors including general plasma proteinase inhibitors and tissue inhibitors of metalloproteinases. Imbalance between the levels of activated enzymes and their inhibitors causes a breakdown of the extracellullar matrix [47,48]. It has been shown that MMPs play a role in primary tumor growth [49]. In addition, they mediate invasion and metastasis, which are the processes that lethally spread cancer cells through the body [50,51]. In order to maintain the balance of MMPs in these pathological process, native inhibitors, such as TIMP-1 [52], and TIMP-2 [53], have been considered for therapeutic aims. Synthetic inhibitors have been developed, such as succinyl hydroxamates, but the use of these compounds is accompanied by various problems such as low water solubility and toxicity [54], thiols [55], and more favorable phosphorous containing compounds [56].

A study of the results led us to observe that the presence of phenyl groups in the vinylphosphonate compounds does not improve inhibition. On the other hand, increasing the chain length slightly increased the inhibition. The introduction of a carbonyl group dramatically enhanced the inhibition of MMP-2 protease. The activity of the compounds varied from weak moderate to interesting, in which 3-aminovinylphosphonates, **1**–**6b**, (Fig. 1), were among the most potent and effective compounds as MMP-2 protease inhibitors as phosphonic esters even at nano molar range, specifically compounds **4b** and **5b** [57].



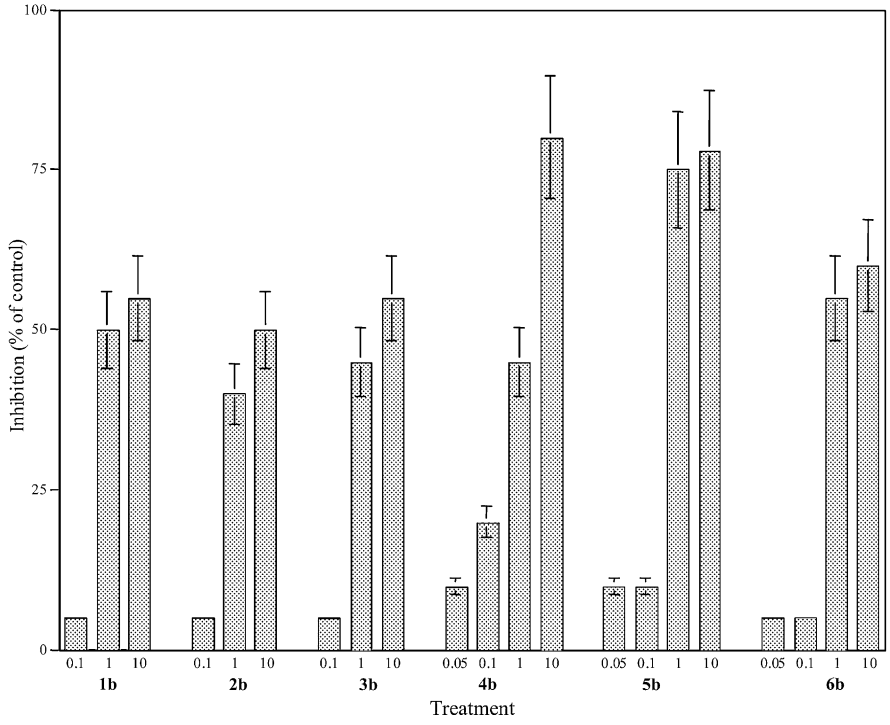


Fig. 1. MMP-2 inhibition of compounds **1**–**6b** (error bars represent the standard deviation, and the experiment was repeated three times).

These results hopefully will revive the field of MMP-2 inhibition.

In summary, various new methods for the preparation of vinylphosphonates were reported by reacting 1-alkynylphosphonate with group (IV) complexes. These methods are general, one-pot, and afford access of compounds that have not been reported in the literature before in a regio- and stereospecific manner. It was observed that generally, the reactions of Ti(II) complexes with 1-alkynylphosphonate occur in different way as with Zr(II) complexes, and afford different product. An in vitro evaluation, as MMP-2 inhibitors for a series of vinylphosphononic acids and phosphonic esters, show that various types exhibit excellent efficiency, and points towards potent, promising compounds. Other types displayed relatively weak to moderate activity.

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