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Hydrophosphonylation of alkenes or nitriles by double radical transfer mediated by titanocene/propylene oxide

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ABSTRACT

Hydrophosphonylation reactions have emerged as efficient processes for the functionalization of alkenes or alkynes. Synthesis of alkylphosphonates was achieved by an original double radical transfer mediated by titanocene and propylene oxide. By the same way, nitriles which are considered as inert functions in radical process lead to aminobisphosphonates.

Considerable efforts have been directed toward the development of radical procedures due to their high selectivity and compatibility with densely functionalized substrates.[1] Beside catalytic transformations, radical-induced chain reactions are generally considered as efficient processes. The most notable aspect of such reactions is supported by the concept of atom economy particularly when only the additions to unsaturated compounds are involved.[2]

Hydroamination reactions and hydrophosphonylations emerged recently as new methodologies for the P–C bond formation from simple and available precursors. Along with metal-catalyzed reactions using complexes of palladium,[3] rhodium,[4] nickel,[5] or even copper,[6] the radical method gained a lot of attention. Due to the nature of the weak P–H bond, P-centered radicals are easily formed in the presence of radical initiators which readily add to alkenes or alkynes. Another feature of P–H phosphorus reagents is related to the fast transfer of hydrogen to a carbon radical thus limiting the polymerization often observed when radical reactions are performed. In pioneering work, the addition of secondary phosphine oxides to terminal alkynes initiated by catalytic amount of benzoyl peroxide was reported. More recently triethylborane/oxygen was used successfully for the radical addition of P–H reagents to terminal alkenes leading to the *anti*-Markovnikov products.[7] The mildness of the radical reaction and the drawback generally associated to the use of tributyltin hydride prompted several research groups to develop alternative radical initiators. In this context, titane-centered radicals are easily formed in the presence of activated zinc and are then usually used to induce homolytical bond cleavage in substituted oxiranes. Subsequently, the newly formed radical adds to various unsaturated functions such as C=O or C=C bonds.[8]

Bisphosphonates are an important family of compounds which are used in the treatment of various bone diseases such as Paget's disease, metastatic bone disease, and osteoporosis because of their effect on the metabolism of calcium.[9] They are analogous to the naturally occurring pyrophosphate,[10] are able to inhibit the action of osteoclasts, thereby reducing the resorption of bone tissue.[11] Bisphosphonates are a well-established class of drugs[12] with important properties and several of these compounds are on the market (Etidronate **1** is used to treat osteoporosis and Pamidronate **2** to treat bone metastases in breast cancer, Fig. 1).[10] The β-aminobisphosphonate Zoledronate **3** and Risedronate **4** sodium salt are among the most

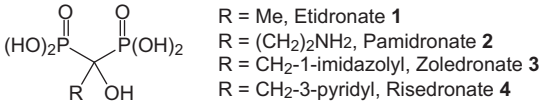

Figure 1. Structures of established bisphosphonate drugs.

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potent bisphosphonates used in therapy.[13] In the context of chemotherapy, recent development on the binding mode opened the way to the design of novel, potent enzyme and cell growth inhibitors that have weak bone-binding affinity.[14] To date little research has been conducted on α-aminobisphosphonates due to the lack of synthetic methods.[15]

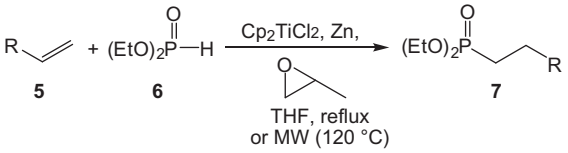
With this in mind, the synthesis of new aminobisphosphonates represents a clear interest for the pharmaceutical industry. Herein, we report a new, mild, and atom economic phosphonylation of alkenes and a double phosphonylation of nitriles to form aminobisphosphonates, using induced phosphorus-centered radicals mediated by titanocene dichloride (Cp_2TiCl_2).

Initial experiments were carried out on the phosphonylation of alkenes as model reaction using bis(cyclopentadienyl)titanium dichloride (Cp_2TiCl_2) in the presence of butene (R = *n*-butyl) **5** and diethyl phosphite **6** (Scheme 1). The results of the optimization are listed in Table 1. Initial conversions were rather low (15–66%), however, these conditions allowed to set-up the influence of each reagent. Entries 1–4 (Table 1) confirmed the necessity of zinc and the titanocene reagent. Interestingly, the hydrophosphonylation was only effective in the presence of propylene oxide. The best solvent proved to be THF with the formation of 66% of **7** while in toluene or dioxane the conversion did not exceed 24%.

In a second set of reactions, the quantities of diethyl phosphite **6** (entries 4–6, Table 1) were lowered, leading to a reduced conversion of the substrate. To insure a high yield and to limit the oligomerization of the alkene **5**, 3 equiv of **6** were used which is notably less than generally employed in radical hydrophosphorylation reactions where 10 equiv are often needed.[7b] Titanocene (5 mol %) resulted in a slight decrease of conversion (60%, entry 8). In optimized conditions, a quantitative yield of diethyl hexylphosphonate was obtained (entry 9).

Further, this titanocene-mediated hydrophosphonylation reaction was confirmed using different alkenes. Using the optimized conditions, the reaction was applied to styrene giving the *anti*-Markovnikov product in 37% yield. For internal alkenes such as cyclohexene, the hydrophosphonylation took place in only 35% yield. Therefore, the reaction was launched for 4 h at 120 °C in the MW leading to a quantitative conversion on ^{31}P NMR.

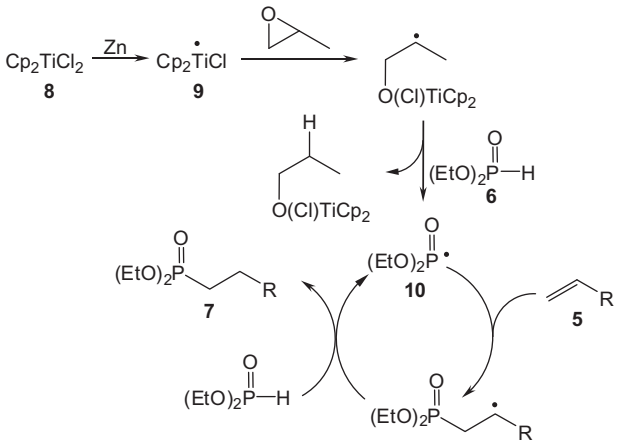
A plausible mechanism for the addition of diethyl phosphite **6** to alkene **5** is given in Scheme 2. Taking into account the required



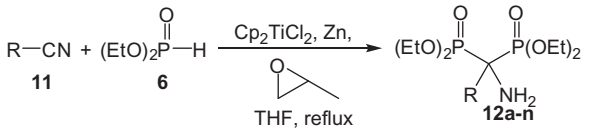
Scheme 1. Radical addition of diethyl phosphite to alkenes.

Table 1
Optimization of the hydrophosphonylation reaction conditions under microwave (R = *n*-butyl)

Entry	Diethyl phosphite (equiv)	Zn (equiv)	Cp_2TiCl_2 (equiv)	Propylene oxide (equiv)	Time (h)	^{31}P NMR yield (%)
1	3	0	0.1	2	1	0
2	3	4	0	2	1	0
3	3	4	0.1	0	1	0
4	3	4	0.1	2	1	66
5	2	4	0.1	2	2	37
6	1	4	0.1	2	2	32
7	2	4	0.1	2	3	28
8	3	4	0.05	2	2	60
9	3	4	0.1	2	2	Quant.



Scheme 2. Radical mechanism of alkene phosphonylation mediated by titanocene.



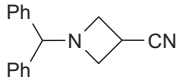
Scheme 3. Double phosphonylation of nitriles – synthesis of α-aminobis phosphonates.

Table 2
Optimization of the Ti-catalyzed phosphonylation of cyclopropylnitrile (R = cyclopropyl)

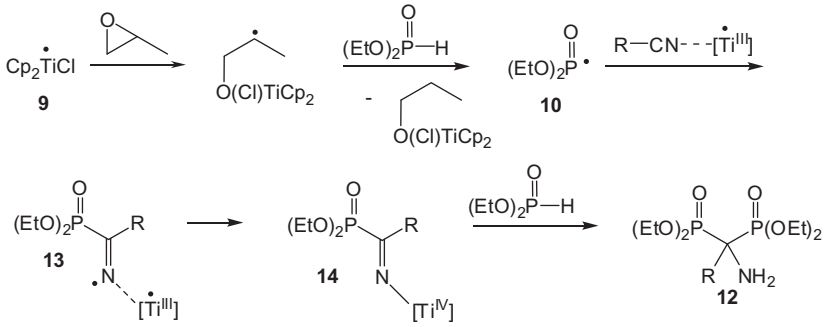
Entry	Reaction conditions	^{31}P-NMR yield (%)
1	2 equiv propylene oxide, 2 h, 120 °C (MW)	35[a]
2	0 equiv propylene oxide, 2 + 2 h, 120 °C (MW)	29 + 29[a]
3	0 equiv propylene oxide, 2 h, 140 °C (MW), THF	10[b]
4	[RCN] = 0.1 M	54[b]
5	[RCN] = 0.2 M	70[b]
6	[RCN] = 0.4 M	90[b]
7	[RCN] = 2.0 M	59[b]
8	[RCN] = 4.0 M	70[b]

[a] Entries 1–3: [RCN] = 0.2 M, 10 mol % Cp_2TiCl_2, THF.
[b] 2 equiv propylene oxide, 10 mol % Cp_2TiCl_2, 17 h, reflux, THF.

Table 3
Double phosphonylation of nitriles – synthesis of aminobisphosphonates

	R-CN	Reaction time	Isolated yield (^{31}P NMR yield)
12a	Me-CN	4 days	43 (77)
12b	*c*-Pr-CN	20 h	94 (Quant.)
12c	*i*-Pr-CN	4 days	0 (2)
12d	$Ph(CH_2)_2$-CN	3 days	25 (53)
12e	*p*-Cl-$C_6H_4CH_2$-CN	18.5 h	34 (83)
12f	FCH_2-CN[a]	4 days	48 (63)
12g	$BrCH_2CH_2$-CN	3 days	0 (10)
12h	$Cl(CH_2)_3$-CN	23.5 h	69 (78)
12i	*p*-Me-C_6H_4-CN	3 days	20 (20)
12j	2-pyridyl-CN	4 days	0 (8)
12k	$PhCH_2NH(CH_2)_2$-CN	40.5 h	0 (32)
12l		4 days	34 (98)
12m	HO_2CCH_2-CN	18.5 h	41 (88)
12n	$MeO(CH_2)_2$-CN	18.5 h	–(74)

[a] Fluorine was reduced from the end product.



Scheme 4. Radical mechanism of nitrile phosphonylation mediated by titanocene.

presence of epoxypropane, the formation of the diethyl alkylphosphonate **7** can be seen as the result of a double radical transfer reaction. Cp_2TiCl radical **9** was generated from the reaction of titanocene dichloride **8** and zinc dust and then transferred to the epoxide leading to the homolytic cleavage of the C–O bond. A second radical transfer to diethyl phosphite **6** occurred to afford the phosphorus-centered radical **10**. In the final stage, hydrophosphonylation of the alkene afforded the desired alkylphosphonate.

Generally nitriles are relatively insensitive to radical conditions and are often used as solvent. In order to determine the influence of the titanocene reagent in such a process, we attempted the reaction using cyclopropanenitrile **11** (R = *c*-propyl) and diethyl phosphite **6** (Scheme 3) in the conditions used for alkenes (3 equiv of **7**, 4 equiv of Zn, 0.1 equiv of titanocene and 2 equiv of propylene oxide). Interestingly, a double phosphonylation on the rather inert nitrile function was observed affording the α-aminobisphosphonate **12b**. The reaction conditions were therefore varied to try to increase the conversion (Table 2).

Unlike the reaction with alkenes, it can be noted that phosphonylation of nitriles can be realized in the absence of propylene oxide under microwaves (entries 1–3). However, the formation of side products was remarkably diminished when using epoxypropane. Reducing the amount of titanocene resulted in lower yield, as changing the temperature of the reaction did. Adding catalyst in two stages did not improve the conversion significantly.

Since microwave conditions are not strictly required, we also used thermal activation. In such conditions, the rate of the reaction is lower and overnight heating is required. A set of experiments was realized under thermal activation to find the optimum nitrile concentration. Optimizations were conducted using cyclopropylnitrile because it gave a better yield. It was found that a cyclopropylnitrile concentration of 0.4 M (entry 6) gave the best conversion. The amount of side-products generally tended to increase with the concentration, but remained at fairly low level for most of the reactions. Formation of by-products only became significant for the high concentrations (2.0 and 4.0 M, entries 7 and 8).

Then, the reaction was run using the best conditions (entry 6, Table 2) with a variety of different nitriles as substrates to determine the scope. The results are summarized in Table 3. It seems that generally the reaction works for alkyl nitriles (compounds **12a–d**). However, the steric hindrance induced by the isopropyl group of isobutyronitrile prevented the reaction and this nitrile did not react as well (**12c**). Surprisingly, some halogenated nitriles appeared to be compatible with these reaction conditions (**12f–h**), although the reactivity was mainly depending on the position of the halogen atom. When it is directly bounded to the alpha or gamma position, relatively high ^{31}P NMR conversions were observed. However, when the halogen is in the beta position, only small amounts of the desired product were obtained.

Generally, the reaction did not work for aromatic nitriles. When it was effective the resulting yields remained quite low (compounds **12i** and **12j**). Stabilisation due to conjugation might be the reason for this low reactivity. For α-aminomethylnitrile, the reaction did not proceed. When a nitrogen atom occupied the beta position, only low yields were obtained for the secondary amines. By contrast, the tertiary amino nitrile gave a good yield (**12n**).

The main difficulty encountered in this reaction was the purification due to the presence of residual diethyl phosphite **6**. Although it would be possible to isolate most of the aminobisphosphonates **12** using column chromatography, a significant amount was lost during this process as such derivatives were highly polar.[16]

From a mechanistic point of view, the formation of bisphosphonate **12** clearly suggests that radical reaction on the cyano group occurs in such a process. The Cp_2TiCl reagent **9** has unambiguously an influence on the behavior of the reaction as no reaction was observed when acetonitrile was reacted with diethyl phosphite with AIBN or with triethyl borane/air. It has been recently proposed that complexation of the nitrile to titanium might occur thus enhancing the radical acceptor character of the cyano group by lowering its LUMO.[17] According to these results, we could propose the mechanism depicted in the Scheme 4. Then, the diethyl phosphonyl radical **10** could add to the titane (III)-activated nitrile leading to the formation of the coordinated iminyl radical **13** which further evolved to afford the N–Ti bond intermediate **14**. The addition mechanism of the second diethyl phosphite remains unclear as both radical and nucleophilic additions to the imino intermediate are possible leading to the bisphosphonate **12**.

In conclusion, titanocene dichloride/zinc reagent has proven for the first time to generate phosphorus radicals. It was successfully employed in the hydrophosphonylation of alkenes by a double radical transfer offering an alternative method to the existing ones. This procedure also proved to be particularly effective in the reaction of nitriles which generally exhibit low or no reactivity under radical conditions. In this way, alkyl aminobisphosphonates can be synthesized in moderate yields.

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16. General procedure for the Ti-mediated double phosphonylation of nitriles: To a mixture of Cp_2TiCl_2 (1.2 mmol) and activated Zn powder (48 mmol), under a nitrogen atmosphere, is added deoxygenated THF (30 mL). To this mixture, nitrile (12 mmol, 0.4 mol mL^{-1}); diethyl phosphite (48 mmol); and propylene oxide (24 mmol) are successively added. The reaction mixture is heated to reflux, with continuous stirring, until no further formation of products can be observed by ^{31}P-NMR monitoring. Depending on the nature of the bisphosphonate different protocols of purification were used and are listed below. *Purification protocol by acid/base extraction:* The reaction mixture was filtered through filter paper and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 or AcOEt (30 mL) and aqueous HCl (1 M) was added. The organic layer was removed and the aqueous layer was washed once more CH_2Cl_2 or AcOEt (30 mL). The aqueous phase was basified to pH = XX with $NaHCO_3$ (1 M) and was extracted three times with CH_2Cl_2 or AcOEt. The combined organic phases are dried over $MgSO_4$ and concentrated in vacuo. *Purification protocol by column chromatography:* Purification by chromatography on silica gel using a gradient of solvents: CH_2Cl_2 to [CH_2Cl_2/EtOH, 9/1]. *Purification protocol by oxidation of the residual diethyl phosphite and extraction:* The reaction mixture is filtered through filter paper and concentrated in vacuo. The oil is redissolved in HCl (30 mL, 1 M). Hydrogen peroxide is added to the mixture (40 mL) and left to stir for 30 min. A color change from yellow, to orange, to red is observed. The mixture is basified using NaOH (25 mL, 4 M). The product is extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo.
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