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## Review on Modern Advances of Chemical Methods for the Introduction of a Phosphonic Acid Group

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### 1. INTRODUCTION

By Nature, the phosphonic acid group ( $R\text{-PO(OH)}_2$ ) is incorporated into a vast number of structural diverse molecules, which are involved in numerous biological functions. Several therapeutic candidates also comprise a phosphonic acid group with prominent examples being anticancer, antibacterial, and anti-HIV agents. From a synthetic chemistry point of view, a wide range of methodologies for the incorporation of a phosphonic acid group have been discovered and reported as early as in 1898.<sup>1</sup> Since then many advances have been made, which will allow for the introduction of the phosphonic acid group onto structurally diverse molecules under mild conditions. Most recently, catalytic methods have been developed, which in some cases have enabled enantioselective protocols.

This review provides the reader with an overview of the physical-organic chemistry properties of the phosphonic acid group in connection to medicinal chemistry aspects, together with an in depth review on advances and modern synthetic methods for its introduction compiled into sections with respect to substrate-carbon hybridization.

### 2. PHYSICAL–CHEMICAL PROPERTIES AND APPLICATIONS OF THE PHOSPHONIC ACID GROUP

The phosphorus atom is found in the fifth main and in the third row of the Periodic Table as its electron configuration is  $1s^2 2s^2 2p^6 3s^2 3p^3$ . The biologically relevant formal oxidation states of phosphorus are +III and +V with trivial names altering with respect to the chemical nature of the groups attached (Table 1).

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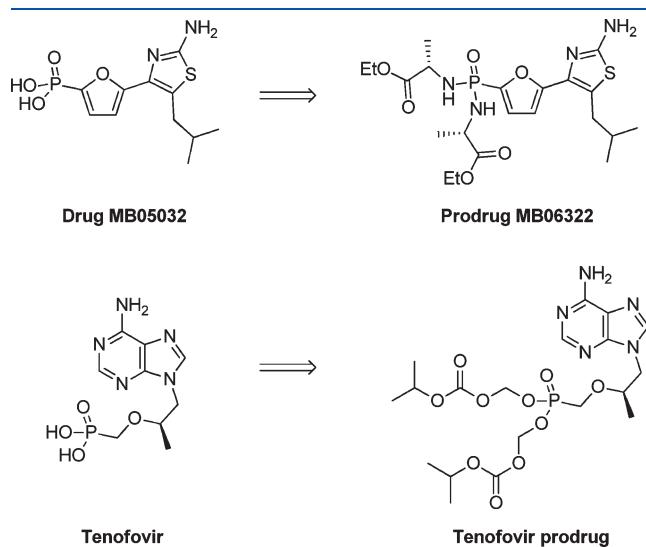
The phosphonic acid group provides unique binding interactions with a biologic target because of its trigonal pyramidal geometry, di- or trivalent chelating properties and possible dual function as a hydrogen acceptor and donor

**Table 1. Trivial Names of Biologically Relevant Phosphorus Groups and Phosphorous Atom Oxidation State**

Trivial Name	Constitutional Formula <sup>a</sup>	Formal Oxidation State
phosphine	R <sup>1</sup> R <sup>2</sup> PR <sup>3</sup>	III
phosphinite	R <sup>1</sup> R <sup>2</sup> P(OR <sup>3</sup> )	III
phosphite	P(OR) <sub>3</sub> or HPO(OR) <sub>2</sub>	III
H-phosphonate or dialkylphosphite	HPO(OR) <sub>2</sub>	III
phosphonite	R <sup>1</sup> P(OR <sup>2</sup> ) <sub>2</sub>	III
trialkylphosphite	P(OR) <sub>3</sub>	III
phosphate	PO(OR) <sub>3</sub>	V
phosphinate	R <sup>1</sup> R <sup>2</sup> PO(OR <sup>3</sup> )	V
phosphine oxide	R <sup>1</sup> R <sup>2</sup> R <sup>3</sup> PO	V
phosphinic acid	R <sup>1</sup> R <sup>2</sup> PO(OH)	V
phosphonate	R <sup>1</sup> PO(OR <sup>2</sup> ) <sub>2</sub>	V
phosphonic acid	RPO(OH) <sub>2</sub> or ROPO(OH) <sub>2</sub>	V
phosphoric acid	ROPO(OH) <sub>2</sub>	V

<sup>a</sup> R-groups comprise a carbon atom as attachment point.

at physiological pH. In water, the pK<sub>a</sub> values for alkyl phosphonic acid have been determined to 2.6 and 7.9,<sup>2</sup> whereas for aryl phosphonic acid the corresponding pK<sub>a</sub> values are 1.42 and 6.92.<sup>3</sup> Introduction of substituents in the vicinity of the phosphonic acid group may influence the



**Figure 1.** Chemical structure of the phosphonic acid comprising drugs MB05032<sup>18</sup> and Tenofovir<sup>13b</sup> and their corresponding prodrug.

**Table 2. Recent Examples of Potential Therapeutic Agents which Comprise a Phosphonic Acid Moiety**

Entry	Structure	Biological target and function	Disease(s)
1 <sup>a</sup>		metallo-β-lactamase inhibitor	Used in co-administration with antibiotic therapy
2 <sup>b</sup>		5'-adenosine monophosphate (AMP) inhibition	Type 2 diabetes mellitus
3 <sup>c</sup>		P2X receptor activation	Heart failure
4 <sup>d</sup>		Inhibitor of the <i>P. falciparum</i>	Malaria
5 <sup>e</sup>		Chain terminator at the DNA polymerase level (reverse transcriptase)	Cytomegalovirus retinitis Human papilloma-, pox-, adeno-, and polyoma virus infections
6 <sup>f</sup>		Chain terminator at the DNA polymerase level (reverse transcriptase)	AIDS (HIV) and HBV

<sup>a</sup> From ref 9b. <sup>b</sup> From ref 6b. <sup>c</sup> From ref 10. <sup>d</sup> From refs 12 and 14. <sup>e</sup> From ref 15. <sup>f</sup> From ref 13a and 16.

$pK_a$  value because of their physical chemical nature.<sup>2,4</sup> In respect to water solubility properties, aryl phosphonic acids display lower logP values (no substituents: 0.88, with interval

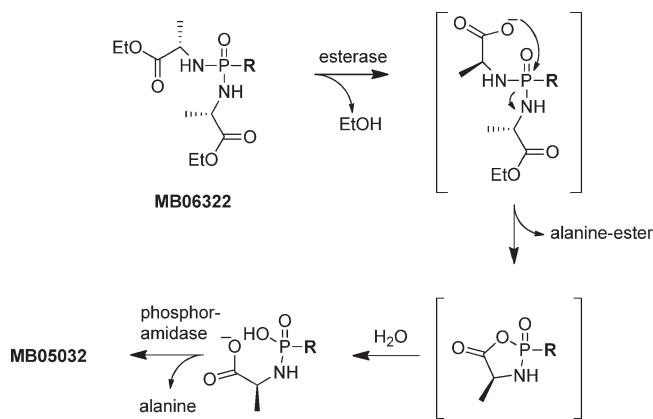
of 0.88–1.70) as compared with the corresponding aryl carboxylic acid (no substituents: 2.04, with interval of 1.57–2.62),<sup>3</sup> which makes it an attractive bioisoster in medicinal chemistry research.

The use of a phosphonic acid group in drug discovery has proven successful in many cases, and over the past 10 years a number of new therapeutic agents for various diseases such as diabetes,<sup>5,6</sup> asthma,<sup>7</sup> inflammation,<sup>8,9</sup> heart failure,<sup>10</sup> cancer,<sup>5,11</sup> malaria,<sup>12</sup> and HIV<sup>13</sup> have been discovered. Examples are listed in Table 2.

In the event that the drug candidate shows poor bioavailability, prodrug strategies for the phosphonic acid group has been developed.<sup>15b,17</sup> Examples are phosphonic diamide **MB06322** (Figure 1), which is a prodrug of fructose 1,6-bisphophatase inhibitor, **MB05032**,<sup>18</sup> and phosphonate ester<sup>13b</sup> of the HIV drug Tenofovir.

Two enzymes are required for the release of **MB05032** from its prodrug **MB06322**. The first enzyme is an esterase, which hydrolyses one of the two ethylesters to give the free carboxylic acid and EtOH as byproduct. Hereafter, an intramolecular rearrangement takes place and a cyclic intermediate

**Scheme 1. Mechanism for the in Vivo Activation of the Phosphonic Diamide Prodrug MB06322<sup>18</sup>**

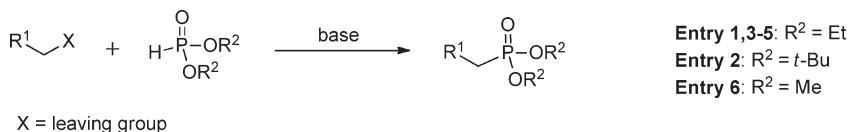


**Table 3. Examples of Introduction of the Dialkyl Phosphonate Group onto an sp<sup>3</sup>-Hybridized Carbon Atom by use of Trialkyl Phosphite as the Reagent (the Arbuzov Reaction)**

Entry	Substrate	Product	Solvent	Temp (°C)	Time (h)	Yield (%)		
							R <sup>1</sup> X	R <sup>2</sup> O <sup>2</sup> P(OR <sup>2</sup> ) <sub>2</sub>
1 <sup>a</sup>			DMF	140	--	50		
2 <sup>b</sup>			neat	135	5	57		
3 <sup>c</sup>			neat	150	--	51		
4 <sup>d</sup>			neat	150	4	80		
5 <sup>e</sup>			neat	150	8	95		
6 <sup>f</sup>			neat	reflux	2.5	86		
7 <sup>g</sup>			benzene	80	2	98		
8 <sup>h</sup>			neat	190	3.17	79 <sup>i</sup>		
9 <sup>h</sup>			neat	190	3.17	81 <sup>i</sup>		
10 <sup>h</sup>			neat	170	0.17	84		

<sup>a</sup> From ref 21c. <sup>b</sup> From ref 21d. <sup>c</sup> From ref 21e. <sup>d</sup> From ref 21f. <sup>e</sup> From ref 21a. <sup>f</sup> From ref 21b. <sup>g</sup> From ref 22. <sup>h</sup> From ref 23. <sup>i</sup> GC-MS yields. — indicates data not available.

Table 4. Michaelis Reaction Illustrated by Recent Examples



Entry	Substrate	Product	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			CsCO <sub>3</sub>	DMF	rt	24	97
2 <sup>b</sup>			NaH	THF	reflux	20	95
3 <sup>c</sup>			KHMDS	THF	0 to 25	12	91
4 <sup>d</sup>			NaH	THF	-78 to rt	overnight	84
5 <sup>e</sup>			NaHMDS	THF	-10	1	78
6 <sup>f</sup>			NaH	THF	rt	24	32-98

<sup>a</sup> From ref 24a. <sup>b</sup> From ref 24c. <sup>c</sup> From ref 24d. <sup>d</sup> From ref 24e. <sup>e</sup> From ref 24f. <sup>f</sup> From ref 21b.

is formed. Upon hydrolysis ring-opening takes place to provide an intermediate, which is a substrate for the enzyme phosphoramidase. Eventually the active drug MB05032 (Scheme 1) is released.<sup>18</sup>

In summary, the physical-chemical properties of the phosphonic acid group are distinct from a carboxylic acid group in terms of solubility, polar surface area, and binding properties to pharmacological targets. Thus, the phosphonic acid group is a potentially interesting carboxylic acid bioisoster, which may in many cases be valuably employed in structure–activity relationship (SAR) studies.

### 3. MODERN CHEMICAL METHODS FOR THE INTRODUCTION OF A PHOSPHONIC ACID GROUP

A review of modern chemical methods for the introduction of a phosphonic acid group is presented in the following section. For readability the various methods are first classed with respect to the hybridization state of the reacting carbon atom, then second by reagents or catalysts. Furthermore, reaction mechanisms have been included and discussed for selected reactions.

#### 3.1.0. Introduction on an $sp^3$ Hybridized Carbon

**3.1.1. Arbuzov Reaction.** The *Arbuzov* reaction was discovered in 1898 by August Michaelis<sup>1</sup> and subsequently explored in details by Aleksander Arbuzov.<sup>19,20</sup> Because of its simplicity, this reaction is still often used for the introduction of a phosphonic acid group via a dialkyl phosphonate intermediate. In brief, the reaction takes place between a nucleophilic phosphite and an electrophilic alkyl halide under elevated

temperature (135–150 °C) to give the dialkyl phosphonate in a moderate to high yield (50–95%) (Table 3). Subsequently, the phosphonate ester can be hydrolyzed to the corresponding phosphonic acid group by various methods (section 4).

On the mechanism, the first step of the *Arbuzov* reaction is nucleophilic attack by the phosphorus atom of the trialkyl phosphite at the electrophilic alkyl halide by an  $S_N2$  mechanism (entry 1–6, Table 3) or at an *in situ* generated carbocation by an  $S_N1$  mechanism (entry 7, Table 3) to give a phosphonium intermediate. The displaced halide anion consecutively reacts with one of the alkoxy moieties of the phosphonium intermediate via an  $S_N2$  mechanism to give the desired product and the corresponding alkyl halide. The driving force for the reaction is the formation of the P=O bond.

Examples listed in Table 3 shows that both saturated- (entry 1–2) as well as activated alkyl halides (entry 3–6) are suitable substrates, and highest yields are in general obtained for the latter group.<sup>21</sup> One noteworthy substrate is triphenylmethylchloride (entry 7), which is readily converted to its corresponding dialkyl phosphonate at only 80 °C and mechanistically via an  $S_N1$  pathway.<sup>22</sup> During the reaction, competition between the alkyl halide substrate and the alkyl halide formed constitute an increasing problem. This problem can be overcome by using an alkyl phosphite reagent, which generates a less reactive alkyl halide than the substrate electrophile. Alternatively, a phosphonate reagent with low molecular weight such as trimethyl- or triethyl phosphite may be used (Table 3) to produce a low boiling alkyl halide as byproduct, which can be removed during the reaction

**Table 5. Examples of the Reaction<sup>a</sup> of Various Benzyl Halide Derivatives with Diethyl Phosphonate<sup>25</sup>**

$\text{R}-\text{X}$	$\text{H}-\text{P}(\text{OEt})_2-\text{OEt}$	$\text{R}-\text{P}(\text{OEt})_2-\text{OEt}$	86–99%
$\text{X} = \text{Cl}, \text{Br}, \text{I}$			
Entry	Substrate	Product	Yield <sup>d</sup> (%)
1			89
2			88
3			87
4			96
5			90
6			86
7			92
8 <sup>b</sup>			92
9 <sup>b</sup>			99
10 <sup>c</sup>			90

<sup>a</sup> Reagents and conditions:  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$  (0.025 equiv), Xantphos (0.05 equiv), *N,N*-diisopropylethylamine (1.2 equiv), reflux, THF, 4 h. <sup>b</sup> Base (2.5 equiv). <sup>c</sup>  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$  (0.04 equiv), Xantphos (0.08 equiv), 6 h.

<sup>d</sup> Determined by  $^{31}\text{P}$  NMR spectroscopy.

to avoid the competition between the two different alkyl halides.

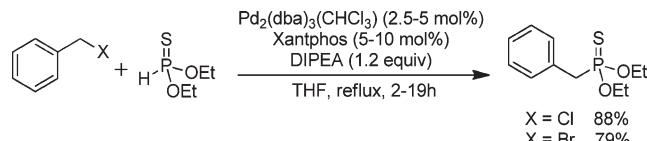
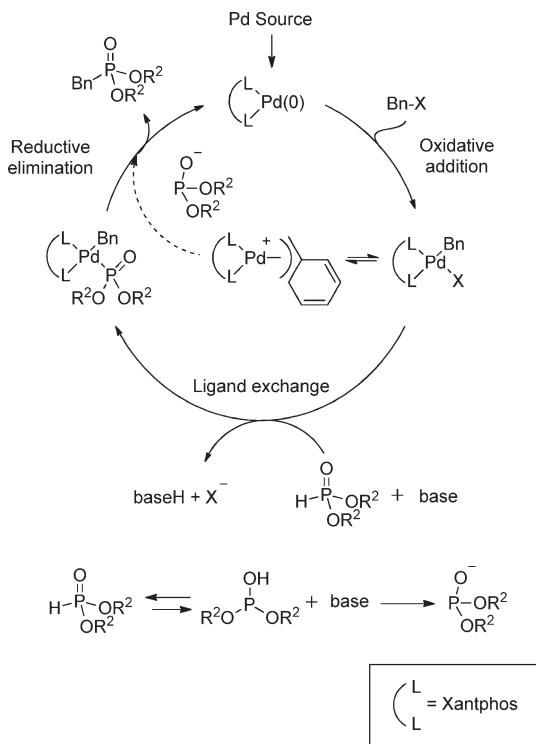
An efficient and green microwave-assisted synthesis of haloalkylphosphonates was developed by Jansa et al. (entry 8–10, Table 3).<sup>23</sup> This method provides an alternative solution for the introduction of phosphonates on volatile reagents. Moreover, the formation of byproducts can be prevented by accurate temperature control and the desired product is obtained in good yields (79–84%).<sup>23</sup>

A disadvantage of this method is the relatively high temperatures ( $150^\circ\text{C}$ ) required for the reaction to take place.<sup>21f</sup> Thus, temperature sensitive functional groups as well as labile protecting groups such as Boc may decompose.

**3.1.2. Michaelis–Becker Reaction.** The *Michaelis–Becker* reaction is similar to the *Arbuzov* reaction in the sense that an alkyl halide or equivalent is the electrophile; however, instead of using a trialkyl phosphite as the nucleophile a dialkyl phosphonate is used in presence of a base (Table 4).<sup>21b,24</sup> The most often applied base is  $\text{NaH}$ , which deprotonates the phosphate, thereby enabling nucleophilic attack on the electrophilic alkyl halide via an  $S_{\text{N}}2$  pathway.

Examples in Table 4 show that a wide range of different electrophiles may be employed. For example, both mesylates and halides are suitable substrates for the reaction and provide the

**Scheme 2. Catalytic Cycle for Palladium(0)-Mediated Benzyl-Phosphonate Formation<sup>25</sup>**



**Figure 2. Examples of the introduction of *H*-phosphononate diesters on benzyl halides.<sup>25</sup>**

desired products in high yields (78–98% with the exception of entry 6, Table 4). Use of microwave irradiation has in some cases been successfully applied reducing the reaction times without affecting the yields.

Both the *Arbuzov* reaction and the *Michaelis–Becker* reaction are effective and complementary stoichiometric strategies for the introduction of a dialkyl phosphonate group. Whereas the *Michaelis–Becker* reaction is carried out at room temperature and is thus compatible with thermally sensitive compounds, the *Arbuzov* reaction is advantageous in cases where a strong base is not tolerated.

**3.1.3. Palladium-Catalyzed Reactions.** An alternative approach for the introduction of a dialkyl phosphonate group onto a benzyl halide is by a palladium(0)-catalyzed cross-coupling reaction, originally developed by Laven et al. (Table 5).<sup>25</sup> The first publication described the use of palladium(II) acetate [ $\text{Pd}(\text{OAc})_2$ ],<sup>26</sup> but shortly after, it was reported that tris(dibenzylideneacetone) dipalladium(0)-(chloroform) [ $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$ ] was superior with respect to reproducibility.<sup>25</sup> In both strategies, the bidentate ligand Xantphos is used with *N,N*-diisopropylethylamine (DIPEA)

**Table 6.** Introduction of a Dialkyl Phosphonate Group by Metal–halogen Exchange or Grignard Reagents

Entry	Substrate	Product	Reagent	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			LiNp, <i>n</i> -BuLi	THF	-40	Overnight	70
2 <sup>b</sup>			LiN(SiMe <sub>3</sub> ) <sub>2</sub> , <i>t</i> -BuLi	THF	-100	2	62
3 <sup>c</sup>			Mg	Et <sub>2</sub> O	reflux	Overnight	21

<sup>a</sup> From ref 29. <sup>b</sup> From ref 30. <sup>c</sup> From ref 31.

as the base.<sup>25,26</sup> Moreover, Stockland et al. showed that a large bite angle of the bidentate phosphine ligand is advantageous as it accelerates the reductive elimination step.<sup>27</sup> The methodology allows for both electron-deficient and electron-rich benzyl halides as substrate and affords the desired product in high yield (86–99%) (Table 5).<sup>25</sup> In addition, the reaction takes place selectively at the benzyl halide functionality and does not react with an aryllic halide if present (entry 4–6, Table 5). The reaction may also occur with compounds comprising heterocycles as exemplified by pyridine and furan (entries 8 and 10, Table 5).<sup>25</sup>

In the presence of the Pd(0) catalyst [Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>)] and Xantphos, a reactive Pd(0)–Xantphos complex is formed, which undergoes oxidative addition to the benzyl halide substrate. This Pd(0)–Xantphos intermediate is in equilibrium with the  $\eta^3$  and  $\eta^1$ -benzylpalladium complexes (Scheme 2), which upon reaction with diethyl *H*-phosphonate and DIPEA may follow two distinct, mechanistic pathways. With the  $\eta^1$ -benzylpalladium complex a ligand exchange process takes place between the phosphonate and the halide. Then, reductive elimination occurs and affords the desired product. Following the other pathway, the desired product results from ligand substitution by a Tsuji–Trost mechanism<sup>28</sup> between the  $\eta^3$ -benzylpalladium complex and a phosphite anion, which is previously formed by reaction between the base and the *H*-phosphonate (Scheme 2).<sup>25</sup> In both cases, the Pd(0)–Xantphos catalyst is regenerated.

The major disadvantage for this method is the chemical restriction to a benzylic halides as substrates.<sup>25</sup> However, this methodology also enables the introduction of a phosphonothionate moiety, which may add interesting information to a structure–activity relationship study (Figure 2).<sup>25</sup>

**3.1.4. Introduction by Metal–Halogen Exchange and Grignard Reagents.** The dialkyl phosphonate group may also be introduced by generating a carbon nucleophile via a metal–halogen exchange reaction. Subsequently, the carbon nucleophile reacts with the electrophilic phosphor reagent dialkyl chlorophosphonate to introduce the dialkyl phosphonate group. However, only few examples are described for  $sp^3$ -hybridized carbons (Table 6).<sup>29,30</sup> In general, metal–halogen exchange is mediated by a strong base such as *n*-BuLi or *t*-BuLi at  $-78\text{ }^\circ\text{C}$ .<sup>29,30</sup> Alternatively, Grignard reagents are formed by an oxidative insertion of magnesium(0) between the carbon–halogen bond at room temperature.<sup>31</sup> The corresponding lithium- or Grignard

reagent undergoes reaction with the electrophilic dialkyl chlorophosphonate to afford the desired product in moderate yields (21–70%).<sup>29–31</sup>

**3.1.5. Summary.** The *Arbuzov* and *Michaelis–Becker* reactions are commonly used for the introduction of the phosphonic acid group on an  $sp^3$  carbon via a dialkyl phosphonate intermediate. In general, both methodologies provide the desired dialkyl phosphonate product in good yields. However, while the *Arbuzov* reaction requires high temperature the *Michaelis–Becker* reaction utilizes a strong base. Thus, care must be taken as to select the method, which is compatible with the given substrate. Alternatively for benzyl halides the introduction of the dialkyl phosphonate group may be accomplished in high yields under palladium-cross-coupling conditions. The disadvantage of all of these methods is of course the need for subsequent hydrolysis of the phosphonate diester to yield the desired free phosphonic acid functionality. This topic will be discussed in section 4.

### 3.2. Introduction on an $sp^2$ -Hybridized Carbon with Retention of Hybridization

**3.2.1. Palladium-Catalyzed Reactions.** The first cross coupling reaction of an aryl halide with a *H*-phosphonate diester was described by Hirao et al. in the beginning of the 1980s with the use of palladium(0).<sup>32,33</sup> The procedure relies on the use of tetrakis(triphenylphosphine)palladium ( $\text{Pd}(\text{PPh}_3)_4$ ) as the catalyst and triethylamine as the base under solvent-free condition. Since then, many improvements have been reported in literature and most recently  $\text{Pd}(\text{OAc})_2$  has become the commonly used source of palladium. According to work by Belabassi et al., the ligand plays a crucial role for the efficiency of the coupling, as with most other cross coupling reactions, and the bidentate phosphorus ligands 1,3-bis(diphenylphosphino)propane (dppp) or 1,1'-bis(diphenylphosphino)ferrocene (dpfp) have been shown to give the best result in several cases.<sup>34</sup>

GooBen and co-workers have described a method for the palladium-cross coupling using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3$  as the catalytic system and  $\text{di}(c\text{-hex})_2\text{NMe}$  as base.<sup>35</sup> As it is shown in Table 7 (entry 1–3), good-to-high yields (80–92%) are obtained for aryl halides as substrates and the method allows for great variety of the electronic nature of substrates such as electron-poor and electron-rich benzyl moieties.<sup>35</sup> On the other hand, some

Table 7. Scope of the Palladium-Catalyzed Substitution on Aryl or Vinyl Compounds

	$R^1, X$	+	$\text{H}-\overset{\text{O}}{\underset{\text{OEt}}{\text{P}}}(\text{OEt})_2$	Pd catalyst	$\text{R}^1-\overset{\text{O}}{\underset{\text{OEt}}{\text{P}}}(\text{OEt})_2$	$R^1 = \text{Aryl, Vinyl}$	$X = \text{halogen}$	
Entry	Substrate		Product	Methods <sup>c</sup>	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>				A	Ethanol	Reflux	16	92
2 <sup>a</sup>				A	Ethanol	Reflux	16	91
3 <sup>a</sup>				A	Ethanol	Reflux	16	80
4 <sup>a</sup>				A	Ethanol	Reflux	16	0
5 <sup>a</sup>				A	Ethanol	Reflux	16	0
6 <sup>b</sup>				B	Ethanol	Reflux	48	73 80 <sup>f</sup>
7 <sup>b</sup>				B	Ethanol	Reflux	48	31
8 <sup>b</sup>				B	Ethanol	Reflux	28	60 <sup>g</sup>
9 <sup>c</sup>				C	THF	120	10min	86
10 <sup>c</sup>				C	THF	120	10min	84
11 <sup>c</sup>				C	THF	120	10min	96
12 <sup>c</sup>				C	THF	120	10min	72
13 <sup>c</sup>				C	THF	120	10min	91
14 <sup>d</sup>				D	THF	Reflux	10	90
15 <sup>d</sup>				D	THF	Reflux	4	98
16 <sup>d</sup>				D	THF	Reflux	23	92
17 <sup>d</sup>				D	THF	Reflux	1.5	92
18 <sup>d</sup>				D	THF	Reflux	3	83 <sup>h</sup>

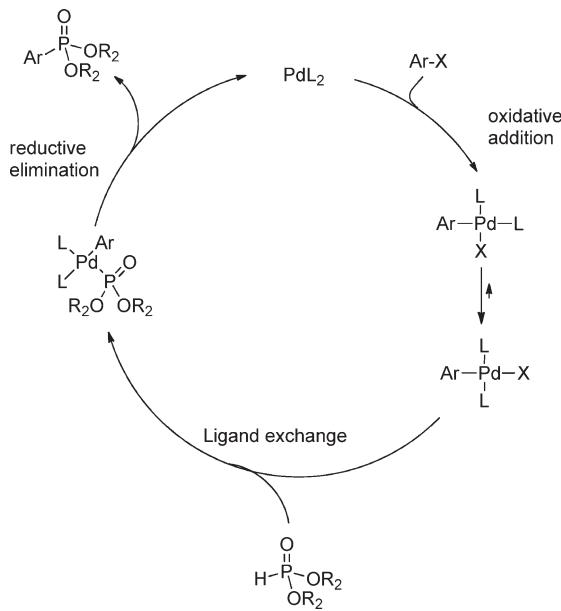
<sup>a</sup> From ref 35. <sup>b</sup> From ref 36. <sup>c</sup> From ref 37. <sup>d</sup> From ref 38. <sup>e</sup> Reagents and conditions: (A) Aryl bromide (1 equiv), diethyl phosphite (1.2 equiv), di(*c*-hex)<sub>2</sub>NMe (1.5 equiv), Pd(OAc)<sub>2</sub> (0.02 equiv), PPh<sub>3</sub> (0.06 equiv). (B) Pyridyl bromide (1 equiv), diethyl phosphate (1.2 equiv), Et<sub>3</sub>N (1.5 equiv), Pd(OAc)<sub>2</sub> (0.12 equiv), PPh<sub>3</sub> (0.30 equiv). (C) Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (1.2 equiv), diethyl phosphite (1 equiv), Ar-X or vinyl-X (1.1 equiv), microwave irradiation. (D) Pd(OAc)<sub>2</sub> (0.024 equiv), dppf (0.048 equiv), Et<sub>3</sub>N (1.2 equiv), KOAc (0.1 equiv), 15 min; then phosphine (1 equiv) and ArX (1.1 equiv) were added. <sup>f</sup> Pd(OAc)<sub>2</sub> (0.05 equiv) and PPh<sub>3</sub> (0.15 equiv) were employed. <sup>g</sup> Pyridyl bromide (1 equiv), diethyl phosphate (2.4 equiv), Et<sub>3</sub>N (3.0 equiv), Pd(OAc)<sub>2</sub> (0.12 equiv), and PPh<sub>3</sub> (0.30 equiv) in EtOH (16 mL) at reflux for 28 h under N<sub>2</sub>. <sup>h</sup> Only 1 equiv of ArX was used.

aromatic heterocycles comprising a bromide substituent are unable to react under these conditions, presumably because of

the reduced reactivity of the substrate.<sup>35</sup> The advantage of this method resides in the use of ethanol as solvent. This is advantages

in case of starting materials, which are only soluble in protic polar solvents. In general, aminopyridines are poor substrates for

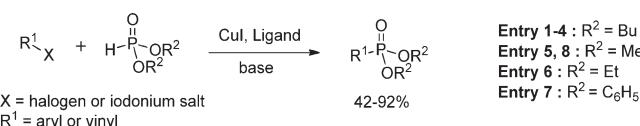
**Scheme 3. General Mechanism for Palladium-Catalyzed Reactions**



palladium-catalyzed reactions because of their strong coordination properties, which may interrupt the catalytic cycle.<sup>36</sup> To overcome these difficulties, specific conditions were developed that address the nature of the solvent as a key parameter. A detailed study identified ethanol as the solvent of choice in many cases.<sup>36</sup> However, despite this improvement the desired product is generally only obtained in low-to-moderate yields (31–80%) as shown in Table 7 (entry 6–8).

Another modification to the palladium catalyzed phosphorylation is the use of microwave irradiations as the source of heating.<sup>37,39</sup> In this case,  $\text{Pd}(\text{PPh}_3)_4$  is used as catalyst and  $\text{Cs}_2\text{CO}_3$  as base in THF.<sup>37</sup> The advantage of this protocol is the short reaction time of 10 min. Moreover, this method may be used with various substrates and affords the corresponding product in good-to-high yields (72–96%).<sup>37</sup> The cross-coupling reaction is efficient with both electron-donating and electron-withdrawing aryl compounds.<sup>37</sup> Furthermore, phosphorylation of bulky aryl groups such as phenanthrene proceed in good yields (72%).<sup>37</sup> The methodology also applies to vinyl bromides, which undergo coupling reaction with retention of the double bond configuration (entry 12, Table 7).<sup>37</sup> In contrast to the first described method, 3-bromopyridine is converted to the desired product in a high yield (86%) (entry 4/9, Table 7).<sup>35,37</sup> In summary, this is an efficient method, which allows for the use of a wide variety of substrates and provides the desired product with retention of configuration.

**Table 8. Copper(I)-Catalyzed Phosphination of Aryl and Vinyl Halides or Iodonium Salts**



Entry	Substrate	Product	Conditions <sup>c</sup>	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			A	Toluene	110	—	88
2 <sup>a</sup>			A	Toluene	110	—	85
3 <sup>a</sup>			A	Toluene	110	—	92
4 <sup>a</sup>			A	Toluene	110	—	64
5 <sup>b</sup>			B	DMF/THF (1/4)	rt	4	82
6 <sup>b</sup>			B	DMF/THF (1/4)	rt	12	79
7 <sup>b</sup>			B	DMF/THF (1/4)	rt	1	42 <sup>d</sup>
8 <sup>b</sup>			B	DMF/THF (1/4)	rt	4	76

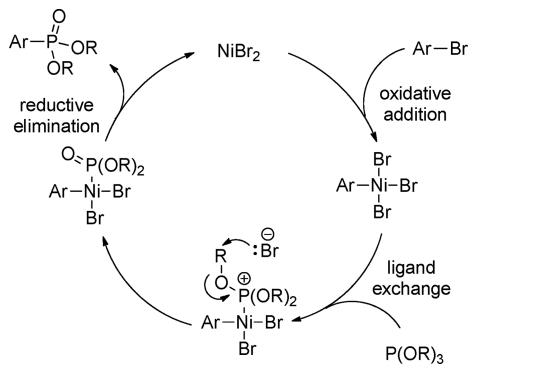
<sup>a</sup> From ref 42. <sup>b</sup> From ref 43. <sup>c</sup> Reagents and conditions: (A) CuI (0.05 equiv), *N,N'*-dimethylethylenediamine (0.2 equiv),  $\text{Cs}_2\text{CO}_3$  (2 equiv), stirred until complete conversion. (B) Iodonium salt (1.5 equiv), TMEDA (1 equiv), CuI (0.3 equiv). <sup>d</sup> Released PhOH during the purification. — indicates data not available

Table 9. Phosphonylation by  $\text{NiBr}_2$  from Halide Compounds and Trialkylphosphine

Entry	Substrate	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	PhMe	110	0.25	95
2 <sup>b</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	Neat	150	1	89
3 <sup>c</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	Neat	165	1	59
4 <sup>d</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	Neat	180	2.5	79
5 <sup>e</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	Mesitylene	150	1	82
6 <sup>f</sup>		$(\text{EtO})_2\text{OP}=\text{CH}-\text{CH}_2-\text{PO}(\text{OEt})_2$	Mesitylene	180	6	89

<sup>a</sup> From ref 45a. <sup>b</sup> From ref 45f. <sup>c</sup> From ref 45d. <sup>d</sup> From ref 45c. <sup>e</sup> From ref 45b. <sup>f</sup> From ref 45e.

**Scheme 4. General Mechanism for the Phosphonylation of Halide Compounds by  $\text{NiBr}_2$**

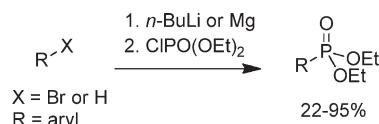


Improvement of the palladium-catalyzed phosphonylation reaction may in some cases be achieved by addition of potassium acetate to exceed 90% yield. The authors explained this effect to the competition between acetate and halide ions at the palladium center.<sup>38</sup> A large variety of substrates comprising both electron-donating and electron-withdrawing aryl groups as well as the bulky phenanthrene moiety are accepted. Also heterocycles such as 3-bromopyridine and 2,5-dibromopyridine (entry 14–18, Table 7) are synthesized in good yields using this protocol.<sup>38</sup> The reaction conditions are mild (refluxing THF) and with relative short-time reaction (generally <10 h). As expected, the rate of reaction is slowed down due to increased steric hindrance of the dialkyl phosphonate deployed (e.g., diisopropyl phosphonate), unfavorable interactions (e.g., with the perihydrogen atom of the phenanthrene) and by a strongly electron-donating group (e.g., *p*-methoxogroup). However, the efficacy (catalyst turnover number) is not affected.<sup>38</sup>

The generally accepted mechanism for phosphorylation by palladium cross-coupling is shown in Scheme 3. The catalytic circle is initiated by oxidative addition of Pd(0) to the aryl halide generating a *cis*-Pd(II) intermediate, which rapidly isomerizes into the trans-intermediate. The second step is exchange of the halogen with dialkyl *H*-phosphonate to give a *cis*-Pd(II)-intermediate, which upon reductive elimination provides the desired product and regenerate the active Pd(0) catalyst. The role of palladium source in combination with anionic additives has been studied in great details by means of  $^{31}\text{P}$  NMR.<sup>40</sup> In case of method D, the mechanism is slightly different due to the presence of the acetate ions that are suggested to act as a bidentate ligand.<sup>38,41</sup>

**3.2.2. Copper(I)-Catalyzed Reactions.** Gelman et al. reported a method for the synthesis of aryl- and vinyl-phosphonic acids using copper(I) iodide and  $\text{Cs}_2\text{CO}_3$  as base in toluene (entry 1–4, Table 8).<sup>42</sup> The efficacy of the reaction increased by addition of the chelating ligand agent, the *N,N'*-dimethylethylenediamine. This methodology is compatible with both bulky and electron rich aryl iodides, as exemplified in Table 8 (entry 2) and generally provides the corresponding product in high yields (85–88%).<sup>42</sup> Moreover, this method allows for the synthesis of vinylphosphonic acids from bromo- and iodo-vinyl compounds in moderate-to-high yields (64–92%) with retention of the original stereochemistry (entry 3,4, Table 8).<sup>42</sup>

A second method for the synthesis of vinylphosphonic acids is by use of vinyliodonium tetrafluoroborates as substrate, CuI, TMEDA and  $\text{Cs}_2\text{CO}_3$  as base in DMF/THF (1/4).<sup>43</sup> Vinyliodonium tetrafluoroborates are readily synthesized from their corresponding vinylmethylsilyl derivatives by a modified Ochiai's method.<sup>44</sup> The phosphorylation reaction is mild and affords the desired product in moderate-to-good yields (42–82%) with retention of the initial configuration of the alkene (entry 5–8, Table 8).<sup>43</sup>

Table 10. Recent Examples of Phosphonylation by Metal–Halogen Exchange, *ortho*-Lithiation, or Grignard Reagents

Entry	Substrate	Product	Conditions	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			<i>n</i> -BuLi	THF	-78 to rt	1	78
2 <sup>a</sup>			<i>n</i> -BuLi	THF	-78 to rt	1	90
3 <sup>a</sup>			<i>n</i> -BuLi	THF	-78 to rt	1	69
4 <sup>b</sup>			<i>n</i> -BuLi	THF	-78	16	95
5 <sup>c</sup>			<i>n</i> -BuLi	THF	-78	2	63
6 <sup>d</sup>			Mg	THF	rt to reflux	14	60
7 <sup>e</sup>			Mg	THF	-78 to rt	3	73

<sup>a</sup> From ref 46c. <sup>b</sup> From ref 46b. <sup>c</sup> From ref 46a. <sup>d</sup> From ref 47b. <sup>e</sup> From ref 47a.

**3.2.3. Nickel-Catalyzed Reactions.** Nickel(II)bromide has also been shown to catalyze the introduction of a phosphonate group (Table 9).<sup>45</sup> However, this class of nucleophilic substitution reactions generally requires harsh reaction conditions to proceed. This reaction may be considered as a variant of the *Arbuzov* reaction<sup>45b</sup> and affords the corresponding products in moderate-to-high yields (59–95%). As it is demonstrated by entry 1–2, the method conserves the initial configuration of the vinyl substrates.<sup>45a,f</sup> Moreover, aryl halides are suitable substrates and the desired product is obtained in moderate-to-good yields (59–79%) (entry 3–4).<sup>45d,c</sup> Noteworthy is also the high efficiency (82–95%) for the simultaneous introduction of more than one phosphonate group (entry 1/5/6).<sup>45a,b,e</sup>

Phosphonylation of aryl halides by use of Ni(II)Br<sub>2</sub> as the catalyst (Scheme 4) follows a mechanistic pathway similar to the one outlined for a Pd(0)L<sub>4</sub> catalyst (Scheme 3). The first step is oxidative addition of the nickel catalyst followed by a ligand exchange to form a nickel–phosphonium intermediate. Then a nucleophilic attack of the halide at the ethyl group allows for formation of the P=O double bond. Finally, a reductive elimination regenerates the Ni(II) catalyst and the desired product is formed (Scheme 4).

**3.2.4. Reactions with Dialkyl Chlorophosphonate as the Electrophile.** Complementary to results shown in Table 6, metal–halogen exchange followed by reaction with a dialkyl chlorophosphonate provides the desired dialkyl phosphonate in moderate-to-high yields (63–95%) (entry 1–5, Table 10).<sup>46</sup> Alternatively, formation of the Grignard reagent is possible (entry 6–7), which upon reaction with dialkyl chlorophosphonate affords

the corresponding product in moderate yields (60–73%).<sup>47</sup> Both of these methods are to be carried out under dry reaction condition due to the high reactivity and water sensitivity of the alkyl lithium- and Grignard reagent. Furthermore, as the reagents and reactive intermediates are strong bases this strategy is incompatible with acidic hydrogens being present elsewhere in the substrate.

**3.2.5. Summary.** The method commonly used for the introduction of a dialkyl phosphonate moiety at an sp<sup>2</sup> hybridized carbon is a palladium-catalyzed reaction. Due to continuous improvements of reaction conditions, this method provides the desired product in good yields and is compatible with a wide range of substrates. An alternative strategy is the use of a copper(I) catalyst. This method is effective, but high temperature is necessary (110 °C) for the reaction to proceed. However, by the use of an iodonium salt instead of a halide, the reaction may be carried out under milder conditions. Complementary to copper(I), introduction of dialkyl phosphonates may be achieved by use of a Ni(II) catalyst, however, this methodology also requires elevated temperature (110–180 °C). Finally, a strategy by formation of an intermediate lithium derivates or Grignard reagents, which then react with dialkyl chlorophosphonate may also be employed. This reaction pathway is attractive due to high yields, but is not compatible with acidic hydrogens elsewhere in the substrate.

### 3.3. Introduction on an sp<sup>2</sup> Hybridized Carbon with Concurrent Rehybridization

**3.3.1. Nucleophilic Addition to Carbonyl Groups.** Compounds comprising an  $\alpha$ -hydroxy phosphonic acid group can

Table 11. Formation of  $\alpha$ -Hydroxyphosphonate from Carbonyl Compounds

Entry	Substrate	Product	Methods <sup>d</sup>	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			A	THF	0	0.25	>99
2 <sup>a</sup>			A	THF	0	1	>99
3 <sup>a</sup>			A	THF	0	2	77
4 <sup>b</sup>			B	neat	80	2.5	95
5 <sup>b</sup>			B	neat	80	1.2	95
6 <sup>b</sup>			B	neat	80	2	77 95 <sup>e</sup>
7 <sup>c</sup>			C	Toluene	25	5 min	94
8 <sup>c</sup>			C	Toluene	25	5 min	95
9 <sup>c</sup>			C	Toluene	25	5 min	97

<sup>a</sup> From ref 48. <sup>b</sup> From ref 49. <sup>c</sup> From ref 50. <sup>d</sup> Reagents and conditions: (A) Carbonyl compound (1 equiv), phosphite (1.3 equiv), KO-*t*-Bu-18-crown-6 (0.05 equiv). (B) Aldehyde (1 equiv), phosphite (1.2 equiv), MoO<sub>2</sub>Cl<sub>2</sub> (0.05 equiv). (C) Aldehyde (1 equiv) and phosphite (1.2 equiv) and [(TMS)<sub>2</sub>N]<sub>3</sub>Ln( $\mu$ -Cl)Li(THF)<sub>3</sub> (0.001 equiv). <sup>e</sup> Reaction was carried out in 24 h in THF.

be synthesized from a carbonyl containing substrate (aldehyde or ketone) and phosphite in the presence of a catalyst. The silylphosphonylation can be performed using a potassium alkoxide-crown ether complex as catalyst (entry 1–3, Table 11).<sup>48</sup> This reaction occurs generally in good-to-high yields (77–99%). Potassium alkoxide-crown ether complexes act as Lewis base catalysts and the counteranion (*t*-BuO<sup>−</sup>) from the complex will activate the phosphite to generate hypervalent silicate.<sup>48</sup> Then, the hypervalent silicate will react with the carbonyl to form a C–P bond.<sup>48</sup> The advantage by the use of a TMS protected phosphite is that TMS protection of tertiary alcohols is effective in preventing or minimizing the undesired retro-reactions.<sup>48</sup>

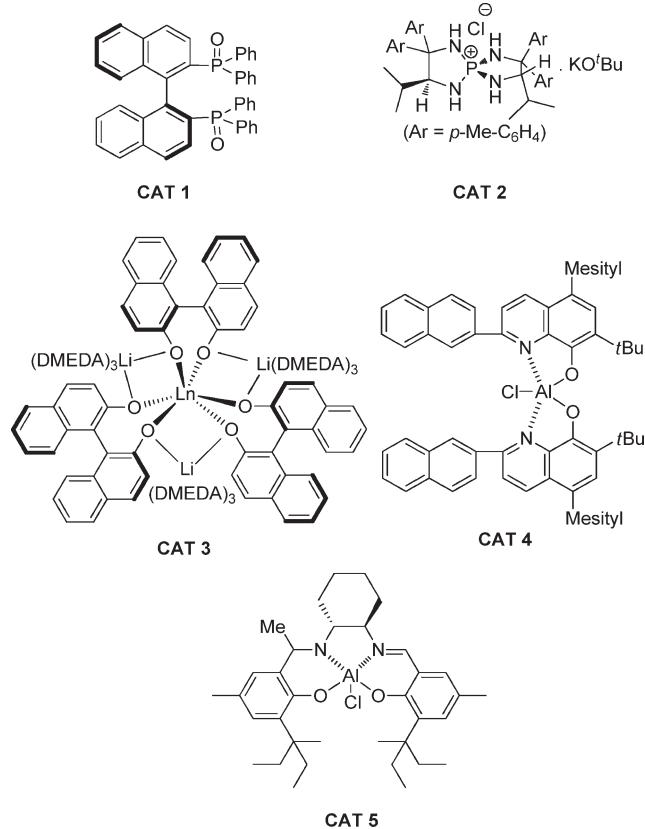
A second method for the preparation of  $\alpha$ -hydroxy phosphonates is the use of MoO<sub>2</sub>Cl<sub>2</sub> under solvent free conditions.<sup>49</sup> Good-to-high yields (77–95%) are reported for distinct substrates (entry 4–6, Table 11).<sup>49</sup> In addition, De Noronha et al. have shown that this method may also be performed in refluxing THF and that these conditions results in a better yield with cinnamaldehyde as the substrate. Furthermore, the addition of the phosphite is chemoselective for the carbonyl group over 1,4-addition to the enone (entry 6, Table 11).<sup>49</sup>

A third interesting strategy is the use of the lanthanide amide: [(TMS)<sub>2</sub>N]<sub>3</sub>Ln( $\mu$ -Cl)Li(THF)<sub>3</sub>, which is highly

efficient for hydrophosphonylation of aromatic aldehydes regardless of electronic and steric effects of the substrates.<sup>50</sup> Moreover, this method is rapid (5 min) and performed under mild conditions. Mechanistically, the lanthanide amide acts as a base to form an intermediate catalyst complex [Ln]PO<sub>2</sub>(OR)<sub>2</sub>.<sup>50</sup> The nucleophilic phosphonic moiety adds to the carbonyl group to generate the desired product in high yield (94–97%). Examples of this reaction are reported in Table 11 (entry 7–9).<sup>50</sup>

Over the past five years and in parallel with previous work, catalysts, which mediate the enantioselective formation of  $\alpha$ -hydroxy phosphonates, have been developed (Figure 3). Five different catalysts have been reported each displaying dissimilar effectiveness. The CAT 1 catalyst facilitates a high yield (83–90%), but with a low enantiomeric excess (9–40% ee) (entry 1–3, Table 14).<sup>51</sup>

In contrary, the remaining four catalysts are highly effective in terms of both yield and % ee. In regard to yield, the best catalyst reported is a chiral phosphonium dialkyl phosphite (CAT 2, Figure 3).<sup>52</sup> As shown in Table 12 (entry 4–6), this catalyst is highly efficient (98–99% yield) and gives an excellent stereo-selectivity (94–98% ee). The methodology is compatible with  $\alpha,\beta$ -unsaturated, as well as aliphatic aldehydes (Table 12).<sup>52</sup> Furthermore, furfural has also been shown to be as a suitable substrate.



**Figure 3.** New catalysts for the stereoselective formation of  $\alpha$ -hydroxyphosphonates.

The heterobimetallic complex CAT 3 (Figure 3) comprises the Lewis acids metal lanthanide(III) and lithium(I).<sup>53</sup> Unfortunately, the only example that has been described for the use of this catalyst is the enantioselective addition of *H*-phosphonate ( $\text{HOP}(\text{OR})_2$ ) to benzaldehyde, which proceeds in 78% *ee* (entry 7, Table 12) and with a yield of 92%.<sup>53</sup> Thus, the scope and limitations of this protocol remains to be investigated.

Catalysts CAT 4 and CAT 5 are similar in the sense that they are both alumina complexes (Figure 3).<sup>54,55</sup> The protocol with CAT 4 requires mild reaction conditions and proceed at room temperature with short times and low catalyst loading (0.01 equiv).<sup>54</sup> However, a limitation to this protocol is that it requires the use of a phosphite reagent, which comprise an electron withdrawing alkyl group such as bis(2,2,2-trifluoroethyl) compared to classical phosphites (diethyl- or dimethyl phosphite).<sup>54</sup> Moreover, the catalyst CAT 4 is most efficient, when the reaction is performed in a nonpolar solvent (93–97% *ee* and 93–96% yield) (entry 8–10, Table 12).<sup>54</sup>

Nevertheless, the second aluminum-salanen catalyst CAT 5 has been reported by Katsuki et al. (Figure 3).<sup>55</sup> In this case, the enantiomeric excess continues to be high (93–98% *ee*) in high yields (94–98%) Table 12 (entry 11–13), which is suggested to origin from the catalyst be able to trap the phosphite anion.<sup>55</sup> The protocol involving CAT 5 has the advantage compared to the previous involving CAT 4 that it does not require the use of an electron deficient phosphite as substrate.

In general, *H*-phosphonates are the active reagent in all the reactions, which exists in two tautomeric forms: the phosphite and

*H*-phosphonate. Deprotonation of the phosphonate provides the corresponding phosphite that has been shown to be a critical problem for the enantioselective reaction.<sup>55</sup>

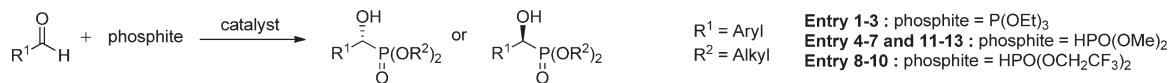
**3.3.2. 1,4-Addition to  $\alpha,\beta$ -Unsaturated Carbonyl Functionalities.** 1,4-Addition of a phosphite substrate to an enone is an effective strategy for the synthesis of compounds comprising a  $\beta$ -carbonylphosphonic acid moiety.<sup>56</sup> A method using a Baylis Hillman adduct, bis(trimethylsilyl)acetamide (BSA) and the corresponding phosphite leads to the unsaturated  $\beta$ -carbonylphosphonate in a relative good yield (56–85%) predominantly with the *Z* configuration (Table 13). This reaction is carried out in a minimal amount of THF at reflux until completion (48–96 h).<sup>56d</sup>

Over the past decade catalytic methodologies were also developed for the 1,4-addition of a phosphonate moiety. One of these reactions makes use of the amine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (CAT 6, Figure 4) and rapidly (5 min) affords the desired product in good-to-high yields (70–99%) (entry 1–3, Table 14).

The 1,4-addition to  $\alpha,\beta$ -unsaturated carbonyl functionalities can also be performed in a stereoselective fashion by use of the chiral catalysts CAT 7 or CAT 8 (Figure 4),<sup>56b,c</sup> which exert their catalytic effect in rather different ways. Whereas CAT 7 reacts with the carbonyl group to form an iminium ion thereby favoring attack at one face of the substrate,<sup>56b</sup> CAT 8 coordinates to the carbonyl group and induces the stereoselectivity due to its C<sub>2</sub>-symmetry formation from the condensation between the carbonyl group and the secondary amine.<sup>56c</sup> Upon the formation of the iminium ion, the phosphite reacts by a 1,4-addition to form a phosphonium ion-enamine intermediate. A nucleophilic substitution then occurs on the alkyl chain of the phosphite protection and facilitates the P=O double bond formation, which is the key step of the mechanism.<sup>56b</sup> Finally, a simple hydrolysis regenerates the carbonyl group as well as the catalyst. As described in Table 14 (entry 4–6), the reaction using CAT 7 is carried out under mild conditions and affords the product in moderate yields (54–67%), but with a good enantiomeric excess (84–88% *ee*).<sup>56b</sup>

A recently developed methodology uses a dinuclear Zinc catalyst CAT 8 (Figure 4) for the enantioselective 1,4-addition of diethyl phosphite. The dinuclear zinc catalyst is thought to function in a dual Lewis acid/Lewis base manner.<sup>56c</sup> In addition to the catalyst itself, this protocol requires the presence of 4 Å molecular sieves to increase conversion and enantioselectivity. As shown in Table 14 (entry 7–10), this method is very effective with a wide range of substrates and affords the desired products in high yields (96–99%) and high enantiomeric excesses (90–98% *ee*).

**3.3.3. Palladium-Catalyzed Reactions.** A methodology has been developed for the synthesis of phosphonate compounds from *H*-phosphinate via Pd-catalyzed tandem carbon–phosphorus bond formation–oxidation process.<sup>57</sup> The protocol uses  $\text{Pd}_2\text{dba}_3$  as the source of palladium and Xantphos as ligand and is performed under aerobic conditions. Two rather different variants of this protocol were later developed: A one-step procedure (method A), where the intermediate is not isolated, and a second method (method B), which is a stepwise process, where the *H*-phosphinic acid is formed under different conditions (under  $\text{N}_2$ , with concentrated  $\text{H}_3\text{PO}_2$ ), followed by in situ Pd-catalyzed oxidation (under aerobic conditions).<sup>57</sup> As shown in Table 15, both methods are effective and afford the desired product in good-to-high yields (81–100%).

Table 12. Scope of the Stereoselective Formation of  $\alpha$ -Hydroxyphosphonate Compounds

Entry	Substrate	Product	Catalyst	Meth <sup>f</sup>	Solvent	Temp (°C)	Time (h)	% ee	Yield (%)
1 <sup>a</sup>			SiCl <sub>4</sub> /CAT 1	A	CH <sub>2</sub> Cl <sub>2</sub>	-78	-- <sup>g</sup>	40	90
2 <sup>a</sup>			SiCl <sub>4</sub> /CAT 1	A	CH <sub>2</sub> Cl <sub>2</sub>	-78	-- <sup>g</sup>	22	87
3 <sup>a</sup>			SiCl <sub>4</sub> /CAT 1	A	CH <sub>2</sub> Cl <sub>2</sub>	-78	-- <sup>g</sup>	9	83
4 <sup>b</sup>			CAT 2	D	THF	-98	4	96	98
5 <sup>b</sup>			CAT 2	D	THF	-98	6.5	98	98
6 <sup>b</sup>			CAT 2	D	THF	-98	8	94	99
7 <sup>c</sup>			CAT 3	C	THF	-78	8	78	92
8 <sup>d</sup>			CAT 4	B	Hexane	r.t.	10min	97	93
9 <sup>d</sup>			CAT 4	B	Hexane	r.t.	10min	93	93
10 <sup>d</sup>			CAT 4	B	Hexane	r.t.	15min	95	96
11 <sup>e</sup>			CAT 5	E	Et <sub>2</sub> O	-30	24	93	98
12 <sup>e</sup>			CAT 5	E	Et <sub>2</sub> O	-30	24	98	98
13 <sup>e</sup>			CAT 5	E	Et <sub>2</sub> O	-30	24	97	94

<sup>a</sup> From ref 51. <sup>b</sup> From ref 52. <sup>c</sup> From ref 53. <sup>d</sup> From ref 54. <sup>e</sup> From ref 55. <sup>f</sup> Reagents and conditions: (A) Aldehyde (1 equiv), (S)-CAT 1 (0.1 equiv), P(OEt)<sub>3</sub> (1.5 equiv), i-Pr<sub>2</sub>NEt (1.5 equiv), and SiCl<sub>4</sub> (1.5 equiv slowly added over 2 h). (B) Aldehyde (1 equiv), phosphite (1.1 equiv), and catalyst (0.01 equiv). (C) Catalyst (0.1 equiv). (D) Catalyst (0.01 equiv), aldehyde (1.0 equiv), and phosphite (1.05 equiv). (E) Aldehyde (1 equiv), P(OMe)<sub>3</sub> (1.05 equiv), K<sub>2</sub>CO<sub>3</sub> (1 equiv), and catalyst (0.02 equiv). <sup>g</sup> Checking completion of the reaction by TLC analysis.

A second application for the palladium-catalyzed reaction is the addition of *H*-phosphonate to 1,3-diene substrates.<sup>58</sup> This coupling is catalyzed by PdMe<sub>2</sub>(dppb) and provides the corresponding product with a high degree of stereoselectivity (81–96% of the *E* isomer).<sup>58</sup> Other palladium catalysts have been studied such as PdMe<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub>, but these catalysts are less stereoselective and afford the product in a *E/Z* ratio of approximately 1/1.<sup>58</sup> In accordance with Scheme 4, oxidative insertion of Pd(0) into the H–P bond occurs in order to form an active Pd(II) complex, which

afterward undergoes ligand-exchange with a 1,3-diene. The catalytic cycle is completed by a reductive elimination affording the desired product in good-to-high yields (76–98%) (Table 16).

The synthesis of alkynylphosphonates may also be achieved by a palladium-catalyzed reaction of 1,1-dibromo-1-alkene and *H*-phosphonate.<sup>59</sup> The optimal protocol for the synthesis of the alkyne products (Table 17) is Pd(OAc)<sub>2</sub> as the palladium source and dppf as the ligand in presence of propylene oxide in DMF at 80 °C. As demonstrated in Table 17, various functionalities are

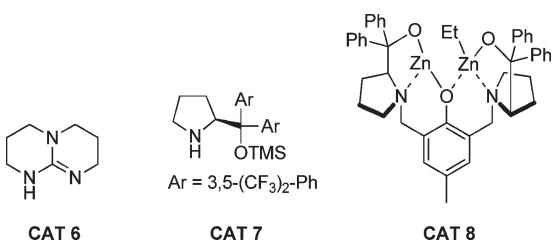
**Table 13. Introduction of a Phosphonate by 1,4-Addition<sup>a</sup> on Substrates Comprising a Leaving Group at the  $\beta'$ -Position<sup>56d</sup>**

AcO<sub>2</sub>C(R)<sub>2</sub>CH=CH<sub>2</sub> + HPO(OR<sup>2</sup>)<sub>2</sub> + OTMS-NTMS → AcO<sub>2</sub>C(R)<sub>2</sub>CH=CH-PO(OR<sup>2</sup>)<sub>2</sub>
  
 Reagents: HPO(OR<sup>2</sup>)<sub>2</sub>, OTMS-NTMS, THF, reflux, 2–4 days

**Entry 1 :** R<sup>1</sup> = Ph; R<sup>2</sup> = Me  
**Entry 2 :** R<sup>1</sup> = Ph; R<sup>2</sup> = Et  
**Entry 3 :** R<sup>1</sup> = Ph; R<sup>2</sup> = i-Pr  
**Entry 4 :** R<sup>1</sup> = p-MeO-C<sub>6</sub>H<sub>4</sub>; R<sup>2</sup> = Me  
**Entry 5 :** R<sup>1</sup> = Me; R<sup>2</sup> = Me

Entry	Substrate	Product	Yield (%)
1			61
2			73
3			57
4			85
5			56

<sup>a</sup> Reagents and conditions: Phosphite (1 equiv), BSA (1 equiv), Baylis–Hillman adduct (1 equiv) in THF at reflux until completion (48–96 h).



**Figure 4.** Catalysts for the 1,4-addition to  $\alpha,\beta$ -unsaturated carbonyl functionalities.

tolerated and afford the corresponding alkynylphosphonates in low-to-good yields (16–76%). Noteworthy, is the increased yield obtained when TFP is used as ligand instead of dppf for the coupling with furan (Table 16, entry 6).

**3.3.4. Manganese-Catalyzed Addition.** Ishii et al. have developed a method for the addition *H*-phosphonate to nucleophilic alkenes, which relies on the use of Mn(OAc)<sub>2</sub> as catalyst (Table 18).<sup>60</sup> The reaction runs at high temperature (100–110 °C), under solvent-free and aerobic conditions. A

mixture of regioisomeric products may be obtained (Table 18, entry 1) and generally moderate-to-good yields (62–82%) are obtained.<sup>60</sup>

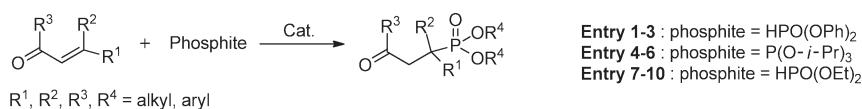
The mechanism of this reaction may be rationalized by a radical process. In the presence of oxygen, manganese reacts with the *H*-phosphonate and an active radical species is generated.<sup>60</sup> Addition to the alkene occurs and the reaction is continued by abstracting a hydrogen from another *H*-phosphonate producing the desired product (Figure 5).<sup>60</sup>

**3.3.5. Nanosized Zinc Oxide.** The synthesis of  $\beta$ -phosphono malonate analogs may be carried out by conjugated addition of a phosphorus nucleophile to  $\alpha,\beta$ -unsaturated cyano malonate analogs in presence of Zinc oxide as the catalyst.<sup>61</sup> Moreover, solvent-free conditions increase the yield of the desired product. A comparison between commercially ZnO catalyst (CM-ZnO) and specially prepared nanosized ZnO flakes (NF-ZnO) shows that the latter is more effective in mediating the 1,4-addition (Table 19).<sup>61</sup> This is suggested to be due to the increased surface area, but also because of the change in surface properties such as surface defects.<sup>61</sup> Etemad et al. have shown that the Lewis basic sites of the catalyst (O<sup>2-</sup>) activates P–H bond, and the Lewis acid moiety (Zn<sup>2+</sup>) activates malonate analogs.<sup>61</sup> As summarized in Table 19 (entry 1–4), NF-ZnO affords the desired  $\beta$ -phosphono cyano malonates analogs in high yields (98%) within relatively short reaction times (0.5 to 7.5 h), as compared to CM-ZnO (2–28 h). Furthermore, by use of HClO<sub>4</sub>–SiO<sub>2</sub> a dialkyl phosphonate was added successfully to diethyl malonate in 55% (entry 5, Table 19).

**3.3.6. Summary.** Over the past decades, a number of methodologies have been developed for the introduction of a phosphonate group at different sp<sup>2</sup>-hybridized carbon centers. Substrates, which comprise a carbonyl group are rehybridized at the carbonyl carbon to sp<sup>3</sup>. The catalysts, both achiral, as well as chiral, exert their action by facilitating the nucleophilic addition of phosphite to the carbonyl functionality. Generally, the corresponding products,  $\alpha$ -hydroxy phosphonates, can be obtained in high yields under these mild conditions. Phosphonylation by 1,4-addition to  $\alpha,\beta$ -unsaturated systems has gained interest during the past decade. The protocols developed require mild conditions and selectively afford the desired 1,4-addition product in moderate-to-high yields. Furthermore, the stereoselectivity can in several cases be controlled by the use of chiral catalysts.

Palladium(0) catalysts are employed in three different reactions for the introduction of dialkyl phosphonates, which in some cases includes rehybridization of the reacting carbon atom generation diverse scaffolds. The first method described is of general nature and involves the synthesis of the phosphonate compounds using *H*-phosphinite as reagent and different substrates including alkenes, alkynes, allylic alcohols, and aryl halides. The protocol thrives on the favorability of the oxidation of phosphinic compounds into phosphonates under aerobic conditions. The reaction may be conducted in one or two steps (with or without isolation of the intermediate) and affords the corresponding product in good-to-high yields. The second method is the addition of *H*-phosphonate into conjugated 1,3-dienes affording the *E* isomer as the main product and favoring addition to the less sterically hindered center in case of asymmetric 1,3-dienes. The reaction proceeds in good yield and with good-to-high stereo-selectivity. The third class of reaction is the formation of alkynyl phosphonates from 1,1-dibromo-1-alkene substrates

Table 14. Methods for 1,4-Additions of the Dialkyl Phosphonate



Entry	Substrate	Product	Cat <sup>d</sup>	Meth <sup>e</sup>	Solv.	Temp (°C)	Time (h)	ee (%)	Yield (%)
1 <sup>a</sup>			CAT 6	A	toluene	rt	5 min	—	85
2 <sup>a</sup>			CAT 6	A	toluene	rt	5 min	—	70
3 <sup>a</sup>			CAT 6	A	toluene	rt	5 min	—	99
4 <sup>b</sup>			CAT 7	B	$\text{CH}_2\text{Cl}_2$	rt	5	84	61
5 <sup>b</sup>			CAT 7	B	$\text{CH}_2\text{Cl}_2$	rt	5	85	54
6 <sup>b</sup>			CAT 7	B	$\text{CH}_2\text{Cl}_2$	rt	5	88	67
7 <sup>c</sup>			CAT 8	C	toluene	rt	12	98	99
8 <sup>c</sup>			CAT 8	C	toluene	rt	12	92	98
9 <sup>c</sup>			CAT 8	C	toluene	rt	12	90	96
10 <sup>c</sup>			CAT 8	C	toluene	rt	12	96	99

<sup>a</sup> From ref 56a. <sup>b</sup> From ref 56b. <sup>c</sup> From ref 56c. <sup>d</sup> See Figure 4. <sup>e</sup> Reagents and conditions: (A) Diphenylphosphite (1.0 equiv), phenylmaleimide (1.0 equiv), and catalyst (0.2 equiv). (B) Enone (3 equiv), tri-*iso*-propyl phosphite (1 equiv), catalyst (0.1 equiv),  $\text{PhCO}_2\text{H}$  (2 equiv), NaI (1 equiv). (C) Enone (1 equiv), phosphite (1.5 equiv) and catalyst (0.2 equiv) in presence of 4 Å molecular sieves.

and *H*-phosphonates. Even though the reaction conditions appear to be compatible with substrates comprising various functionalities, the alkyne products are only obtained in low-to-good yields.

A direct addition of *H*-phosphonate on nucleophilic alkenes can also be accomplished by the use of a manganese catalyst. However, this method does not allow for regioselective addition and high temperature is required. The product is obtained in moderate-to-good yields and the fact that radical intermediates are involved should be taken into consideration in order to avoid undesired side reactions.

$\beta$ -Phosphono malonate analogs may be synthesized by use of ZnO as catalyst. An increased efficiency for this method is observed, when nanosized ZnO particles are applied instead of the technical bulk standard. The desired product is synthesized under solvent free conditions and in high yields.

### 3.4. Introduction on an $\text{sp}^1$ -Hybridized Carbon

**3.4.1. Copper-Catalyzed Reactions.** The synthesis of alkynyl phosphonates has previously been discussed in section 3.3.3; however, another method was coincidentally discovered by Gao et al.<sup>63</sup> The method builds on the use of a copper salt as the catalyst in the presence of a base in DMSO at 55 °C and under aerobic conditions. Suitable copper catalysts are CuI, CuBr, CuCl, and  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ , whereas other metals salts, such as AgI, NiCl<sub>2</sub>, PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, and FeCl<sub>3</sub>, do not or only poorly catalyze this reaction. Both organic and inorganic bases, such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Et<sub>2</sub>NH, and Et<sub>3</sub>N, may be applied.<sup>63</sup> The solvent is also very important and only DMSO and DMF have resulted in effective conversion.<sup>63</sup> As shown in Table 20, the reaction is selective for alkynes and compatible with functionalities such as alcohols, cyanides, amides, chlorides or  $\alpha,\beta$ -unsaturated carbonyl groups. The reaction affords the corresponding alkynyl phosphonate compounds in good-to-high yields.

Table 15. Synthesis of Phosphonic Acids via Tandem C–P Bond Formation–Oxidation Reactions<sup>57</sup>

Entry	Substrate	Product	Meth <sup>a</sup>	Solvent	Temp (°C)	(a) Time (h)	(b) Temp (°C)	(b) Time (h)	Yield (%)
1a			A	DMF	110	20	—	—	100
1b			B	DMF	85	12	110	24	100
2a			A	DMF	110	50	—	—	81
2b			B	DMF	85	12	110	64	97
3			A	DMF	110	50	—	—	95
4			B	DMF	85	12	110	22	89
5			B	DMF	85	12	110	50	91
6 <sup>b</sup>			B	DMF	85	12	110	22	82 <sup>c</sup>

<sup>a</sup> Reagents and conditions: Method A (a) Substrate (1 equiv), Pd<sub>2</sub>dba<sub>3</sub>/Xantphos (0.02 equiv), 50% aq. H<sub>3</sub>PO<sub>2</sub> (2 equiv), DMF, 110 °C, aerobic conditions. Method B (a) Substrate (1 equiv), Pd<sub>2</sub>dba<sub>3</sub>/Xantphos (0.02 equiv), conc. H<sub>3</sub>PO<sub>2</sub>, (2 equiv), DMF, 85 °C, N<sub>2</sub> (b) Oxidation: DMF, 110 °C, aerobic conditions. <sup>b</sup> Pd<sub>2</sub>dba<sub>3</sub>/dppe (0.02 equiv) and Et<sub>3</sub>N (3 equiv). <sup>c</sup> Purified by recrystallization.

(72–90%).<sup>63</sup> At this point, a detail reaction mechanism remains to be elucidated, however, the authors have proposed that the reaction follows the classical pathway similar to the one described for cross-coupling reactions.<sup>63</sup>

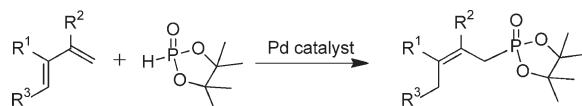
**3.4.2. Palladium-Catalyzed Reactions.** The transition-metal-catalyzed hydrophosphorylation of alkynes was discovered by Han and Tanaka in 1996.<sup>64</sup> They reported the use of *cis*-PdMe<sub>2</sub>(PPh<sub>2</sub>Me)<sub>2</sub> as the catalyst in THF under inert conditions, which in general affords the 2-substituted product in case of terminal alkynes.<sup>65</sup> Ananikov et al. have reported an improved catalytic system for this type of reaction using Pd<sub>2</sub>(dba)<sub>3</sub> and Ph<sub>3</sub>P in THF under acidic condition.<sup>65</sup> Noteworthy is the use of TFA, which not only increases the yield, but also the rate of the reaction. The use of triethylamine instead does not facilitate the reaction and the desired product is not obtained.<sup>65</sup> The study further concludes that the use of benzene or THF as solvent provides the best yields in case of small terminal alkynes. The regioisomeric outcome of the reaction is controlled by the formation of the more stabilized carbocation intermediate. As shown in Table 21, a wide range of functionalities are compatible with this method such as chlorides, alcohols, cyanides and silyl derivates, and the desired product is obtained in moderate-to-high yields (65–91%).<sup>65</sup>

A palladium(0) catalyst may also be employed for the synthesis of 1,2-diphosphonate compounds, which are known to be active in treatment of bones diseases.<sup>66</sup> They are prepared from alkynes, which undergo two consecutive additions of H-phosphonate.<sup>67</sup> The method uses Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst in toluene at 110 °C; however, it only proceeds

with electron-deficient terminal alkynes. Noteworthy, the reaction provides the best yield, when diethyl phosphite is employed. The use of dimethyl phosphite only gives the monoaddition product.<sup>67</sup> As shown in Table 22, this double addition may be carried out on functionalized ethynylbenzenes as well as heterocyclic alkynes such as 2- or 4-ethynylpyridine and 2-ethynylthiazole. The corresponding products are generally obtained in good-to-high yields (72–90%).<sup>67</sup>

**3.4.3. Nickel-Catalyzed Reaction.** An efficacious method for the addition of dimethyl phosphonate to terminal alkynes has been developed by Han et al. in 2004.<sup>68</sup> This method mainly generates the 1- or 2-regioisomeric product by a slight modification of the reaction conditions. Moreover, these reaction conditions are both practical and mild. The 1-regioisomeric product is obtained using Ni(PPh<sub>2</sub>Me) as the catalyst in EtOH, whereas the 2-regioisomeric product is obtained in the presence of a combination of the catalysts Ni(cod)<sub>2</sub>, PPhMe<sub>2</sub> and Ph<sub>2</sub>PO(OH) using THF as the solvent.<sup>68</sup> As demonstrated in Table 23, both methods are efficient with aryl- and aliphatic alkynes. Furthermore, moderate-to-high yields (72–96%), as well as stereoselectivity (90–99%) are observed for both methods.<sup>68</sup>

**3.4.4. Molybdenum-Catalyzed Addition.** A regio- and stereospecific phosphonylation of phenylacetylene was developed by Kuramshin et al. using Mo(CO)<sub>6</sub> as catalyst (Figure 6).<sup>69</sup> This method facilitates the formation of the 1,2-*cis* regioisomeric product in a simple fashion without formation of the 1,1-regioisomer.

Table 16. Palladium-Catalyzed Hydrophosphorylation of 1,3-Dienes<sup>58a</sup>

Entry	Substrate	Product	Catalyst	Solvent	Temp (°C)	Time (h)	Stereo selectivity (E / Z)	GC yield (%)
1			PdMe₂(dppb)	dioxane	100	12	—	97 (76) <sup>b</sup>
2			PdMe₂(dppb)	dioxane	100	12	—	87 (80) <sup>b</sup>
3			PdMe₂(binap)	dioxane	100	12	83 / 17	98
4			PdMe₂(dppf)	dioxane	80	16	93 / 7	89
							96 / 4	7
5			PdMe₂(dppf)	dioxane	60	12	—	82
							81 / 19	16

<sup>a</sup> Reagents and conditions: phosphite (1 equiv), diene (1–10 equiv), and palladium catalyst (0.05 equiv) in 1,4-dioxane (~0.7M). <sup>b</sup> Figures in parentheses are isolated yields.

The selectivity is explained by the formation of the (alkyne)<sub>3</sub>Mo(CO) complex via a direct interaction of three alkyne substrates with one hexacarbonyl-molybdenum(0) (Scheme 5).<sup>69</sup> This coordination results in a reduction of the electronic density on the triple bond. Moreover, the steric repulsion between the phenyl groups of the substrate plays a crucial role for the observed regioselectivity.<sup>69</sup> Only one reaction has been reported using this protocol and thus no conclusion can be drawn as to the general applicability of this method.

**3.4.5. Phosphine-Catalyzed Addition to Phosphonic Alkynes.** A simple route to the formation of 1,1-bis(dialkyl phosphonates) from electron-deficient 1-dialkyl phosphonate alkynes is catalyzed by the reaction of a highly nucleophilic tertiary phosphine such as *n*-Bu<sub>3</sub>P in refluxing EtOH. The presence of ethanol is essential to achieve complete conversion of the substrate due to its ability to act as cocatalyst.<sup>70</sup> This methodology affords the desired product in good-to-high yields (80–97%) as shown in Table 24.

Mechanistically, the first step is the nucleophilic addition of the trialkyl phosphine to the triple bond forming a reactive phosphonium intermediate (Scheme 6). The hydrogen of the diethyl phosphonate is transferred to the phosphonium intermediate, which facilitates the attack of the diethyl phosphonate anion leading to the formation of an ylide.<sup>70</sup> A proton shift then generates a more stabilized zwitterion. The unfavorable disruption of the ylide is counteracted by resonance stabilization of

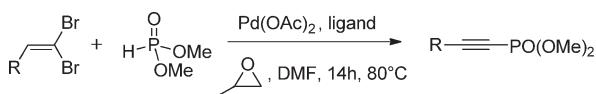
the anion by two phosphonate groups. Alkene formation and consecutive extrusion of the tributyl-phosphine afterward afford the desired product.<sup>70</sup>

**3.4.6. Formation of Alkynyl Phosphonates by Lithiation and by Alkyne Sulfones Substitutions.** The most often used route for the syntheses of alkynyl phosphonates from terminal alkynes is by the formation of the corresponding lithium species by using strong bases, such as BuLi, LDA, or a combination thereof.<sup>71</sup> The anionic intermediate undergoes reaction with an electrophilic diethyl chlorophosphonate to afford the desired product. Generally, the reaction is carried out in ether at low temperature (−78 °C) and the product is obtained in low-to-high yields (35–96%) (Table 25).<sup>71</sup>

Yatsunomiji et al. have developed an alternative method for the formation of alkynyl phosphonates from alkyne sulfones.<sup>72</sup> According to a method reported by Bieber, alkynyl sulfones can be prepared by the copper(I) iodide-catalyzed reactions of terminal alkynes with diphenyl disulfides in excellent yields.<sup>73</sup> The phosphonate can then be introduced by substitution of the sulfone moiety using different trialkyl phosphites in THF at 60 °C. This method affords the desired product in good-to-high yields (70–98%).<sup>72</sup>

As shown in Table 26 this protocol also tolerates more sterically hindered phosphites such as tri-*iso*-propyl phosphites. This methodology works well with aliphatic alkynes, however, the efficiency remains to be investigated with

**Table 17.** Palladium-Catalyzed Formation of Alkynyl Phosphonates from Dibromo Alkenes<sup>59a</sup>



Ent	Substrate	Product	Ligand	Yield (%)
1	<i>n</i> -heptyl- <i>trans</i> -1,2-dibromopropane	<i>n</i> -heptyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dppf TFP	66 27
2	cyclohexyl- <i>trans</i> -1,2-dibromopropane	cyclohexyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dppf TFP	76 35
3	phenyl- <i>trans</i> -1,2-dibromopropane	phenyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dffp	63
4	4-methoxyphenyl- <i>trans</i> -1,2-dibromopropane	4-methoxyphenyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dffp	73
5	4-nitrophenyl- <i>trans</i> -1,2-dibromopropane	4-nitrophenyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dppf TFP	27 31
6	2-furyl- <i>trans</i> -1,2-dibromopropane	2-furyl- <i>cis</i> -1,2-dibromoethyne-1,2-diphenylphosphonate	dppf TFP	16 60

<sup>a</sup> Reagents and conditions: Pd(OAc)<sub>2</sub> (0.2 equiv), ligand (0.4 equiv), H-phosphonate (2.0 equiv), propylene oxide (3.0 equiv), DMF, 80 °C, 14 h.

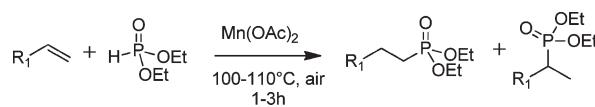
substrates containing substituents that affect the electron density of the alkyne.

**3.4.7. Summary.** Several methods for introduction of a phosphonic ester on alkynes have been described in the literature. One involves formation of alkynyl phosphonates from terminal alkynes using a copper(I) catalyst in the presence of base. The protocol is compatible with functionalities, such as alcohols, cyanides, or chlorides, and affords the desired product in good-to-high yields.

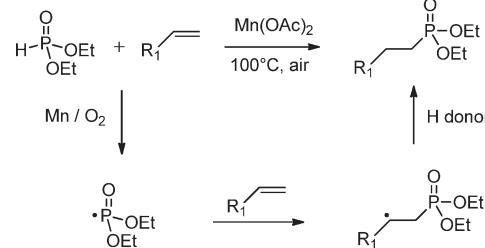
Monoaddition of a dialkyl phosphonate to an alkyne may be achieved by use of a palladium catalyst. Exclusively, the terminal regioisomeric product is obtained in moderate-to-high yields and functionalities such as alcohols and chlorides are well-tolerated. By use of Pd(PPh<sub>3</sub>)<sub>4</sub> as the palladium catalyst and diethyl phosphonate as reagent, diaddition to the alkyne is promoted and the 1,2-diphosphonate compounds, is obtained in good-to-high yields.

Two methods have been reported for the selective addition of phosphonate to alkynes with concurrent rehybridization to an alkene. Both methods are performed by Nickel catalysis using dimethyl phosphonate at room temperature. The regioselectivity may be controlled by the catalyst ligand and different phosphor additives. Both methods afford the desired product in good-to-high yields with selectivity for either the geminal product or the trans isomer.

**Table 18.** Manganese-Catalyzed Addition of H-Phosphonate on Alkenes<sup>60</sup>



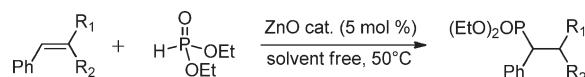
Entry	Substrate	Product	Temp (°C)	Time (h)	Yield (%)
1	$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_{11}$	$\begin{array}{c} \text{O} \\    \\ \text{EtO}-\text{P}-\text{Et} \\   \\ \text{EtO}-\text{CH}-\text{CH}-\text{C}_6\text{H}_{11} \end{array}$ $\begin{array}{c} \text{O} \\    \\ \text{EtO}-\text{P}-\text{Et} \\   \\ \text{EtO}-\text{CH}-\text{CH}-\text{C}_6\text{H}_{11} \end{array}$	110	2	49
2	cyclohexene	cyclohexyl- <i>cis</i> -1,2-diphenylphosphonate	100	1	80
3	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{COOEt}$	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{COOEt}-\text{CH}_2-\text{P}(\text{OEt})_3$	100	1	82
4	$\text{Ph}-\text{CH}=\text{CH}_2$	$\text{Ph}-\text{CH}_2-\text{CH}_2-\text{P}(\text{OEt})_3$	110	3	62



**Figure 5.** Radical mechanism for manganese-catalyzed addition on alkenes.<sup>60</sup>

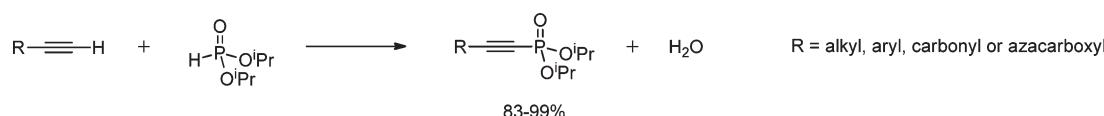
Addition of a phosphonate to a terminal alkyne generating the 1,2-cis stereoisomer of the corresponding alkene can be accomplished by use of Mo(CO)<sub>6</sub> as catalyst under inert conditions. The method has only been investigated for ethynylbenzene as substrate, which provides the product in quantitative yield, thus, the scope of this reaction remains elusive.

When an alkynyl phosphonate is the substrate, the corresponding *geminal* bisphosphonate analog is obtained. This can be accomplished in the presence of a highly nucleophilic trialkyl phosphine reagent such as *n*-Bu<sub>3</sub>P, which is required to catalyze the addition. Moreover, ethanol as solvent is essential to achieve complete conversion. The corresponding product is obtained in good-to-high yields. Alkynyl phosphonates may also be synthesized by lithiation of terminal alkynes and reaction with diethyl chlorophosphonate. This reaction is generally carried out at -78 °C and with strong bases such as LDA or BuLi or a combination. The lithium intermediate is highly nucleophilic

Table 19. Formation of  $\beta$ -Phosphono Malonate Analogs by ZnO Catalyst

Entry	Substrate	Product	Catalyst <sup>a</sup>	Temp (°C)	Time (h)	Yield (%)
1 <sup>b</sup>			CM-ZnO NF-ZnO	50	10	83
					2.5	98
2 <sup>b</sup>			CM-ZnO NF-ZnO	50	2	80
					0.5	98
3 <sup>b</sup>			CM-ZnO NF-ZnO	50	28	75
					5	98
4 <sup>b</sup>			CM-ZnO NF-ZnO	50	28	50
					7.5	98
5 <sup>c</sup>			HClO <sub>4</sub> -SiO <sub>2</sub>	60	1	55

<sup>a</sup> CM-ZnO: Commercial ZnO; NF-ZnO: nanofalke ZnO. <sup>b</sup> From ref 61. <sup>c</sup> From ref 62.

Table 20. Copper-Catalyzed Coupling between Alkynes and Dialkyl Phosphonates under Aerobic Conditions<sup>63a</sup>

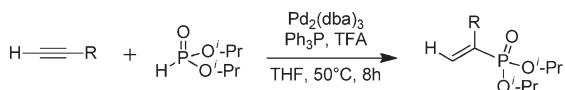
Entry	Substrate	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>b</sup>			DMSO	55	Overnight	72
2 <sup>b</sup>			DMSO	55	Overnight	83
3 <sup>b</sup>			DMSO	55	Overnight	88
4 <sup>b</sup>			DMSO	55	Overnight	82
5 <sup>b</sup>			DMSO	55	Overnight	85
6 <sup>c</sup>			DMSO	55	Overnight	88
7 <sup>d</sup>			DMSO	55	Overnight	90

<sup>a</sup> Reagents and conditions: Alkyne (1.2 equiv), phosphine (1 equiv), Cu catalyst (0.1 equiv), base (0.2 equiv), DMSO (1 mL), 55 °C, overnight under dry air. <sup>b</sup> CuI, Et<sub>3</sub>N. <sup>c</sup> CuI, Et<sub>2</sub>NH. <sup>d</sup> Alkyne (1 equiv), phosphine (1.5 equiv), CuI (0.1 equiv), and Et<sub>3</sub>N (0.2 equiv).

and reacts readily with the electrophilic diethyl chlorophosphonate to afford the desired product in low-to-high yields. Finally, a

strategy for the synthesis of alkynyl phosphonates is by substitution of readily available alkynyl sulfones. These sulfur-based

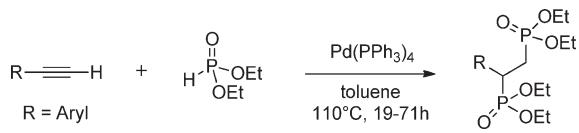
**Table 21.** Examples of Hydrophosphorylation<sup>a</sup> of Terminal Alkynes<sup>65</sup>



Entry	Substrate	Product	Yield (%)
1 <sup>a</sup>			91
2 <sup>a</sup>			85
3 <sup>a</sup>			65
4 <sup>a</sup>			89
5 <sup>a</sup>			83

<sup>a</sup> Reagents and conditions: Alkyne (1 equiv), phosphite (1 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (0.03 equiv), Ph<sub>3</sub>P (0.12 equiv), TFA (0.1 equiv).

**Table 22.** Formation of Bisphosphonates<sup>a</sup> from Alkynes<sup>67</sup>



Entry	Substrate	Product	Yield (%)
1			90
2			89
3			87
4			87
5			72

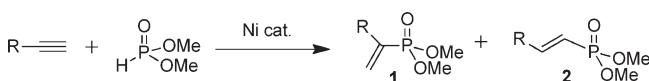
<sup>a</sup> Reagents and conditions: Alkynes (1 equiv), dialkyl phosphites (3 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 equiv) in toluene, 110°C, 19–71 h.

substrates are reacted with a trialkyl phosphite under gentle reflux in THF to afford the corresponding product in good-to-high yields (Table 26).<sup>72</sup>

#### 4. METHODS FOR THE HYDROLYSIS OF MONO AND DIALKYL PHOSPHONATES

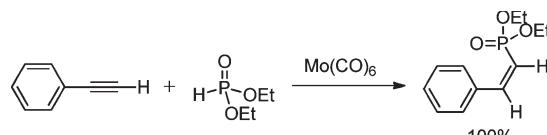
The vast majority of the above-described chemical methods introduce a dialkyl phosphonate group, which subsequently has to undergo hydrolysis to provide the corresponding phosphonic acid functionality. As shown in Scheme 7, dialkyl phos-

**Table 23.** Nickel-Catalyzed Addition<sup>a</sup> of Dimethyl Phosphonate on Alkyne Derivatives<sup>68</sup>



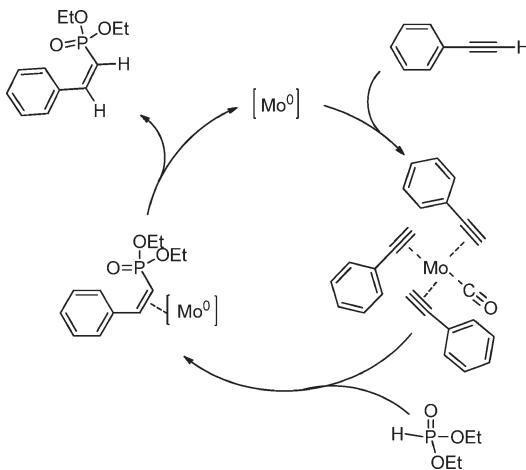
entry	substrate (R)	condition	yield % (1/2)
1	Ph	A	91 (1/99)
2	Ph	B	72 (90/10) <sup>b</sup>
3	n-C <sub>6</sub> H <sub>13</sub>	A	96 (7/93)
4	n-C <sub>6</sub> H <sub>13</sub>	B	91 (92/8)

<sup>a</sup> Reagents and conditions: (A) Ni(PPh<sub>2</sub>Me)<sub>4</sub> (0.005 equiv), 1M EtOH, 20 °C, Sh. (B) Ni(cod)<sub>2</sub> (0.01 equiv), PPh<sub>2</sub>Me<sub>2</sub> (0.04 equiv), Ph<sub>2</sub>PO(OH) (0.02 equiv), 1 M THF, 20 °C, 2 h. <sup>b</sup> 67 °C, 3 h.



**Figure 6.** Molybdenum-catalyzed addition on phenyl acetylene.<sup>69</sup>

**Scheme 5.** Proposed Mechanism the Molybdenum-Catalyzed Addition<sup>69</sup>

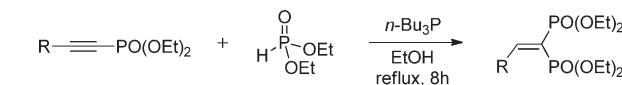


phonates may be hydrolyzed stepwise to the monoprotected phosphonic acid and then by a second step into the free phosphonic acid, or in one step directly into the free phosphonic acid. Both pathways are discussed in the following section.

For complete hydrolysis into the free phosphonic acid, two types of reagents are generally used. One method makes use of a strong, concentrated, inorganic acid, such as HCl or HBr, in a polar solvent. As demonstrated in Table 27 (entry 1–3), this method affords the corresponding free acid phosphonic in high yields (91–94%). In these cases, aqueous HCl at reflux is required. In contrary, room temperature is adequate with the use of HBr. However, since hydrochloride and -bromide are strong acids, concurrent reactions may take place as exemplified by the simultaneous deprotection of esters or imines (entry 2–3, Table 27). The second class of reagents used is

trimethylsilyl halides, such as TMSBr, TMSI, or a combination of TMSCl and NaI, in a polar aprotic solvent such as

**Table 24.** Phosphine-Catalyzed<sup>a</sup> 2-Aryl-1-vinyl-1,1-Diphosphonic Acids Derivatives<sup>70</sup>

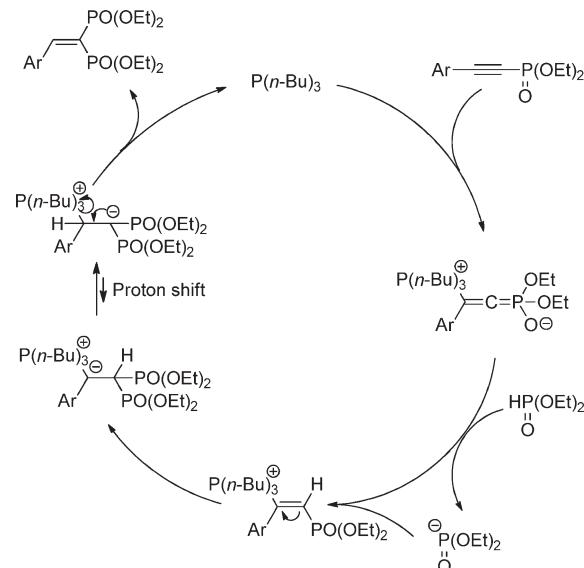


Entry	Substrate	Product	Yield (%)
1	Ph-C≡PO(OEt) <sub>2</sub>		95
2			95
3			80
4			97

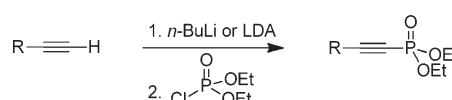
<sup>a</sup> Reagents and conditions: Alkyne (1 equiv), phosphite (1.1 equiv), *n*-Bu<sub>3</sub>P (0.2 equiv), inert conditions, reflux, 8 h.

dichloromethane or acetone. As shown in Table 27 (entry 4–6), these reagents afford the desired phosphonic acid in good yields (72–89%); however, hydrolysis of other labile protection groups such as acetals may still occur under these conditions.

**Scheme 6.** Mechanism for the Formation of 2-Aryl-1-vinyl-1,1-diphosphonates Catalyzed by Phosphine<sup>70</sup>



**Table 25.** Formation of Alkynylphosphonates from Alkyne Lithiation



Entry	Substrate	Products	Reagents	Solvent	Temp (°C)	Time (h)	Yield (%)
1 <sup>a</sup>			<i>n</i> -BuLi	THF	-78 to rt	24	56
2 <sup>b</sup>			<i>n</i> -BuLi	THF	-78 to rt	0.75	47
3 <sup>c</sup>			LDA / <i>n</i> -BuLi	THF	-78 to rt	6	85
4 <sup>c</sup>			LDA / <i>n</i> -BuLi	THF	-78 to rt	6	35
5 <sup>c</sup>			LDA / <i>n</i> -BuLi	THF	-78 to rt	6	86
6 <sup>d</sup>			LDA / <i>n</i> -BuLi	Et <sub>2</sub> O	-78 to -30	4	80
7 <sup>e</sup>			LDA / <i>n</i> -BuLi	THF	-78 to rt	1	95
8 <sup>e</sup>			LDA	THF	-78 to rt	1	96

<sup>a</sup> From ref 71b. <sup>b</sup> From ref 71d. <sup>c</sup> From ref 71a. <sup>d</sup> From ref 71c. <sup>e</sup> From ref 71e.

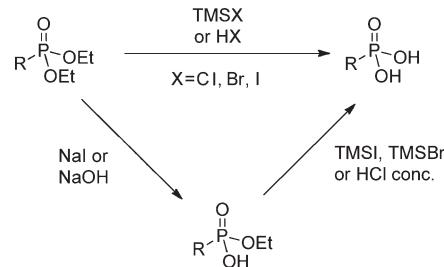
**Table 26. Conversion of Alkynyl Sulfones into Alkynyl Phosphonates by Substitution<sup>72</sup>**

Entry	R <sup>1</sup>	Phosphite (R <sup>2</sup> )	Yield (%)
1	Phenyl	Me	96
2	Phenyl	Et	98
3	Phenyl	i-Pr	71
4	Ph—CH <sub>2</sub>	Me	93
5	Ph—CH <sub>2</sub>	Et	90
6	Ph—CH <sub>2</sub>	i-Pr	70
7	Hexane	Me	90
8	Hexane	Et	95
9	Hexane	i-Pr	71
10	Cyclohexane	Me	90
11	Cyclohexane	Et	95
12	Cyclohexane	i-Pr	70

Selective deprotection of only one of the phosphonic ester groups is facilitated by reagents such as diluted hydrochloric acid, alkali metal halides, PhSH/NEt<sub>3</sub>, and TMSOK. The selectivity arises from the use of less reactive reagents than the ones used for complete hydrolysis into free phosphonic acids. As shown in Table 28, all these reagents afford the mono protected product in moderate-to-high yields (60–98%). Moreover, various solvents are used depending on the reagent applied.

Hydrolysis of a monoprotected phosphonic acid into the free acid phosphonic may be achieved by use of the same reagents as described for the direct complete hydrolysis of dialkyl phosphonates, such as concentrated HCl, TMSBr, or TMSI. As illustrated in Table 29, the corresponding free phosphonic acid is obtained in good-to-high yields (78–99%).<sup>85</sup>

**Scheme 7. General Methods for the Hydrolysis of the Dialkyl Phosphonate into the Free Phosphonic Acid or via Mono-deprotected Phosphonic Acid**



**Table 27. Methods for the Direct Hydrolysis of Dialkyl Phosphonate into Free Phosphonic Acid**

Entry	Starting Material	Products	Reagents	Solvent	Temp (°C)	Time (h)	Yields (%)
1 <sup>a</sup>			HCl	H <sub>2</sub> O	100	14	91
2 <sup>b</sup>			HCl	H <sub>2</sub> O	100	12	93
3 <sup>c</sup>			HBr	AcOH	rt	20	94
4 <sup>d</sup>			TMSBr	CH <sub>2</sub> Cl <sub>2</sub>	rt	24	72
5 <sup>e</sup>			TMSCl / NaI	CH <sub>3</sub> CN	rt	18	89
6 <sup>f</sup>			TMSI	CH <sub>2</sub> Cl <sub>2</sub>	rt	17	78

<sup>a</sup> From ref 74. <sup>b</sup> From ref 75. <sup>c</sup> From ref 76. <sup>d</sup> From ref 9b. <sup>e</sup> From ref 77. <sup>f</sup> From ref 10.

Table 28. Scope of the Different Reagents used for the Monodeprotection of the Dialkyl Phosphonate

Entry	Starting Material	Products	Reagents	Solvent	Temp (°C)	Time (h)	Yields (%)
1 <sup>a</sup>			20% HCl	H <sub>2</sub> O	Reflux	6	80
2 <sup>b</sup>			1)LiBr 2)HCl resin	pentan-2-one	Heat	3	95
3 <sup>c</sup>			NaI	Pyridine	110	--	90
4 <sup>d</sup>			1)NaI 2)HCl	MeOH	-- <sup>h</sup>	0.5	60
5 <sup>e</sup>			NaOH	H <sub>2</sub> O	80	Over night	69
6 <sup>f</sup>			PhSH, NEt <sub>3</sub>	THF/DMF	rt	48	98
7 <sup>g</sup>			TMSOK	THF	50	4	85

<sup>a</sup> From ref 78. <sup>b</sup> From ref 79. <sup>c</sup> From ref 80. <sup>d</sup> From ref 81. <sup>e</sup> From ref 82. <sup>f</sup> From ref 83. <sup>g</sup> From ref 84. <sup>h</sup> 10 min under microwave irradiation conditions (100 W) followed by cooling to room temperature. — indicates data not available.

Table 29. Different Reagents Used for the Fully Deprotection of the Monoprotected Phosphonate

Entry	Starting material	Products	Reagents	Solvent	Temp (°C)	Time (h)	Yields (%)
1 <sup>a</sup>			2N HCl Dowex-50W	H <sub>2</sub> O	80	72	99
2 <sup>b</sup>			TMSI	CH <sub>3</sub> CN	rt	3	86
3 <sup>c</sup>			TMSBr	CH <sub>3</sub> CN	rt	24	78

<sup>a</sup> From ref 85c. <sup>b</sup> From ref 85b. <sup>c</sup> From ref 85a.

## 5. CONCLUSION

In this paper, we have reviewed modern synthetic methods for the introduction of a phosphonic acid group. Except for one strategy described herein (Table 15) its introduction is carried out as a two-step process. First a dialkyl phosphonate is introduced, which is subsequently hydrolyzed to the corresponding

phosphonic acid group. To the organic chemist, the field presents a large number of diverse methodologies, from which a selection may be made on the basis of the hybridization state ( $sp^1$ ,  $sp^2$ , or  $sp^3$ ) of the carbon-atom at which the introduction is to take place, as well as compatibility of functional groups in the substrate. However, it is essential to recognize that complete hydrolysis of the phosphonate

ester is carried out under aqueous strongly acidic conditions or with the use of a strong Lewis acid (Table 28 and Table 29). This limits the compatibility with other functional groups and should be taken into account during retrosynthetic planning.

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## BIOGRAPHIES



Charles Demmer obtained his MSc degree in 2010 in organic chemistry from Université Blaise Pascal (UBP, Clermont-Ferrand in France). He did his master thesis at the Faculty of Pharmaceutical Sciences, University of Copenhagen working on the chemical synthesis of kainic acid analogs during which he did extensive work within introduction of a phosphonic acid group. In April 2011, he commenced his PhD studies in the Chemical Neuroscience Group at the University of Copenhagen working at the development of new synthetic methodology and the discovery of novel ligands acting at the central nervous system.



Niels Krogsgaard-Larsen obtained his MSc in 2004 in pharmaceutical sciences from The Faculty of Pharmaceutical Sciences at the University of Copenhagen. After being employed as research assistant, working as an external consultant at H. Lundbeck A/S, he received a Drug Research Academy PhD scholarship. The PhD studies were conducted in collaboration between the Department of Medicinal Chemistry at FARMA, H. Lundbeck A/S and The University at Buffalo, State University of

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Lennart Bunch obtained his BSc degree in 1996 in chemical engineering from the Technical University of Denmark (DTU). Shortly thereafter he relocated to the U.S.A. to complete an MSc study program in organic chemistry at Florida State University. In 1998, he returned to his home country to commence his PhD studies at the Royal Danish School of Pharmacy with focus on organic chemistry and rational drug design/medicinal chemistry. He received his PhD degree in 2002, and afterwards he did a one-year postdoctoral work within the field organometallic chemistry, at the Department of Chemistry, DTU. He was following awarded a 3-year Assistant Professorship from the Danish Medical Research Council for the medicinal chemistry studies of glutamate transporters. In 2006, he was promoted to Associate Professor and established his own research group named Chemical Neuroscience Group at the Faculty of Pharmaceutical Sciences, University of Copenhagen. His research interests are rational design and synthesis of neuroactive ligands, development of new methodology, computer-aided molecular modeling. He is dedicated to making a significant contribution to the discovery of novel psychiatric and neurological therapeutics.

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## GLOSSARY

**BINAP** 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl  
**BSA** bis(trimethylsilyl)acetamide  
**cod** 1,5-cyclooctadiene  
**dba** dibenzylideneacetone  
**DEP** diethylphosphite  
**DIPEA** *N,N*-diisopropylethylamine  
**DMF** dimethylformamide  
**dppf** 1,1'-bis(diphenylphosphino)ferrocene  
**dppp** 1,3-bis(diphenylphosphino)propane  
**KHMDS** potassium bis(trimethylsilyl)amide  
**LDA** lithium diisopropylamide  
**NaHMDS** sodium bis(trimethylsilyl)amide

rt room temperature  
TBD 1,5,7-triazabicyclo[4.4.0]dec-5-ene  
TFP tris(2-furyl)phosphine  
TMEDA tetramethylethylenediamine  
TMSBr trimethylsilyl bromide  
TMSCl trimethylsilyl chloride  
TMSI trimethylsilyl iodide

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