# Titanocene Dichloride as an Efficient Catalyst for One-Pot Synthesis of α-Aminophosphonates

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**Abstract:** Commercially available titanocene dichloride was firstly used as an extremely efficient catalyst for a three-component one-pot reaction of an amine, an aldehyde (ketone), and a dialkyl phosphite to form α-aminophosphonates under solvent-free conditions at ambient temperature in good to high yields, providing a green, rapid and convenient method for the synthesis of α-aminophosphonates.

**Keywords:** α-Aminophosphonates, multi-component reaction, titanocene dichloride.

## INTRODUCTION

As a kind of natural amino analogues, α-aminophosphonates constitute an important class of compounds with diverse biological activities [1]. α-Aminophosphonates are used as peptidomimetics [2], enzyme inhibitors [3], pharmacogenetical agents [4], inhibitors of serine hydrolases [5] and antitumor agents [6-8]. Thus, the development of synthetic methodologies for α-aminophosphonates has attracted much attention of medicinal/organic chemists. A large number of methods for the preparation of diverse α-aminophosphonates have been published since the first synthesis by Fields in 1952 [9-22]. However, one-pot synthesis of α-aminophosphonates remains a favor due to its simple procedure and excellent yields. Recently, three-component synthesis starting from aldehydes, amines and diethylphosphite or triethylphosphite have been reported by using Lewis or Bronsted acid catalysts such as $LiClO_4$ [23-26], $InCl_3$ [27], $ZrCl_4$ [28], $SbCl_3/Al_2O_3$ [29], $TaCl_5$-$SiO_2$ [30], amberlyst-15 [31], $Al_2O_3$-MW [32], $CF_3COOH$ [33], sulfamic acid [34], $BF_3{\cdot}Et_2O$ [35], M(OTf)n [36], M($ClO_4$)n [37] and $TiO_2$ [38]. Unfortunately, many of these methods suffer from some drawbacks such as long reaction times, requirement of solvents, additional reagents, heating, costly and moisture sensitive catalysts, or special apparatus. Therefore, it is necessary to develop an efficient method to construct such significant compounds.

Titanocene dichloride is a kind of Lewis acid, since α-aminophosphonates could be synthesized through three-component reactions catalyzed by Lewis acid, we had predicted that titanocene dichloride could be used an active catalyst for the synthesis of α-aminophosphonates. At the same time, titanocene dichloride is commercially available, non-toxic, inexpensive, highly active, and easy to handle. Herein, for the first time, titanocene dichloride is reported as a new and efficient catalyst for the synthesis of α-aminophosphonates under solvent-free conditions.

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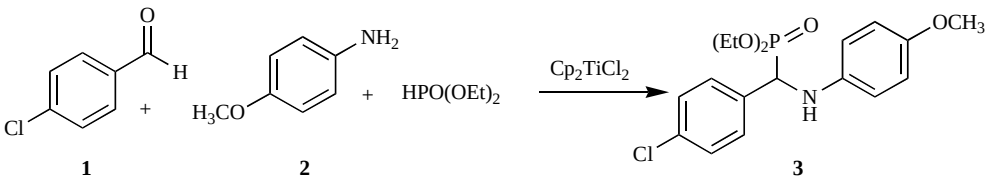
## RESULTS AND DISCUSSION

To optimize the experimental conditions, the reaction between 4-chlorobenzaldehyde, *p*-methoxyaniline and diethylphosphite was chosen as a model reaction (Table **1**). It was found that the reaction afforded medium yields with 10 mol% $Tp_2TiCl_2$ within longer reaction time when certain solvent such as EtOH, $CH_2Cl_2$, $CH_3Cl$, THF, EtOAc or PhMe was employed (entries 1-6). While under solvent-free condition, the reaction gave 95% isolated yield within 30 minutes at room temperature (entry 7). Reducing catalyst amount (3 mol%) led to the formation of α-aminophosphonates in lower yield (80%) even in 60 minute (entry 9). When the reaction was conducted by using 5 mol % of $Cp_2TiCl_2$ at room temperature for 50 min under solvent-free condition, 95% isolated yield was obtained (entry 8).

To evaluate the generality of the reaction, various aldehydes/ketons and aniline were subjected to the one-pot three-component reaction catalyzed by $Cp_2TiCl_2$ (Table **2**). First, various aromatic aldehydes with different functional groups such as Cl, OMe, $NO_2$, OH, $NMe_2$, and $CH_3$ were checked (entries 1-10). Electronic or steric effects from aromatic aldehydes seemed to have little impact on the reaction. The reaction proceeded smoothly to give the desired products in high yields. To our delight, heteroaromatic aldehydes also gave high yields catalyzed by $Cp_2TiCl_2$ under solvent-free conditions (entries 11-13). It is noteworthy, product **3la** and **3ma** from heteroaromatic

1875-6255/11 $58.00+.00 

**Table 1. Optimization of the Reaction Conditions for the Synthesis of α-Aminophosphonates 3 Catalyzed by $Tp_2TiCl_2$[a]**

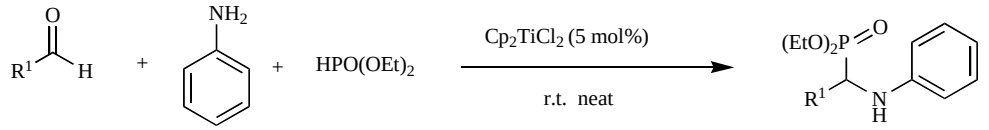



**1** **2** **3**

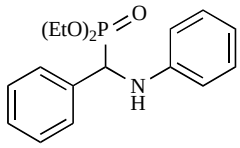
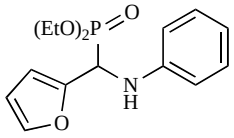
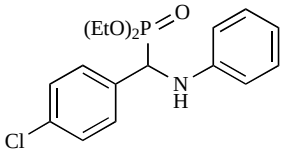
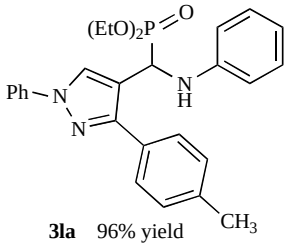
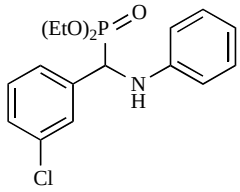
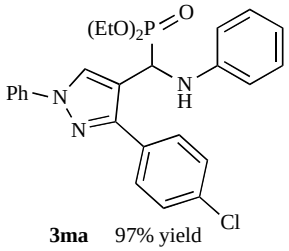
| Entry | Catalyst (mol%) | Solvent/Temp ($^oC$) | Time | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 10 | EtOH/50 | 28 h | 83 |
| 2 | 10 | $CH_2Cl_2$/50 | 24 h | 86 |
| 3 | 10 | $CHCl_3$/50 | 20 h | 78 |
| 4 | 10 | EtOAc/50 | 28 h | 87 |
| 5 | 10 | THF/50 | 18 h | 65 |
| 6 | 10 | $PhCH_3$/50 | 18 h | 76 |
| 7 | 10 | Solvent-free/r.t. | 30 min | 95 |
| 8 | 5 | Solvent-free/r.t. | 50 min | 95 |
| 9 | 3 | Solvent-free/r.t. | 60 min | 80 |

[a]Reaction conditions: diamine (0.5 mmol), aldehyde (0.5 mmol) and diethyl phosphite (1.5 mmol). [b]Isolated yields based on aldehydes.

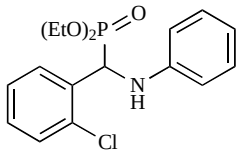
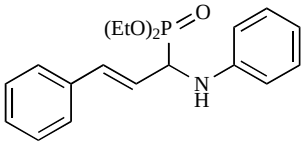
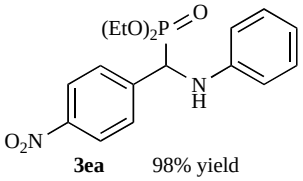
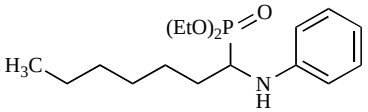
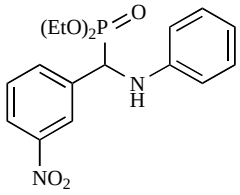
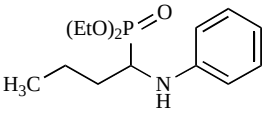
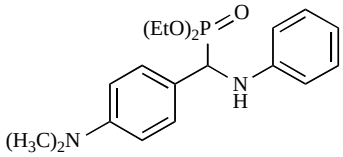
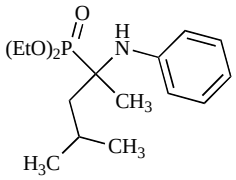
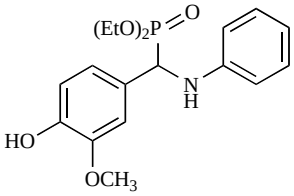
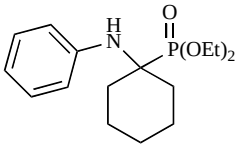
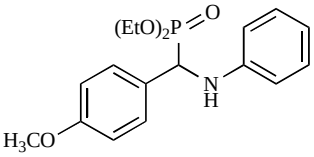
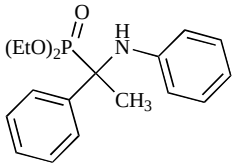
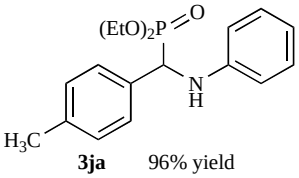
**Table 2. Synthesis of α-Aminophosphonates with Various Aldehydes/Ketons and Aniline[a]**




**1** **2a** **3**

| Entry | Time (min) | Products[b] | Entry | Time (min) | Products[b] |
|---|---|---|---|---|---|
| 1 | 30 |  **3aa** 96% yield | 11 | 60 |  **3ka** 90% yield |
| 2 | 30 |  **3ba** 96% yield | 12 | 60 |  **3la** 96% yield |
| 3 | 30 |  **3ca** 94% yield | 13 | 60 |  **3ma** 97% yield |

**(Table 2). Contd…..**

| Entry | Time (min) | Products [b] | Entry | Time (min) | Products [b] |
|---|---|---|---|---|---|
| 4 | 50 |  **3da** 90% yield | 14 | 60 |  **3na** 86% yield |
| 5 | 30 |  **3ea** 98% yield | 15 | 60 |  **3oa** trace |
| 6 | 30 |  **3fa** 88% yield | 16 | 60 |  **3pa** 66% yield |
| 7 | 60 |  **3ga** 86% yield | 17[c] | 60 |  **3qa** NR |
| 8 | 70 |  **3ha** 96% yield | 18[d] | 50 |  **3ra** 89% yield |
| 9 | 50 |  **3ia** 96% yield | 19[c] | 120 |  **3sa** NR |
| 10 | 60 |  **3ja** 96% yield | | | |

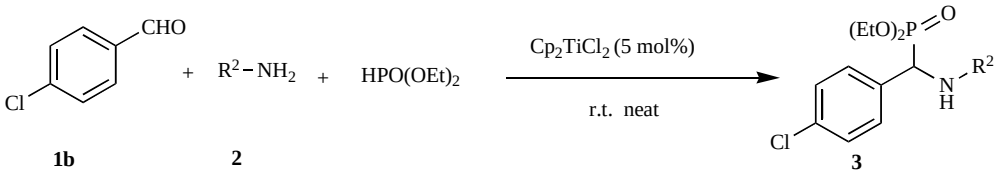
[a]Reaction conditions: diamine (0.5 mmol), aldehyde (0.5 mmol) and diethyl phosphite (1.5 mmol). [b]Isolated yields based on aldehydes. [c]No Reaction, the reaction was carried out at 100 °C. [d]The reaction was performed at 50 °C.

aldehydes are important scaffolds with biochemical activities. For aliphatic aldehydes, the reactions gave trace product or lower yields (Table **2**, entries 14-16). Futhermore, excellent chemoselectivities were observed for *α,β*-unsaturated carbonyl substrates (Table **2**, entry 14) that no competitive conjugate addition reaction occurred.

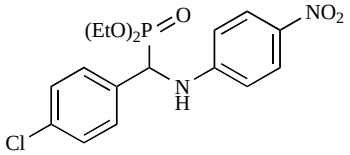
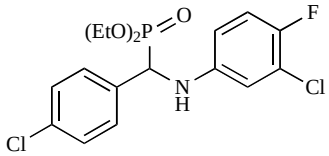
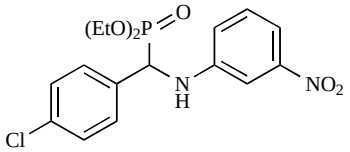
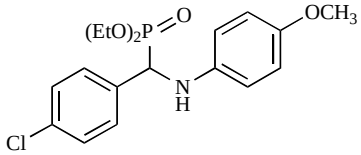
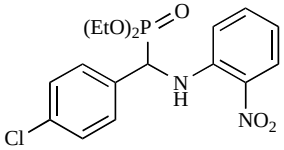
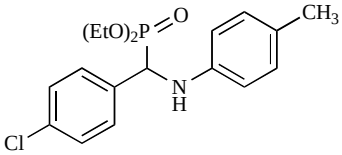
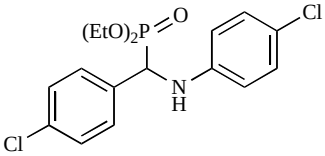
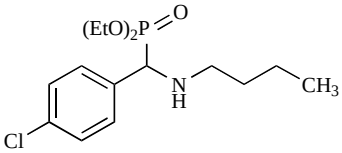
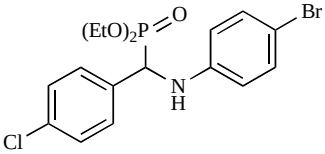
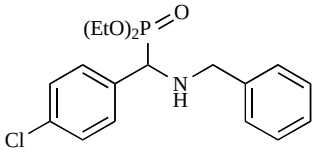
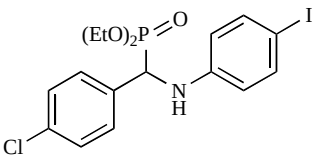
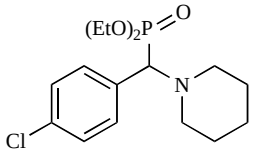
In addition to aldehydes, some ketones were also screened to the three-component coupling reaction catalyzed by $Cp_2TiCl_2$ under solvent-free conditions (Table **2**, entries 17-19). Due to the lower reactivities than that of aldehydes, both straight-chain aliphatic ketones like 4-methyl-2-pentanone (entry 17) and aromatic ketones like 4-methoxy-acetophenone (entry 19) gave no product even the reaction was carried out at 100 °C. While cyclic ketones like cyclohexanone (entry 18) smoothly gave the expected product in 89 % yield at 50 °C.

To study the influence of amines, a series of aromatic and aliphatic amines were employed as the substrates under the optimized reaction conditions (Table **3**). For aromatic amines,

**Table 3. Synthesis of α-Aminophosphonates with *p*-Chlorobenzaldehyde and Various Amines[a]**




**1b** **2** **3**

| Entry | Time (min) | Products[b] | Entry | Time (min) | Products[b] |
|---|---|---|---|---|---|
| 1 | 60 |  **3bb** 96% yield | 7 | 30 |  **3bh** 85% yield |
| 2 | 60 |  **3bc** 96% yield | 8 | 50 |  **3bi** 95% yield |
| 3 | 60 |  **3bd** 92% yield | 9 | 30 |  **3bj** 96% yield |
| 4 | 30 |  **3be** 96% yield | 10[c] | 60 |  **3bk** 90% yield |
| 5 | 30 |  **3bf** 96% yield | 11 | 60 |  **3bl** 85% yield |
| 6 | 50 |  **3bg** 87% yield | 12[d] | 60 |  **3bm** NR |

[a]Reaction conditions: diamine (0.5 mmol), aldehyde (0.5 mmol) and diethyl phosphite (1.5 mmol). [b]Isolated yields based on aldehydes. [c]The reaction was performed at 50 °C. [d]No Reaction.

it was found there were no remarkable electronic and steric effects on the three-component couplings, since anilines with *p*-, *o*-, and *m*-substituents resulted in the corresponding α-aminophosphonates in excellent yields (entries 1-9). Apart from aromatic amines, aliphatic amines were also selected to the three-component couplings. Primary amines, like *n*-butyl amine, phenyl-methanamine (entries 10-11) could provide the target products in reasonable yields, while secondary amines like piperidine (entry 12) were ineffective partners for such a reaction.

## CONCLUSIONS

In conclusion, commercially available $Cp_2TiCl_2$ was firstly found to be a new and extremely efficient catalyst for the synthesis of α-aminophosphonates by a three-component one-pot reaction. With the increasing concern for need of green synthetic procedures, the advantages such as the solvent-free reaction condition, ambient temperature, high yields, excellent chemoselectivities, the use of easily available and safe catalyst, and low catalyst amount make the present methodology attractive and environmentally benign.

## EXPERIMENTAL SECTION

### General

Elemental analyses were performed on a PE-2400 elemental analyzer. Melting points were determined with a XRC-1 micro melting point apparatus and were uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for $^1$H-NMR, 100 MHz for $^{13}$C-NMR. Proton chemical shifts δ were given in ppm relative to tetramethylsilane (0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent DMSO-d6 (2.50 ppm) for $^1$H and $^{13}$C NMR. For column chromatography 200-300 mesh silica gel (GF254) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All regents were purchased from commercial sources and purified commonly before used.

### Typical Procedure

To a glass vial, the required carbonyl compound (0.5 mmol), an amine (0.5 mmol), diethyl phosphite (1.5 mmol), and $Cp_2TiCl_2$ (5 mol %) were added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (eluent: EtOAc/petroleum ether, 20:80). After the reaction was completed, EtOAc (20 mL) was added to the reaction mixture and the catalyst was separated by filtration. The organic solvent was removed under reduced pressure. After purification by chromatography on silica gel (EtOAc/petroleum ether, 20:80) the α-amino phosphonates were obtained. All new products were characterized by NMR and elemental analyses.

### $^1$H NMR Spectral Data for all the Products

**3aa:** White solid, mp 88-90 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (3H, t, $J_{HH}$ 7.2 Hz), 1.28 (3H, t, $J_{HH}$ 7.2 Hz), 3.62-3.72 (1H, m), 3.89-3.98 (1H, m), 4.06-4.17 (2H, m), 4.76 (1H, d, $J_{HP}$ 24.0 Hz), 6.59 (2H, d, *J* 8.4 Hz), 6.69 (1H, t, *J* 7.6 Hz), 7.10 (2H, *J* 8.0 Hz), 7.25-7.28 (1H, m), 7.33 (2H, t, *J* 7.6 Hz), 7.47 (2H, d, *J* 7.6 Hz).

**3ba:** White solid, mp 57-59 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.06 (3H, t, $J_{HH}$ 6.8 Hz), 1.71 (3H, t, $J_{HH}$ 6.8 Hz), 3.73-3.80 (1H, m), 3.87-3.93 (1H, m), 4.00-4.07 (2H, m) 5.06 (1H, d, $J_{HP}$ 24.8 Hz), 6.27-6.31 (2H, m), 6.51 (1H, br s), 6.75 (2H, d, *J* 8.4 Hz), 6.96-7.01 (2H, m), 7.36 (2H, d, *J* 8.4 Hz), 7.52 (2H, dd, *J* 8.4, 1.6 Hz).

**3ca:** White solid, mp 88-90 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.06 (3H, t, $J_{HH}$ 7.2 Hz), 1.17 (3H, t, $J_{HH}$ 6.8 Hz), 3.72-3.82 (1H, m), 3.87-3.94 (1H, m), 4.02-4.06 (2H, m) 5.03 (1H, 2d, $J_{HP}$ 27.6, 7.2 Hz), 6.27-6.30 (1H, m), 6.50-6.54 (1H, m), 6.74-6.76 (2H, m), 6.99 (2H, d, *J* 8.0 Hz), 7.45-7.51 (4H, m).

**3da:** White solid, mp 87-89 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (3H, t, $J_{HH}$ 8.0 Hz), 1.34 (3H, t, $J_{HH}$ 7.2 Hz), 3.64 (1H, t, $J_{HH}$ 7.6 Hz), 3.89-3.93 (1H, m), 4.18-4.25 (2H, m), 5.06 (1H, 2d, $J_{HP}$ 24.0 Hz), 6.58 (2H, d, *J* 7.6 Hz), 6.69 (1H, t, *J* 7.2 Hz), 7.11 (2H, t, *J* 7.2 Hz), 7.20-7.26 (2H, m), 7.38 (1H, d, *J* 7.2 Hz), 7.52 (1H, d, *J* 7.2 Hz).

**3ea:** Yellow solid, mp 112-124 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (3H, t, $J_{HH}$ 7.2 Hz), 1.30 (3H, t, $J_{HH}$ 7.2 Hz), 3.83-3.93 (1H, m), 3.99-4.06 (1H, m), 4.07-4.21 (2H, m), 4.86 (1H, d, $J_{HP}$ 24.8 Hz), 6.53 (2H, d, *J* 8.0 Hz), 6.74 (1H, t, *J* 7.2 Hz), 7.12 (2H, t, *J* 7.6 Hz), 7.66 (2H, dd, *J* 8.8, 2.0 Hz), 8.20 (2H, d, *J* 8.4 Hz).

**3fa:** Yellow solid, mp 152-154 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (3H, t, $J_{HH}$ 6.8 Hz), 1.30 (3H, t, $J_{HH}$ 6.8 Hz), 3.86-3.93 (1H, m), 3.94-4.06 (1H, m), 4.11-4.19 (2H, m), 4.86 (1H, d, $J_{HP}$ 26.8 Hz), 6.56 (2H, d, *J* 8.0 Hz), 6.74 (1H, t, *J* 7.2 Hz), 7.13 (2H, t, *J* 7.2 Hz), 7.26 (1H, s), 7.52 (1H, t, *J* 8.0 Hz), 7.83 (1H, d, *J* 7.6 Hz), 8.14 (1H, d, *J* 7.6 Hz).

**3ga:** White solid, mp 72-74 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.14 (3H, t, $J_{HH}$ 6.8 Hz), 1.28 (3H, t, $J_{HH}$ 7.2 Hz), 2.91 (6H, s), 3.63-3.72 (1H, m), 3.73-3.97 (1H, m), 4.03-4.16 (2H, m), 4.67 (1H, d, $J_{HP}$ 24.0 Hz), 6.60 (2H, d, *J* 7.6 Hz), 6.67 (3H, t, *J* 8.4 Hz), 7.09 (2H, t, *J* 7.6 Hz), 7.30 (2H, dd, *J* 8.8, 2.4 Hz).

**3ha:** White solid, mp 86-88 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.05 (3H, t, $J_{HH}$ 6.8 Hz), 1.18 (3H, t, $J_{HH}$ 7.2 Hz), 3.57 (3H, s), 3.72-3.80 (1H, m), 3.84-3.92 (1H, m), 4.04 (2H, t, $J_{HH}$ 6.8 Hz), 5.00 (1H, d, $J_{HP}$ 24.0 Hz), 5.90 (1H, br s), 6.61 (2H, d, *J* 9.2 Hz), 6.70 (2H, d, *J* 9.2 Hz), 7.35 (2H, d, *J* 8.0 Hz), 7.50 (2H, d, *J* 6.8 Hz).

**3ia:** White solid, mp 96-98 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.14 (3H, t, $J_{HH}$ 7.2 Hz), 1.28 (3H, t, $J_{HH}$ 6.8 Hz), 3.67-3.72 (1H, m), 3.77 (3H, s), 3.91-3.97 (1H, m), 4.08-4.15 (2H, m), 4.71(1H, 2d, $J_{HP}$ 24.0 Hz), 6.59 (2H, d, *J* 7.6 Hz), 6.69 (1H, t, *J* 7.6 Hz), 6.86 (2H, d, *J* 8.0 Hz), 7.10 (2H, t, *J* 7.6 Hz), 7.38 (2H, dd, *J* 8.4, 2.0 Hz).

**3ja:** White solid, mp 58-60 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.14 (3H, t, $J_{HH}$ 6.8 Hz), 1.29 (3H, t, $J_{HH}$ 6.8 Hz), 2.31 (3H, s), 3.67-3.73 (1H, m), 3.92-3.97 (1H, m), 4.10-4.16 (2H, m), 4.75 (1H, 2d, $J_{HP}$ 24.0 Hz), 6.61 (2H, d, *J* 7.2 Hz), 6.69 (1H, t, *J* 7.6 Hz), 7.12 (4H, t, *J* 8.0 Hz), 7.35 (2H, d, *J* 6.8 Hz).

**3ka:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (3H, t, $J_{HH}$ 6.8 Hz), 1.29 (3H, t, $J_{HH}$ 7.2 Hz), 3.70-3.74 (1H, m), 4.00-4.04 (1H, m), 4.15-4.21 (2H, m), 4.90 (1H, d, $J_{HP}$ 23.2 Hz), 6.35 (2H, d, *J* 24.0 Hz), 6.67 (2H, d, *J* 8.0 Hz), 6.74 (1H, t, *J* 7.2 Hz) , 7.15 (2H, t, *J* 7.6 Hz), 7.37 (1H, d, *J* 6.4 Hz).

**3la:** White solid, mp 178-180 °C. $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (3H, t, $J_{HH}$ 6.4 Hz), 1.25 (3H, t, $J_{HH}$ 6.0 Hz), 2.43 (3H, s), 3.87-3.93 (1H, m), 4.03-4.13 (2H, m), 4.17-4.25 (1H, m), 4.89 (1H, d, $J_{HP}$ 20.4 Hz), 6.51 (2H, d, *J* 7.2 Hz), 6.69 (1H, t, *J* 7.2 Hz), 7.07 (2H, d, *J* 6.8 Hz), 7.27 (3H, d, *J* 8.0 Hz), 7.42 (2H, t, *J* 7.2 Hz), 7.59 (2H, t, *J* 6.4 Hz), 7.73 (2H, t, *J* 7.2 Hz); $^1$C NMR ($CDCl_3$, 100 MHz) δ: 16.3, 16.5, 21.3, 46.8, 48.6 (d, $J_{CP}$ 180 Hz), 63.3, 63.4, 113.5, 113.8, 116.8, 117.2, 118.5, 118.9, 126.4, 128.4, 129.1, 129.4, 131.7, 138.1, 139.8, 147.6; elemental analysis, $C_{27}H_{30}N_3PO_3$ requires: C, 68.20; H, 6.36; N, 8.84 %.; Found: C, 68.18; H, 6.38; N, 8.85 %. LRMS (FAB) m/z (pos) 476.7 $[M+1]^+$.

**3ma:** White solid, mp 148-150 °C. $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (3H, t, $J_{HH}$ 6.8 Hz), 1.26 (3H, t, $J_{HH}$ 6.0 Hz), 3.89-3.95 (1H, m), 4.04-4.13 (2H, m), 4.17-4.23 (1H, m), 4.89 (1H, 2d, $J_{HP}$ 20.8 Hz), 6.50 (2H, d, *J* 8.0 Hz), 6.71 (1H, t, *J* 6.4 Hz), 7.07-7.10 (2H, m), 7.25-7.30 (1H, m), 7.44 (4H, t, *J* 2.4 Hz), 7.64-7.66 (2H, m), 7.72 (2H, t, *J* 3.0 Hz); $^1$C NMR ($CDCl_3$, 100 MHz) δ: 16.2, 16.4, 45.9, 47.6 (d, $J_{CP}$ 170 Hz), 63.3, 63.6, 107.0, 113.8, 116.9, 118.8, 126.7, 127.7, 128.9, 129.2, 129.4, 129.8, 131.2, 134.4, 139.6, 145.7, 151.2; elemental analysis, $C_{26}H_{27}ClN_3PO_3$ requires: C, 62.97; H, 5. 49; N, 8.47 %.; Found: C, 62.99; H, 5.50; N, 8.46 %. LRMS (FAB) m/z (pos) 496.6 $[M+1]^+$.

**3na:** White solid, mp 102-104 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (3H, t, $J_{HH}$ 7.2 Hz), 1.24 (3H, t, $J_{HH}$ 6.8 Hz), 3.67-3.72 (1H, m), 3.91-3.97 (1H, m), 4.08-4.15 (2H, m), 4.81(1H, d, $J_{HP}$ 24.0 Hz), 5.48 (1H, m), 5.62 (H, m), 6.60 (2H, d, *J* 7.6 Hz), 6.69 (2H, d, *J* 7.6 Hz), 6.86 (2H, d, *J* 8.0 Hz), 7.12 (2H, t, *J* 7.6 Hz), 7.48 (2H, d, *J* 8.0 Hz).

**3pa:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 0.84-1.66 (13H, m), 4.09-4.17 (4H, m), 5.92 (1H, d, $J_{HP}$ 23.2 Hz), 6.62-6.76 (2H, m) , 7.14 (2H, t, *J* 7.2 Hz), 7.66 (1H, s).

**3ra:** White solid, mp 100-102 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (6H, t, $J_{HH}$ 6.8 Hz), 1.52 (4H, t, *J* 9.2 Hz), 1.65 (1H, d, *J* 9.2 Hz), 1.76-1.84 (2H, m), 2.17-2.22 (2H, m), 2.94 (2H, br s), 3.95-4.11(4H, m), 6.79 (1H, t, *J* 7.2 Hz), 7.02 (2H, t, *J* 7.6 Hz), 7.15 (2H, t, *J* 8.4 Hz).

**3bb:** Yellow solid, mp 141-143 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.06 (3H, t, $J_{HH}$=6.8 Hz), 1.15 (3H, t, $J_{HH}$ 6.8 Hz), 3.76-3.82 (1H, m), 3.89-3.95 (1H, m), 4.00-4.06 (2H, m), 5.38 (1H, 2d, $J_{HP}$ 23.6 Hz), 6.93 (2H, *J* 9.2 Hz), 7.42 (2H, d, *J* 8.8 Hz), 7.54 (2H, dd, *J* 8.4, 1.6 Hz), 7.94 (3H, d, *J* 9.2 Hz).

**3bc:** Yellow solid, mp 126-130 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (3H, t, $J_{HH}$ 6.8 Hz), 1.20 (3H, t, $J_{HH}$ 6.8 Hz), 3.66-3.78 (1H, m), 3.92-4.00 (1H, m), 4.05-4.21 (2H, m), 4.78 (1H, d, $J_{HP}$ 24.8 Hz), 6.68 (2H, s), 6.89 (1H, d, *J* 8.0 Hz), 7.18 (1H, *t*, *J* 8.0 Hz), 7.29 (1H, d, *J* 8.4 Hz), 7.41-7.49 (3H, m).

**3bd:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (3H, t, $J_{HH}$ 6.8 Hz), 1.30 (3H, t, $J_{HH}$ 6.8 Hz), 3.86-3.93 (1H, m), 3.94-4.06 (1H, m), 4.11-4.19 (2H, m), 4.86 (1H, d, $J_{HP}$ 26.8 Hz), 4.92 (1H,br s), 6.56 (2H, d, *J* 8.0 Hz), 6.74 (1H, t, *J* 7.2 Hz), 7.13 (2H, t, *J* 7.2 Hz), 7.26 (1H, s), 7.52 (1H, t, *J* 8.0 Hz), 7.83 (1H, d, *J* 7.6 Hz), 8.14 (1H, d, *J* 7.6 Hz).

**3be:** White solid, mp 114-116 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (3H, t, $J_{HH}$ 6.8 Hz), 1.30 (3H, t, $J_{HH}$ 7.2 Hz), 3.71-3.81 (1H, m), 3.94-4.00 (1H, m), 4.08-4.17 (2H, m), 4.66 (1H, d, $J_{HP}$ 24.0 Hz), 6.47 (2H, d, *J* 8.8 Hz), 7.04 (1H, t, *J* 8.8 Hz), 7.31 (2H, d, *J* 8.4 Hz), 7.38 (2H, dd, *J* 8.4, 2.0 Hz).

**3bf:** White solid, mp 124-126 °C; $^1$H NMR (DMSO, 400 MHz) δ: 1.06 (3H, t, $J_{HH}$ 7.2 Hz), 1.17 (3H, t, $J_{HH}$ 7.2 Hz), 3.75-3.79 (1H, m), 3.87-3.91 (1H, m), 4.01-4.06 (2H, m), 5.07 (1H, d, $J_{HP}$ 24.0 Hz), 6.74 (1H, t, $J_{NH}$ 7.2 Hz, 7.13 (2H, d, *J* 8.8 Hz), 7.38 (2H, t, $J_{HH}$ 8.6 Hz), 7.50 (2H, d, *J* 8.8 Hz), 7.52 (2H, d, *J* 8.8 Hz); $^1$C NMR (DMSO, 100 MHz) δ: 16.5, 16.7, 52.3 (d, $J_{CP}$ 151.2 Hz), 62.7, 62.8, 63.1, 65.5, 113.6, 114.6, 116.9, 117.2, 119.6, 128.4, 130.5, 132.6, 136.0, 145.0, 148.9, 151.3. HRMS: calcd for $C_{17}H_{21}BrClNO_3P$ $[M+H^+]$ 432.0131, found 432.0131.

**3bg:** White solid, mp 136-138 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.05 (3H, t, $J_{HH}$ 7.2 Hz), 1.15 (3H, t, $J_{HH}$ 6.8 Hz), 3.72-3.78 (1H, m), 3.84-3.94 (1H, m), 4.02-4.05 (2H, m), 5.08 (1H, 2d, $J_{HP}$ 24.8 Hz), 6.63 (3H, t, *J* 8.4 Hz), 6.90 (1H, 2d, *J* 8.8Hz), 7.26 (1H, d, *J* 8.4 Hz), 7.37 (2H, d, *J* 8.0 Hz), 7.50 (2H, d, *J* 8.4 Hz). HRMS: calcd for $C_{17}H_{21}ClINO_3P$ $[M+H^+]$ 479.9992, found 479.9995.

**3bh:** White solid, mp 72-74 °C; $^1$H NMR (DMSO, 400 MHz) δ: 1.05 (3H, t, $J_{HH}$ 6.8 Hz), 1.17 (3H, t, $J_{HH}$ 6.8 Hz), 3.72-3.80 (1H, m), 3.86-3.92 (1H, m), 4.00-4.06 (2H, m), 5.14 (1H, 2d, $J_{HP}$ 24.8 Hz), 6.63 (1H, br s), 6.73-6.76 (1H, m), 6.95 (1H, dd, *J* 6.4 2.8 Hz), 7.03 (1H, t, *J* 8.8 Hz), 7.38 (2H, d, *J* 8.4 Hz), 7.50 (2H, d, *J* 8.8 Hz). $^1$C NMR (DMSO, 100 MHz) δ: 16.5, 16.7, 53.5 (d, $J_{CP}$ 151.8 Hz), 62.7, 62.8, 63.1, 108.3, 115.9, 114.6, 124.3, 117.2, 124.8, 128.4, 130.5, 131.5, 132.6, 136.2, 146.8, 146.9. HRMS: calcd for $C_{17}H_{20}Cl_2FNO_3P$ $[M+H^+]$ 406.0542, found 406.0544.

**3bi:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (3H, t, $J_{HH}$ 6.8 Hz), 1.29 (3H, t, $J_{HH}$ 7.2 Hz), 3.69 (3H, s), 3.76-3.82 (1H, m), 3.95-4.02 (1H, m), 4.06-4.17 (2H, m), 4.65 (1H, d, $J_{HP}$ 23.6 Hz), 6.50 (2H, d, *J* 8.8 Hz), 6.69 (2H, d, *J* 8.8 Hz), 7.29 (2H, t, *J* 8.4 Hz), 7.39 (2H, dd, *J* 8.4, 1.5 Hz).

**3bj:** White solid, mp 90-92 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (3H, t, $J_{HH}$ 6.8 Hz), 1.29 (3H, t, $J_{HH}$ 6.8 Hz), 2.19 (3H, s), 3.75-3.82 (1H, m), 3.94-4.00 (1H, m), 4.06-4.18 (2H, m), 4.66 (1H, d, $J_{HP}$ 24.0 Hz), 6.43 (2H, d, *J* 7.6 Hz), 7.16-7.19 (2H, m), 7.30-7.32 (2H, m), 7.37 (2H, d, *J* 6.8 Hz).

**3bk:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 0.78 (3H, t, $J_{HH}$ 7.2 Hz), 1.04 (3H, t, $J_{HH}$ 6.8 Hz), 1.17-1.25 (3H, m), 1.71-1.83 (6H, m), 2.62-2.65 (2H, m), 3.46-3.52 (1H, m), 3.59-3.67 (1H, m), 4.66 (1H, d, $J_{HP}$ 17.2 Hz), 7.36 (2H, d, *J* 8.4 Hz), 7.68 (2H, dd, *J* 6.8, 2.0 Hz). HRMS: calcd for $C_{15}H_{26}ClNO_3P$ $[M+H^+]$ 334.1339, found 334.1341.

**3bl:** Viscous colourless oil; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (3H, t, $J_{HH}$ 7.0 Hz), 1.27 (3H, t, $J_{HH}$ 7.0 Hz), 3.50 (1H, d, *J* 13.2 Hz), 3.77 (1H, d, *J* 13.2 Hz), 3.97-4.10 (6H, m), 7.23-7.37 (10H, m).

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## REFERENCES

[1] Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M. R.; Jafari, A. A.; Zare, H. R. Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity. *Eur. J. Med. Chem.*, **2009**, *44*, 4266-4275.

[2] Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids, *Phosphorus, Sulfur Silicon Relat. Elem.*, **1991**, *63*, 193-215.

[3] Allen, M. C.; Fuher, W.; Tuck, B.; Wade, R.; Wood, J. *M.* Renin inhibitors. Synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond, *J. Med. Chem.*, **1989**, *32*, 1652-1661.

[4] Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. 1-Aminoalkylphosphonous acids. Part 1. Isosteres of the protein amino acids, *J. Chem. Soc., Perkin Trans.* **1984**, *1*, 2845-2853.

[5] Makhaeva, G. F.; Malygin, V. V.; Aksinenko, A. Y.; Sokolov, V. B.; Strakhova, N. N.; Rasdolsky, A.N.; Richardson, R. J.; Martynov, I. V. Fluorinated alpha-aminophosphonates--a new type of irreversible inhibitors of serine hydrolases, *Dokl Biochem. Biophys.* **2005**, *400*, 92-95.

[6] Bloemink, M. J.; Diederen, J. J. H.; Dorenbos, J. P.; Heetebrij, R. J.; Keppler, B. K.; Reedijk, Calcium Ions Do Accelerate the DNA Binding of New Antitumor-Active Platinum Aminophosphonate Complexes, J. *Eur. J. Inorg. Chem.* **1999**, *10*, 1655-1657;

[7] Jin, L.; Song, B.; Zhang, G.; Xu, R.; Zhang, S.; Gao, X.; Hu, D.; Yang, S. Synthesis, X-ray crystallographic analysis, and antitumor activity of *N*-(benzothiazole-2-yl)-1-(fluorophenyl)-*O*,*O*-dialkyl-α-aminophosphonates, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1537-1543;

[8] Rao, X.; Song, Z.; He, L. Synthesis and antitumor activity of novel α-aminophosphonates from diterpenic dehydroabietylamine, *Heteroat. Chem.* **2008**, *19*, 512-516.

[9] Fields, E. K. The Synthesis of Esters of Substituted Amino Phosphonic Acids, J. *Am. Chem. Soc.* **1952**, *74*, 1528-1531;

[10] Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P. Elektrochemische Decarboxylierung von L.-Threonin- und Oligopeptid-Derivaten unter Bildung von *N*-Acyl-N, O-acetalen: Herstellung von Oligopeptiden mit Carboxamid-oder Phosphonat-C-Terminus, *Helv. Chim. Acta* **1989**, *72*, 401-425;

[11] Kuntz, H.; Laschat, S. Carbohydrates as Chiral Templates: Stereoselective Synthesis of (*R*)- and (*S*)-α-Aminophosphonic Acid Derivatives, *Synthesis* **1992**, 90-94;

[12] Shatzmiller, S.; Dolitzky, B. -Z.; Meirovich, R.; Neidlein, R.; Weik, C. Synthesis of -amino phosphonic acids *via* oxoiminium salts, *Liebigs Ann. Chem.* **1991**, *161-164*;

[13] Smith III, A. B.; Yager, K. M.; Taylor, C. *M.* Enantioselective Synthesis of Diverse .alpha.-Amino Phosphonate Diesters, *J. Am. Chem. Soc.* **1995**, *117*, 10879-10888;

[14] Yokommatsu, T.; Shibuya, S. Enantioselective synthesis of α-amino phosphonic acids by an application of stereoselective opening of homochiral dioxane acetals with triethyl phosphite, *Tetrahedron: Asymmetry* **1992**, *3*, 377-378;

[15] Hanessian, S.; Bennani, Y. L. Electrophilic Amination and Azidation of Chiral α-Alkyl Phosphonamides: Asymmetric Syntheses of α-Amino α-Alkyl Phosphonic Acids, *Synthesis* **1994**, 1272-1274;

[16] Schmidt, U.; Oehme, G.; Kraus, H. Catalytic stereoselective synthesis of α-Amino phosphonic acid derivatives by asymmetric hydrogenation, *Synth. Commun.* **1996**, *26*, 777-781;

[17] Schőllkopf, U.; Hoppe, I.; Thiele, A. Asymmetric synthesis of -aminophosphonic acids, I enantioselective synthesis of L-(1-aminoethyl)phosphonic acid by asymmetric catalytic hydrogenation of ***N***-[1-(dimethoxyphosphoryl)ethenyl]formamide, *Liebigs Ann. Chem.* **1985**, 555-559;

[18] Sawamura, M.; Ito, Y.; Hayashi, T. Conformational isomers of 14-hydroxy-9-epi-β-caryophyllene isolated from the wood of Juniperus oxycedrus, *Tetrahedron Lett.* **1989**, *30*, 247-250;

[19] Kim, D. Y.; Rhie, D. Y. Synthesis of α-aminoalkylphosphonates from vinylphosphonates *via* aziridinylphosphonates, *Tetrahedron* **1997**, *53*, 13603-13608;

[20] Lefebvre , I. M.; Evans Jr., S. A. Studies toward the Asymmetric Synthesis of α-Amino Phosphonic Acids *via* the Addition of Phosphites to Enantiopure Sulfinimines, *J. Org. Chem.* **1997**, *62*, 7532-7533;

[21] Heydari, A.; Karimian, A.; Ipaktschi, J. Lithium perchlorate/diethylether catalyzed aminophosphonation of aldehydes, *Tetrahedron Lett*. **1998**, *39*, 6729-6732;

[22] Yang, R.; Zhao, R.; Zhao, L.; Yun, L.; Wang, H. An Auto-catalyzed Mannich-Type Reaction for Synthesis of Highly Substituted α-Aminomethylphosphonates, *Synthesis* **2003**, 887-893.

[23] 8. Saidi, M. R.; Azizi, N. A New Protocol for a One-pot Synthesis of α-Amino Phosphonates by Reaction of Imines Prepared In Situ with Trialkylphosphites, *Synlett*, **2002**, 1347-1349;

[24] Azizi, N.; Rajabi, F.; Saidi, M. R. A mild and highly efficient protocol for the one-pot synthesis of primary α-amino phosphonates under solvent-free conditions, *Tetrahedron Lett.* **2004**, *45*, 9233-9236;

[25] Azizi, N.; Saidi, M. R. Synthesis of tertiary α-amino phosphonate by one-pot three-component coupling mediated by LPDE, *Tetrahedron*, **2003**, *59*, 5329-5332;

[26] Azizi, N.; Saidi, M. R. Lithium Perchlorate-Catalyzed Three-Component Coupling: A Facile and General Method for the Synthesis of -Aminophosphonates under Solvent-Free Conditions, *Eur. J. Org. Chem.* **2003**, *23*, 4630-4633;

[27] Ranu, B. C.; Hajra, A.; Jana, U. General Procedure for the Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Using Indium(III) Chloride as a Catalyst, *Org. Lett.* **1999**, *1*, 1141-1143;

[28] Manjula, A.; Rao, B. V.; Neelakantan, P. One-Pot Synthesis of α-Aminophosphonates: An Inexpensive Approach, *Synth. Commun.* **2003**, *33*, 2963-2969;

[29] Ambica, Kumar, S.; Taneja, S. C.; Hundal, M. S., Kapoor, K. K. One-pot synthesis of α-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina, *Tetrahedron Lett.* **2008**, *49*, 2208-2212;

[30] Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. Three component coupling catalyzed by TaCl5−SiO2: synthesis of α-amino phosphonates, *Tetrahedron Lett.* **2001**, *42*, 5561-5563;

[31] Tajbakhsh, M.; Heydari, A.; Alinezhad, H.; Ghanei, M.; Khaksar, S. Coupling of Aldehydes, Amines, and Trimethyl Phosphite Promoted by Amberlyst-15: Highly Efficient Synthesis of α-Aminophosphonates, *Synthesis* **2008**, 352-354;

[32] Kaboudin, B.; Nazari, R. Microwave-assisted synthesis of 1-aminoalkyl phosphonates under solvent-free conditions, T*etrahedron Lett*. **2001**, *42*, 8211-8213;

[33] Akiyama, T.; Sanada, M.; Fuchibe, K. Brønsted Acid-Mediated Synthesis of α-Amino Phosphonates under Solvent-Free Conditions, *Synlett*, **2003**, 1463-1464;

[34] Mitragotri, S. D.; Pore, D. M.; Desai, U. V.; Wadgaonkar, P. P. Sulfamic acid: An efficient and cost-effective solid acid catalyst for the synthesis of α-aminophosphonates at ambient temperature, *Catal. Commun.* **2008**, *9*, 1822-1826;

[35] Ha, H.-J.; Nam, G.-S. An Efficient Synthesis of Anilinobenzylphosphonates, *Synth. Commun.* **1992**, *22*, 1143-1148;

[36] Firouzabadi, H.; Iranpoor, N.; Sobhani, S. Metal Triflate-Catalyzed One-Pot Synthesis of α-Aminophosphonates from Carbonyl Compounds in the Absence of Solvent, *Synthesis* **2004**, 2692:

[37] Bhagat, S.; Chakraborti, A. K. An Extremely Efficient Three-Component Reaction of Aldehydes/Ketones, Amines, and Phosphites (Kabachnik−Fields Reaction) for the Synthesis of α-

Aminophosphonates Catalyzed by Magnesium Perchlorate, *J. Org. Chem*. **2007**, *72*, 1263-1270.

[38] Hosseini-Sarvari, M. TiO2 as a new and reusable catalyst for one-pot three-component syntheses of α-aminophosphonates in solvent-free conditions, *Tetrahedron* **2008**, *64*, 5459-5466.