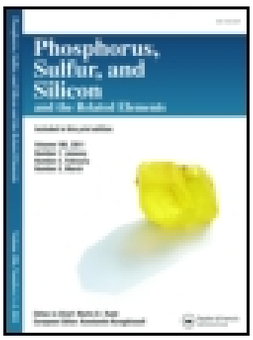


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

# $CeCl_3 \cdot 7H_2O$-catalysed hydrophosphonylation of aldehydes and ketones: An expeditious route to α-hydroxyphosphonates under solvent-free conditions

R. Mahesh, Rupali Sharma, Parteek Kour & Anil Kumar

**To cite this article:** R. Mahesh, Rupali Sharma, Parteek Kour & Anil Kumar (2019): $CeCl_3 \cdot 7H_2O$-catalysed hydrophosphonylation of aldehydes and ketones: An expeditious route to α-hydroxyphosphonates under solvent-free conditions, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2019.1633532

**To link to this article:** https://doi.org/10.1080/10426507.2019.1633532

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2019.1633532

Taylor & Francis
Taylor & Francis Group

SHORT COMMUNICATION

# $CeCl_3 \cdot 7H_2O$-catalysed hydrophosphonylation of aldehydes and ketones: An expeditious route to α-hydroxyphosphonates under solvent-free conditions

R. Mahesh, Rupali Sharma, Parteek Kour, and Anil Kumar

Synthetic Organic Chemistry Lab, Faculty of Sciences, Shri Mata Vaishno Devi University, Katra, Jammu & Kashmir, India

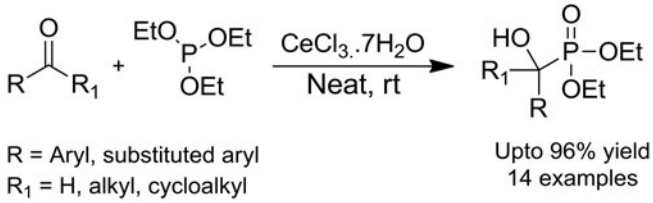
**ABSTRACT**

A cerium(III) chloride-catalysed expeditious synthesis of α-hydroxyphosphonates via a modified Abramov synthetic protocol has been developed. The scope of the current protocol is broad, with a range of aromatic, α,β-unsaturated and heterocyclic aldehydes being efficiently converted to the anticipated products in very good to excellent yields (89–96%) in 15 min using low catalytic loading. The protocol was efficiently extended to hitherto unactivated cyclic ketones such as cyclopentanone and cyclohexanone to afford the required products in excellent yields. However, the reaction with cyclohexenone delivered a Michael product instead of the anticipated α-hydroxyphosphonates. The solvent-free conditions, low catalytic loadings, avoidance of toxic reagents and good to excellent yields are significant advantages of this protocol.

**ARTICLE HISTORY**
Received 25 February 2019
Accepted 15 June 2019

**KEYWORDS**
Cerium(III) chloride; hydrophosphonylation; α-hydroxyphosphonates; solvent-free

**GRAPHICAL ABSTRACT**




## Introduction

The α-hydroxyphosphonates represent an elite class of compounds known to exhibit wide-ranging biological activities.[1] They have been extensively utilized as key intermediates to obtain biologically relevant natural and synthetic products, unnatural amino acids and potential drug candidates.[2a–e] Further, as shown in Figure 1, type a and b α-hydroxyphosphonates are potent anti-cancer agents and type c and d are potent renin/ligase and autotaxin inhibitors, respectively.[2f–g] Owing to these attractive biological, industrial and synthetic applications, a plethora of protocols have been devised and reviewed in the literature for the synthesis of α-hydroxyphosphonates. However, most of these synthetic routes were primarily inspired by the older methods of Abramov and Pudovik.

These protocols have been carried out using various kinds of catalysts, including basic catalysts such as tetramethylguanidine,[3] lithium diisopropylamide (LDA),[4] guanidine hydrochloride,[5] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[6] $K_3PO_4$,[7] $K_2CO_3$,[8] CaO,[9] $Na_2CO_3$,[10] triethylamine,[11] KF/$Al_2O_3$,[12] polystyrene tetraalkylammonium hydroxide ion exchange resin [Rexyn 201 (OH)],[13] magnesia[14] and 1,5,7-triazabicyclo[4.4.0]dec-1-ene[15] and acidic catalysts such as amberlyst-15,[16] camphor sulfonic acid,[17] oxalic acid,[18] silica-supported tungstic acid,[19] $AlCl_3$ or HCl,[20] $MoO_2Cl_2$,[21] Ti(O-*i*-Pr)$_4$,[22] trimethylsilyl chloride[23] and $NH_4VO_3$.[24]

Recently there has been a surge in organometallic catalysts such as $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$,[25] lanthanide anilido complexes,[26] *n*-BuLi[27] and organo-bimetallic catalysts[28] that have been elegantly applied for this transformation. Although these protocols for synthesizing α-hydroxyphosphonates have their advantages, most suffer from one or more disadvantages such as high catalytic loading,[6,12] prolonged reaction time,[9] expensive catalysts,[22] acidic and harsh reaction conditions,[20] tedious procedure.[26,28] Therefore, the development of a new strategy that avoids most of these drawbacks would be highly desirable.

It has been well documented that Lewis acids are a very useful class of catalysts for the hydrophosphonylation of aldehydes that work via the activation of alkyl phosphite and simultaneously avoid the shortcomings of the base-catalysed reaction, but surprisingly these have rarely been applied for the synthesis of α-hydroxyphosphonates.[29] Further, after a careful survey of the literature, it was

CONTACT Anil Kumar anilsharmachemistry@gmail.com Synthetic Organic Chemistry Lab, Faculty of Sciences, Shri Mata Vaishno Devi University, Katra, Jammu & Kashmir 182 320, India.

Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2019.1633532.

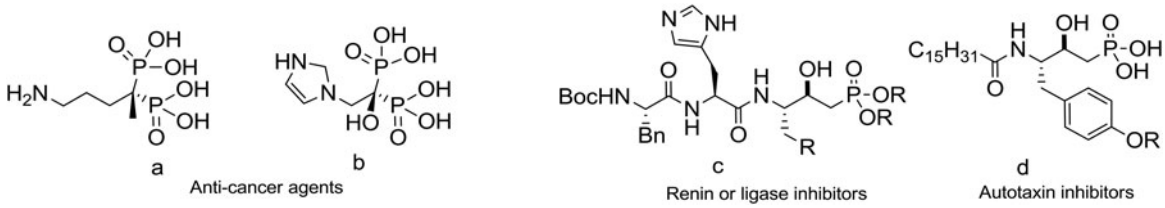
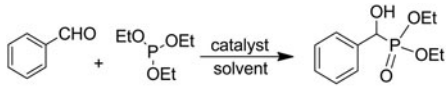



**Figure 1.** Biologically active α-hydroxyphosphonates.

**Table 1.** Experiment for optimization of reaction conditions[a].




1a 2 3a

| Entry | Catalyst (mol%) | Solvent | Time | Temp.[b] | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | $ZrO_2Cl_2$ (10) | Neat | 25 h | 80 °C | 83 |
| 2 | DMAP (10) | Neat | 30 h | 80 °C | 89 |
| 3 | Cinchonine (10) | Neat | 15 h | 80 °C | 90 |
| 4 | $CeCl_3$ .$7H_2O$ (10) | Neat | 15 min | 80 °C | 96 |
| 5 | $CeCl_3$ .$7H_2O$ (10) | Neat | 15 min | rt | 95 |
| 6 | No catalyst | Neat | 10 h | rt | NR[d] |
| 7 | $CeCl_3$ ·$7H_2O$ (15) | Neat | 15 min | rt | 97 |
| 8 | $CeCl_3$ ·$7H_2O$ (1) | Neat | 25 h | rt | 94 |
| 9 | $CeCl_3$ ·$7H_2O$ (1) | $CHCl_3$ | 32 h | rt | 87 |
| 10 | $CeCl_3$ ·$7H_2O$ (1) | EtOH | 34 h | rt | 92 |
| 11 | $CeCl_3$ ·$7H_2O$ (1) | DCM | 32 h | rt | 89 |
| 12 | $CeCl_3$ ·$7H_2O$ (1) | $CH_3CN$ | 32 h | rt | 90 |
| 13 | $CeCl_3$ ·$7H_2O$ (1) | $CH_3OH$ | 33 h | rt | 91 |
| 14 | $CeCl_3$ ·$7H_2O$ (1)/KI(1) | Neat | 22 h | rt | 95 |

[a]Reaction was carried out by taking 1.0 mmol each of benzaldehyde and triethylphosphite.
[b]rt, room temperature.
[c]Yield of isolated and purified product **3a**.
[d]NR, no reaction.

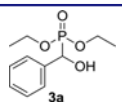
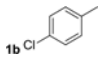
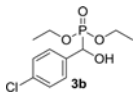
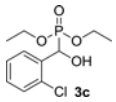
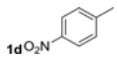
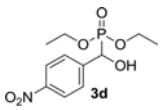
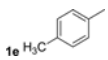
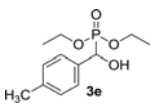
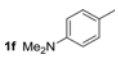
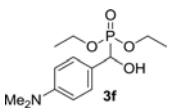
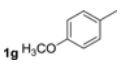
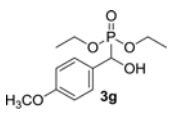
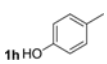
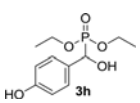
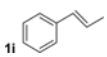
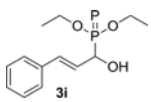
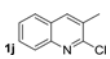
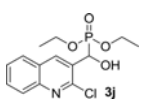
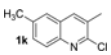
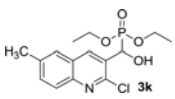
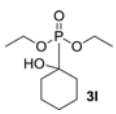
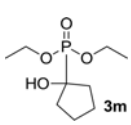
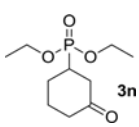
noticed that although significant progress has been achieved with aldehydes, reaction with ketones has scarcely been investigated and exploited.[3,9,15,20b] Recently, several complexes have been reported to efficiently catalyze the hydrophosphonylation of both aldehydes and ketones at a very low catalytic loading and with a shorter reaction time, but these require an additional and somewhat tedious step of preparing the ligands to produce the corresponding organolanthanide complexes.[25,26,28] Further, most of these complexes need to be used in Schlenk-tube techniques under dried argon to avoid traces of moisture and air, both of which could be detrimental for the efficiency of organolanthanide complexes.

It was thus deemed worthwhile and meaningful to explore the direct use of an economic and easily accessible Lewis acid catalyst that would work effectively with a wide range of substrates to generate different α-hydroxyphosphonates. Cerium(III) chloride heptahydrate in particular has received considerable attention as a Lewis acid catalyst because of its unique attributes, which include water tolerance, non-toxicity, easy handling, inexpensive and readily available, and it has been used extensively for a wide range of organic transformations.[30] Further, green protocols under solvent-free conditions have currently come to the forefront of contemporary research, strictly following the principles of green chemistry because this could lead to considerable reduction of waste by avoiding the use of toxic solvents.[31] Due to our active pursuit to expand our efforts to develop novel synthetic strategies,[32] especially for organophosphorus compounds,[32a–c] we report herein our findings regarding the $CeCl_3.7H_2O$-catalysed solvent-free synthetic route to different α-hydroxyphosphonates via a modified Abramov reaction.

## Results and discussion

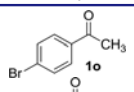
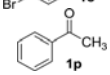
Based on the preceding discussion we thought it worthwhile to develop a new synthetic route that would be effective with a wide range of aldehydes and ketones for the synthesis of diverse α-hydroxyphosphonates. Hence, we started our investigation by selecting a model reaction of benzaldehyde (1.0 mmol) and triethylphosphite (1.0 mmol) to investigate the different catalytic systems shown in Table 1. The reaction was heated at 80 °C in the presence of 10 mol% of different catalysts such as zirconium oxychloride, $CeCl_3·7H_2O$, 4-dimethylaminopyridine (DMAP) and cinchonine under neat conditions (Table 1, entries 1-4). The reaction proceeded well with all the catalysts but maximum yield (96%) was obtained with $CeCl_3·7H_2O$ to afford the desired product **3a** (Table 1, entry 4), as authenticated with the literature.[14] Interestingly, the reaction also delivered a very good yield with zirconium oxychloride, cinchonine and DMAP (Table 1, entries 1–3). Next, it was established that 10 mol% $CeCl_3·7H_2O$ could trigger the reaction even at room temperature (Table 1, entry 5). When the reaction was performed without catalyst, the product was not observed even after a prolonged reaction time (Table 1, entry 6). Increasing

**Table 2.** A cerium(III) chloride-catalysed synthesis of diverse α-hydroxyphosphonates[a].

| Entry | Aldehydes/ Ketones 1(a–p) | Product 3(a-n) | Time | | Yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | 1 mol% of catalyst | 10 mol% of catalyst | 1 mol% of catalyst | 10 mol% of catalyst |
| 1 |  |  | 25 h | 15 min | 94 | 95 |
| 2 |  |  | 24 h | 15 min | 88 | 91 |
| 3 |  |  | 24 h | 15 min | 93 | 95 |
| 4 |  |  | 28 h | 15 min | 87 | 89 |
| 5 |  |  | 24 h | 15 min | 89 | 93 |
| 6 |  |  | 22 h | 15 min | 90 | 96 |
| 7 |  |  | 23 h | 15 min | 88 | 91 |
| 8 |  |  | 24 h | 15 min | 92 | 96 |
| 9 |  |  | 24 h | 15 min | 88 | 91 |
| 10 |  |  | 24 h | 15 min | 86 | 92 |
| 11 |  |  | 24 h | 15 min | 84 | 95 |
| 12 |  |  | – | 12 h | 50 | 95 |
| 13 |  |  | – | 10 h | – | 92 |
| 14 |  |  | – | 6 h | – | 96[c] |

(*continued*)

**Table 2.** Continued.

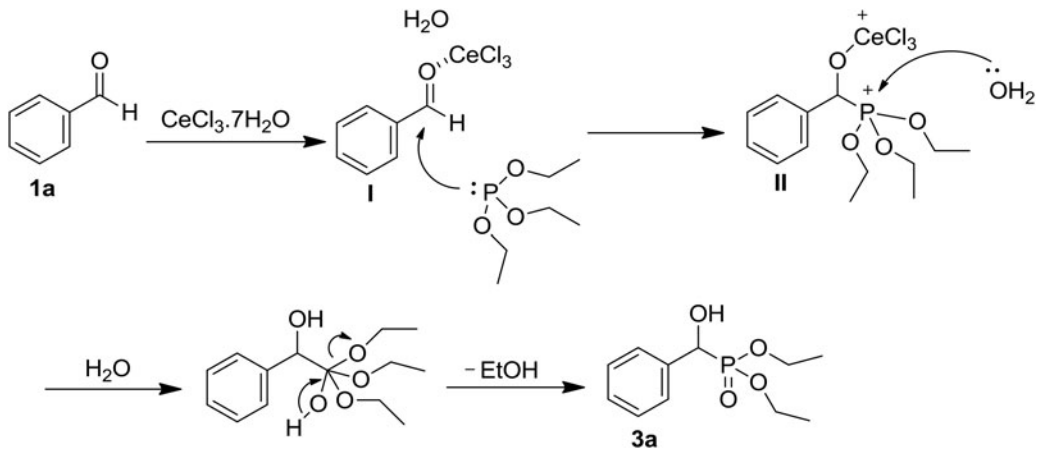
| Entry | Aldehydes/ Ketones 1(a–p) | Product 3(a-n) | Time | | Yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | 1 mol% of catalyst | 10 mol% of catalyst | 1 mol% of catalyst | 10 mol% of catalyst |
| 15 |  1o | – | – | 15 h | – | No reaction |
| 16 |  1p | – | – | 15 h | – | No reaction |

[a]Reactions were carried out by stirring aldehydes/ketones (1.0 mmol), triethyphosphite (1.0 mmol) and $CeCl_3.7H_2O$ (1/10 mol %) at room temperature.
[b]Yield of isolated and purified product.
[c]A Michael product was formed instead of the anticipated product.

**Table 3.** Comparison of $CeCl_3{\cdot}7H_2O$ for the preparation of 3i[a].

| Entry | Catalyst (g/mol%) | Phosphite | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $CeCl_3{\cdot}7H_2O$ (10 mol%) | Triethyl | 15 min | 95[b] |
| 2 | *n*-Butyllithium (0.1 mol%) | Diethyl | 5 min [27] | 95 |
| 3 | Tetramethylguanidine | Diethyl | 12 h [3] | 66 |
| 4 | 1,5,7-Triazabicyclo[4.4.0]dec-1-ene systems (10 mol%) | Diethyl | 3 h [15] | 78 |
| 5 | KF–$Al_2O_3$(2.5 g each, mixed) | Diethyl | 15 min [12] | 95 |
| 6 | La-anilido (0.1 mol%) | Diethyl | 20 min [26] | 96 |
| 7 | $NH_4VO_3$ (10 mol%) | Diethyl | 24 h [24] | 0 |

[a]Reactions were carried out by taking 1.0 mmol each of cyclohexanone and triethylphosphite with 0.1 mmol of $CeCl_3{\cdot}7H_2O$.
[b]Isolated and purified yield.




**Scheme 1.** Proposed mechanism for the synthesis of **3a**.

the catalytic concentration to 15 mol% did not influence the yield by any considerable extent (Table 1, entry 7). However, on decreasing the concentration of catalyst to 1 mol% an incremental decrease of yield was observed (Table 1, entry 8) and the reaction time increased drastically compared to reaction with 10 mol% of catalyst (25 h vs 15 min). Next, we examined the effect of solvents such as chloroform, ethanol, dichloromethane, acetonitrile and methanol, and the results (Table 1, entries 9–13) indicated that the best conditions for the envisaged reaction were the use of $CeCl_3$ (1 mol%) at ambient temperature under solvent-free conditions, although the time required is much longer compared to reaction with 10 mol% of catalyst. Before shifting our attention towards substrate scope we tried to observe the effect of potassium iodide on the efficiency of $CeCl_3$, especially reaction time, but did not find any substantially positive outcome (Table 1, entry 14).

To further expand the synthetic utility of this protocol, optimal conditions were applied to convert the diverse range of aldehydes into the corresponding α-hydroxyphosphonates. Reaction with aromatic aldehydes containing electron-withdrawing groups such as *o*/*p*-chloro and *p*-nitro, electron-donating groups such as *p*-methyl, *p*-*N*,*N*-dimethyl, *p*-methoxy, *p*-OH and α,β-unsaturated aldehydes proceeded smoothly within 15 min to deliver good yields of products **3 b-i** (Table 2, entries 2-9). Furthermore, heterocyclic aldehydes such as 2-chloroquinoline-3-carbaldehyde and 2-chloro-6-methylquinoline-3-carbaldehyde also gave high yields of anticipated products (Table 2, entries 10-11). Importantly, the position as well as the nature of substituents on the aromatic/heteroaromatic aldehydes do not have any considerable impact on the yield of reaction, which is quite evident from Table 2. Furthermore, as depicted in Table 2, with 10 mol% loading the reaction was completed

in just 15 min compared to 22–28 h with 1 mol%. Hence for comparative purposes, we studied the substrate scope with respect to both 10 mol% and 1 mol% of catalyst, and the results are outlined in Table 2.

Next, the versatility of this strategy was further explored with various ketones, considering the fact that reaction with ketones has scarcely been investigated in the literature. In this context, we conducted a test reaction by taking 1.0 mmol each of cyclohexanone and triethylphosphite under the standardized conditions, and product formation was observed, albeit in low yield. Fascinatingly, we were able to raise the level of yield to 95% with 10 mol% of catalyst (Table 2, entry 12), hence 10 mol% of catalyst was the optimum concentration that was subsequently applied with different ketones. With cyclopentanone 92% yield of product was obtained (Table 2, entry 13). Interestingly, cyclohexenone undergoes a phospha-Michael reaction instead of hydrophosphonylation to give the corresponding product in 96% yield (Table 2, entry 14). Conversely, reaction with *p*-bromoacetophenone and acetophenone did not afford the desired product; instead we recovered the unreacted starting material, despite heating for a long time (Table 2, entries 15, 16).

Comparative data for the reaction of **3i** are summarized in Table 3 (entries 1-7). It is indicated that the current protocol delivered comparable or better yield than the reported catalysts, with an additional advantage of easy and direct availabilty of $CeCl_3{\cdot}7H_2O$, thus avoiding the use of a moisture-sensitive catalyst that requires special handling techniques and a tedious multistep route for synthesis, especially for cyclic ketones such as cyclopentanone and cyclohexanone.

## Mechanism

The proposed mechanism for the synthesis of **3a** is shown in Scheme 1. The carbonyl carbon of aldehyde, **1a** is activated by coordinating with cerium(III) chloride to gave the intermediate **I** which underwent nucleophilic attack of phosphorus atom of triethylphosphite to form the intermediate **II** which finally delivers the formation of desired product, **3a**.

## Experimental

All starting materials and reagents were commercially available and applied without further purification. Analab melting point apparatus was used to determine melting points. NMR spectra was recorded on a Bruker spectrometer respectively in $CDCl_3$ solvent at following frequencies: $^1$H NMR at 400 MHz, $^{13}$C NMR at 100 MHz and $^{31}$P NMR at 162 MHz. All compounds, **3a-n** are known and their spectral data was compared with the reported literature.[14,20c,27,33,34] The Supplemental Materials contains sample $^1$H, $^{13}$C and $^{31}$P NMR spectra for the products 3 (Figures S1 – S42).

## General procedure for preparation of α-hydroxyphosphonates

A mixture of aldehyde/ketone (1.0 mmol), triethylphosphite (1.0 mmol) and $CeCl_3.7H_2O$ (10 mol%) was stirred at room temperature under neat conditions for appropriate time (Table 2). After completion of the reaction, the resulting reaction mixture was isolated and products were purified by crystallization with ethanol. In some cases (Table 2, entries 10, 11, 12, 13 and 14) column chromatography (using ethyl acetate and *n*-hexane) was performed for the purification of the crude product.

## Conclusion

In conclusion, we have reported a new route to α-hydroxyphosphonates that tolerates a wide range of aldehydes under solvent-free conditions. The use of a cheap, commercially available, moisture-tolerant catalyst, an easy work-up procedure and the avoidance of solvents are all advantages of the current methodology. Furthermore, the current methodology has been successfully extended by the addition of triethyl phosphite to unactivated cyclic ketones such as cyclohexanone and cyclopentanone.

## Acknowledgements

P.K. thanks the University Grants Commission for a BSR fellowship. The contribution of IIIM Jammu and the Department of Chemistry at University of Jammu for providing spectral data is also acknowledged.

## ORCID

Anil Kumar http://orcid.org/0000-0002-2415-1255

## References

[1] (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. Preparation of Peptidic α-Hydroxy Phosphonates a New Class of Transition State Analog Renin Inhibitors. *Tetrahedron Lett.* **1990**, *31*, 5587–5590. DOI: 10.1016/S0040-4039(00)97903-6. (b) Stowasser, B.; Budt, K.-H.; Jia n-Qi, L.; Peyman, A.; Ruppert, D. New Hybrid Transition State Analog Inhibitors of HIV Protease with Peripheric $C_2$-Symmetry. *Tetrahedron Lett.* **1992**, *33*, 6625–6628. DOI: 10.1016/S0040-4039(00)61002-X. (c) Alder, M.; Nicholson, J. D.; Starks, D. F.; Kane, C. T.; Cornille, F.; Hackley, B. E. Evaluation of Phosphoramidon and Three Synthetic Phosphonates for Inhibition of Botulinum Neurotoxin B Catalytic Activity. *J. Appl. Toxicol.* **1999**, *19*, S5–S11. DOI: 10.1002/(SICI)1099-1263(199912)19. (d) Cox, R. J.; Gibson, J. S.; Martín, M. B. M. Aspartyl Phosphonates and Phosphoramidates: The First Synthetic Inhibitors of Bacterial Aspartate-semialdehyde Dehydrogenase. *Chem. Bio. Chem.* **2002**, *3*, 874–886. DOI: 10.1002/1439-7633(20020902)3:9 < 874::AID-CBIC874 > 3.0.CO;2-V. (e) Bubenik, M.; Rej, R.; Nguyen-Ba, N.; Attardo, G.; Ouellet, F.; Chan, L. Novel Nucleotide Phosphonate Analogues with Potent Antitumor Activity. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3063–3066. DOI: 10.1016/S0960-894X(02)00679-0. (f) Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van Den Oord, J.; De Clercq, E.; Andrei, G. Antivaccinia Activities of Acyclic Nucleoside Phosphonate Derivatives in Epithelial Cells and Organotypic Cultures. *Antimicrob. Agents Chemother.* **2002**, *46*, 3356–3361.

DOI: 10.1128/AAC.46.11.3356-3361.2002. (g) Košiová, I.; Šimák, O.; Panova, N.; Buděšínský, M.; Petrova, M.; Rejman, D.; Liboska, R.; Páv, O.; Rosenberg, I. Inhibition of Human Thymidine Phosphorylase by Conformationally Constrained Pyrimidine Nucleoside Phosphonic Acids and Their "Open-structure" Isosteres. *Eur. J. Med. Chem.* **2014**, *74*, 145–168. DOI: 10.1016/j.ejmech.2013.12.026.

[2] (a) Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. Herbicidal Activity of Phosphonic, Phosphinic, and Phosphonous Acid Analogues of Phenylglycine and Phenylalanine. *J. Plant Growth Regul.* **1995**, *14*, 199–203. DOI: 10.1007/BF00204912 (b) Yan, B.; Spilling, C. D. Stereospecific Pd(O)-Catalyzed Malonate Additions to Allylic Hydroxy Phosphonate Derivatives: A Formal Synthesis of (−)-Enterolactone. *J. Org. Chem.* **2004**, *69*, 2859–2862. DOI: 10.1021/jo035795h. (c) Sobhani, S.; Tashrifi, Z. Synthesis of α-Functionalized Phosphonates from α-Hydroxyphosphonates. *Tetrahedron* **2010**, *66*, 1429–1439. DOI: 10.1016/j.tet.2009.11.081. (d) Yan, B.; Spilling, C. D. Synthesis of Cyclopentenones via Intramolecular HWE and the Palladium-catalyzed Reactions of Allylic Hydroxy Phosphonate Derivatives. *J. Org. Chem.* **2008**, *73*, 5385–5396. DOI: 10.1021/jo8004028. (e) Song, Y.; Niederer, D.; Lane-Bell, P. M.; Lam, L. K. P.; Crawley, S.; Palcic, M. M.; Pickard, M. A.; Pruess, D. L.; Vederas, J. C. Stereospecific Synthesis of Phosphonate Analogs of Diaminopimelic Acid (DAP), their Interaction with DAP Enzymes, and Antibacterial Activity of Peptide Derivatives. *J. Org. Chem.* **1994**, *59*, 5784–5793. DOI: 10.1021/jo00098a045. (f) Dellaria, J. F.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. New Inhibitors of Renin that Contain Novel Phosphostatine Leu-Val Replacements. *J. Med. Chem.* **1990**, *33*, 534–542. DOI: 10.1021/jm00164a011. (g) Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Mellin, T. N. (3-Amino-2-oxoalkyl)phosphonic Acids and Their Analogs as Novel Inhibitors of D-Alanine:D-alanine Ligase. *J. Med. Chem.* **1989**, *32*, 1886–1890. DOI: 10.1021/jm00128a033.

[3] Simoni, D.; Invidiata, F. P.; Manferdini, M.; Lampronti, I.; Rondanin, R.; Roberti, M.; Pollini, G. P. Tetramethylguanidine (TMG)-Catalyzed Addition of Dialkyl Phosphites to α,β-Unsaturated Carbonyl Compounds, Alkenenitriles, Aldehydes, Ketones and Imines. *Tetrahedron Lett* **1998**, *39*, 7615–7618. DOI: 10.1016/S0040-4039(98)01656-6.

[4] Blazis, V. J.; Koeller, K. J.; Spilling, C. D. Reactions of Chiral Phosphorous Acid Diamides: The Asymmetric Synthesis of Chiral.alpha.-Hydroxy Phosphonamides, Phosphonates, and Phosphonic Acids. *J. Org. Chem.* **1995**, *60*, 931–940. DOI: 10.1021/jo00109a025.

[5] Heydari, A.; Arefi, A.; Khaksar, S.; Tajbakhsh, M. Hydrophosphonylation of Aldehydes Catalyzed by Guanidine Hydrochloride in Water. *Catal. Commun* **2006**, *7*, 982–984. DOI: 10.1016/j.catcom.2006.04.014.

[6] Pamies, O.; Backvall, J. E. An Efficient Route to Chiral α- and β-Hydroxyalkanephosphonates. *J. Org. Chem* **2003**, *68*, 4815–4818. DOI: 10.1021/jo026888m.

[7] Kulkarni, M. A.; Lad, U. P.; Desai, U. V.; Mitragotri, S. D.; Wadgaonkar, P. P. Mechanistic Approach for Expeditious and Solvent-Free Synthesis of α-Hydroxy Phosphonates Using Potassium Phosphate as Catalyst. *C. R. Chimie* **2013**, *16*, 148–152. DOI: 10.1016/j.crci.2012.10.009.

[8] Jeanmaire, T.; Hervaud, Y.; Boutevin, B. Synthesis of Dialkyl-Hydroxymethylphosphonates in Heterogeneous Conditions. *Phosphorus Sulfur Silicon Relat. Elem* **2002**, *177*, 1137–1145. DOI: 10.1080/10426500211718.

[9] Martinez-Castro, E.; Lopez, O.; Maya, I.; Fernandez-Balanos, J. G.; Petrini, M. A Green Procedure for the Regio- and Chemoselective Hydrophosphonylation of Unsaturated Systems Using CaO under Solventless Conditions. *Green Chem.* **2010**, *12*, 1171–1174. DOI: 10.1039/c0gc00026d.

[10] Keglevich, G.; Toth, V. R.; Drahos, L. Microwave-Assisted Synthesis of α-Hydroxy-Benzylphosphonates and -Benzylphosphine Oxides. *Heteroatom Chem.* **2011**, *22*, 15–17. DOI: 10.1002/hc.20649.

[11] Dolle, R. E.; Herpin, T. F.; Shimshock, Y. C. Solid-Phase Synthesis of α-Hydroxy Phosphonates and Hydroxystatine Amides. Transition-State Isosteres Derived from Resin-Bound Amino Acid Aldehydes. *Tetrahedron Lett* **2001**, *42*, 1855–1858. DOI: 10.1016/S0040-4039(01)00097-1.

[12] Textier-Boullet, F.; Lequitte, M. An Unexpected Reactivity of Simple Heterogeneous Mixture of γ-Alumina and Potassium Fluoride: 1-Hydroxyalkane Phosphonic Esters Synthesis from Non-Activated Ketones in "Dry Media. *Tetrahedron Lett* **1986**, *27*, 3515–3516. DOI: 10.1016/S0040-4039(00)84837-6.

[13] Alexander, C. W.; Albiniak, P. A.; Gibson, L. R. Synthesis of α-Hydroxy Phosphonates Using a Solid Supported Base. *Phosphorus Sulfur Silicon Relat. Elem* **2000**, *167*, 205–209. DOI: 10.1080/10426500008082399.

[14] Sardarian, A. R.; Kaboudin, B. Surface-Mediated Solid Phase Reactions: Preparation of Diethyl 1-Hydroxyarylmethylphosphonates on the Surface of Magnesia. *Synth. Commun* **1997**, *27*, 543–551. DOI: 10.1080/00397919708003324.

[15] Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. 1,5,7-Triazabicyclo[4.4.0]Dec-1-Ene (TBD), 7-methyl-TBD (MTBD) and the Polymer-Supported TBD (P-TBD): Three Efficient Catalysts for the Nitroaldol (Henry) Reaction and for the Addition of Dialkyl Phosphites to Unsaturated Systems. *Tetrahedron Lett* **2000**, *41*, 1607–1610. DOI: 10.1016/S0040-4039(99)02340-0.

[16] Tajbakhsh, M.; Heydari, A.; Khalilzadeh, M.; Lakouraj, M.; Zamenian, B.; Khaksar, S. Amberlyst-15 as a Heterogeneous Reusable Catalyst for the Synthesis of α-Hydroxy Phosphonates in Water. *Synlett* **2007**, *2007*, 2347–2350. DOI: 10.1055/s-2007-985595.

[17] Shinde, P. V.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. An Organocatalyzed Facile and Rapid Access to α-Hydroxy and α-Amino Phosphonates under Conventional/Ultrasound Technique. *Tetrahedron Lett* **2011**, *52*, 2889–2892. DOI: 10.1016/j.tetlet.2011.03.138.

[18] Vahdat, S. M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S. M.; Khaksar, S. Organocatalytic Synthesis of α-Hydroxy and α-Aminophosphonates. *Tetrahedron Lett* **2008**, *49*, 6501–6504. DOI: 10.1016/j.tetlet.2008.08.094.

[19] Santhisudha, S.; Sreelakshmi, P.; Jayaprakash, S. H.; Kumar, B. V.; Reddy, C. S. Silica-Supported Tungstic Acid Catalyzed Synthesis and Antioxidant Activity of α-Hydroxyphosphonates. *Phosphorus Sulfur Silicon Relat. Elem* **2015**, *190*, 1479–1488. DOI: 10.1080/10426507.2014.991825.

[20] (a) Kharasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. Organophosphorus Chemistry. Addition Reactions of Diethyl phosphonate and the Oxidation of Triethyl phosphate. *J. Org. Chem.* **1960**, *25*, 1000–1006. DOI: 10.1021/jo01076a035. (b) Goldeman, W.; Soroka, M.; Wrocawska, P. The Preparation of Dialkyl 1-hydroxyalkylphosphonates in the Reaction of Trialkyl phosphites with Oxonium Salts Derived from Aldehydes or Ketones. *Synthesis* **2006**, 3019–3024. DOI: 10.1055/s-2006-950200. (c) Congsiglio, G.; Failla, S.; Finocchiaro, P. A General Synthetic Approach to α-Hydroxy Phosphoryl Compounds. *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *117*, 37–54. DOI: 10.1080/10426509608038773.

[21] de Noronha, R. G.; Costa, P. J.; Romao, C. C.; Calhorda, M. J.; Fernandes, A. C. $MoO_2Cl_2$ as a Novel Catalyst for C − P Bond Formation and for Hydrophosphonylation of Aldehydes. *J. Organometallics* **2009**, *28*, 6206–6212. DOI: 10.1021/om9005627.

[22] Yokomatsu, T.; Yamagishi, T.; Shibuya, S. Enantioselective Synthesis of α-Hydroxyphosphonates through Asymmetric Pudovik Reactions with Chiral Lanthanoid and Titaniumalkoxides. *J. Chem. Soc, Perkin Trans.* **1997**, *1*, 1527–1534. DOI: 10.1039/a608161d.

[23] Olah, G. A.; Wu, A. Synthetic Methods and Reactions. 159. Preparation of 1,2-Diketones from Nonenolizable Aliphatic and Aromatic Acyl Chlorides with Diethyl 1-Alkyl(Aryl)-1-(Trimethylsiloxy)-Methanephosphonates. *J. Org. Chem.* **1991**, *56*, 902–904. DOI: 10.1021/jo00002a085.

[24] Sonar, S. S.; Kategaonkar, A. H.; Ware, M. N.; Gill, C. H.; Shingate, B. B.; Shingare, M. S. Ammonium Metavanadate: An Effective Catalyst for Synthesis of α-Hydroxyphosphonates. *Arkivoc* **2009**, *2009*, 138–148. DOI: 10.3998/ark.5550190.0010.215.

[25] Wu, Q.; Zhou, J.; Yao, Z.; Xu, F.; Shen, Q. Lanthanide Amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ Catalyzed Hydrophosphonylation of Aryl Aldehydes. *J. Org. Chem.* **2010**, *75*, 7498–7501. DOI: 10.1021/jo101743e.

[26] Liu, C.; Qian, Q.; Nie, K.; Wang, Y.; Shen, Q.; Yuan, D.; Yao, Y. Lanthanide Anilido Complexes: Synthesis, Characterization, and Use as Highly Efficient Catalysts for Hydrophosphonylation of Aldehydes and Unactivated Ketones. *Dalton Trans.* **2014**, *43*, 8355–8362. DOI: 10.1039/c4dt00522h.

[27] Liu, C.; Zhang, Y.; Qian, Q.; Yuan, D.; Yao, Y. n. BuLi as a Highly Efficient Precatalyst for Hydrophosphonylation of Aldehydes and Unactivated Ketones. *Org. Lett.* **2014**, *16*, 6172–6175. DOI: 10.1021/ol5030713.

[28] (a) Nie, K.; Liu, C.; Zhang, Y.; Yao, Y. Syntheses of Bimetallic Rare-earth Bis(cyclopentadienyl) Derivatives Supported by Bridged Bis(guanidinate) Ligands and their Catalytic Property for the Hydrophosphonylation of Aldehydes. *J. Organomet. Chem.* **2016**, *804*, 59–65. DOI: 10.1016/j.jorganchem.2015.12.033. (b) Nie, K.; Liu, C.; Zhang, Y.; Yao, Y. Syntheses of Bimetallic Lanthanide Bis(amido) Complexes Stabilized by Bridged Bis(guanidinate) Ligands and Their Catalytic Activity Toward the Hydrophosphonylation Reaction of Aldehydes and Ketones. *Sci China Chem.* **2015**, *58*, 1451–1460. DOI: 10.1007/s11426-015-5407-9.

[29] Yokomatsu, T.; Yoshida, Y.; Shibuya, S. Stereoselective Synthesis of.beta.-Oxygenated.alpha.-Hydroxyphosphonates by Lewis Acid-Mediated Stereoselective Hydrophosphonylation of.alpha.-Benzyloxy Aldehydes. An Application to the Synthesis of Phosphonic Acid Analogs of Oxyamino Acids. *J. Org. Chem.* **1994**, *59*, 7930–7933. DOI: 10.1021/jo00104a064.

[30] (a) Dhara, D.; Gayen, K. S.; Khamarui, S.; Pandit, P.; Ghosh, S.; Maiti, D. K. $CeCl_3{\cdot}7H_2O$ Catalyzed C–C and C–N Bond-forming Cascade Cyclization with Subsequent Side-chain Functionalization and Rearrangement: A Domino Approach to Pentasubstituted Pyrrole Analogues. *J. Org. Chem.* **2012**, *77*, 10441–10449. DOI: 10.1021/jo301796r. (b) Jafari, A. A.; Nazarpour, M.; Abdollahi-Alibeik, M. $CeCl_3{\cdot}7H_2O$-catalyzed One-pot Kabachnik–Fields Reaction: A Green Protocol for Three-component Synthesis of α-Aminophosphonates. *Heteroatom Chem.* **2010**, *21*, 397–403. DOI: 10.1002/hc.20635. (c) Khan, A. T.; Choudhury, L. H.; Parvin, T.; Ali, M. A. $CeCl_3{\cdot}7H_2O$: An Efficient and Reusable Catalyst for the Preparation of β-Acetamido Carbonyl Compounds by Multicomponent Reactions (MCRs). *Tetrahedron Lett.* **2006**, *47*, 8137–8141. DOI: 10.1016/j.tetlet.2006.09.041. (d) Silveira, C. C.; Mendes, S. R.; Líbero, F. M.; Lenardão, E. J.; Perin, G. Glycerin and $CeCl_3{\cdot}7H_2O$: A New and Efficient Recyclable Medium for the Synthesis of Bis(indolyl)methanes. *Tetrahedron Lett.* **2009**, *50*, 6060–6063. DOI: 10.1016/j.tetlet.2009.08.062. (e) Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S.; Yadav, J. S. $CeCl_3{\cdot}7H_2O$-Catalyzed Synthesis of 1-Oxo-hexahydroxanthene Derivatives in Aqueous Media. *Synthetic Commun.* **2008**, *38*, 3439–3446. DOI: 10.1080/00397910802154253.

[31] (a) Kanagaraj, K.; Pitchumani, K. Solvent-free Multicomponent Synthesis of Pyranopyrazoles: Per-6-amino-β-cyclodextrin as a Remarkable Catalyst and Host. *Tetrahedron Lett.* **2010**, *51*, 3312–3316. DOI: 10.1016/j.tetlet.2010.04.087. (b) Singh, M. S.; Chowdhury, S. Recent Developments in Solvent-free Multicomponent Reactions: A Perfect Synergy for Eco-compatible Organic Synthesis. *RSC Adv.* **2012**, *2*, 4547–4592. DOI:10.1039/C2RA01056A.

[32] (a) Kour, P.; Kumar, A.; Rai, V. K. Aqueous Microwave-assisted DMAP Catalyzed Synthesis of β-Phosphonomalonates and 2-Amino-4*H*-chromen-4-ylphosphonates via a Domino Knoevenagel-phospha-Michael Reaction *C. R. Chimie* **2017**, *20*, 140–145. DOI: 10.1016/j.crci.2016.05.013. (b) Kour, P.; Kumar, A.; Sharma, R.; Chib, R. ; Khan, I. A.; Rai, V. K. Synthesis of 2-Amino-4*H*-chromen-4-ylphosphonates and β-Phosphonomalonates via Tandem Knoevenagel–Phospha-Michael Reaction and Antimicrobial Evaluation of Newly Synthesized β-Phosphonomalonates. *Res Chem Int.* **2017**, *43*, 7319–7329. DOI: 10.1007/s11164-017-3077-2. (c) Kumar, A.; Jamwal, S.; Khan, S.; Singh, N.; Rai, V. K. $Bi(NO_3)_3{\cdot}5H_2O$ Catalyzed Phosphonylation of Aldehydes: An Efficient Route to α-Hydroxyphosphonates. *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 381–385. DOI: 10.1080/10426507.2016.1247085. (d) Kour, P.; Singh, V. P.; Khajuria, B.; Singh, T.; Kumar, A. Al(III) Chloride Catalyzed Multi-component Domino Strategy: Synthesis of Library of Dihydrotetrazolo[1,5-*a*]pyrimidines and Tetrahydrotetrazolo[1,5-*a*]quinazolinones. *Tetrahedron Lett.* **2017**, *58*, 4179–4185. DOI: 10.1016/j.tetlet.2017.09.052. (e) Singh, N.; Kumar, A.; Rai, V. K. Aqueous Mortar–pestle Grinding: An Efficient, Attractive, and Viable Technique for the Regioselective Synthesis of β-Amino Alcohols. *C. R. Chimie* **2018**, *21*, 71–79. DOI: 10.1016/j.crci.2017.11.004.

[33] Pokalwar, R. U.; Hangarge, R. V.; Maske, P. V.; Shingare, M. S. Synthesis and Antibacterial Activities of α-Hydroxyphosphonates and α-Acetyloxyphosphonates Derived from 2-Chloroquinoline-3-Carbaldehyde. *Arkivoc* **2006**, *2006*, 196–204. DOI: 10.3998/ark.5550190.0007.b20.

[34] Verbicky, C. A.; Zercher, C. K. Zinc-Mediated Chain Extension of β-Keto Phosphonates. *J. Org. Chem.* **2000**, *65*, 5615–5622. DOI: 10.1021/jo000343f.