

## Green-inspired synthetic drives for organophosphorus compounds under solvent-free conditions

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Dedicated to Professor György Keglevich on the occasion of his 65th birthday

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### Abstract

Organophosphorus chemistry is an exciting field of research. Phosphorus-functionalized organic molecules find practical and useful applications in such diverse areas as medicinal, pharmaceutical, agrochemical, and materials chemistries, both on laboratory and industrial scales. Green-chemistry principles are motivating the design and development of newer synthetic methodologies for such beneficial organophosphorus compounds and their analogues. Solvent-free conditions are associated with several practical benefits, including operational simplicity, cost-effectiveness, minimization of waste generation, and reduced pollution, all of which are very much crucial for industrial process development. This review summarizes solvent-free synthetic methodologies for functionalized organophosphorus compounds reported during the period 2016 through 2021.



**Keywords:** Organophosphorus compounds, synthetic methods, solvent-free, green chemistry

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## 1. Introduction

Organophosphorus compounds are fascinating to researchers involved in diverse scientific fields. Phosphorus-functionalized organic compounds find numerous applications in industrial, agricultural, flame retardant, material science, and medicinal chemistry, owing to their inherent biological and physical properties.<sup>1-11</sup> They offer immense possibilities for structural, synthetic, and mechanistic studies.<sup>12-15</sup> Therefore, synthetic chemists are continuously searching for novel series of diversely functionalized organophosphorus molecules.<sup>16-22</sup> As part of their synthetic endeavors, designing and developing methodologies following green-chemistry principles have become routine.<sup>23-27</sup> Recently, various 'greener' pathways as alternatives to traditional chemical syntheses and transformations have been invented in diverse fields of organic chemistry, including organophosphorus chemistry, to attain greater sustainability through newer concepts.<sup>28-33</sup> The practice of 'green' chemistry comprises many aspects. Among them, designing solvent-free techniques is noteworthy. Implementing solvent-free (or solid-state) reactions by avoiding toxic organic solvents imparts several key benefits to the development processes, including operational simplicity, cost-effectiveness, minimization of waste generation, and reduced pollution—all of which are very much crucial for industrial-process development.<sup>34-43</sup> This review aims to present a recent update on the green-inspired synthetic drives for functionalized organophosphorus compounds under solvent-free conditions, reported during the period 2016 through 2021.

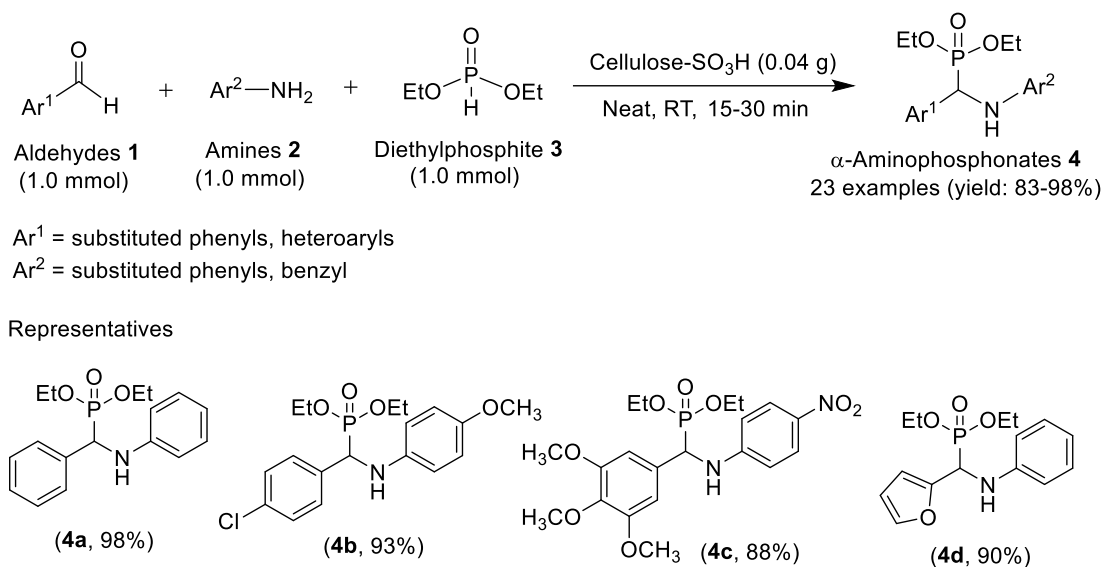
## 2. Solvent-free Synthesis of Organophosphorus Compounds

### 2.1. Synthesis of $\alpha$ -aminophosphonates

Owing to their multifaceted biological activity,  $\alpha$ -aminophosphonates stand as evergreen targets for biochemists.<sup>44-51</sup> Functionalized  $\alpha$ -aminophosphonates are considered the mimic of natural amino acids and have, therefore, invoked tremendous interest in medicinal and industrial chemistries.<sup>44-65</sup> These organophosphorus compounds are known to exhibit a wide array of biological properties including antimicrobial activity,<sup>56-63</sup> antimalarial activity,<sup>66</sup> antitumor activity,<sup>64,65,67-70</sup> and enzymatic-inhibitory activity against rennin,<sup>71</sup> serine protease,<sup>61,70</sup> dialkylglycine decarboxylase,<sup>72</sup> leucine aminopeptidase,<sup>73</sup> among many

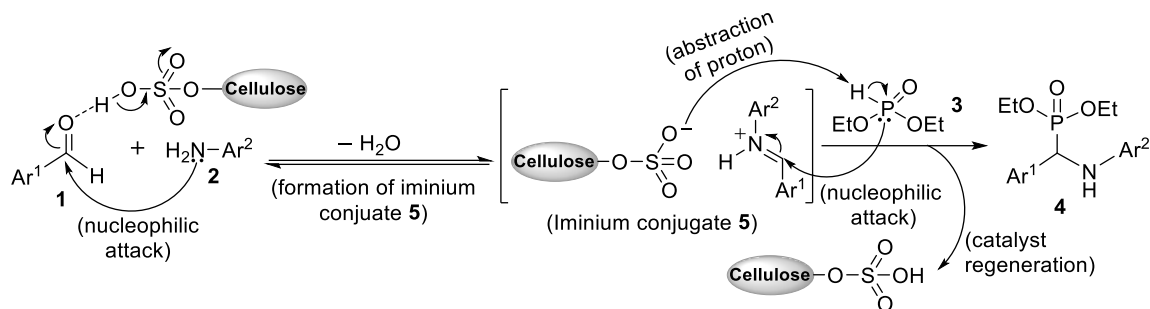
others.<sup>74-80</sup> Certain  $\alpha$ -aminophosphonate derivatives showed efficacy in designing continuous drug-release systems due to their ability to enhance the membrane permeability of a hydrophilic probe molecule.<sup>81</sup> In addition,  $\alpha$ -functionalized phosphonic-acid esters serve as synthones for many organic compounds and dyes in phosphonate chemistry, and also find use in laser technology, and as fluorescent materials for visualization of biomolecules.<sup>82,83</sup> Solvent-free synthetic drivers for diverse  $\alpha$ -aminophosphonates reported in the recent past are overviewed herein.

Cellulose-SO<sub>3</sub>H has recently been reported as a useful solid-acid organocatalyst for many organic transformations.<sup>84-88</sup> Reddy and his group utilized this eco-friendly solid-acid catalyst for the synthesis of a diverse series of  $\alpha$ -aminophosphonates (**4**) from a one-pot, three-component reaction between aromatic aldehydes (**1**), aromatic amines (**2**) and diethyl phosphonate (**3**) under solvent-free conditions at room temperature (Scheme 1).<sup>89</sup> Operational simplicity, use of eco-friendly and reusable organocatalysts, and good-to-excellent yields with short reaction times are major advantages of this protocol.



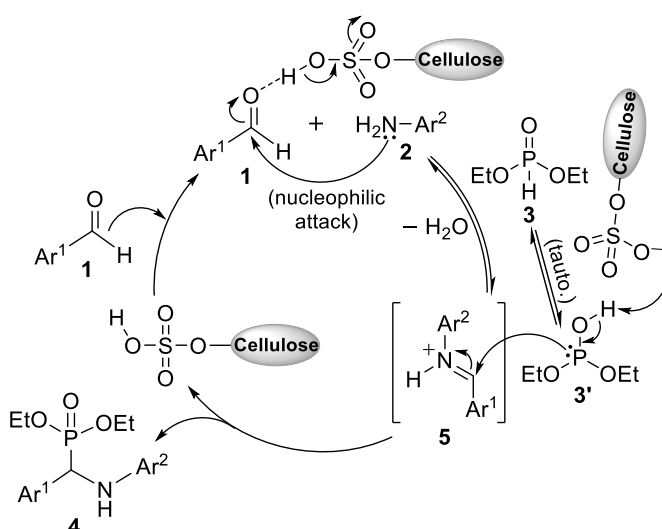
**Scheme 1.** Cellulose-SO<sub>3</sub>H catalyzed synthesis of  $\alpha$ -aminophosphonates at room temperature

The investigators proposed a plausible mechanism for this reaction as depicted in Scheme 2a. The solid-acid catalyst cellulose-SO<sub>3</sub>H first activates aldehyde **1** through hydrogen bonding, thereby facilitating nucleophilic attack by amine **2** to form an iminium-conjugate intermediate **5**. The cellulose sulfate anion subsequently abstracts a proton from the H-phosphonate **3**, making the phosphorus centre more nucleophilic for its attack of the electrophilic imine carbon atom, resulting in the desired product **4**. The catalyst is regenerated for the next cycle.



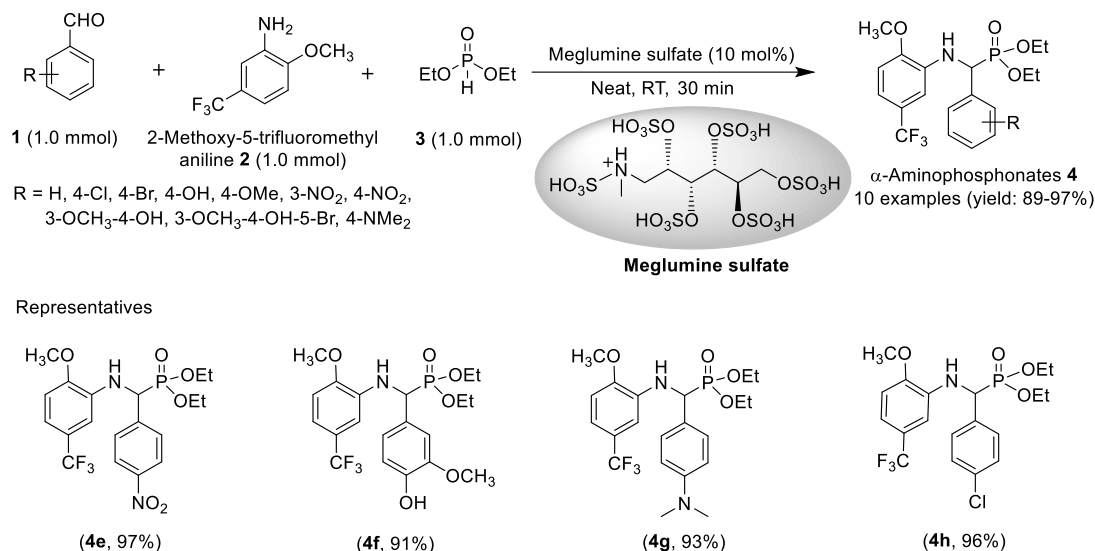
**Scheme 2a.** Proposed mechanism of cellulose- $\text{SO}_3\text{H}$  catalyzed synthesis of  $\alpha$ -aminophosphonates **4**

Based on their own research experience and available literature reports, however, the authors of this article felt it more pertinent to suggest a modified mechanism involving tautomerization of the diethyl phosphonate **3** to the tautomer **3'**, which, in turn, attacks the iminium carbon atom through its nucleophilic phosphorus centre, giving rise to the desired product **4** (Scheme 2b).



**Scheme 2b.** The suggested mechanism of cellulose- $\text{SO}_3\text{H}$  catalyzed synthesis of  $\alpha$ -aminophosphonates **4**

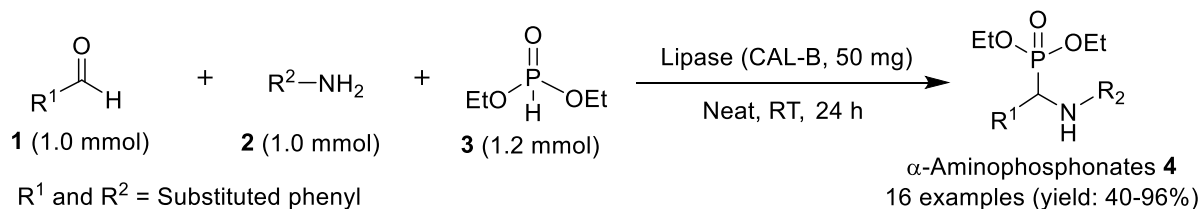
The same group of investigators synthesized ten more  $\alpha$ -aminophosphonate derivatives using 2-methoxy-5-trifluoromethylaniline (**2**) under meglumine sulfate catalysis at room temperature (Scheme 3).<sup>90</sup>



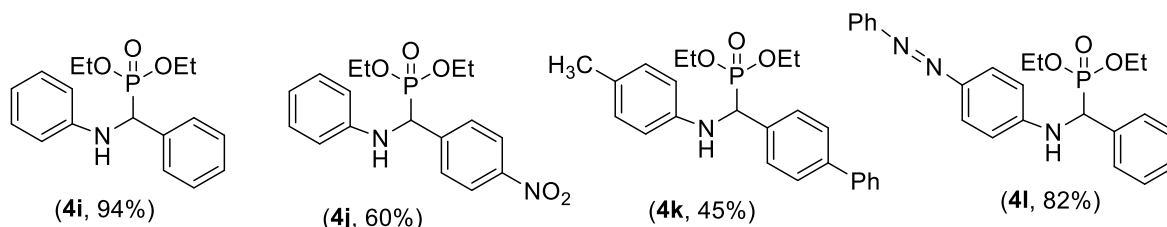
**Scheme 3.** Meglumine sulfate-catalyzed synthesis of  $\alpha$ -aminophosphonates at room temperature

They also evaluated *in vitro* antioxidant properties of the synthesized compounds by determining their radical-scavenging activity in three different assays, including DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate), NO (nitric oxide), and H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide). Compounds diethyl (((2-methoxy-5-(trifluoromethyl)phenyl)amino)(4-nitrophenyl)methyl)phosphonate (**4e**) and diethyl ((4-hydroxy-3-methoxyphenyl)((2-methoxy-5-(trifluoromethyl)phenyl)amino)methyl)phosphonate (**4f**) showed the highest activity among the series with respective IC<sub>50</sub> values of 31.88, 37.0, and 38.63 mg/mL, respectively, and 33.78, 33.78, and 35.21 mg/mL, respectively, which were found to be more potent than ascorbic acid (IC<sub>50</sub> values: 31.88, 37.0, and 38.63 mg/mL, respectively) used as the standard.<sup>47</sup>

The application of lipase enzyme as a biocatalyst for implementing this Kabachnik-Fields reaction was demonstrated by Aribi-Zouiouche and coworkers for the first time.<sup>91</sup> Biocatalysis has now emerged as a powerful tool in synthetic organic chemistry, and, among many enzymes, lipase has already found significant applications in organic transformations.<sup>92,93</sup> The investigators synthesized  $\alpha$ -aminophosphonate derivatives in good yields *via* a one-pot Kabachnik-Fields reaction between aldehydes **1**, amines **2** and diethyl phosphonates **3** in the presence of immobilized *Candida antarctica* lipase (CAL-B) as a biocatalyst under solvent-free conditions at room temperature (Scheme 4). The notable advantages of this method were the simple operational process, easy purification avoiding column chromatography, reusability of the biocatalyst, mild reaction conditions, good atom economy, and eco-friendliness.

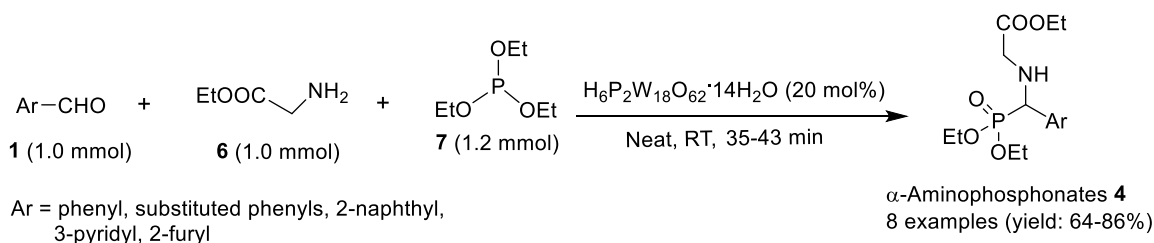


Representatives

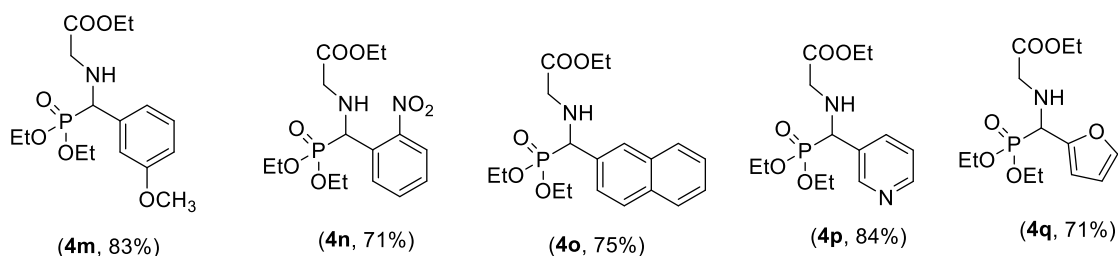


#### Scheme 4. Lipase-catalyzed synthesis of $\alpha$ -aminophosphonates at room temperature

In another report in 2020 by Boughaba *et al.*, a total of eight new versions of  $\alpha$ -aminophosphonate derivatives were accessed out of the Kabachnik-Fields reaction between aromatic aldehydes **1**, amino-acid esters **6**, and triethyl phosphite **7** under the solvent-free catalytic influence of  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \cdot 14\text{H}_2\text{O}$ , at room temperature (Scheme 5).<sup>94</sup> Mild reaction conditions, good yields within short reaction times, atom economy and reusability of the inexpensive catalyst are the notable features of this protocol. The scope of the present method, however, is limited.



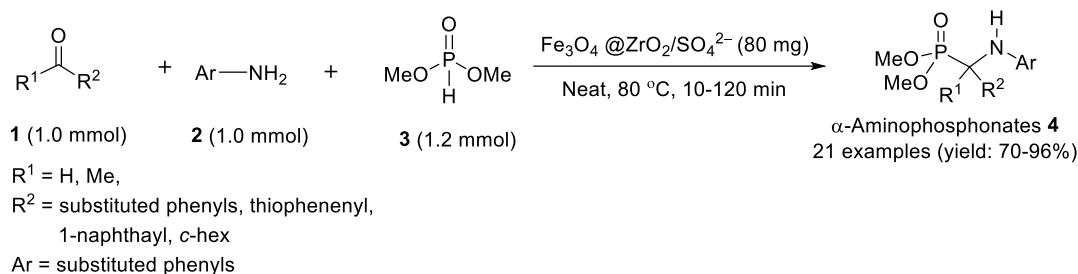
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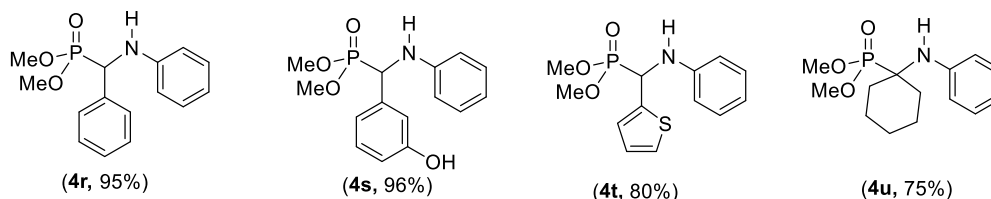
#### Scheme 5. $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \cdot 14\text{H}_2\text{O}$ -catalyzed synthesis of $\alpha$ -aminophosphonates at room temperature

The application of sulfated zirconia ( $\text{Fe}_3\text{O}_4 @ \text{ZrO}_2 / \text{SO}_4^{2-}$ ) impregnated on magnetic iron oxide nanoparticles as a reusable heterogeneous acid catalyst, was demonstrated by Ghafuri and coworkers to successfully implement Kabachnik-Fields reaction for synthesizing a series of substituted  $\alpha$ -aminophosphonate derivatives from a one-pot, three-component reaction between aldehydes/ketones, aromatic amines and dimethyl phosphonate with heating at 80 °C under neat conditions (Scheme 6).<sup>95</sup> Easy separation by the external

magnetic field, and reusability of the nanocatalyst, short reaction times, and good to excellent yields are the key advantages of this method.

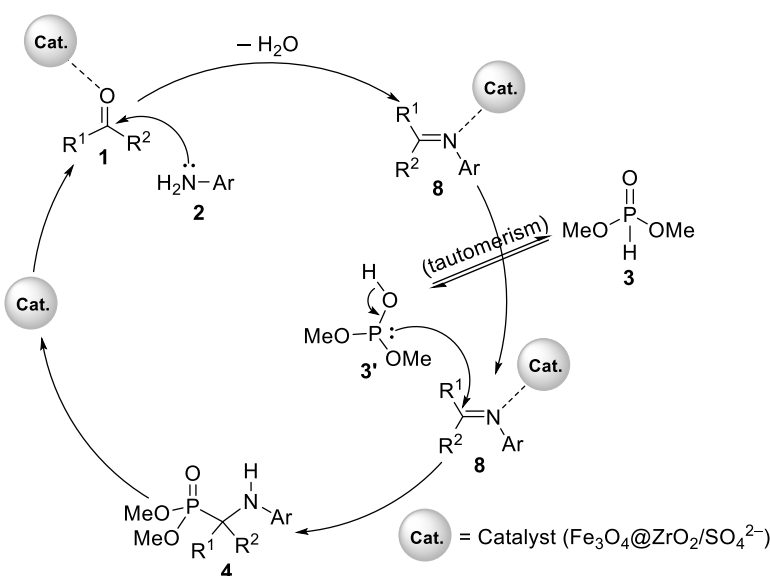


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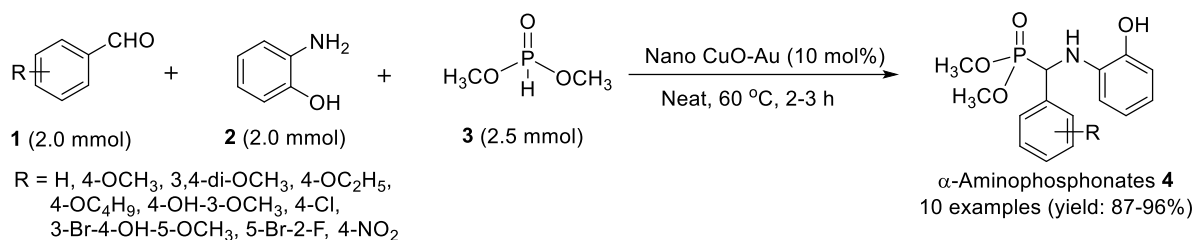
**Scheme 6.** Nanomagnetic sulfated zirconia-catalyzed synthesis of  $\alpha$ -aminophosphonates under heating

The investigators proposed a possible mechanism for this transformation, i.e., the acidic nanocatalyst facilitates the formation of imine intermediate **8** and also the subsequent nucleophilic attack by the tautomeric form of P-reagent (Scheme 7).

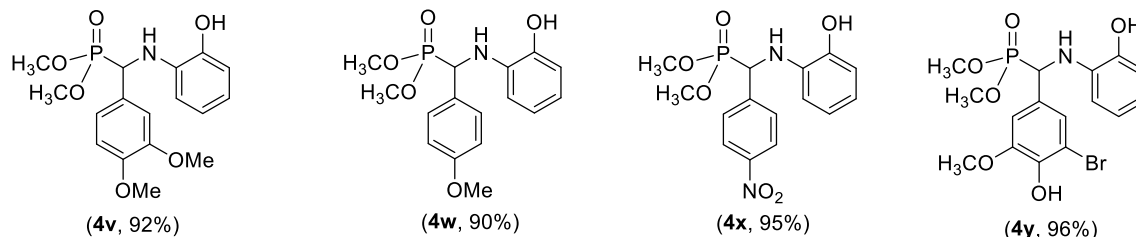


**Scheme 7.** Proposed mechanism for sulfated zirconia nanocatalyst-catalyzed synthesis of  $\alpha$ -aminophosphonates

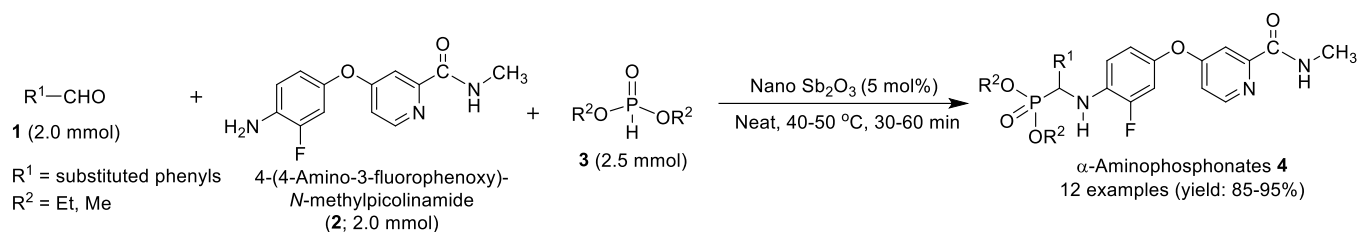
In a recent report, the synthesis of a new version of  $\alpha$ -aminophosphonate derivatives with antioxidant and  $\alpha$ -glucosidase enzyme-inhibition activity was accomplished by Suresh Reddy and his group using nano copper oxide-gold (nano  $\text{CuO-Au}$ ) as an effective metal catalyst upon heating a mixture of aldehydes, *ortho*-aminophenol and dimethyl phosphonate under solvent-free conditions (Scheme 8).<sup>96</sup>



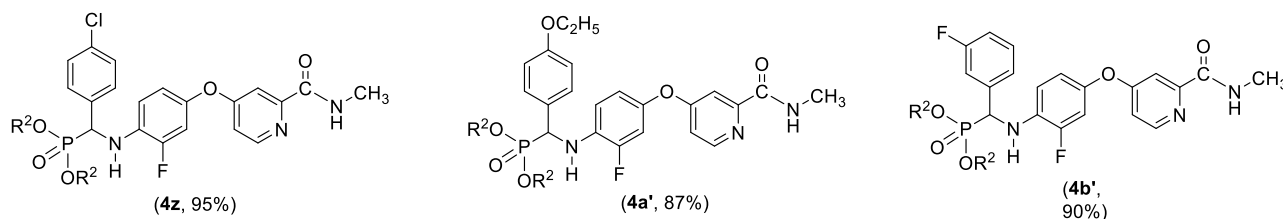
Representatives

**Scheme 8.** Nano CuO-Au-catalyzed synthesis of  $\alpha$ -aminophosphonates under heating

The same group also reported another version of similar compounds with anticancer potential under almost identical conditions exploring nano antimony oxide (Sb<sub>2</sub>O<sub>3</sub>) as the nanocatalyst (Scheme 9).<sup>97</sup>

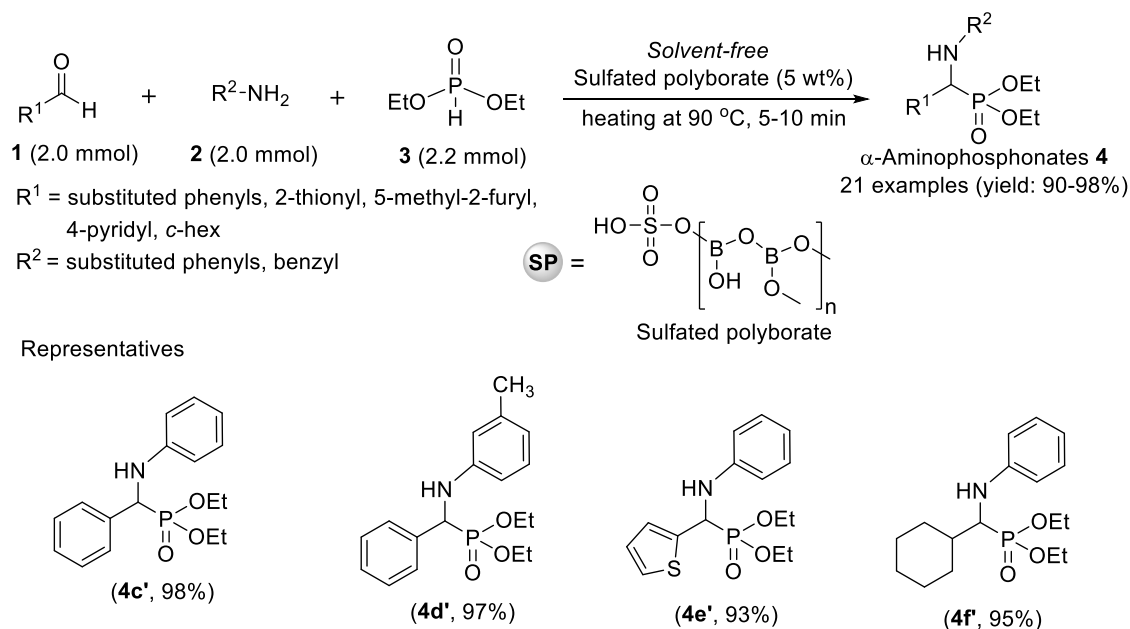


Representatives

**Scheme 9.** Nano Sb<sub>2</sub>O<sub>3</sub>-catalyzed synthesis of  $\alpha$ -aminophosphonates under heating

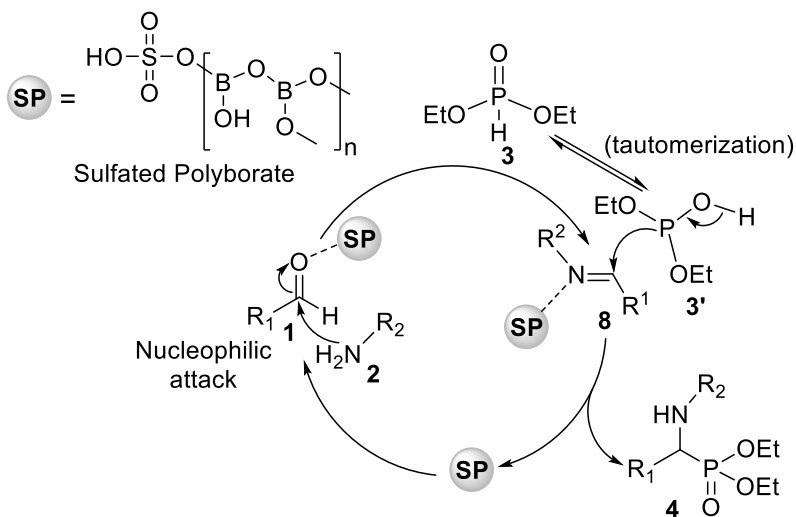
Chaturbhuj and his group accomplished an efficient protocol for a three-component Kabachnik-Fields reaction of aldehydes, amines, and diethyl phosphonate in the presence of sulfated polyborate as an organocatalyst to have a series of  $\alpha$ -aminophosphonate derivatives under solvent-free conditions (Scheme 10).<sup>98</sup> The notable advantages of the present method are high yields, short reaction times, inexpensiveness, an eco-friendly and reusable catalyst, and solvent-free reaction conditions.





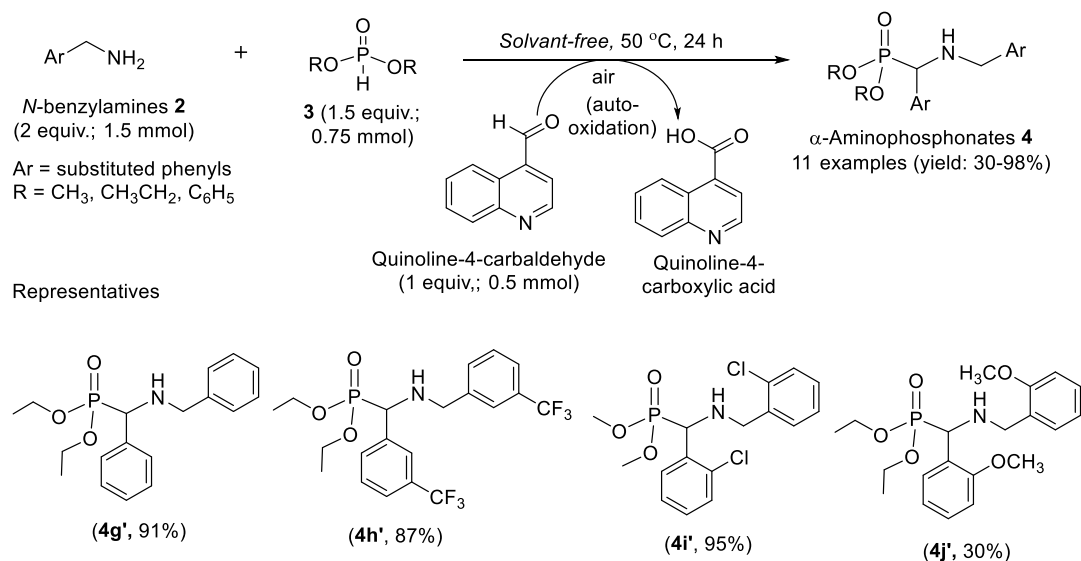
**Scheme 10.** Sulfated polyborate-catalyzed synthesis of  $\alpha$ -aminophosphonates under heating

Scheme 11 offers a possible mechanistic path for the transformation that involves a nucleophilic attack of an amine on sulfated polyborate-activated aldehydes, followed by a further nucleophilic attack of the P-reagent on the sulfated polyborate-activated imine intermediate **8**, leading to the formation of the desired product.



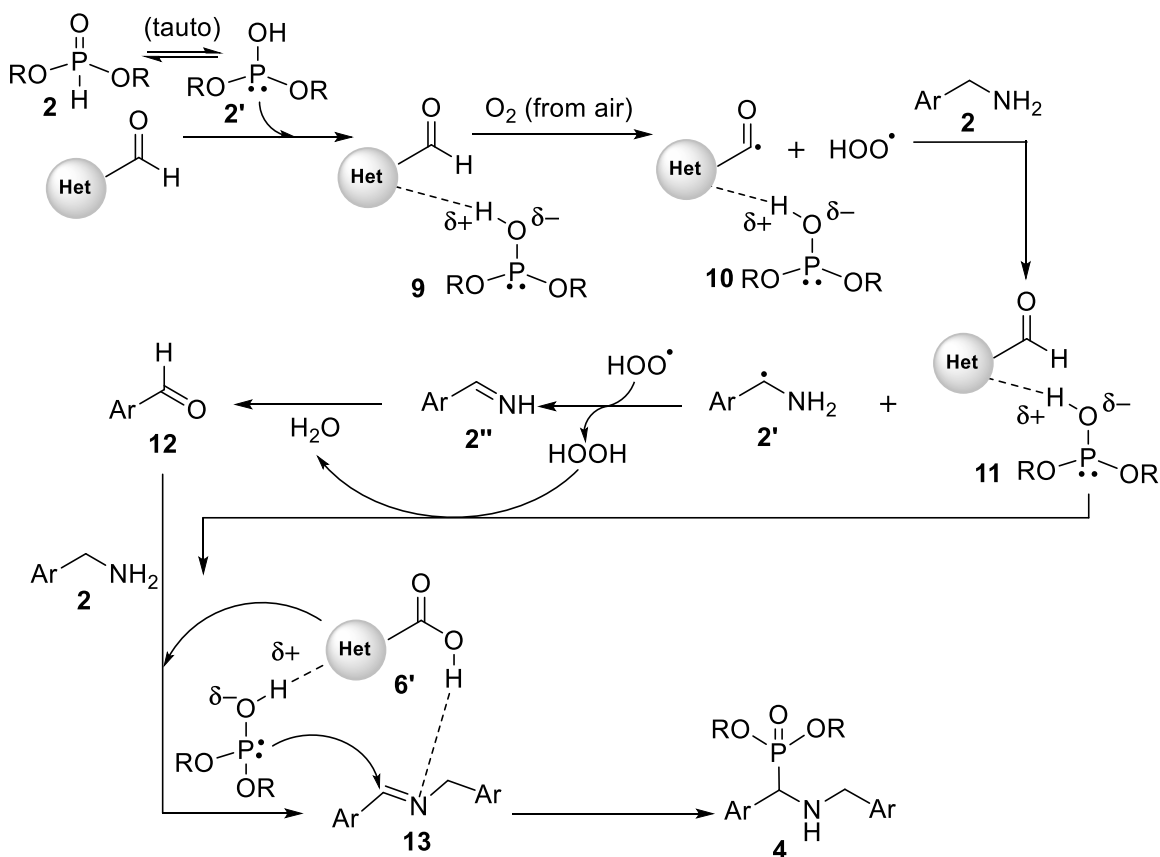
**Scheme 11.** A suggested mechanism for the sulfated polyborate-catalyzed synthesis of  $\alpha$ -aminophosphonates

Recently, Aghahosseini *et al.* developed, for the first time, a selective radical reaction, promoted *via* the auto-oxidation of quinoline-4-carbaldehyde as an effective organocatalyst in the synthesis of  $\alpha$ -aminophosphonates from a dialkyl phosphite and two molecules of the same *N*-benzylamine upon heating the reaction mixture in the presence of air (Scheme 12).<sup>99</sup> Interestingly, this is a new version of the Kabachnik-Fields reaction that avoids the use of carbonyl compound(s) as one component of this three-component reaction. Instead, the heteroaromatic aldehyde generates a stable acyl radical out of its aerobic auto-oxidation.



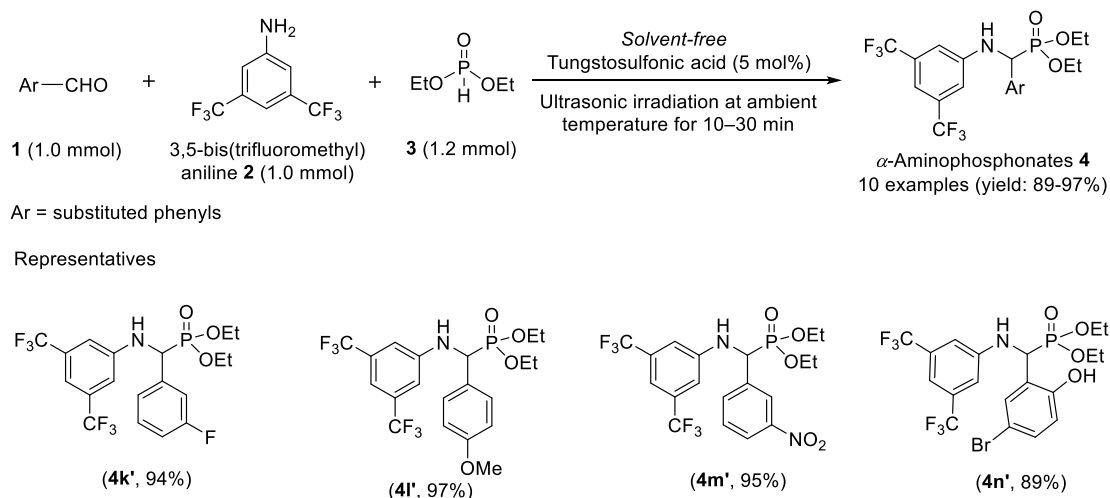
**Scheme 12.** Quinoline-4-carbaldehyde-promoted synthesis of  $\alpha$ -aminophosphonates under heating in the presence of air

The investigators assumed that the *in-situ* generated pyridine-based heteroaromatic aldehydic species provides a hydrogen-bonding framework, which plays a crucial role in defining the reaction pathway (Scheme 13).



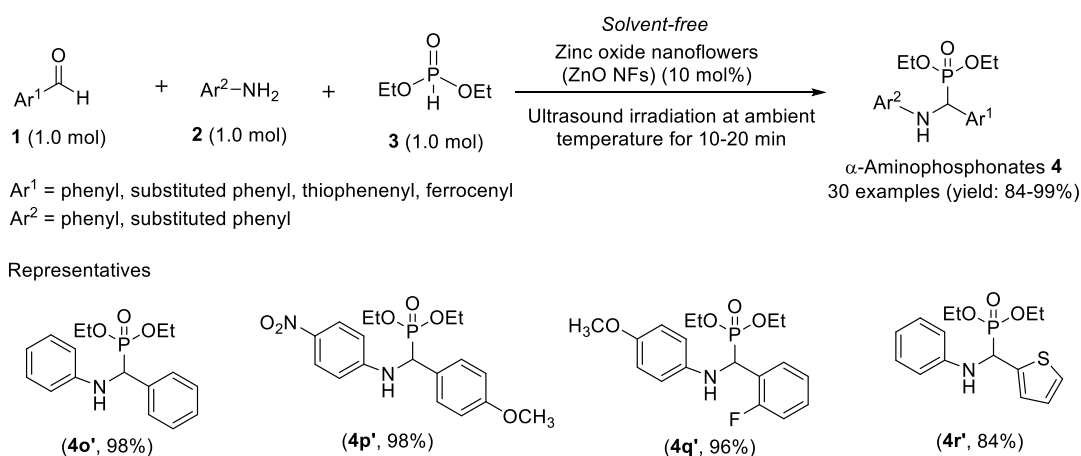
**Scheme 13.** Proposed mechanism for quinoline-4-carbaldehyde-promoted synthesis of  $\alpha$ -aminophosphonates under heating in the presence of air

Ultrasonic irradiation has recently emerged as a functional 'green' tool in implementing a plethora of chemical transformations.<sup>100-104</sup> This technique is associated with several benefits, including safety, energy savings, waste prevention, improvement in the mass transfer, product selectivity and enhancement in reaction rates. Suresh Reddy and coworkers demonstrated an ultrasound-assisted synthetic protocol for substituted  $\alpha$ -aminophosphonate derivatives containing a biologically potent trifluoromethyl group ( $-\text{CF}_3$ ), using tungstosulfonic acid as an efficient and reusable heterogeneous solid-acid catalyst under solvent-free conditions (Scheme 14).<sup>105</sup> All of the synthesized compounds were evaluated for their antioxidant and antimicrobial potential.



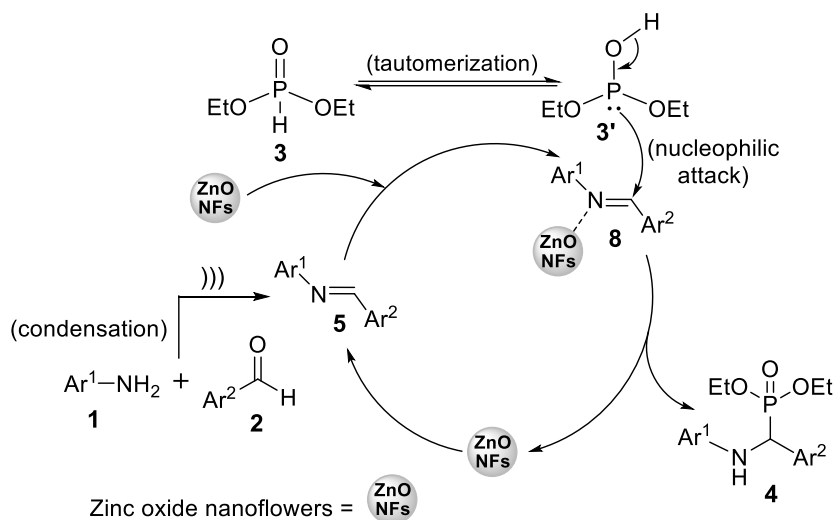
**Scheme 14.** Tungstosulfonic acid-catalyzed synthesis of  $\alpha$ -aminophosphonates under ultrasonication

The application of zinc oxide nanoflowers (ZnO NFs) as an alternative, reusable heterogeneous metal catalyst under the influence of ultrasound irradiation was also explored by Rasal *et al.* for a similar type of reaction (Scheme 15).<sup>106</sup> Operational simplicity, a broad scope of potential substrates, reusability of the heterogeneous nanocatalyst, and good yields within a short reaction time are the notable advantages of this protocol.



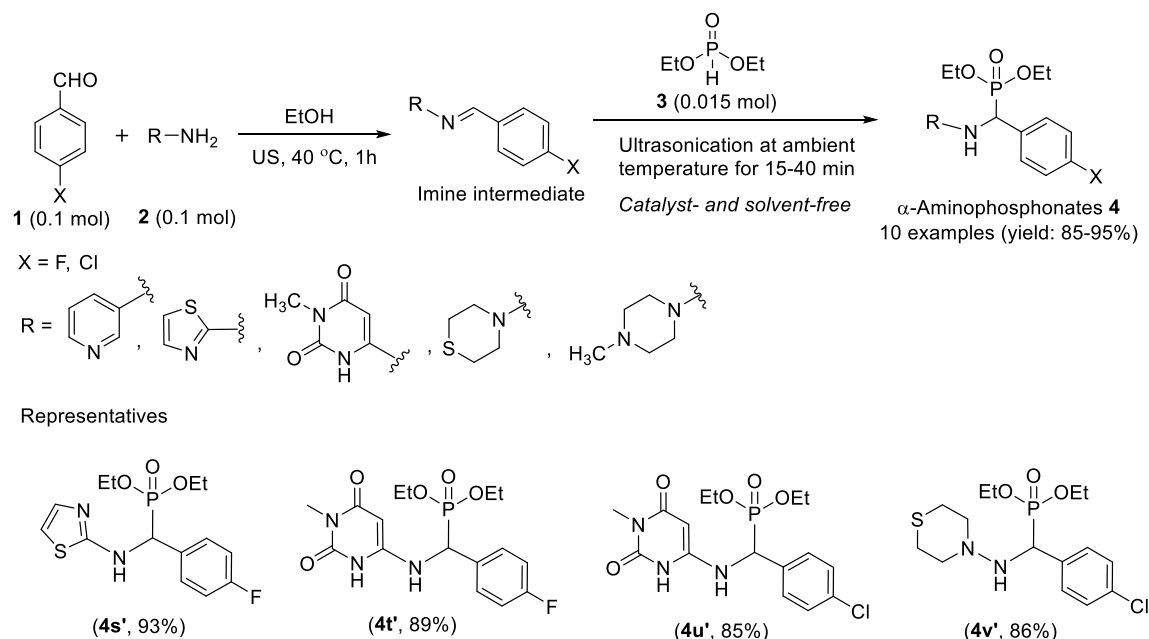
**Scheme 15.** ZnO NFs-catalyzed synthesis of  $\alpha$ -aminophosphonates under ultrasonication

A plausible mechanism for this ultrasound-assisted ZnO NFs-catalyzed transformation is depicted in Scheme 16.



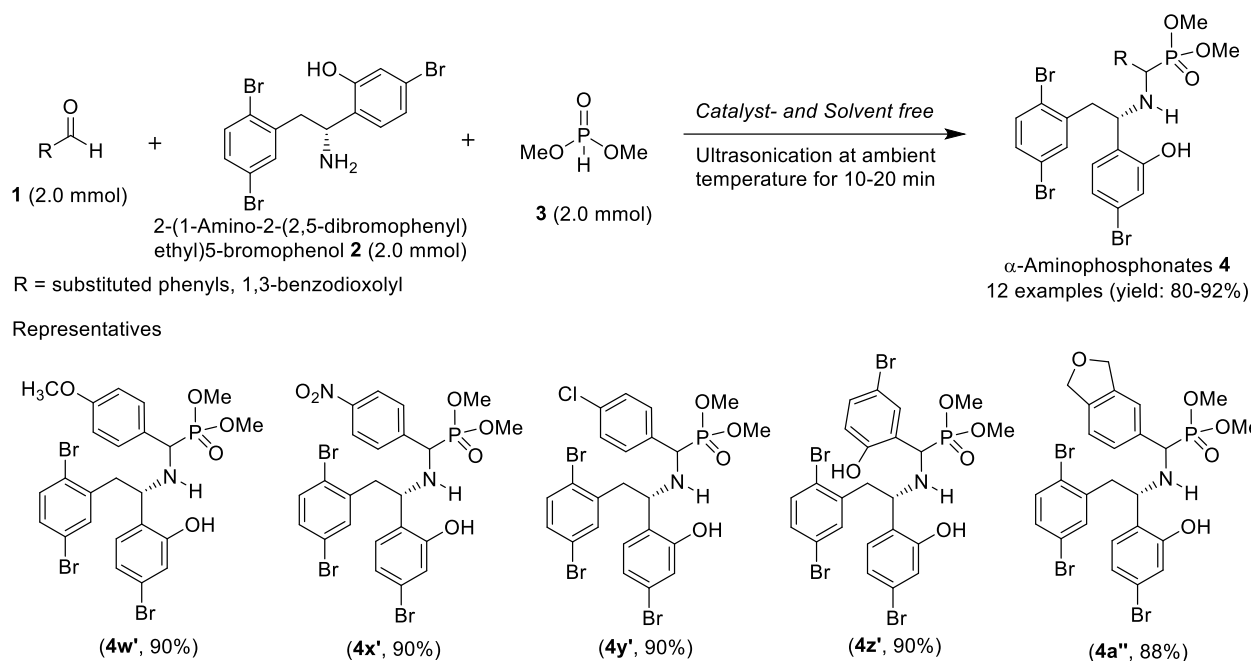
**Scheme 16.** A plausible mechanism for the ZnO NFs-catalyzed synthesis of  $\alpha$ -aminophosphonates under ultrasonication

A catalyst-free, ultrasound-assisted protocol for the synthesis of a series of antioxidant  $\alpha$ -aminophosphonate derivatives by Pudovik reaction was developed by Rao and coworkers (Scheme 17).<sup>107</sup> Operational simplicity, avoidance of catalysts and solvent, good yields within short reaction times, and eco-friendliness are also the major benefits of this protocol.



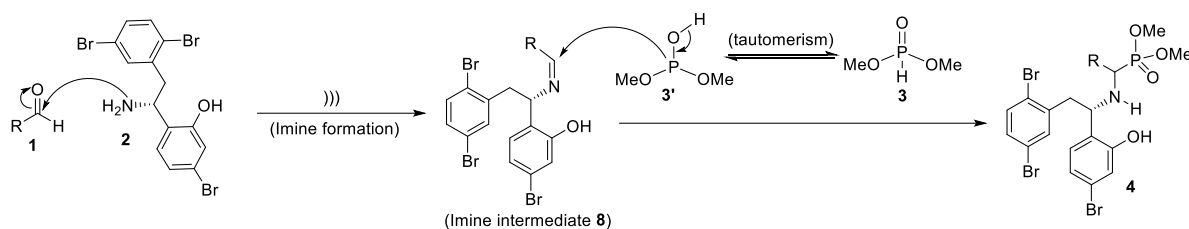
**Scheme 17.** Catalyst- and solvent-free synthesis of  $\alpha$ -aminophosphonates under ultrasonication

Suresh Reddy and coworkers extended this protocol to synthesize another version of such molecules and evaluated their antimicrobial properties (Scheme 18).<sup>108</sup>



**Scheme 18.** Catalyst- and solvent-free synthesis of  $\alpha$ -aminophosphonates under ultrasonication

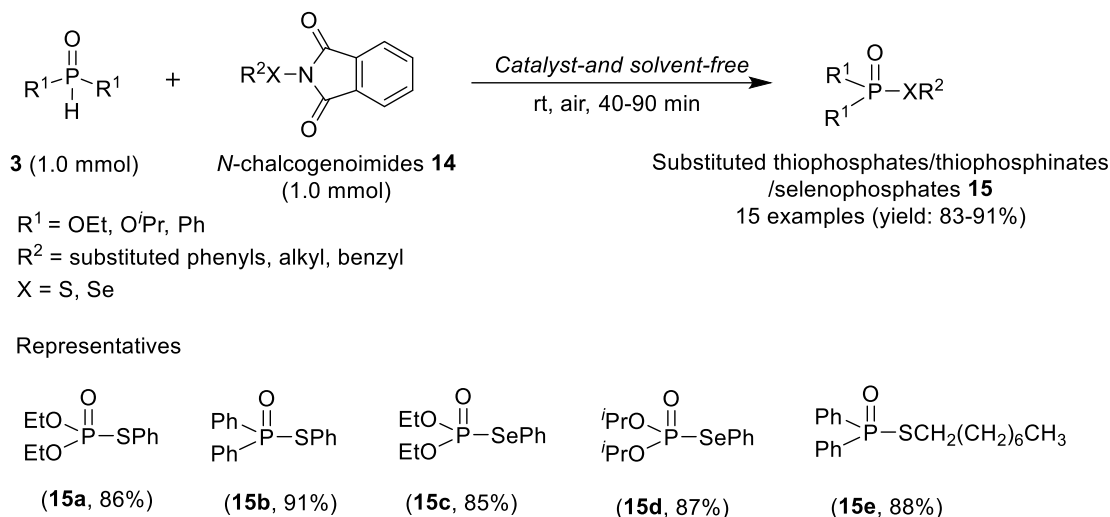
A possible mechanism for this transformation is shown in Scheme 19.



**Scheme 19.** A suggested mechanism for the ultrasound-assisted synthesis of  $\alpha$ -aminophosphonates

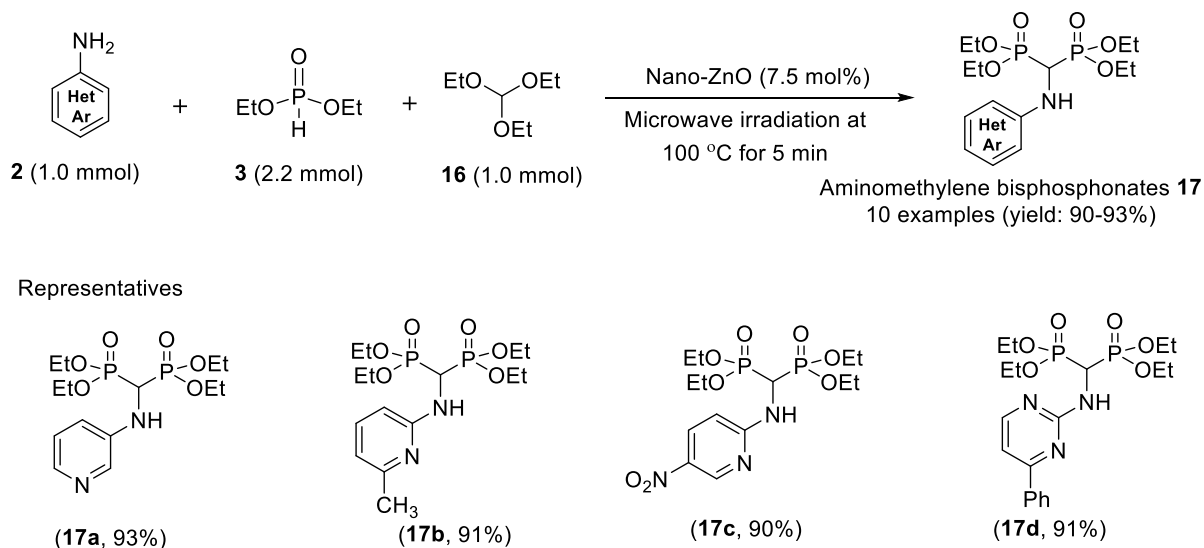
## 2.2. Synthesis of organophosphorus compounds through P-H functionalization

Accessing organophosphorus compounds through P-H bond functionalization has received much attention from synthetic organic chemists.<sup>109</sup> As part of such endeavors, Mondal and Saha developed an elegant catalyst- and solvent-free, room-temperature-based protocol for the syntheses of a series of diverse thiophosphates/thiophosphinates/selenophosphates **15** from the reaction between H-phosphonates and *N*-chalcogenoimides **14** *via* P-H bond functionalization (Scheme 20).<sup>110</sup> Good-to-excellent yields, a clean reaction profile, and eco-friendliness are notable advantages of this protocol.



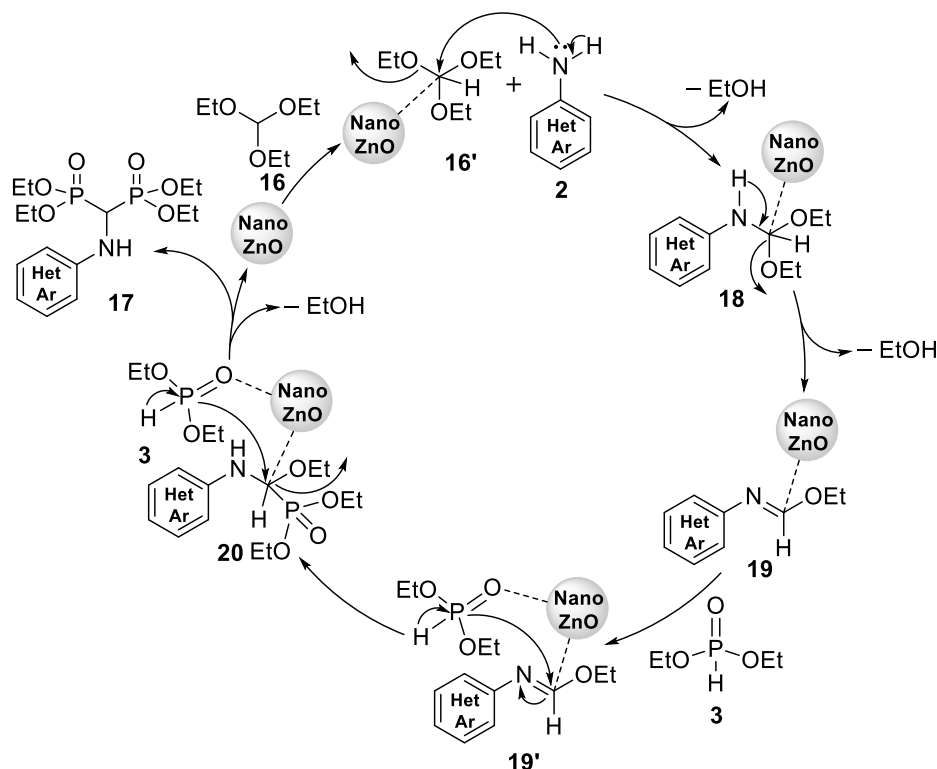
**Scheme 20.** Catalyst- and solvent-free syntheses of substituted thiophosphates/thiophosphinates/selenophosphates at room temperature

In another report, Reddy and his group disclosed a microwave-assisted protocol for synthesizing aminomethylene bisphosphonates **17** in good-to-excellent yields from a three-component reaction of an amine, diethyl phosphonate, and triethyl orthoformate (**16**), in the presence of a catalytic amount of nano ZnO as a heterogeneous catalyst under solvent-free conditions (Scheme 21).<sup>111</sup> The synthesized compounds were evaluated and showed promising *in vitro* anticancer activity against a series of human cancer cell lines, including breast (MCF-7), prostate (DU-145), osteosarcoma (MG-63), fibrosarcoma (HT-1080), multiple myeloma (RPMI-8226) cancer cell lines using sulforhodamine-B (SRB) assay method, and adriamycin as reference drug.<sup>111</sup>



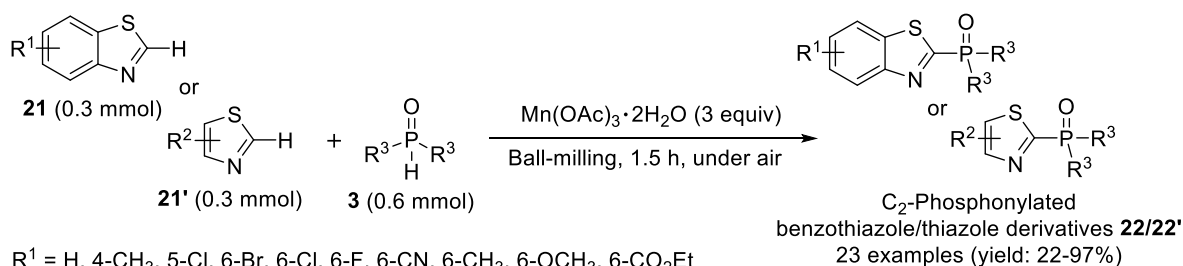
**Scheme 21.** Nano ZnO-catalyzed syntheses of pyridinyl and pyrimidinyl bisphosphonates under microwave irradiation

The investigators outlined the possible mechanistic pathway for this transformation as depicted in Scheme 22.



**Scheme 22.** Proposed mechanism for the microwave-assisted and nano ZnO-catalyzed synthesis of pyridinyl and pyrimidinyl bisphosphonates

Wang and coworkers, for the first time, accomplished the direct phosphonylation of benzothiazoles **21** and thiazole derivatives **21'** with phosphine oxides/phosphinate ester/phosphonate diesters, promoted by manganese(III) acetate under ball milling to access a diverse series of C<sub>2</sub>-phosphonylated benzothiazole/thiazole derivatives **22/22'** in good yields (Scheme 23).<sup>112</sup>

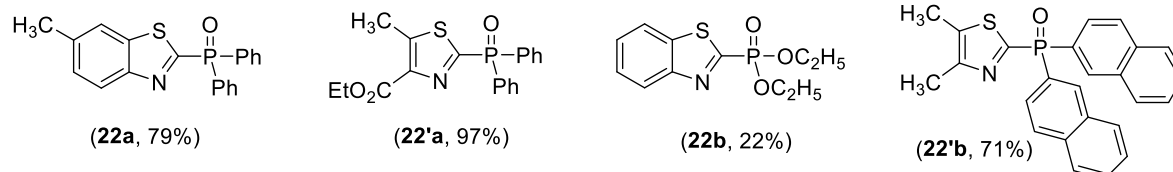


R<sup>1</sup> = H, 4-CH<sub>3</sub>, 5-Cl, 6-Br, 6-Cl, 6-F, 6-CN, 6-CH<sub>3</sub>, 6-OCH<sub>3</sub>, 6-CO<sub>2</sub>Et

R<sup>2</sup> = H, 4,5-di-CH<sub>3</sub>, 4-CO<sub>2</sub>Et-5-CH<sub>3</sub>

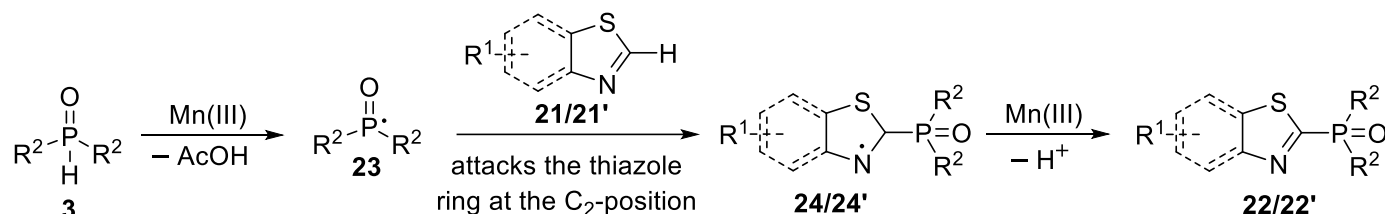
R<sup>3</sup> = phenyl, substituted phenyl, 2-naphthyl, *c*-hexyl, *n*-butyl, alkoxy

Representatives



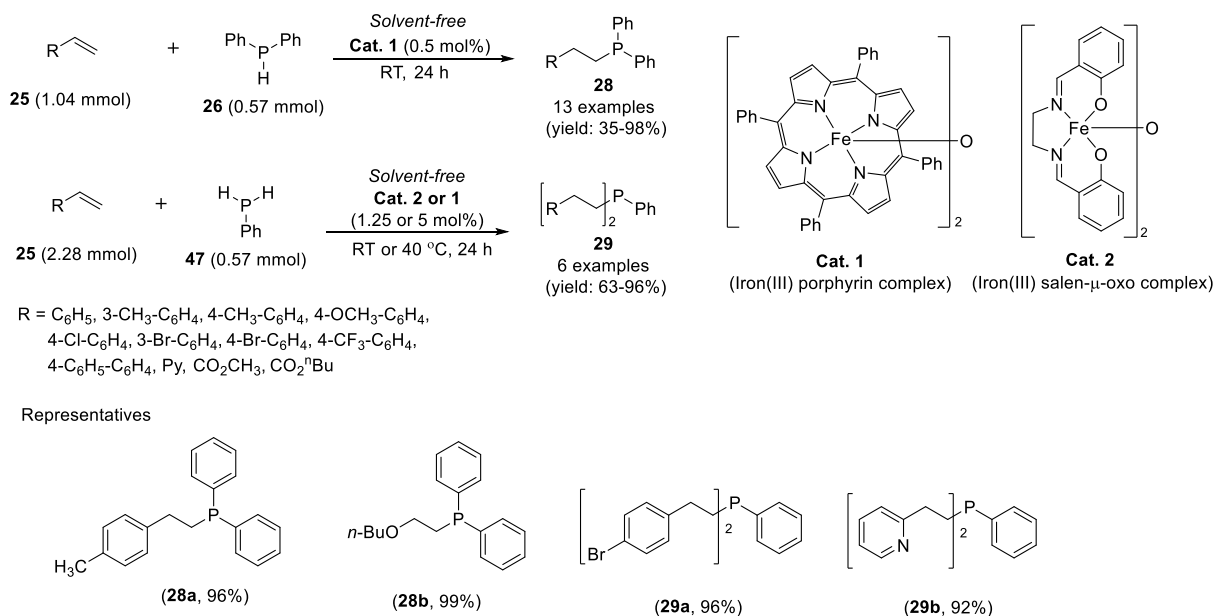
**Scheme 23.** Manganese acetate-catalyzed synthesis of C<sub>2</sub>-phosphonylated benzothiazole/thiazole derivatives under ball milling

The investigators proposed that the phosphoryl radical **23** is initially generated from organophosphorus compounds **3** under the oxidative influence of manganese(III) acetate, which, in the next step, attacks the thiazole ring at the C<sub>2</sub>-position of **21/21'** to give the radical intermediate **24**. The intermediate **24** undergoes subsequent aromatization of the thiazole ring *via* oxidation by the Mn(III) species to furnish the desired product **22/22'** (Scheme 24).<sup>112</sup>



**Scheme 24.** Proposed mechanism for manganese acetate-catalyzed synthesis of C<sub>2</sub>-phosphonylated benzothiazole/thiazole derivatives under ball milling

Recently, Webster and coworkers also accomplished room temperature-based hydrophosphination of activated alkenes **25** with phenyl/diphenylphosphine **26/47** using two individual iron(III) porphyrin complexes (**Cat.1** and **Cat. 2**) as the biocompatible catalysts under solvent-free conditions (Scheme 25).<sup>113</sup>

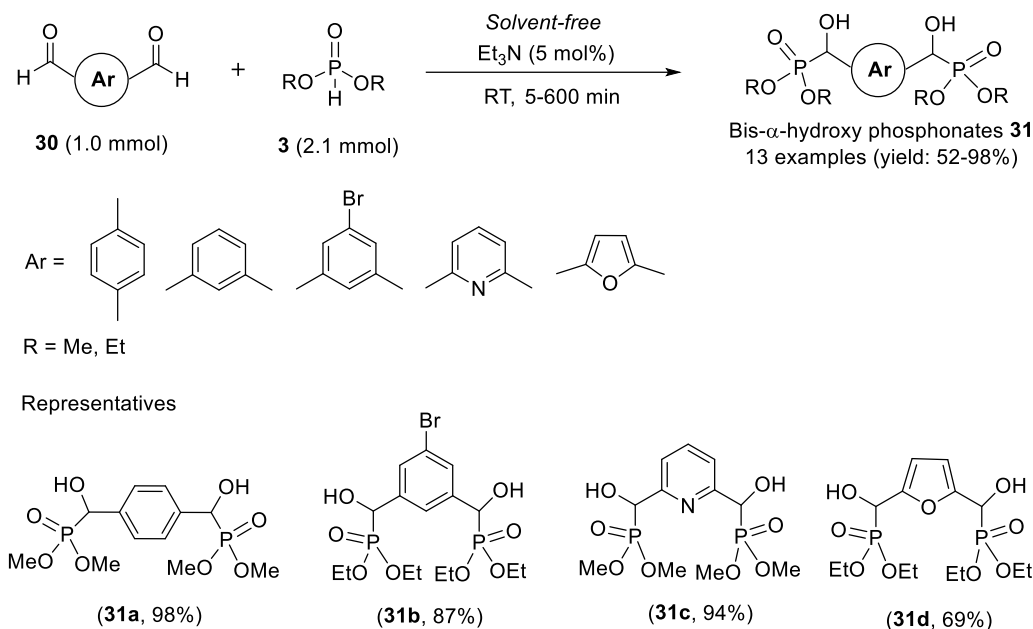


**Scheme 25.** Room temperature-based hydrophosphination of activated alkenes with phenyl/diphenylphosphine using iron(III) porphyrin complexes as the biocompatible catalysts

## 2.3. Synthesis of miscellaneous organophosphorus compounds

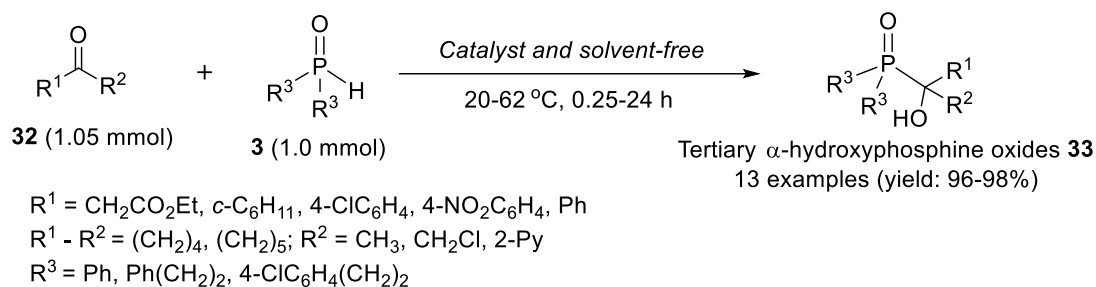


$\alpha$ -Hydroxyphosphonates, particularly the bis- $\alpha$ -hydroxyphosphonate version, are useful organophosphorus compounds with multifaceted pharmaceutical activities, flame-retardant properties and synthetic applications.<sup>114-119</sup> Recently, Mou *et al.* accomplished a metal-free green method to prepare bis- $\alpha$ -hydroxyphosphonates **31** via an atom-economical Pudovik reaction between aromatic/heteroaromatic dialdehydes **30** and dialkyl phosphonates using triethylamine as catalyst (Scheme 26).<sup>120</sup> The reaction proceeded smoothly under mild conditions with high activity, atom economy, and operational simplicity.

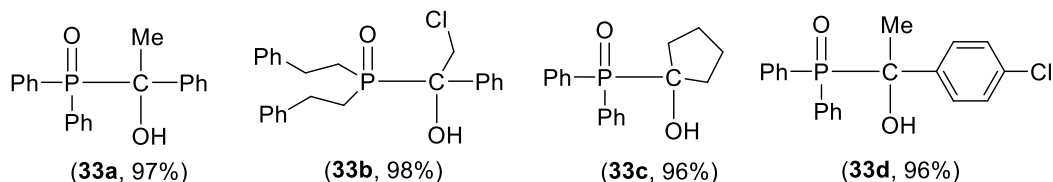


**Scheme 26.** Triethylamine-catalyzed synthesis of bis- $\alpha$ -hydroxy phosphonates at room temperature

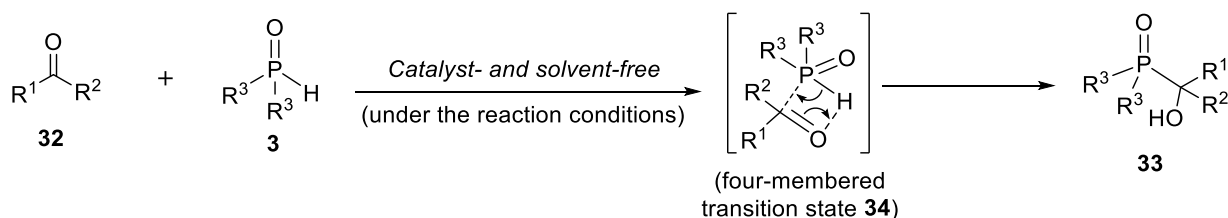
Tertiary phosphine oxides find useful applications as ligands in extractive metallurgy,<sup>121,122</sup> preparation of metal-complex catalysts<sup>123-126</sup> and organic syntheses,<sup>127,128</sup> in medicinal chemistry, and many other uses.<sup>129,130</sup> Therefore, designing functionalized tertiary-phosphine oxides is a valid exercise.<sup>131,132</sup> Very recently, Trofimov and his group reported on developing a catalyst- and solvent-free synthesis of tertiary  $\alpha$ -hydroxyphosphine oxides by hydrophosphorylation of ketones with secondary phosphine oxides (Scheme 27).<sup>133</sup> Mild reaction conditions, excellent yields, high atom economy, operational simplicity and eco-friendliness are the key advantages of this protocol.



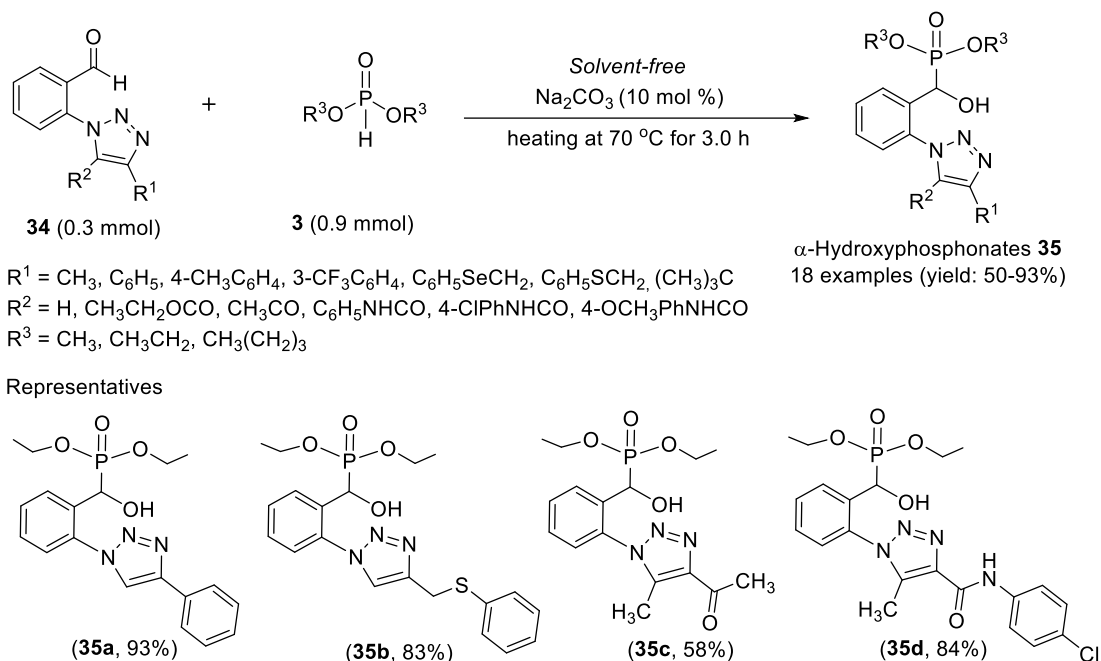
Representatives

**Scheme 27.** Catalyst- and solvent-free synthesis of tertiary  $\alpha$ -hydroxyphosphine oxides

The investigators assumed the addition reaction proceeds through a four-membered transition state **34** involving a concerted electron pair (or single-electron transfer) without preliminary formation of ions or radicals (Scheme 28).

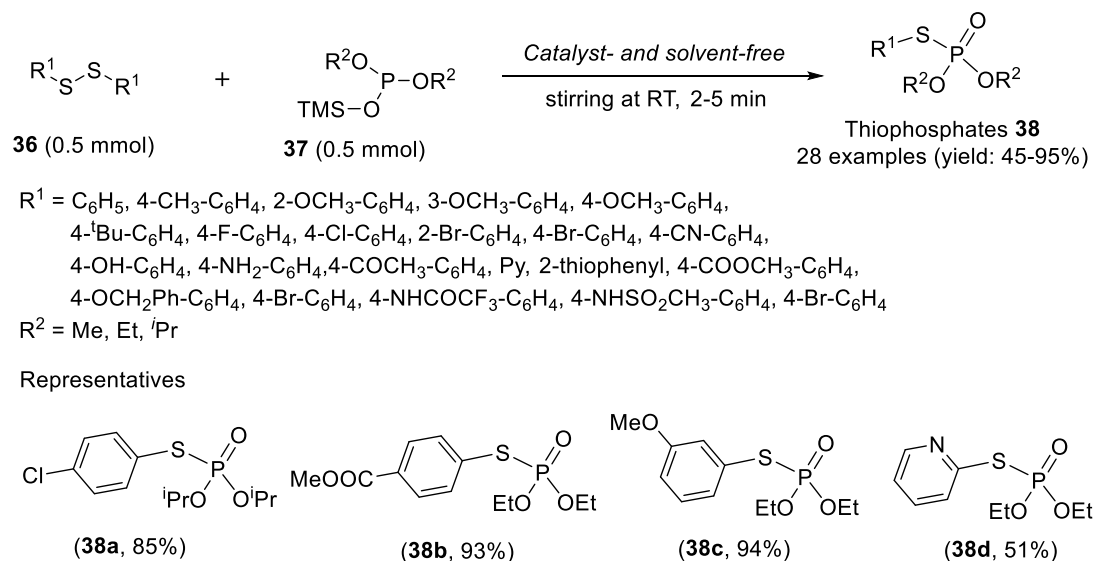
**Scheme 28.** Proposed synthetic pathway for tertiary  $\alpha$ -hydroxyphosphine oxides

Silva and his group recently developed a solvent-free synthesis of  $\alpha$ -hydroxyphosphonates **35** containing a 1,2,3-triazole moiety in moderate-to-excellent yields through the Abramov reaction between 2-(1*H*-1,2,3-triazol-1-yl)benzaldehydes **34** and dialkyl phosphonates **3**, using sodium carbonate as catalyst and heating at 70 °C (Scheme 29).<sup>134</sup>



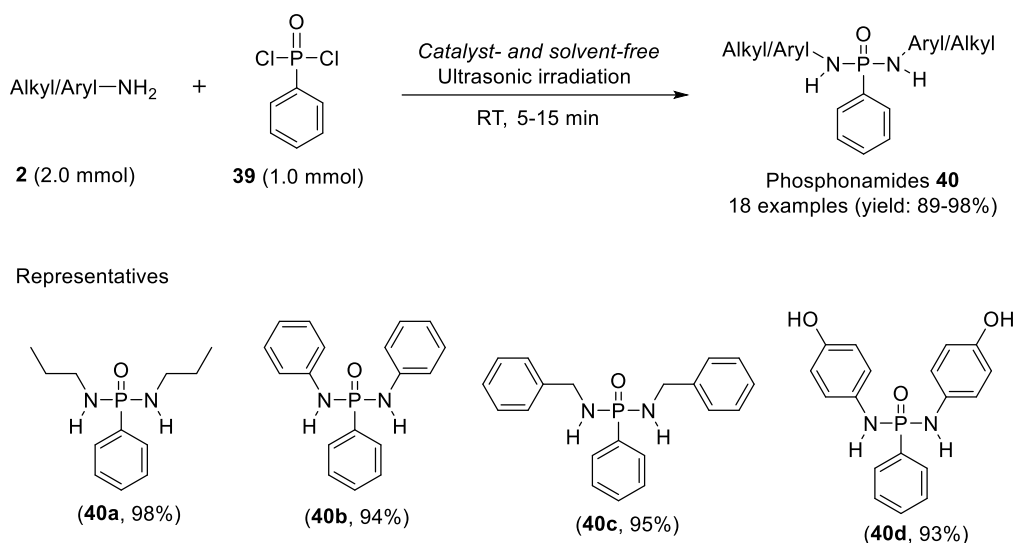
**Scheme 29.** Sodium carbonate-catalyzed solvent-free synthesis of  $\alpha$ -hydroxyphosphonates containing functionalized 1,2,3-triazoles with heating

Thiophosphates are valuable organophosphorus compounds finding wide applications as therapeutic agents in medicinal chemistry<sup>135-138</sup> and as pesticides in agrochemistry.<sup>139-141</sup> In a recent report, Wu and his group demonstrated a green and simple protocol for synthesizing a series of thiophosphates **38** through coupling reactions between disulfides **36** and dialkyl trimethylsilyl phosphites **37**, under neat reaction conditions at ambient temperature and pressure (Scheme 30).<sup>142</sup> Easy operation, moderate-to-excellent yields, short reaction times, scalable syntheses, and good functional-group tolerability are the notable benefits of this protocol.



**Scheme 30.** Catalyst- and solvent-free synthesis of thiophosphates at room temperature

Phosphoramidates are a group of useful organophosphorus compounds.<sup>143-146</sup> Bouchareb *et al.* synthesized a series of phosphoramidate derivatives **40** from a catalyst- and solvent-free reaction between primary amines and phenylphosphonic dichloride **39** under ultrasound irradiation (Scheme 31).<sup>147</sup> Good yields, short reaction times, avoidance of catalyst and solvent, and easy scale-up are the benefits of this present method.



**Scheme 31.** Ultrasound-promoted synthesis of phosphoramidate derivatives under catalyst and solvent-free conditions

### 3. Conclusions

Organophosphorus chemistry is an exciting field of research since phosphorus-functionalized organic molecules find practical and useful applications in such diverse areas as medicinal, pharmaceutical, agrochemical, and materials chemistries, both on laboratory and industrial scales. Synthetic organic chemists are also deeply involved in designing green-inspired protocols for the generation of organophosphorus compounds of both known and unknown skeletons, and their analogues, that may offer different physical and biological properties. These advantages are very important for industrial-process developments since solvent-free conditions are associated with several practical benefits, including operational simplicity, cost effectiveness, minimization of waste generation, and reduced pollution. This review has attempted to provide a comprehensive update on the green-inspired synthetic drivers for functionalized organophosphorus compounds under solvent-free conditions reported from 2016 to 2021. Many significant developments, particularly those involving green-chemistry approaches, have been documented in some detail.. We sincerely believe this overview would be helpful to researchers and scientists interested in this field of work.

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**Goutam Brahmachari**, after receiving his Ph.D. in 1997 at Visva-Bharati University (India) joined his alma mater the very next year and has held the position of a full professor of organic chemistry since 2011. The research interests of his group include organic synthesis, green chemistry and medicinal chemistry of natural and natural product-inspired synthetic molecules. With more than 23 years of experience in teaching and research, he has produced over 200 scientific publications, including original research papers, review articles, books, and invited book chapters in organic synthesis, green chemistry, and natural products. He has already authored/edited 26 books and 50 book chapters from internationally reputed leading scientific publication houses. He is the *Founder Series Editor* of the Elsevier Book Series '*Natural Product Drug Discovery*'. Prof. Brahmachari is a Fellow of the Royal Society of Chemistry, and a recipient of CRSI (Chemical Research Society of India) Bronze Medal-2021 (contributions to research in chemistry), INSA (Indian National Science Academy) Teachers Award-2019, Dr. Kalam Best Teaching Faculty Award-2017, and Academic Brilliance Award-2015 (Excellence in



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