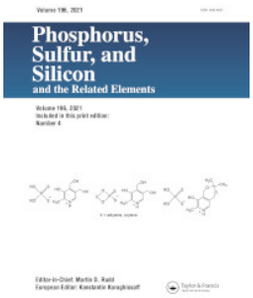
Taylor & Francis
Taylor & Francis Group



Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Synthesis of α-aminophosphonates by the Kabachnik-Fields reaction

G. Sravya, A. Balakrishna, Grigory V. Zyryanov, G. Mohan, C. Suresh Reddy & N. Bakthavatchala Reddy

To cite this article: G. Sravya, A. Balakrishna, Grigory V. Zyryanov, G. Mohan, C. Suresh Reddy & N. Bakthavatchala Reddy (2021) Synthesis of α-aminophosphonates by the Kabachnik-Fields reaction, Phosphorus, Sulfur, and Silicon and the Related Elements, 196:4, 353-381, DOI: 10.1080/10426507.2020.1854258

To link to this article: https://doi.org/10.1080/10426507.2020.1854258

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
2021, VOL. 196, NO. 4, 353–381
https://doi.org/10.1080/10426507.2020.1854258

Taylor & Francis
Taylor & Francis Group

REVIEW

Synthesis of α-aminophosphonates by the Kabachnik-Fields reaction

G. Sravya[a], A. Balakrishna[b], Grigory V. Zyryanov[a,c], G. Mohan[d,e], C. Suresh Reddy[d], and N. Bakthavatchala Reddy[a]

[a]Chemical Engineering Institute, Ural Federal University, Yekaterinburg, Russian Federation; [b]Rajeev Gandhi Memorial College of Engineering and Technology (Autonomous), Nandyal, Andhra Pradesh, India; [c]I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, Yekaterinburg, Russian Federation; [d]Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India; [e]DST-PURSE Centre, Sri Venkateswara University, Tirupati, Andhra Pradesh, India

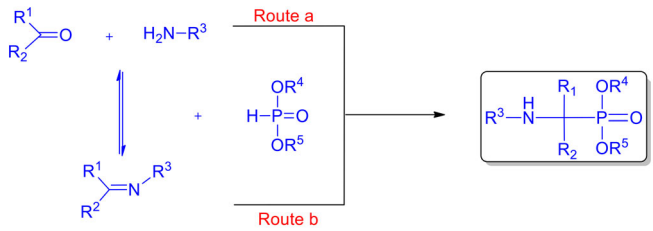
ABSTRACT

The review discusses recent achievements in the development of more ecofriendly and economically viable processes for the synthesis of biologically potent α-aminophosphonates via Kabachnik-Fields reaction by three-component coupling of carbonyl, amine and hydrophosphoryl compounds. These α-aminophosphonates exhibited promising antioxidant, antimicrobial and anticancer activity. Some recent developments on the synthesis of biologically active α-aminophosphonates in the presence of various catalysts, in catalytic solvent medium, in catalyst-free solvent medium, under solvent-free conditions, and reactions in solution are discussed. Miscellaneous reactions are also included.

ARTICLE HISTORY
Received 28 September 2020
Accepted 9 November 2020

KEYWORDS
Synthesis; α-aminophosphonates; Kabachnik-Fields reaction

GRAPHICAL ABSTRACT



Introduction

α-Aminophosphonates represent a fascinating class of molecules with unique properties which have thrived structural analogy to α-aminoacids[1] and significant biological activities. These molecular components act as peptide mimics,[2] enzyme inhibitors,[3] antibiotics and pharmacological agents.[4] These structurally diversified important scaffolds have been synthesized by various routes: (i) addition of a P-H function to imines and enamines[5] (ii) addition of a P-H function to nitriles[6] (iii) Arbuzov and Michaelis–Becker reactions[7] (iv) condensation of X-NH_2 with acyl phosphorus species[8] (v) Curtius and Hofmann rearrangement of substituted phosphonoacetic esters[9] and (vi) alkylation of nucleophilic precursors such as Schiff bases.[10] Apart from this wide range of synthetic methods for the synthesis of α-aminophosphonates,[11] little effort has been made to convert the readily accessible α-hydroxyphosphonates into α-aminophosphonates. For the first time, a variety of α-aminophosphonates were synthesized from α-hydroxyphosphonates in the presence of acidic alumina using microwave irradiation.[12]

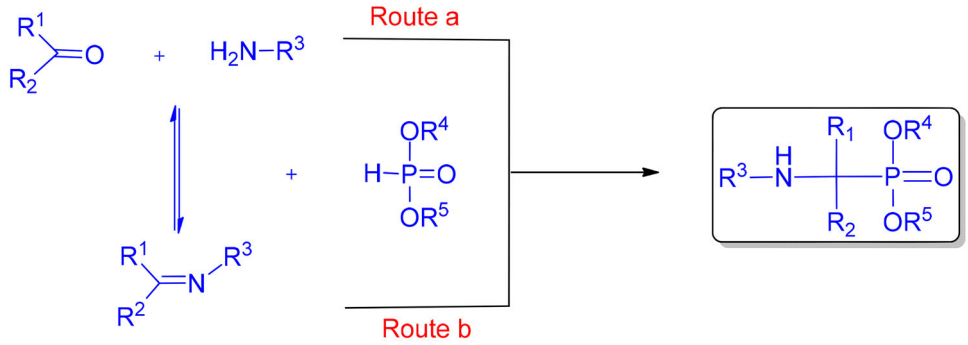
The interest in the synthesis and study of α-aminophosphonates emerged naturally from intense studies over the last century. Among these synthetic methods, the Kabachnik-Fields reaction appears to be the simplest and most direct approaches.[13] This reaction proceeds via an imine formed by the reaction of carbonyl compounds and amines, where it is converted to the corresponding aminophosphonates by phosphite addition.

It is accepted that this one-pot reaction can be promoted by acid or base catalysts, microwave irradiation or by heating.[14] Several acid catalysts, such as Lewis acids e. g. $BiCl_3$,[15] or $Al(OTf_3)$,[16] Bronsted acids such as sulfamic acid,[17] or heteropoly acids,[18] and base catalysts such as $CaCl_2$[19] and PPh_3[20] as well as other catalysts such as ZnO,[21] TiO_2,[22] tosylchloride,[23] have been used to promote this reaction.

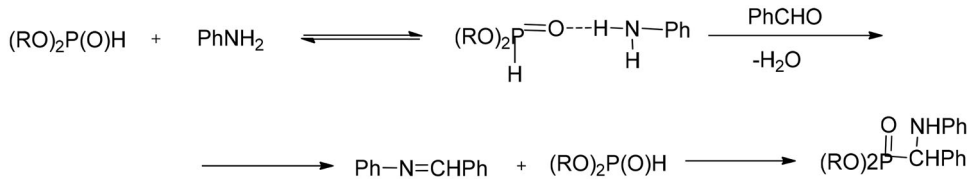
Mechanistic pathways for the synthesis of α-aminophosphonates

Designing α-aminophosphonates is majorly carried through a one-pot reaction.[24] This reaction was individually

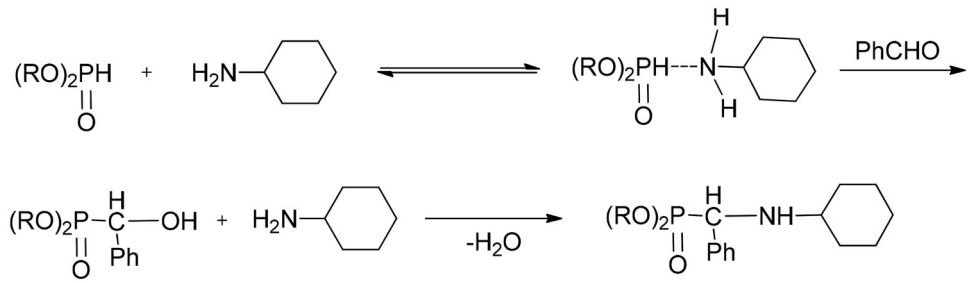
CONTACT N. Bakthavatchala Reddy drbvreddyn@gmail.com; Grigory V. Zyryanov bvreddysvu@gmail.com Ural Federal University, Chemical Engineering Institute, Yekaterinburg, 620002, Russian Federation.



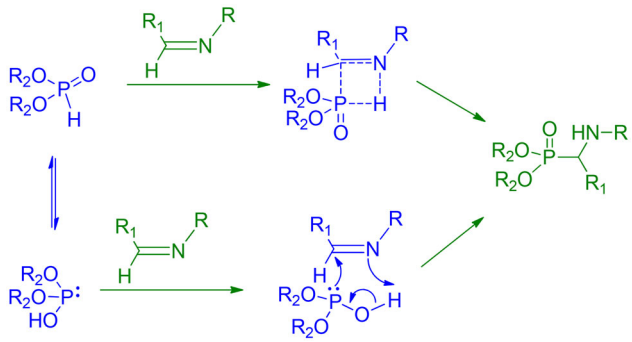
Scheme 1. Formation of α-aminophosphonates by three-component (a) or two component (b) route.



Scheme 2. Imine mechanism proposed for Kabachnik-Fields reaction.



Scheme 3. α-hydroxy phosphonate mechanism proposed for Kabachnic-Fields reaction.



Scheme 4. Synthesis of α-aminophosphonates.

reported by both Kabachnik[25] and Fields[26] in 1952. An alternative method is the so-called Pudovik reaction,[27] in which a dialkyl phosphite reacts with the corresponding imine (Scheme 1).

Plausible mechanism of the Kabachnik-Fields reaction

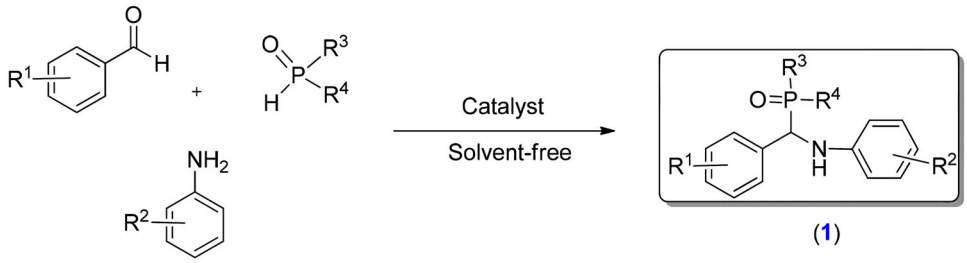
As noted above, the Kabachnik-Fields reaction is a three-component reaction of hydrophosphoryl compounds with ammonia, amines or other NH-compounds and aldehydes or ketones. It represents an exclusive method for the formation of the α-aminophosphonates framework [N-C-P(O)]. However, the detailed mechanism of this reaction has not been established. On the basis of kinetic studies, it was concluded that the mechanism is dependent on the nature of the reactants.

The main difficulty in the understanding of the Kabachnik-Fields reaction mechanism is the determination of the sequence of separate steps involved in this process. In their initial studies, Kabachnik and Medved thought that it was similar to the Rodionov reaction employed for the synthesis of β-aminoacids or the Zelinsky reaction, i.e., the formation of aminonitriles upon treatment of aldehydes with ammonium cyanide.

$$\mathrm{RCHO + NH_3 + CH_2(COOH)_2 \longrightarrow RCH(NH_2)CH_2COOH + H_2O + CO_2}$$

$$\mathrm{RCHO + HCN \longrightarrow RCH(CN)OH \longrightarrow NH_3RCH(NH_2)CN + H_2O}$$

In another study, it was noticed that the pathway of the Kabachnik-Fields reaction depends on the nature of the



Scheme 5. General scheme for the solvent-free catalyzed Kabachnik-Fields reactions studied.

substrates. The amine and hydrophosphoryl compound form a complex in which either one of the partners may react with the carbonyl compound. Often, the nucleophilicity of the amine determines the reaction pathway. Weak basic amines such as anilines, which can act as proton donors, favor the formation of an imine, where the H-bond is formed between the P = O function of the phosphite and the HN unit of the amine (Scheme 2).[28,29]

Cherkasov et al. proposed that the reaction of the more nucleophilic cyclohexyl-amine, benzaldehyde and a dialkyl phosphite takes place through the formation of hydroxyphosphonate intermediates. Here again an interaction was substantiated to precede the addition of the dialkylphosphite on the C = O unit of the oxo-compound, in which a H-bond is formed between the P(O)*H* moiety of the phosphite and the nitrogen atom of the amine (Scheme 3).[28,30]

R. Gancarz and I. Gancarz proved that the formation of hydroxyphosphonate is succeeded by a dead-end route mechanism[31] via rearrangement of the corresponding phosphate/phosphite. It can be said that in the Kabachnik-Fields reaction a soft nucleophile (the dialkyl phosphite) and a hard nucleophile (the amine) compete for the electrophilic carbonyl compound. The softer the carbonyl compound the faster it reacts with the softer P-nucleophile and the slower it reacts with the harder amine nucleophile.[32]

If additional catalysts are used, both acids and bases can have a positive influence on the reaction rate. Sometimes, the chemical yield and the diastereoselectivity of the formation of α-aminophosphonates are higher in two-component systems using preformed imines. In this case, due to the phosphonate/phosphite tautomerism the addition to the imine could occur by either a four or five-membered transition state (Scheme 4).

Thus, in the analysis of the Kabachnik-Fields reaction the important statement has been made that the aminoalkylation of the hydrophosphoryl compounds might occur through a step-wise formation of an imine and its subsequent involvement in the Pudovik reaction.

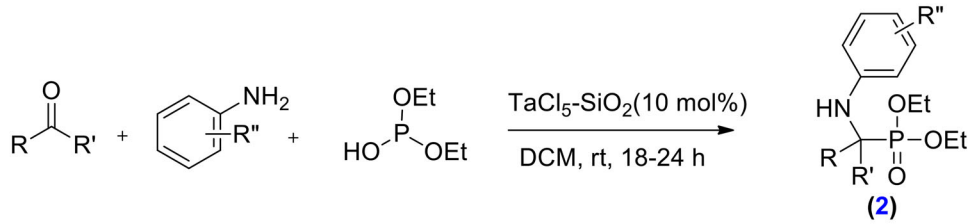
Synthesis of α-aminophosphonates in the presence of various catalysts

In recent years, solvent-free reactions have gained much attention since this method was valuable not only for ecological and economic reasons but also for operational simplicity and to obtain high yields of products. Emphasis was also done toward the development of clean and green chemical processes. Due to this reason a library of α-aminophosphonates were synthesized via three-component Kabachnik-Fields reaction by use of different carbonyl compounds, amines and hydrophosphoryl compounds. The α-aminophosphonate derivatives are represented by structure **1** in the general Scheme 5.

The detailed results are listed in Table 1.

Synthesis of α-aminophosphonates in presence of catalysts in solvent medium

Chandrasekhar et al.[42] developed a three-component reaction of aldehydes, amines and diethyl phosphite catalyzed by the Lewis acid $TaCl_5$-SiO_2 affording the corresponding α-aminophosphonates (**2**) in good yields under mild reaction conditions.



R = alkyl, aryl
R' = H, alkyl
R" = H, NO_2, OMe, OH, F

Table 1. *N*-Substituted a-aminophosphonates obtained by the Kabachnik-Fields reaction under solvent-free conditions.

Entry	Catalyst	R^1	R^2	R^3	R^4	Yield(%)	Ref
1	Lewis acid Fe_3O_4	Ph	Ph	OEt	OEt	94	[33]
		4-MeC_6H_4	Ph	OEt	OEt	91	
		4-ClC_6H_4	Ph	OEt	OEt	92	
		4-BrC_6H_4	Ph	OEt	OEt	91	
		4-$OMeC_6H_4$	Ph	OEt	OEt	87	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	86	
		Picolinyl	Ph	OEt	OEt	86	
		n-Pentyl	Ph	OEt	OEt	76	
		Cyclohexanone	Ph	OEt	OEt	79	
		Cinnamyl	Ph	OEt	OEt	85	
		Ph	4-MeC_6H_4	OEt	OEt	90	
		Ph	4-FC_6H_4	OEt	OEt	91	
		Ph	3-Cl,4-FC_6H_3	OEt	OEt	86	
		Ph	2,4-$Cl_2C_6H_3$	OEt	OEt	88	
		Ph	4-$MeOC_6H_4$	OEt	OEt	92	
		Ph	3,4,5-$(MeO)_3C_6H_2$	OEt	OEt	93	
		Ph	4-$NO_2C_6H_4$	OEt	OEt	86	
		4-$OMeC_6H_4$	4-BrC_6H_4	OEt	OEt	92	
		Ph	2-Pyridyl	OEt	OEt	82	
		Ph	Piperidine	OEt	OEt	80	
		Ph	Morpholine	OEt	OEt	79	
2	Lewis acid choline chloride-2 $ZnCl_2$	Ph	Ph	OEt	OEt	96	[34]
		3-BrC_6H_4	Ph	OEt	OEt	89	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	70	
		3-ClC_6H_4	Ph	OEt	OEt	85	
		4-$MeOC_6H_4$	Ph	OEt	OEt	98	
		4-OHC_6H_4	Ph	OEt	OEt	90	
		4-BrC_6H_4	Ph	OEt	OEt	92	
		2-ClC_6H_4	Ph	OEt	OEt	85	
		Ph	$PhCH_2$	OEt	OEt	98	
		Ph	4-FC_6H_4	OEt	OEt	70	
		Ph	4-ClC_6H_4	OEt	OEt	87	
		3-ClC_6H_4	4-ClC_6H_4	OEt	OEt	83	
		Ph	4-BrC_6H_4	OEt	OEt	90	
		4-$MeOC_6H_4$	4-BrC_6H_4	OEt	OEt	94	
		4-$MeOC_6H_4$	4-FC_6H_4	OEt	OEt	80	
3	Lewis acid $MgFe_2O_4$	Ph	Ph	OMe	OMe	94	[35]
		4-MeC_6H_4	Ph	OMe	OMe	90	
		2-$MeOC_6H_4$	Ph	OMe	OMe	91	
		4-ClC_6H_4	Ph	OMe	OMe	87	
		4-$(CH_3)_2NC_6H_4$	Ph	OMe	OMe	85	
		Phenylacetone	Ph	OMe	OMe	81	
		2-Thienyl	Ph	OMe	OMe	88	
		Cyclohexanone	Ph	OMe	OMe	89	
4	Lewis acid $Yb(PFO)_3$	Ph	Ph	OEt	OEt	90	[36]
		Ph	2-ClC_6H_4	OEt	OEt	86	
		Ph	3-ClC_6H_4	OEt	OEt	90	
		Ph	4-ClC_6H_4	OEt	OEt	84	
		Ph	4-FC_6H_4	OEt	OEt	86	
		Ph	4-$NO_2C_6H_4$	OEt	OEt	84	
		Ph	4-$CH_3C_6H_4$	OEt	OEt	90	
		Ph	4-$MeOC_6H_4$	OEt	OEt	92	
		2-$NO_2C_6H_4$	Ph	OEt	OEt	93	
		3-$NO_2C_6H_4$	Ph	OEt	OEt	90	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	95	
		4-ClC_6H_4	Ph	OEt	OEt	88	
		4-$CH_3C_6H_4$	Ph	OEt	OEt	90	
		4-$MeOC_6H_4$	Ph	OEt	OEt	86	
		4-$MeOC_6H_4$	4-$NO_2C_6H_4$	OEt	OEt	90	
		Isopropyl	Ph	OEt	OEt	50	
		Ph	Cyclohexyl	OEt	OEt	55	
5	NP or KF/NP	Ph	Ph	OEt	OEt	82	[37]
		4-$CH_3C_6H_4$	Ph	OEt	OEt	84	
		4-$MeOC_6H_4$	Ph	OEt	OEt	86	
		4-ClC_6H_4	Ph	OEt	OEt	77	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	71	
		2-OHC_6H_4	Ph	OEt	OEt	67	
		Cinnamyl	Ph	OEt	OEt	87	
		Ph	Ph	OMe	OMe	83	
		4-$MeOC_6H_4$	Ph	OMe	OMe	85	
		Cyclohexanone	Ph	OEt	OEt	76	
		Ph	2-MeC_6H_4	OEt	OEt	61	
		4-$MeOC_6H_4$	2-MeC_6H_4	OEt	OEt	68	
		Ph	$PhCH_2$	OEt	OEt	70	

(*continued*)

Table 1. Continued.

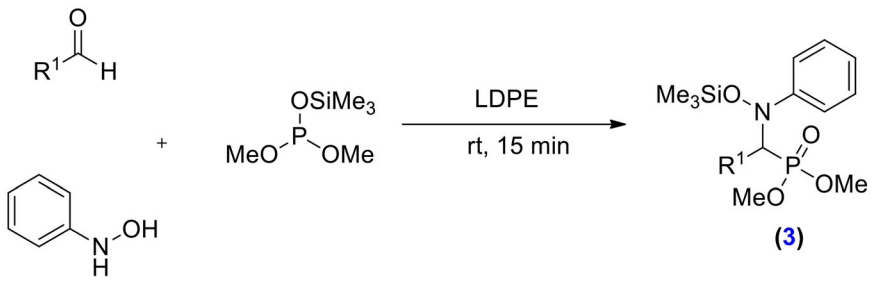
Entry	Catalyst	R^1	R^2	R^3	R^4	Yield(%)	Ref
		Cyclopentanone	Ph	OEt	OEt	64	
6	Lewis acid Amberlite-IR 120	Ph	Ph	OEt	OEt	90	[38]
		4-$MeOC_6H_4$	Ph	OEt	OEt	81	
		3-$MeOC_6H_4$	Ph	OEt	OEt	92	
		2-$MeOC_6H_4$	Ph	OEt	OEt	87	
		4-MeC_6H_4	Ph	OEt	OEt	89	
		2-OHC_6H_4	Ph	OEt	OEt	91	
		4-FC_6H_4	Ph	OEt	OEt	87	
		4-$N(CH_3)_2C_6H_4$	Ph	OEt	OEt	70	
		4-(2,3-dihydroxypropoxy)C_6H_4	Ph	OEt	OEt	67	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	95	
		3-$NO_2C_6H_4$	Ph	OEt	OEt	88	
		2-$NO_2C_6H_4$	Ph	OEt	OEt	75	
		2-$COOHC_6H_4$	Ph	OEt	OEt	78	
		3,4-$(MeO)_2$-C_6H_3	Ph	OEt	OEt	90	
		2-OH,3-$MeOC_6H_3$	Ph	OEt	OEt	95	
		3-MeO,4-OHC_6H_3	Ph	OEt	OEt	90	
		3-OH,4-$MeOC_6H_3$	Ph	OEt	OEt	87	
		3,4-$CH_2O_2C_6H_3$	Ph	OEt	OEt	92	
		3,4-$CH_2O_2C_6H_3$	4-OHC_6H_4	OEt	OEt	98	
		3,4-$CH_2O_2C_6H_3$	2-OHC_6H_4	OEt	OEt	79	
		3,4-$CH_2O_2C_6H_3$	2-$MeOC_6H_4$	OEt	OEt	91	
		3,4-$CH_2O_2C_6H_3$	$PhCH_2$	OEt	OEt	81	
		Ph	$PhCH_2$	OEt	OEt	87	
		Citryl	Ph	OEt	OEt	11	
		Cyclohexanone	Ph	OEt	OEt	78	
		Cyclohexanone	$PhCH_2$	OEt	OEt	84	
7	Lewis acid sulfamic acid (SA)	4-ClC_6H_4	Ph	OEt	OEt	94	[17]
		Ph	4-MeC_6H_4	OEt	OEt	76	
		4-ClC_6H_4	4-MeC_6H_4	OEt	OEt	82	
		4-IsopropylC_6H_4	$PhCH_2$	OEt	OEt	86	
		4-IsopropylC_6H_4	4-$MeOC_6H_4$	OEt	OEt	78	
		4-FC_6H_4	4-MeC_6H_4	OEt	OEt	91	
		4-$MeOC_6H_4$	Ph	OEt	OEt	87	
		4-$MeOC_6H_4$	4-$MeOC_6H_4$	OEt	OEt	89	
		2-Furyl	4-MeC_6H_4	OEt	OEt	87	
		2-Thienyl	3-MeC_6H_4	OEt	OEt	86	
		4-$MeOC_6H_4$	n-butyl	OEt	OEt	82	
		4-MeC_6H_4	Cyclohexyl	OEt	OEt	84	
		Ph	$PhCH_2$	OEt	OEt	79	
		4-ClC_6H_4	4-$MeOC_6H_4$	OEt	OEt	86	
		4-ClC_6H_4	$PhCH_2$	OEt	OEt	74	
		3,4$CH_2O_2C_6H_3$	3-MeC_6H_4	OEt	OEt	87	
		4-$MeOC_6H_4$	diethylamine	OEt	OEt	86	
		Cinnamyl	Ph	OEt	OEt	—	
		Isobutyryl	Ph	OEt	OEt	—	
8	Lewis acid TiO_2	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	OEt	OEt	98	[22]
		4-$MeOC_6H_4$	Ph	OEt	OEt	98	
		Ph	Ph	OEt	OEt	98	
		4-ClC_6H_4	Ph	OEt	OEt	98	
		3-ClC_6H_4	Ph	OEt	OEt	90	
		2-ClC_6H_4	Ph	OEt	OEt	87	
		4-MeC_6H_4	Ph	OEt	OEt	98	
		4-OHC_6H_4	Ph	OEt	OEt	98	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	95	
		2,6-$Cl_2C_6H_3$	Ph	OEt	OEt	72	
		3-Thienyl	Ph	OEt	OEt	90	
		Cinnamyl	Ph	OEt	OEt	87	
		Isobutyl	Ph	OEt	OEt	75	
		Cyclohexanone	Ph	OEt	OEt	90	
		3,3-dimethyl-2-butanone	Ph	OEt	OEt	55	
		Acetophenone	Ph	OEt	OEt	—	
		4-$MeOC_6H_4$	3-$NO_2C_6H_4$	OEt	OEt	87	
		4-$MeOC_6H_4$	3-$CF_3C_6H_4$	OEt	OEt	93	
		4-$MeOC_6H_4$	3-CNC_6H_4	OEt	OEt	85	
		4-$MeOC_6H_4$	4-BrC_6H_4	OEt	OEt	80	
		4-$MeOC_6H_4$	3-BrC_6H_4	OEt	OEt	90	
		4-$MeOC_6H_4$	2-BrC_6H_4	OEt	OEt	80	
		4-$MeOC_6H_4$	4-FC_6H_4	OEt	OEt	80	
		4-$MeOC_6H_4$	3-OHC_6H_4	OEt	OEt	93	
		4-$MeOC_6H_4$	2-OHC_6H_4	OEt	OEt	95	
		4-$MeOC_6H_4$	4-MeC_6H_4	OEt	OEt	70	
		4-$MeOC_6H_4$	3-MeC_6H_4	OEt	OEt	87	
		4-$MeOC_6H_4$	2-MeC_6H_4	OEt	OEt	85	

(*continued*)

Table 1. Continued.

Entry	Catalyst	R^1	R^2	R^3	R^4	Yield(%)	Ref
		4-$MeOC_6H_4$	4-$MeOC_6H_4$	OEt	OEt	98	
		4-$MeOC_6H_4$	2-CH_3pyridyl	OEt	OEt	76	
		4-$MeOC_6H_4$	n-Propyl	OEt	OEt	85	
		4-$MeOC_6H_4$	1,2-ethelenediamine	OEt	OEt	50	
		4-$MeOC_6H_4$	3-amino,1-propanol	OEt	OEt	78	
		4-$MeOC_6H_4$	Morpholine	OEt	OEt	—	
		4-$MeOC_6H_4$	Piperidine	OEt	OEt	—	
		4-$MeOC_6H_4$	2-amino,2-phenylacetic acid	OEt	OEt	90	
9	Lewis acid ZnO nanoparticles	Ph	Ph	OEt	OEt	83	[39]
		Ph	4-ClC_6H_4	OEt	OEt	70	
10	Lewis acid Amberlyst-15	3-Indolyl	1-OH,2,6-$Cl_2C_6H_2$	OEt	OEt	84	[40]
		4-$(CH_3)_2NC_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OEt	OEt	86	
		2-OHC_6H_4	1-OH,2,6-$Cl_2C_6H_2$	OEt	OEt	89	
		3-$NO_2C_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OEt	OEt	92	
		2-$OCH_2phC_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OEt	OEt	83	
		3-Indolyl	1-OH,2,6-$Cl_2C_6H_2$	OMe	OMe	89	
		4-$(CH_3)_2NC_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OMe	OMe	90	
		2-OHC_6H_4	1-OH,2,6-$Cl_2C_6H_2$	OMe	OMe	83	
		3-$NO_2C_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OMe	OMe	88	
		2-$OCH_2phC_6H_4$	1-OH,2,6-$Cl_2C_6H_2$	OMe	OMe	85	
11	Bronsted as well as Lewis acid sulfated polyborate	Ph	Ph	OEt	OEt	98	[41]
		2-ClC_6H_4	Ph	OEt	OEt	94	
		3-ClC_6H_4	Ph	OEt	OEt	95	
		4-ClC_6H_4	Ph	OEt	OEt	95	
		2-$NO_2C_6H_4$	Ph	OEt	OEt	93	
		3-$NO_2C_6H_4$	Ph	OEt	OEt	94	
		4-$NO_2C_6H_4$	Ph	OEt	OEt	94	
		2-$MeOC_6H_4$	Ph	OEt	OEt	92	
		4-$MeOC_6H_4$	Ph	OEt	OEt	94	
		4-BrC_6H_4	Ph	OEt	OEt	95	
		4-MeC_6H_4	Ph	OEt	OEt	94	
		4-OHC_6H_4	Ph	OEt	OEt	93	
		2-Thienyl	Ph	OEt	OEt	93	
		5-Me,2-Furyl	Ph	OEt	OEt	95	
		Isonicotinyl	Ph	OEt	OEt	90	
		Cyclohexyl	Ph	OEt	OEt	95	
		Ph	4-ClC_6H_4	OEt	OEt	97	
		Ph	4-BrC_6H_4	OEt	OEt	95	
		Ph	4-$NO_2C_6H_4$	OEt	OEt	93	
		Ph	4-MeC_6H_4	OEt	OEt	97	
		Ph	$PhCH_2$	OEt	OEt	94	

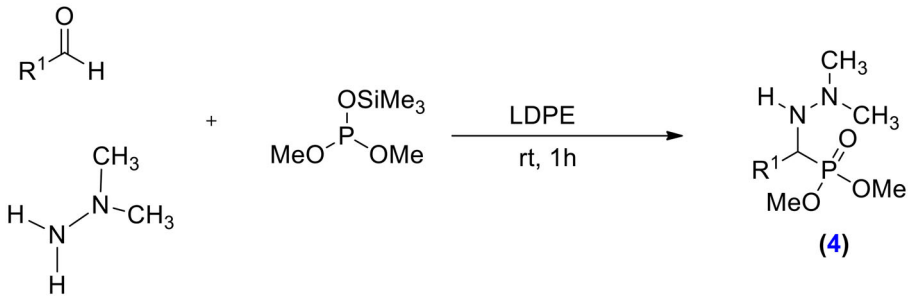
Heydari et al.[43] developed a simple and efficient one-pot method to give *N*-(trimethylsilyloxy)aminophosphonate derivatives (**3**) from aldehydes, hydroxylamines, and dimethyl trimethylsilyl phosphite in Lewis acid lithium perchlorate/diethyl ether solution (LPDE) in high yields.



(3)

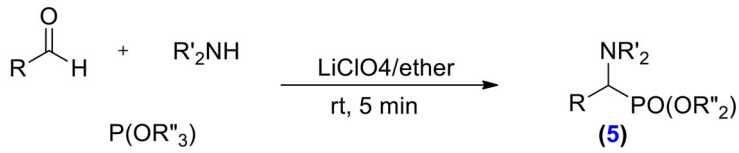
R^1 = *i*-propyl, *n*-propyl, *n*-butyl, *c*-hexyl, *n*-hexyl, phenyl, *p*-MeO-phenyl, 2-Furyl, 3-pyridyl, *trans*-cinnamyl.

Heydari et al.[44] also prepared various hydrazinophosphonates (**4**) on the basis of three-component coupling of aldehydes, *N*,*N*-dimethylhydrazine and dimethyl trimethylsilyl phosphite via Lewis acid $LiClO_4$-catalyzed tandem reactions under moderate reaction conditions.



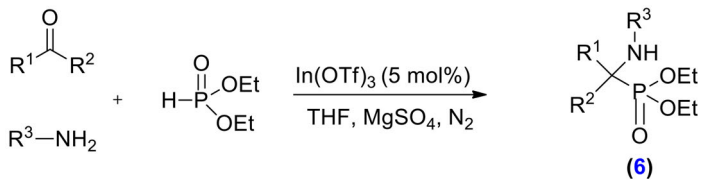
R^1 = *n*-ethyl, *i*-propyl, *n*-propyl, *ter*-butyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *c*-hexyl.

Saidi et al.[45] reported a very mild, efficient and simple method for the synthesis of tertiary α-aminophosphonates (**5**) by reaction of an aldehyde, a secondary amine and trialkyl phosphite in Lewis acid ethereal solution of lithium perchlorate, at ambient temperature with short reaction times.



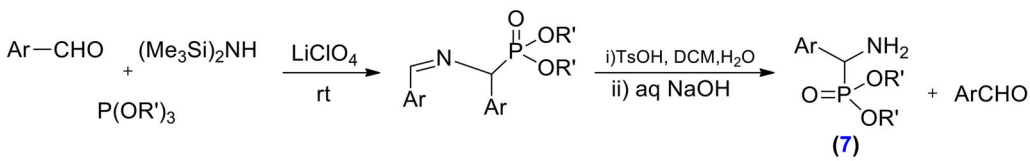
R = Ph, 2,4-diClC_6H_3, o-$MeOC_6H_4$, m-$NO_2C_6H_4$, p-ClC_6H_4, i-propyl.
R'_2NH = pyrrolidine, diethylamine, piperidine,Me_2NSiMe_3.
R" = Et, Me.

Ghosh et al.[46] synthesized α-aminophosphonates (**6**) from nitro-substituted anilines, aldehydes and diethyl phosphite by employing 5 mol% of $In(OTf)_3$ as Lewis acid. The method was equally effective for the generation of α-aminophosphonates from various carbonyl compounds and other amines.



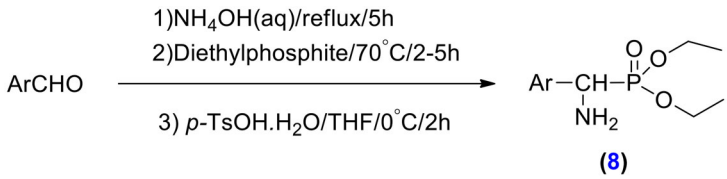
R^1 = Ph, *m*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4$, m-OHC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *trans*-cinnamyl, *i*-propyl, C_9H_{19}, Cyclohexanone.
R^2 = H
R^3 = Ph, *m*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4$, $PhCH_2$, *p*-$MeOC_6H_4$.

Saidi et al.[47] described a novel and mild protocol for the one-pot, three-component synthesis of primary α-aminophosphonates (**7**) under solvent-free reaction conditions and in the presence of solid $LiClO_4$ as Lewis acid from an aldehyde, hexamethyldisilazane and trialkyl phosphite with high yields and within short reaction times.



Ar = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *m*-$NO_2C_6H_4$, *o*-$MeOC_6H_4$, *p*-BrC_6H_4.
R' = Et, Me.

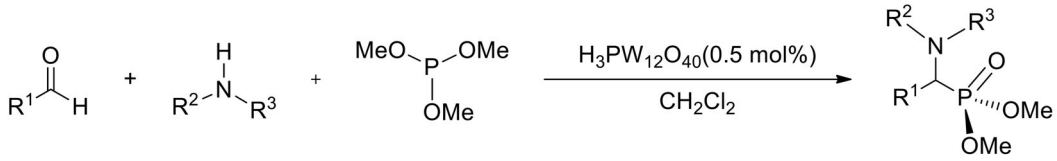
Kaboudin et al.[48] have developed a Lewis acid mediated simple, efficient, and possible industrial process for the synthesis of 1-aminophosphonic acids by the treatment of aromatic aldehydes with ammonia and reaction with diethyl phosphite which gives diethyl *N*-(arylmethylene)-1-amino-1-arylmethanephosphonates. The latter can be easily hydrolyzed to diethyl 1-amino-1-arylmethanephosphonates. This method is easy, rapid, and good yielding for the synthesis of 1-aminoalkylphosphonates (**8**) from simple starting materials.



(8)

Ar = Ph, *p*-ClC_6H_4, *p*-isopropylC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *m*-ClC_6H_4, *m*-MeC_6H_4, 1-Naphthyl, 2-Naphthyl, *n*-C_6H_{13}.

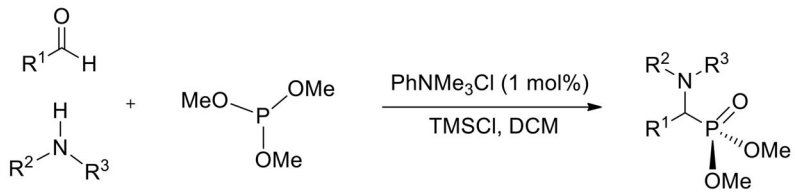
Heydari et al.[18] described a new and highly flexible procedure for the synthesis of α-aminophosphonates (**9**) from *in situ* generated imines or iminium salts by use of the Bronsted acid dodecatungstophosphoric acid (0.5 mol%) as catalyst in dichloromethane at room temperature in short reaction times.



(9)

R^1 = ter-butyl, n-pentyl, phenyl, 4-Cl-phenyl, 4-NO2-phenyl, 4-pyridyl, 4-Me-phenyl, 2-Furyl, i-propyl.
R^2 = H, ethyl. R^3 = phenyl, benzyl, ethyl.

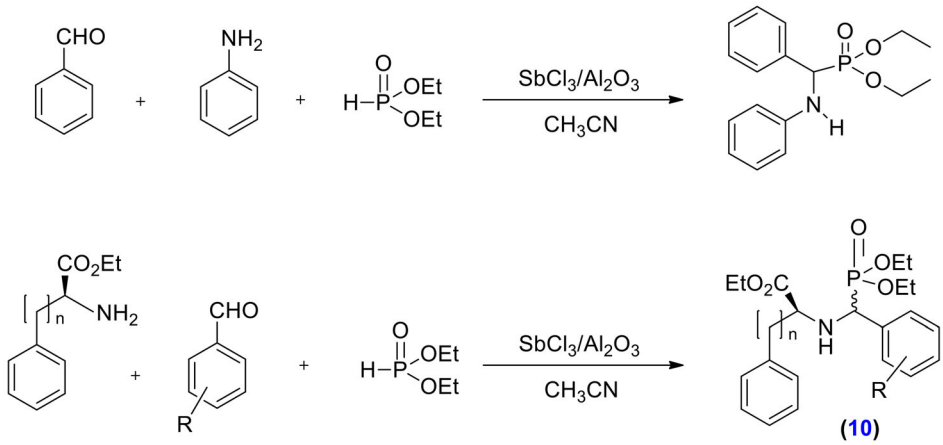
A new and highly flexible procedure[49] was described for the synthesis of α-amino-α-hydrazino-, and α-*N*-hydroxyaminophosphonates (**9**) by reaction between trimethyl phosphite and *in situ* generated imines (iminium salts, oximes, hydrazones, nitrones) by use of phenyltrimethylammonium chloride as catalyst (1 mol%) in reagent grade dichloromethane at 40 °C.



(9)

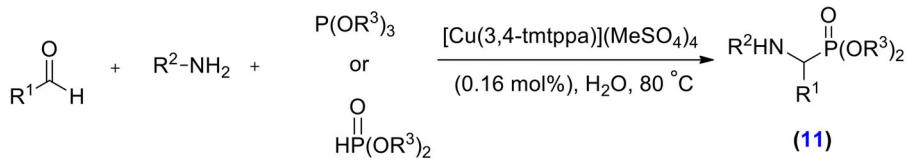
R^1 = n-propyl, n-pentyl, phenyl, 4-Clphenyl, 4-NO_2phenyl, phenylCH_2CH_2, 2-Furyl, i-propyl, Cinnamyl.
R^2 = H, Ethyl, OH. R^3 = phenyl, ethyl, phenylCH_2CH_2, O-TMSi, NMe_2.

Kapoor et al.[50] described $SbCl_3$ adsorbed on Al_2O_3 to be an efficient and recyclable Lewis acid catalyst for the promotion of three-component coupling reactions of aldehydes (aromatic and aliphatic), amines (aromatic and aliphatic amines) and esters of (*S*)-α-aminoacids) and dialkyl phosphites to afford the corresponding α-aminophosphonates (**10**) in high yields. The ethyl ester of (*S*)-phenylalanine led to the corresponding α-aminophosphonate as (*S*,*S*)-diastereoisomer formed in predominance over the (*S*,*R*)-diastereoisomer.



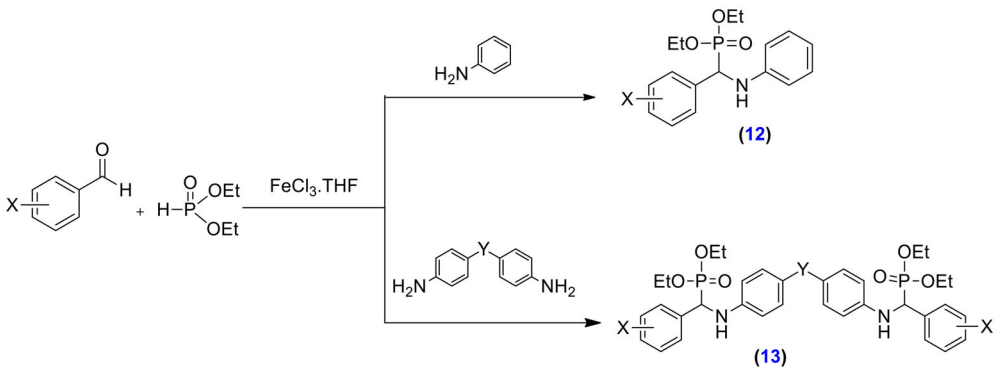
R = Ph, *p*-MeC6H4, 3,4,5-triMeOC$_6$H$_2$, *p*-NO$_2$C$_6$H$_4$, trans-cinnamyl, *p*-MeOC$_6$H$_4$, butyryl, *m*-MeC$_6$H$_4$, *p*-ClC$_6$H$_4$, *o*-ClC$_6$H$_4$.
Amines = Aniline, Benzylamine, *p*-toluidine, 2-aminopyridine, piperidine, 2-aminobenthiazole, ethyl ester of S- phenyl glycine.
phosphite = ethyl phosphite, methyl phosphite.

A new, convenient and highly flexible procedure[51] was reported for the synthesis of diethyl α-aminophosphonates (**11**) in water by three-component, one-pot reaction of aldehydes, amines, tri/dialkyl phosphites in the presence of a low amount of [Cu(3,4-tmtppa)](MeSO$_4$)$_4$ (0.16 mol%) as a highly stable and reusable catalyst.



R^1 = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,6-diClC$_6$H$_3$, 2-Thienyl, 2-Furyl, Cinnamyl, propyl, 2-Naphthyl, terephethyl.
R^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Benzyl, 4-NH$_2$C$_6$H$_4$. R^3 = Et, Me, i-propyl.

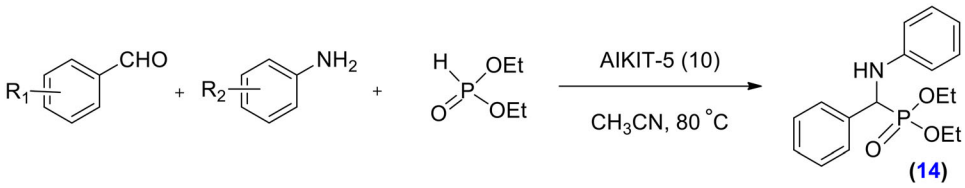
Rezaei et al.[52] described the highly efficient synthesis of α-aminophosphonates (**12**) *via* a three-component system comprising of aldehydes, amines and diethyl phosphite catalyzed by FeCl$_3$·THF-solution as Lewis acid. This protocol was also applied to the one-pot preparation of bis(α-aminophosphonates) (**13**). This method is advantageous because of the eco-friendly mild reaction conditions and the high yields of the produced α-aminophosphonates.



X= Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-OHC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-MeO-4-OHC$_6$H$_3$, Cinnamyl.
Amines= Aniline, N-Methylaniline. Y= CO, O, CH$_2$, SO$_2$.

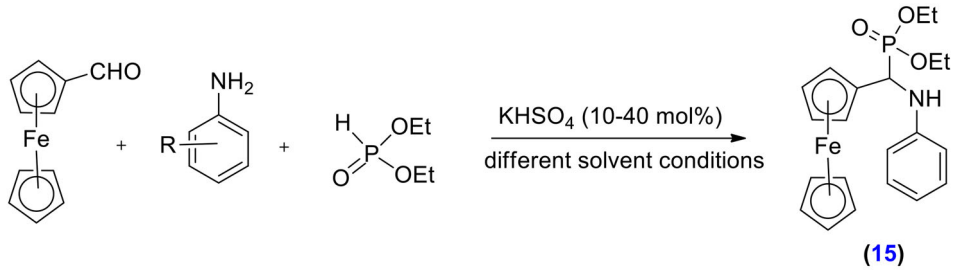
Subba Reddy et al.[53] described the preparation of α-aminophosphonates (**14**) through the three-component coupling reaction of aldehydes, amines, and diethyl phosphite by using 3D mesoporous aluminosilicate nanocages as Lewis acid

catalyst which gave excellent yields with a high selectivity in a short reaction time due to the high acidity of the 3D pores and a huge space in the nanocages.



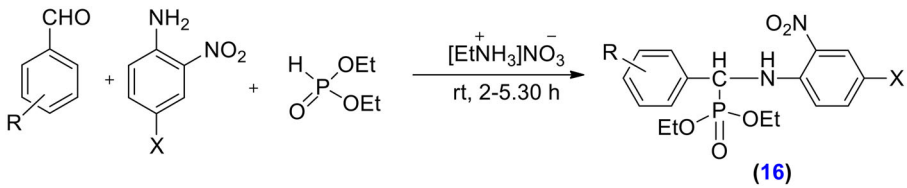
R_1 = Ph, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, *o*-$NO_2C_6H_4$, *o*-OHC_6H_4, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, Pyridyl, 2-Thienyl, *n*-Propyl, *n*-Pentyl, *n*-Hexyl.
R_2 = Ph, 3,4-dimethoxyphenyl ethyl, C_8H_7O, $C_{13}H_9O$, Piperidine.

Perumal et al.[54] have accomplished a simple and efficient method for the synthesis of α-aminophosphonates (**15**) from aromatic aldehydes, diethyl phosphite, and aromatic or aliphatic amines using acidic potassium hydrogen sulfate as a catalyst under solvent free conditions.



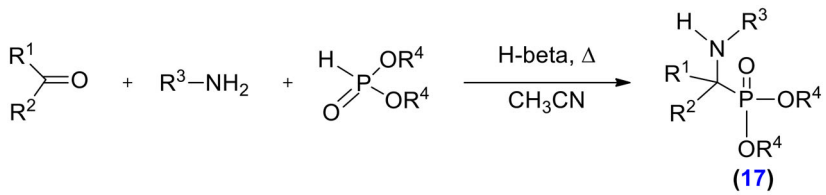
R= Ph, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, 3,4-diFC_6H_3, *p*-OHC_6H_4, Picolinyl.

Novel α-aminophosphonates[55] (**16**) were synthesized by the three-component one-pot reaction of aldehydes, amines and diethyl phosphite at room temperature in the presence of the ionic liquid ethyl ammonium nitrate as catalyst and solvent. Among the various catalysts, the preparation of ethyl ammonium nitrate is an eco-friendly, cost effective and recyclable catalyst.



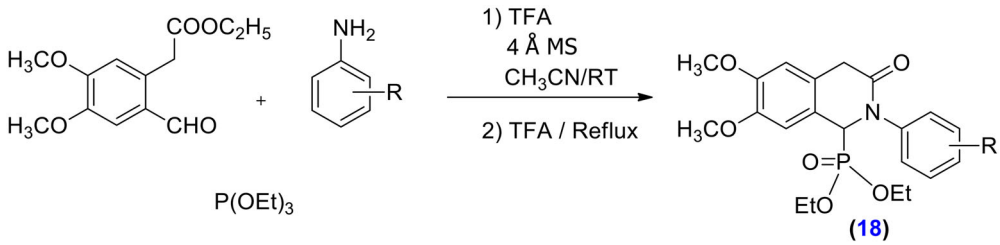
R = 4-OHC_6H_4, 3-MeO-4-OHC_6H_3, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 2-OHC_6H_4, 2-NO_2-5-OHC_6H_3, 3,4-di$MeOC_6H_3$, 3-ClC_6H_4, 2-$COOHC_6H_4$, 3-Indolyl. X=Cl, I.

Choudhary et al.[13] synthesized α-aminophosphonates (**17**) by the reaction between carbonyl compound, primary amine, and substituted phosphite via Kabachnik-Fields reaction with high yields and in a short period, using Lewis acid H-beta zeolite as a reusable catalyst.



R^1 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Cinnamyl, 3-indolyl, *n*-butyl, Ph, 4-MeC_6H_4, 2-Furyl.
R^2 = H, CH_3, Cyclohexanone.
R^3 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Benzyl, 3-$NO_2C_6H_4$, 4-BrC_6H_4, *n*-Propyl.
R^4 = Et, Me, DiBenzyl.

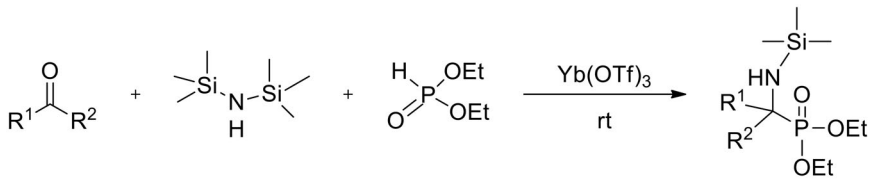
Borse et al.[56] described a convenient one-pot three-component synthesis of novel *N*-phenylisoquinolone-1-phosphonate derivatives (**18**) by reacting aldehydes with substituted anilines and triethyl phosphite in acetonitrile using trifluoroacetic acid as catalyst in good yields.



(18)

R= 4-F, 4-Cl, H, 4-Br, 3-Cl, 4-CH_3, 4-C_2H_5.

Doo Ok Jang and coworkers[57] developed an efficient three-component one-pot synthesis of *N*-silylated α-aminophosphonates and α,α-disubstituted α-aminophosphonates (**19**) using $Yb(OTf)_3$ as Lewis acid catalyst at room temperature under mild conditions.

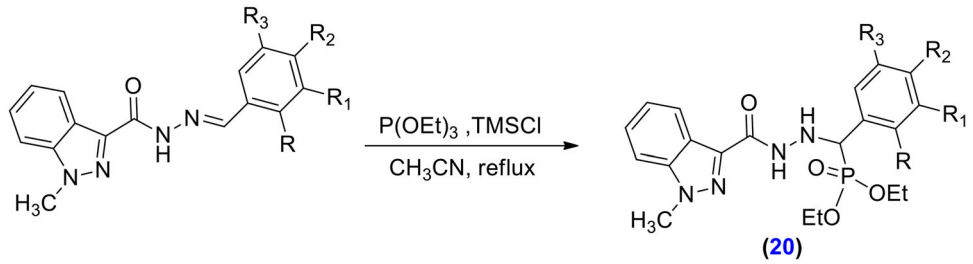


(19)

R^1 = Ph, *p*-$MeOC_6H_4$, *p*-N-acetylC_6H_4, *p*-$NO_2C_6H_4$, *iso*-Butyl, *n*-Butyl.

R^2 = H, CH_3, Ph, Cyclohexanone, Cyclohexenone, 2-Dodecanone, Methylvinylketone.

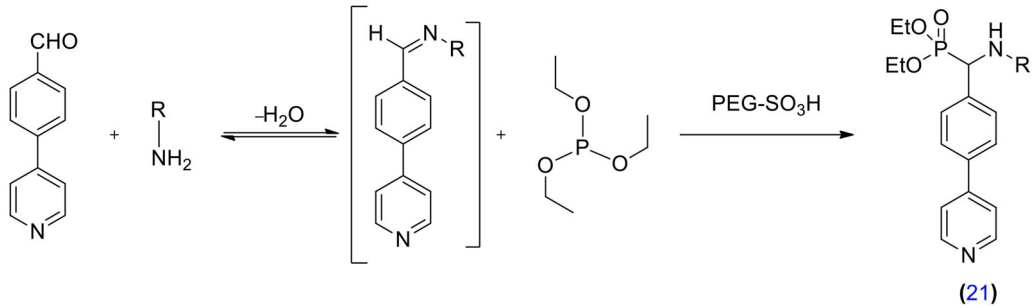
A new series of α-aminophosphonates[58] (**20**) containing a bioactive indazole moiety was synthesized in two steps. In the first step, the imine of the indazole component was synthesized and in the next step it was converted to α-aminophosphonates using chlorotrimethylsilane (TMSCl) and triethyl phosphite.



(20)

R = H, Br. R_1 = H, F. R_2 = H, CF3. R_3 = H.

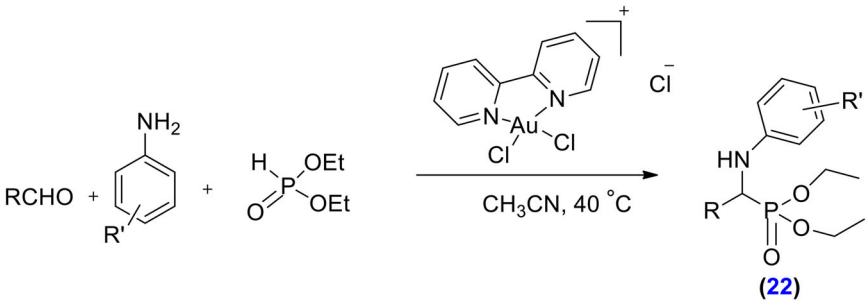
Reddy et al.[59] reported the one-pot three-component, Lewis acid PEG-SO_3H catalyzed synthesis of structurally diversified α-aminophosphonates (**21**) by use of 4-(pyridin-4-yl)benzaldehyde and triethyl phosphite with various primary amines with high yields by the Kabachnik-Field's reaction.



(21)

R = Ph, 3-Cl-4-FC_6H_3, 3-BrC_6H_4, 3-NO_2-4-ClC_6H_3, 3-$NO_2C_6H_4$, 4-Pyridinyl, 3-pyridinyl methyl, 2-thiazolyl, 2-Benzthiazolyl, 6-NO2-Benzthiazolyl.

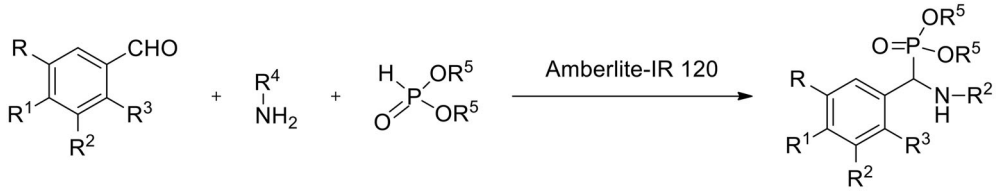
Chengjian Zhu et al.[60] have developed an efficient protocol for the construction of C-P bonds under formation of (**22**) with high yields under mild conditions by employing the three-component reaction of an amine, an aldehyde and a dialkyl phosphite, catalyzed by a gold complex.



(**22**)

R = 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, Ph, 4-ClC_6H_4, 2-Furyl, Ethyl.
R' = H,CH_3, OCH_3, Cl.

A small library of structurally diversified α-aminophosphonates[61] (**23**) has been synthesized by reacting alkyl/aryl aldehydes, alkyl/aryl amines and alkyl/aryl phosphites in one-pot reactions catalyzed by the Lewis acid Amberlite-IR 120 resin.



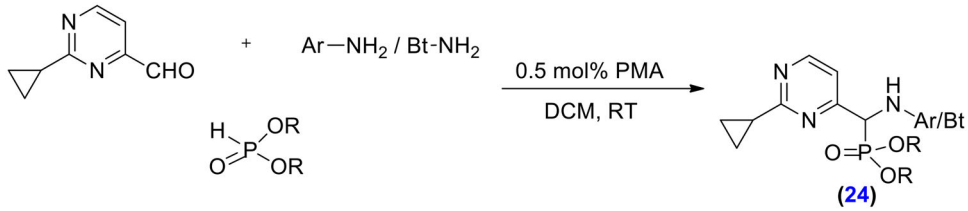
(**23**)

R = R^1 = R^2 = R^3 =H, R, R^1 =OCH_2O R^2 = R^3 = H, R = R^1 = R^2 = H, R^3=OMe,
R = R^2 = R^3 =H, R^1= F, R = R^3 = H, R^1 = R^2 =OMe, R = R^3 = H, R^1 =OMe, R^2 = OH
R = R^2 = R^3 = H, R^1 =NO2, R = R^1 = R^3 =H, R^2 = NO2, R = R^2 = R^3 = H, R^1= Me
R = R^2 = R^3 = H, R^1= OMe, Citral.

R^4 = Bn, 4-OHC_6H_4, 2-OHC_6H_4, 2,6-diMeC_6H_3, 3,4-$OCH_2CH_2OC_6H_3$,*n*-C_3H_7, 3,4-$OCH_2OC_6H_3$, 3-FC_6H_4, 2-MeC_6H_4, 3-ClC_6H_4, Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$,(R)-1-Phenylethyl, (S)-1-Phenylethyl.

R^5 = Et, n-Bu, Ph, Allyl.

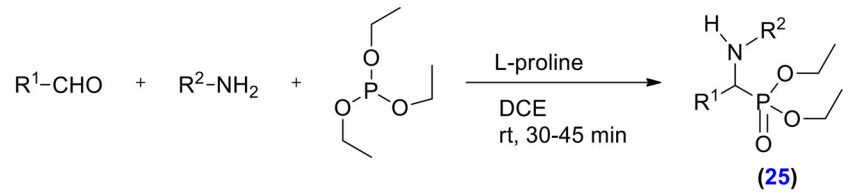
A convenient synthesis of α-aminophosphonates (**24**) has been developed by Reddy et al.[62] who used 0.5 mol % of phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) as Lewis acid catalyst for the coupling of 2-cyclopropylpyrimidin-4-carbaldehyde, anilines/benzothiazole amines and different phosphites in dichloromethane at room temperature in good to excellent yields within short reaction times.



(**24**)

R = Ph, Bu, Et, Me. Ar = Ph, Cl-Ph, Br-Ph, CH_3-Ph. Bt = Benzothiazol.

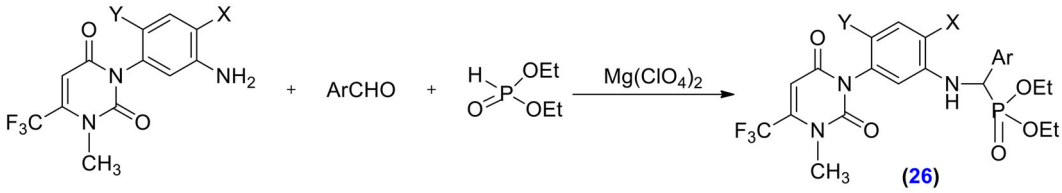
An efficient and robust method[63] has been developed for the synthesis of α-aminoalkanephosphonates (**25**) by treatment of aldehydes, amines and triethyl phosphate at room temperature by employing L-proline as an organocatalyst at room temperature. The products are formed in excellent yields (82-94%) within 30–45 min.



(25)

R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-isoPropylC_6H_4, 4-Cl,3-FC_6H_3, 2,4-$Cl_2C_6H_3$, 4-BrC_6H_4, iso-Propyl, Pentyl.
R^2 = Ph, 4-MeC_6H_4, 4-OHC_6H_4, 4-MeOOC-C_6H_4.

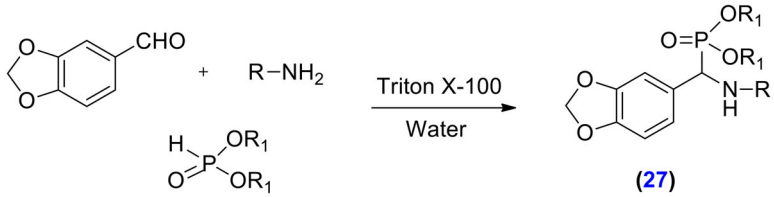
Che et al.[64] were designed and synthesized a series of novel α-aminophosphonates (**26**) containing a uracil moiety by use of the Lewis acid, $Mg(ClO_4)_2$ as catalyst in a the Kabachnik-Fields reaction.



(26)

X = Cl. Y= Cl, H.
Ar = Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-MeC_6H_4.

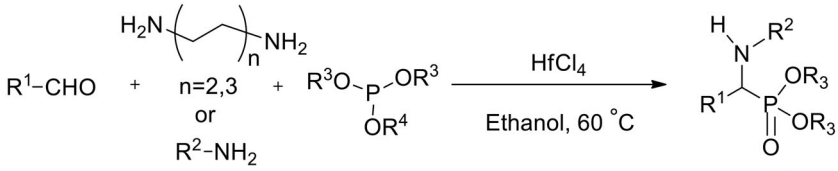
A convenient synthesis of α-aminophosphonates (**27**) has been developed by Reddy *et al.*[65] *via* a nonionic surfactant Triton X-100 catalyzed coupling of aldehyde, amines and dialkyl phosphites at 70 °C in aqueous medium.



(27)

R = Ph, 4-ClPh, 4-BrPh, 3-Cl-4-FPh,4-MeOPh.
R_1= Et, Me.

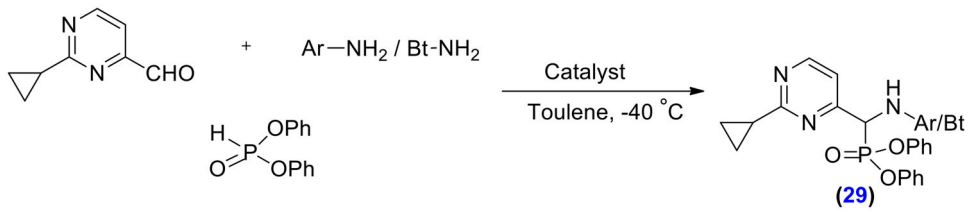
Li et al.[66] have reported an efficient protocol for one-pot synthesis of α-aminophosphonates (**28**) via three-component reaction of aldehyde, amine and phosphite using only 2 mol % $HfCl_4$ as the catalyst. The NMR evidence strongly indicated the catalytic roles of Hf^{4+} on the activation of aldehyde, phosphite, and imine intermediate.



(28)

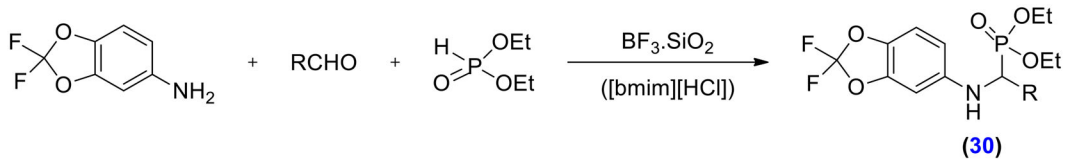
R^1, R^2 = alkyl (or) aryl roups
R^3 = Me, Et, Ph
R^4 = H (or) R^3

Reddy et al.[67] reported camphor-derived thioureas as Lewis base organocatalysts for the reaction of 2-cyclopropylpyrimidin-4-carbaldehyde with amines, and diphenyl phosphite to yield the corresponding enantioselective α-aminophosphonates (**29**) in 74–82% yields and 14–35% ee.



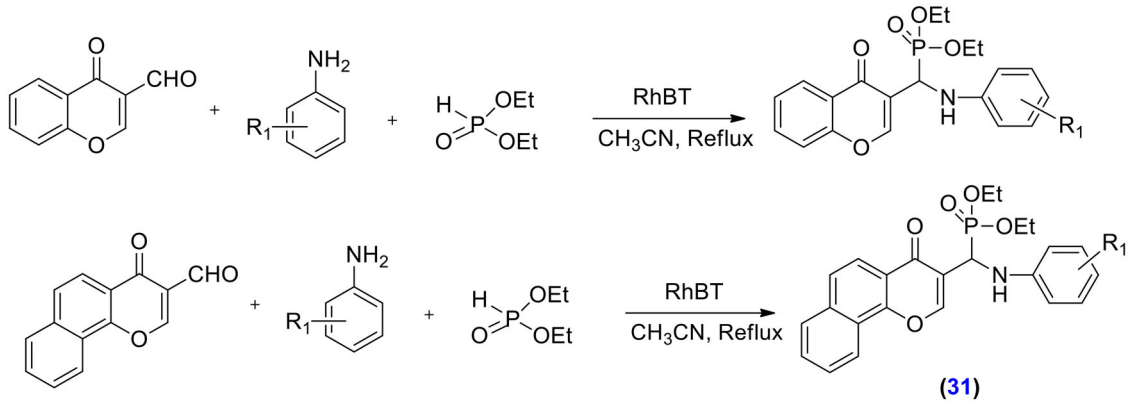
Ar= Ph, 4-ClPh, 4-MePh. Bt=Benzothiazol.

A novel and robust method was developed for the synthesis of α-aminophosphonates[68] (**30**) by the three-component condensation reaction of 5-amino-2,2-difluoro-1,3-benzodioxole, aromatic aldehydes, and diethyl phosphite. Silica-supported boron trifluoride (BF_3-SiO_2) in ionic liquid ([bmim][HCl]) was used as Lewis acid at room temperature to give good to excellent yields within short reaction times.



R= 4-BrC_6H_4, 4-ClC_6H_4, 4-$EtOC_6H_4$, 4-OHC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-isopropylC_6H_4, 2-OHC_6H_4, 2-$NO_2C_6H_4$, 3-ClC_6H_4, 3-$MeOC_6H_4$, 5-Cl-2-OHC_6H_3,Picolinyl.

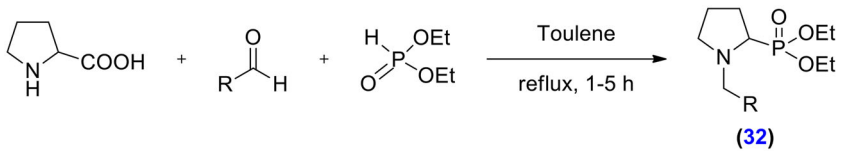
Jaiyeola et al.[69] described a new series of α-aminochromonephosphonates (**31**) (ACPs) which were obtained from chromone based aldehydes, aniline derivatives and diethyl phosphite with RhBT as catalyst.



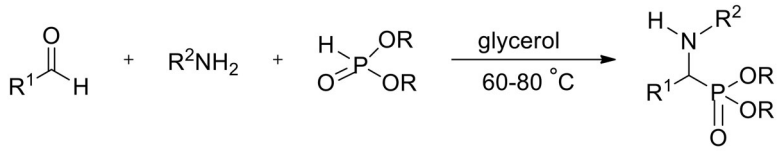
R_1 = H, 4-Cl, 4-Br, 2-NO_2, 2-Me, 3,4-Cl, 4-Me, 2-MeO, 4-MeO, 3-NO_2.

Synthesis of α-aminophosphonates in catalyst free conditions in solvent medium

Kaboudin et al.[70] described a simple, efficient, and feasible method for the synthesis of α-aminophosphonates (**32**) *via* a three-component, catalyst-free decarboxylative coupling of aminoacids with aldehydes and H-dialkyl phosphite. Treatment of aminoacids with aldehydes and diethyl phosphite in the absence of catalyst, base, and ligand give α-aminophosphonates in moderate to good yields.



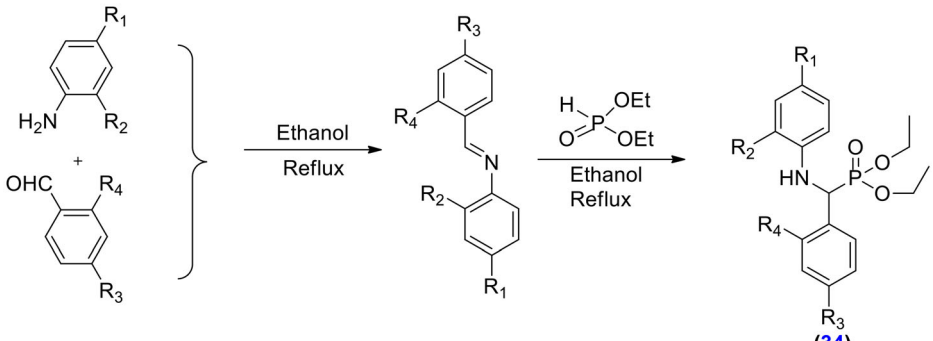
Azizi et al.[71] described a simple and efficient catalyst-free method for the synthesis of α-aminophosphonates (**33**) via condensation of amines, phosphites, and carbonyl compounds with high purity using glycerol as a solvent. The method does not require a toxic catalyst.



(**33**)

R^1 = Ph, 2-Thienyl, Cyclohexanone.
R^2 = Ph, Bu, $O(CH_2CH_2)_2NH$.
R = Me, Et, Ph.

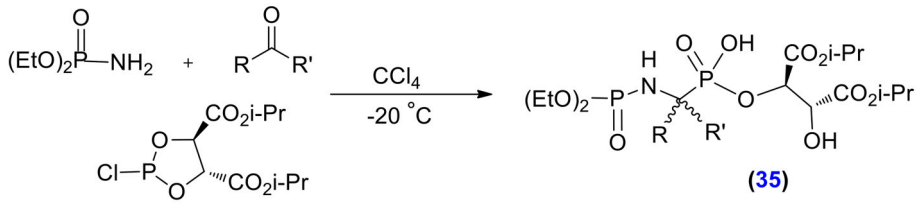
Wang et al.[72] prepared new α-aminophosphonate *N*-derivatives (**34**), and their binding interactions have been investigated by UV-visible and fluorescence emission spectrometry.



(**34**)

R_1 = Cl, R_2 = H, R_3 = H, R_4 =OCH_3
R_1 = Cl, R_2 = H, R_3 = OCH_3, R_4 =H
R_1 = Cl, R_2 = H, R_3 = H, R_4 =NO_2
R_1 = Cl, R_2 = H, R_3 =NO_2, R_4 =H
R_1 = NO_2, R_2 = H, R_3 = Cl, R_4 =H

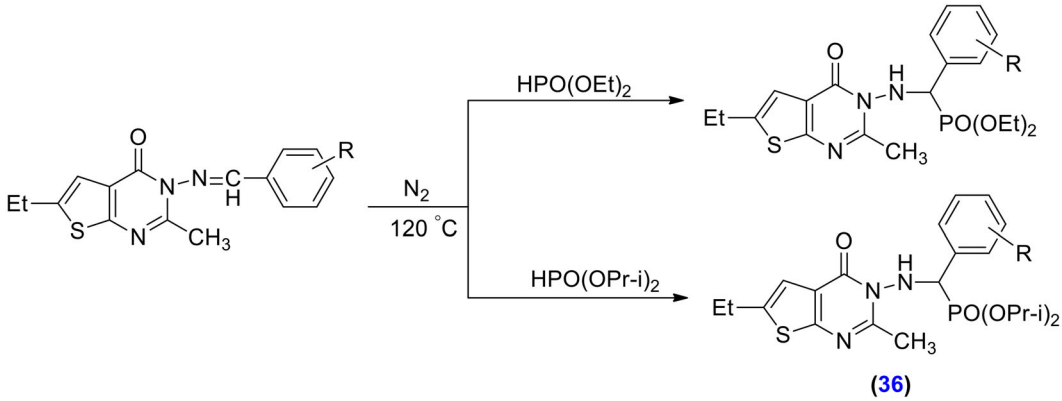
Fang et al.[73] reported the synthesis of α-aminophosphonates (**35**) as a mixture of two diastereoisomers in moderate to good yield by the one-pot three-component reaction of chiral isopropyl (*4R,5R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate with several aromatic aldehydes and diethyl phosphoramidate in CCl_4 at −20 °C. When acetophenone was used, the quaternary α-aminophosphonate was obtained in 62% yield and 67:33 diastereoisomeric ratio.



(**35**)

R = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$.
R' = H, Me.

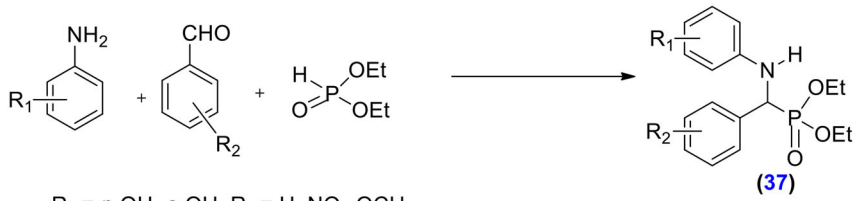
Guo et al.[74] were designed and synthesized two series of thieno[2,3-d]pyrimidine derivatives (**36**) in which bioactive α-aminophosphonate subunits were introduced at the N3 position through an N–N bond connection.



(36)

R = H, 3-CH_3, 4-CH_3, 3-NO_2, 4-NO_2, 3-Cl, 4-Cl, 3-Br, 4-Br, 4-OCH_3, 2,4-Cl_2.

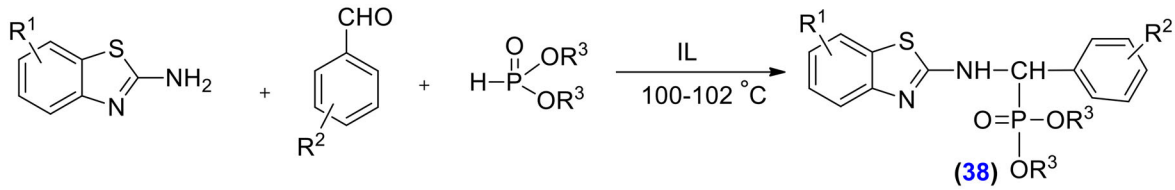
A series of α-aminophosphonates[75] (**37**) containing aminophenol substituents have been synthesized *via* Kabachnik-Fields reaction. DFT calculations on the B3LYP/6-31G (d,p) level have been used to analyze the electronic and geometric characteristics deduced for the stable structure of the compounds and also correlated the principal quantum chemical descriptors (HOMO, LUMO, MESP).



(37)

R_1 = *p*-OH, *o*-OH. R_2 = H, NO_2,OCH_3.

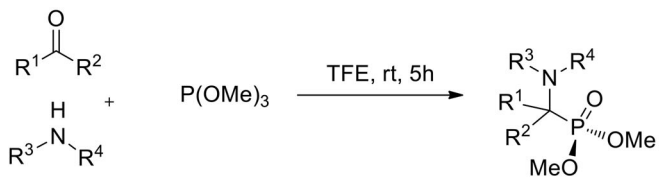
Song et al.[76] synthesized α-aminophosphonates (**38**) containing benzothiazole and fluorine substituents by Mannich-type addition in ionic liquid media with high yield and short reaction time.



(38)

R^1 = 4-Me, 6-MeO. R^2 = 2-F, 4-CF_3. R^3 = Et, Me, n-Pr, n-Bu.

Heydari et al.[77] synthesized α-aminophosphonates (**39**) by one-pot, three-component coupling reactions of aldehydes or ketones, amines and trimethyl phosphite in presence of trifluoroethanol as efficient and recyclable medium in high yields. This protocol does not require the use of an acid or base catalyst.

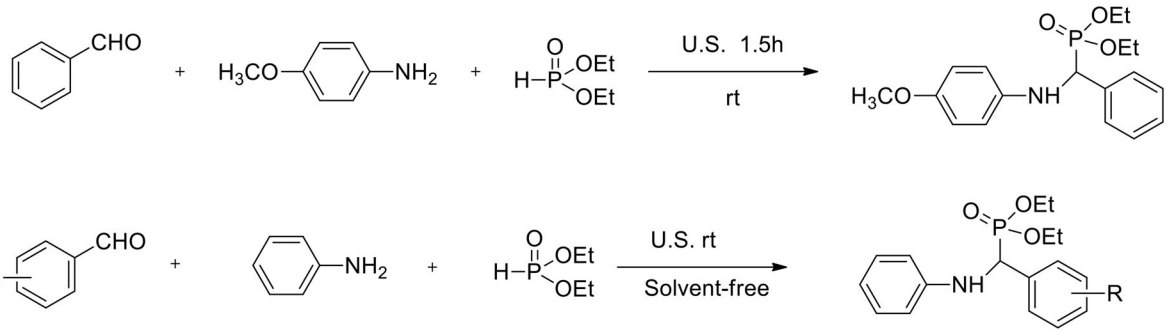


(39)

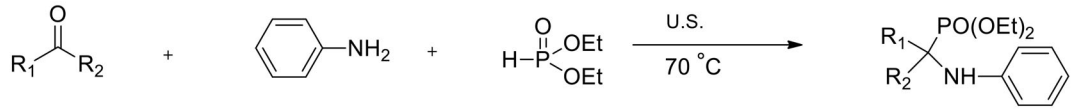
R^1 = Ph, 4-ClC_6H_4, 4-CNC_6H_4, propyl, 2-Furyl, Cyclohexanone, Cyclopentanone.
R^2 = H. R^3 = Ph, $PhCH_2$, 4-ClC_6H_4, 4-$MeOC_6H_4$. R^4 = H, Morpholine, Dibenzyl amine.

Synthesis of α-aminophosphonates under solvent free conditions

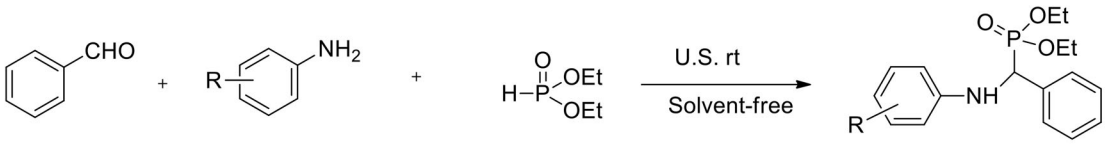
Min Xia et al.[78] prepared α-aminophosphonates (**40**) in good to excellent yields by the three-component coupling of aldehydes, amines and diethyl phosphite in a one-pot procedure under ultrasound-assisted solvent-free and catalyst-free conditions.



R= 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 2-Furyl, Cinnamyl, isopropyl.



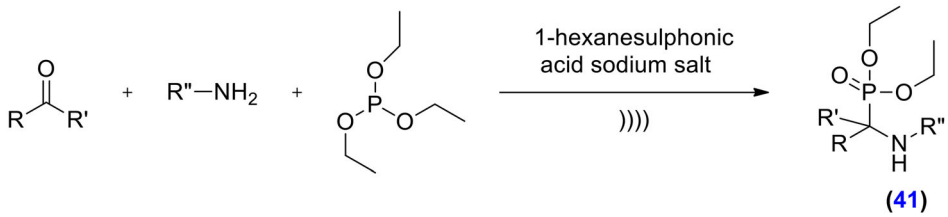
R_1COR_2= Cyclohexanone, 2-butanone, Acetophenone.



(40)

R= 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 3-$CF_3C_6H_4$, Benzyl, Butyl, Piperidine.

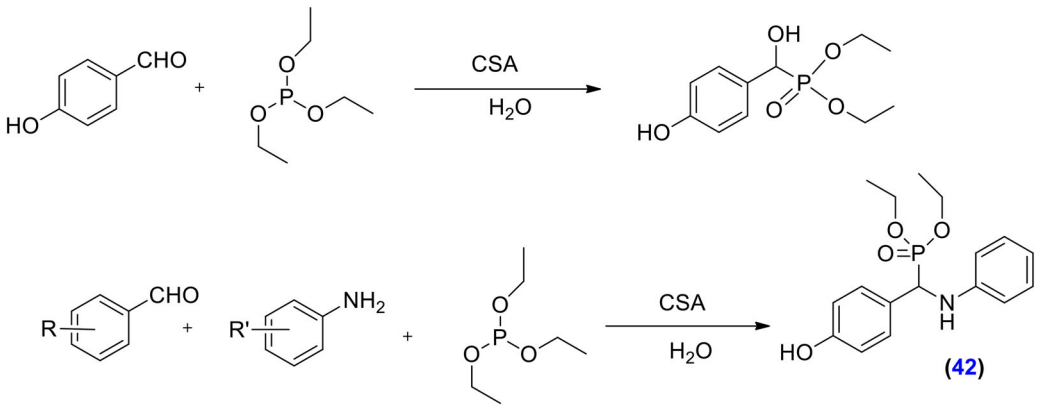
A simple, efficient, inexpensive, eco-friendly and robust method has been reported for the green synthesis of α-aminophosphonates[79] (**41**) by the coupling of aldehydes/ketone, an amine and triethyl phosphite in the presence of sodium hexane-1-sulphonate as a catalyst under ultrasound irradiation to furnish the desired product in good to excellent yield under solvent-free condition. This catalyst provides clean conversion, greater selectivity and easy workup which make this protocol practical and economically attractive.



(41)

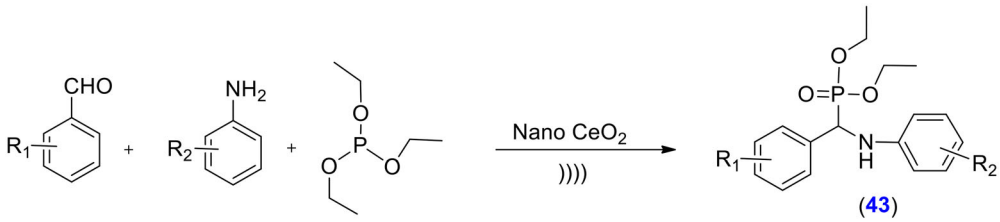
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2,6-$Cl_2C_6H_3$, 3-ClC_6H_4, 4-OHC_6H_4, 2-Furyl, 2-Thienyl, Cyclohexanone, Acetophenone. R' = H, R
R" = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$.

Shingare and coworkers[80] demonstrated the successful implementation of ultrasound irradiation for the rapid synthesis of α-hydroxy- and α-aminophosphonates (**42**) in the presence of the novel catalyst camphor sulfonic acid.



R= 4-OHC_6H_4, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3,4-MethelenedioxyC_6H_3, 2-Furyl, 2-Cl-3-quinolinyl, Tetrazolo[1,5-*a*]-4-quinolinyl.
R'= Ph, 4-$CH_3C_6H_4$, 4-FC_6H_4.

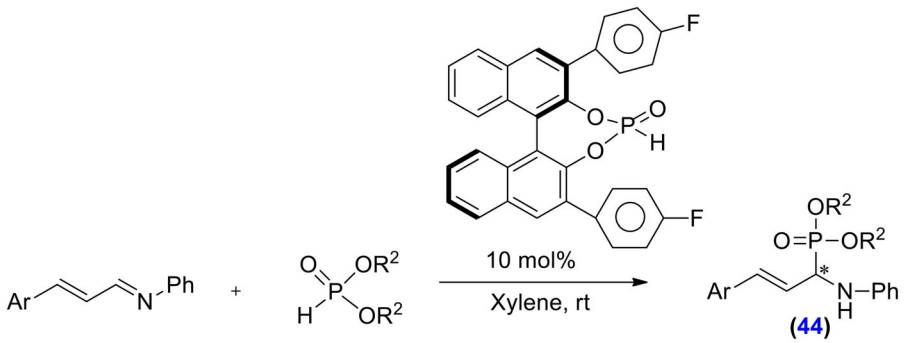
A simple, efficient and general method[81] has been developed for the one-pot three-component syntheses of α-aminophosphonates (**43**) from aldehydes, amine and triethyl phosphite by employing CeO_2 nanoparticles as catalyst under ultrasound irradiation and solvent-free condition. This catalyst provides cleaner conversion, short reaction time and high selectivity which makes the protocol feasible and economical viable.



R_1 = Ph, 4-ClC_6H_4, 4-OHC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-Furyl.
R_2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-OHC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4, Benzyl, Pyridyl.

Miscellaneous synthesis of α-aminophosphonates

Xu et al.[82] described the asymmetric synthesis of α-aminophosphonates (**44**) under mild conditions of dialkyl phosphites on aldimines derived from cinnamaldehyde by using the inexpensive chiral organocatalyst (R)-3,3′-bis[4-fluorophenyl]-1,1′-binaphthyl phosphate in moderate yields (30–65%) and enantiomeric excess (8.4–61.9%).

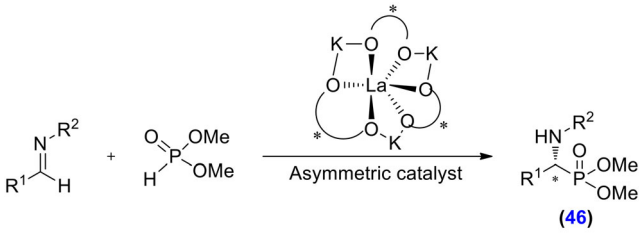


Ar = Ph, 2-FC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4.
R^2 = Et, n-Pr, i-Pr, n-Bu.

Kaur et al.[83] reported various chiral α-aminophosphonates (**45**) in excellent yields (94-97%) and diastereoselectivities (93:7–99:1) by reacting chiral *N*-phosphonylimines with lithium phosphites.

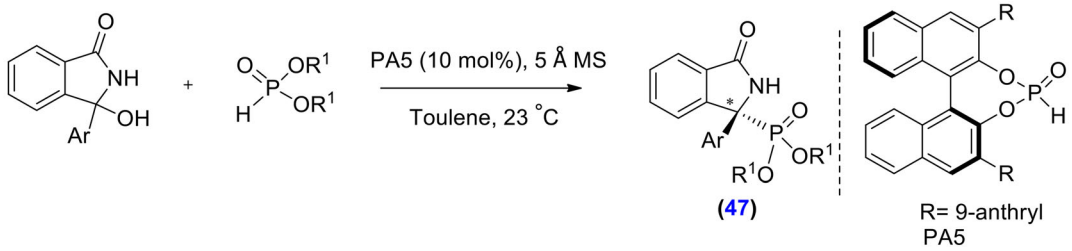
Ar= Ph, 2-ClC$_6$H$_4$, 2-FC$_6$H$_4$, 2-BrC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$.

Sasai and coworkers[84] accounted the first example of a catalytic asymmetric hydrophosphonylation to imines using lanthanoid-potassium-BINOL heterobimetallic complexes (LnPB, Ln = lanthanoid metal) to afford optically active α-aminophosphonates (**46**) in good to high enantiomeric excess.



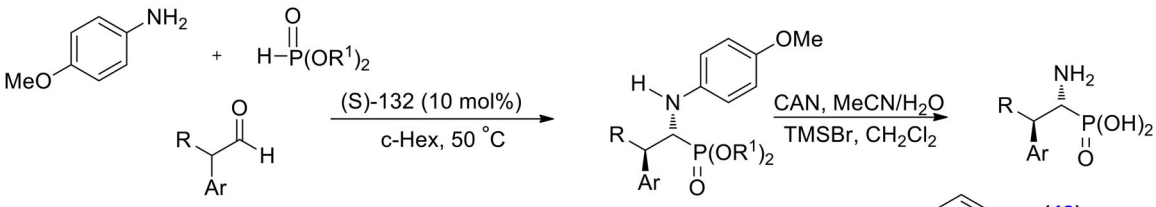
R^1 = Et, *i*-Pr, Me, C$_5$H$_{11}$, *trans*-Cinnamyl, Cyclohexyl.
R^2 = Tr, DAM, CHph$_2$, p-MeOC$_6$H$_4$.

A novel and efficient method was described for the synthesis of various α-aminophosphonates[85] (**47**) with a quaternary stereogenic centers embedded in isoindolinone motifs in high yields with excellent enantiomeric ratios (up to 98.5:1.5 e.r.) via asymmetric hydrophosphonylation of *in situ* generated ketimines by employing BINOL-derived phosphoric acid as chiral catalyst.



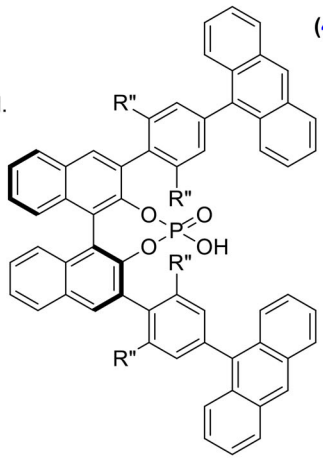
Ar = 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 4-OBnC$_6$H$_4$, 4-O^{i}PrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$, 3,4-diMeOC$_6$H$_3$
R^1 = Me, Et, CH$_2$CF$_3$, Ph.

Cheng et al.[86] furnished the α-aminophosphonates (**48**) by one-pot three-component reaction of 2-arylalkanecarbaldehydes, *p*-anisidine, and di(pent-3-yl) phosphite in the presence of chiral Bronsted acid (*S*)-132 (10 mol %) in cyclohexane at 50 °C, with high diastereoselectivity and moderate to high enantioselectivity. This process combines a dynamic kinetic resolution with the parallel creation of an additional stereogenic center. Cleavage of the *p*-methoxyphenyl and phosphonic ester groups with cerium ammonium nitrate (CAN) and TMSBr gave the α-aminophosphonic acid in 54% yield.



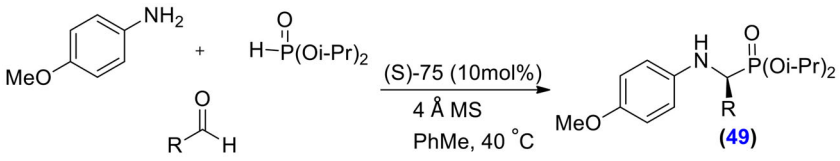
(48)

R= *c*-Pent, Me, Et, *i*-Pr, c-Hex. R^1 = pent-3-yl
Ar= Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 2-Naphthyl, 2-Thienyl.



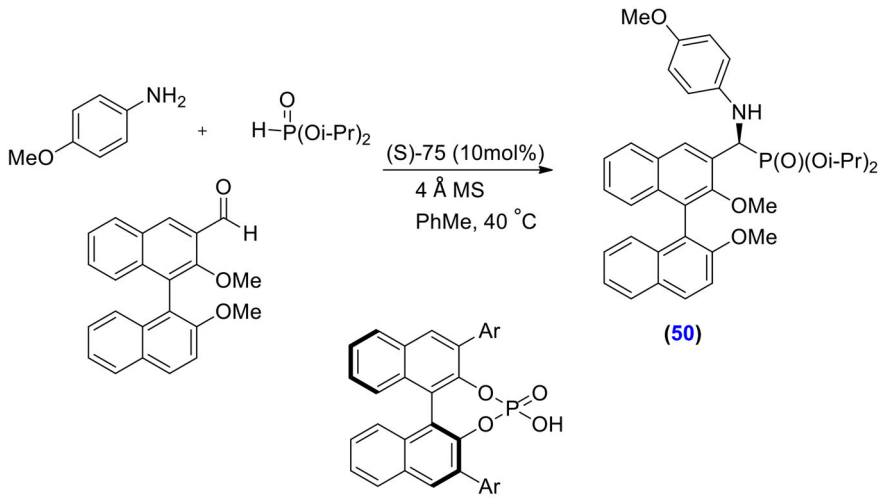
(S)-132, R" = i-pr

Wang et al.[87] synthesized α-aminophosphonates (**49**) in moderate yields and enantioselectivity by asymmetric one-pot three-component reaction of aldehydes with *p*-methoxyaniline and diisopropyl phosphite in the presence of catalytic amounts of chiral Bronsted acid (*S*)-75 and powdered 4 Å MS in toluene at 40 °C. This reaction was further extended to the chiral (R_{ax})- and (S_{ax})-1,10-binaphthyl-3-formaldehyde obtaining the α-aminophosphonates (**50**) in good yield and 94:6 and 80:20 diastereoisomeric ratio.



(49)

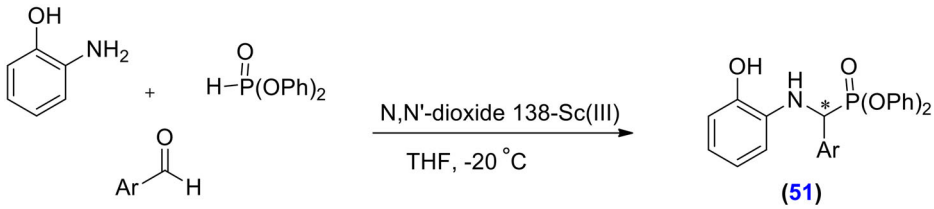
R = Ph, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 2-ClC_6H_4,cinnamyl, 4-MeO-cinnamyl, 2-NO_2-cinnamyl, 4-NO_2-cinnamyl, 1-naphthyl-C_2H_2, 9-anthracenyl-C_2H_2.



(50)

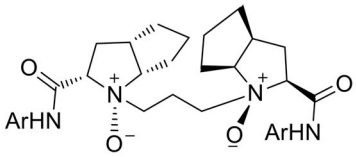
(S)-75, Ar = 3,5-$(CF_3)_2C_6H_3$

On the other hand, asymmetric syntheses of α-aminophosphonates (**51**) were carried out under mild reaction conditions by one-pot three-component reaction of aromatic aldehydes with 2-aminophenol and diphenyl phosphite catalyzed by chiral *N*,*N*'-dioxide **138**-Sc(III) complex in THF at Lewis acid −20 °C in good yields and with 80-87% enantiomeric excess. Further, this can be used for large scale synthesis of these α-aminophosphonates.[88]



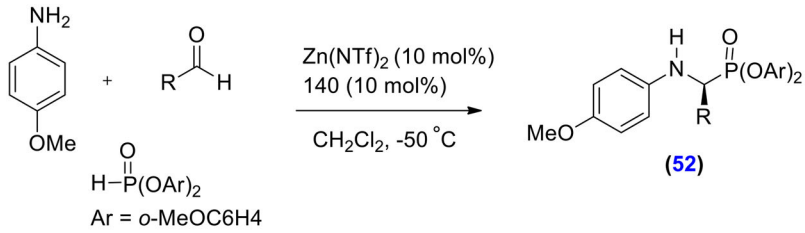
(51)

Ar = Ph, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 2-naphthyl, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-$MeOC_6H_4$, 4-phC_6H_4, 3,4-$(OCH_2O)C_6H_3$, 3-phO-4-FC_6H_3.



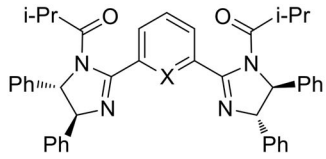
138, Ar = 2,6-$(i\text{-}Pr)_2C_6H_3$

Ohara et al.[89] developed the α-aminophosphonates (**52**) by reacting various aldehydes with *p*-anisidine and di(*o*-methoxyphenyl) phosphite, catalyzed by $Zn(NTf)_2$ (10 mol %) using **140** as chiral ligand in CH_2Cl_2 at −50 °C, in excellent yields and with moderate to high enantiomeric excess.



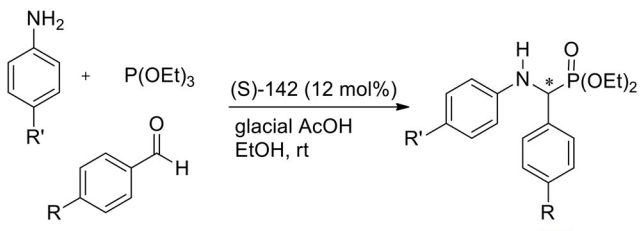
(52)

R = Ph, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 4-$MeOOCC_6H_4$, 2-naphthyl, 2-thienyl, 2-furyl, 2-benzofuryl, cinnamyl, *i*-Bu, *c*-Hex.



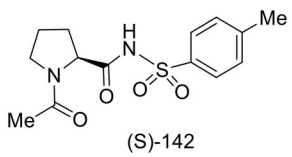
140, X = N(pybim)

Bhusare et al.[90] reported the enantioselective one-pot three-component reaction of aromatic aldehydes with several *para*-substituted anilines and triethyl phosphite for the synthesis of optically enriched α-aminophosphonates (**53**) employing (*S*)-1-acetyl-*N*-tosylpyrrolidine-2-carboxamide **142** as organocatalyst in glacial acetic acid at room temperature up to 71-90% yield and with 73-92% enantiomeric excess.



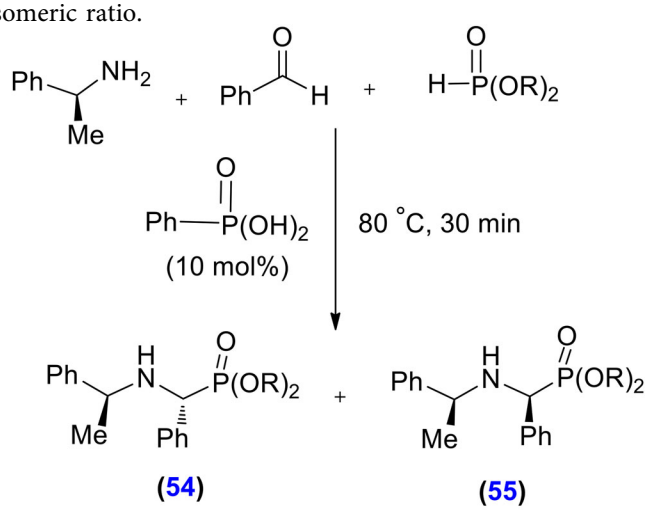
R = H, NO_2, Cl, OH, OMe. R' = H, F, Cl, Me.

(53)



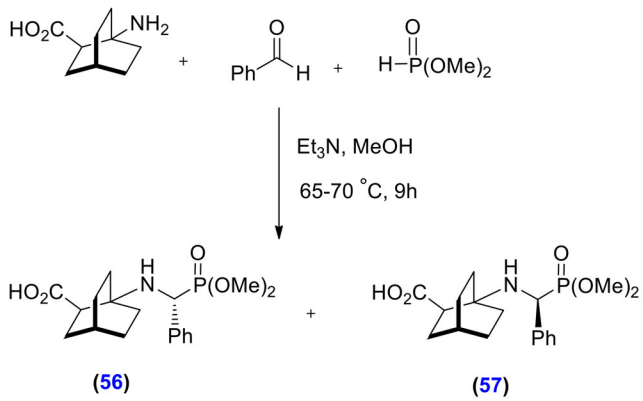
(S)-142

Bedolla-Medrano et al.[91] accomplished the synthesis of α-aminophosphonates by the one-pot three-component reaction of benzaldehyde with (*S*)-α-methylbenzylamine and diethyl or dimethyl phosphite in the presence of 10 mol % of phenylphosphonic acid as catalyst at 80 °C under solvent free conditions, obtaining the α-aminophosphonates (**54, 55**) in good yield, 80:20 and 76:24 diastereoisomeric ratio.

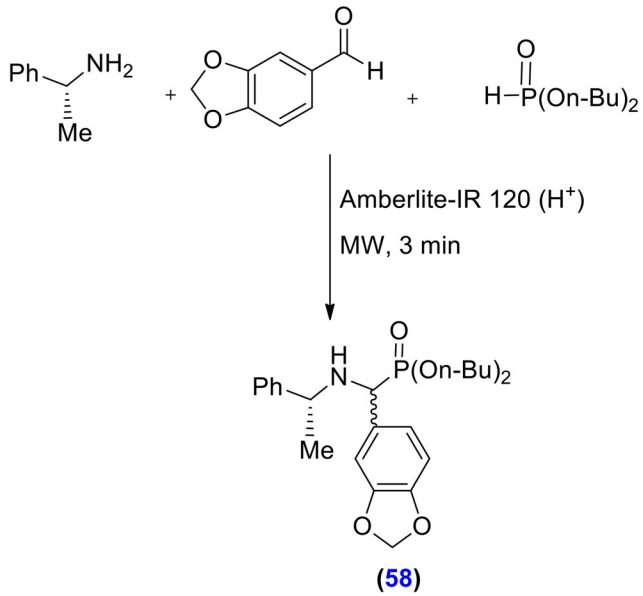


R= Et, Me

Todorov et al.[92] synthesized optically active, constrained α-aminophosphonates (**56**, **57**) by the reaction of (*R*)-1-aminobicyclo[2.2.2]octane-2-carboxylic acid with benzaldehyde and dimethyl phosphite in the presence of triethylamine in methanol with up to 34% yield and 60:40 diastereoisomeric ratio.

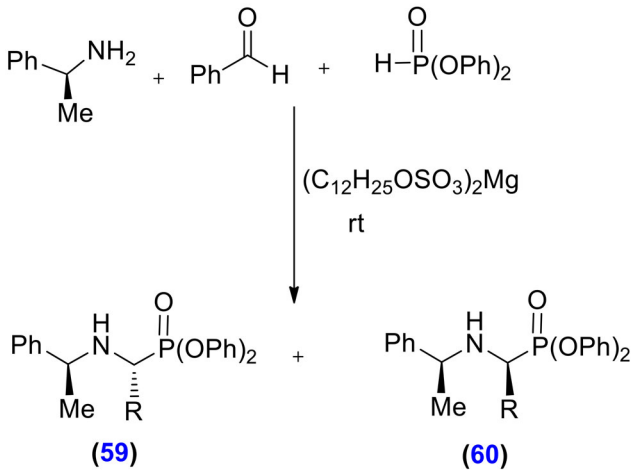


Bhattacharya and coworkers[61] reported the synthesis of α-aminophosphonates (**58**) by the one-pot three-component reaction of piperonal with (*R*)-α-methylbenzylamine and dibutyl phosphite catalyzed by Amberlite-IR 120 under microwave irradiation in 92% yield. Identical results were obtained using (*S*)-α-methylbenzylamine.



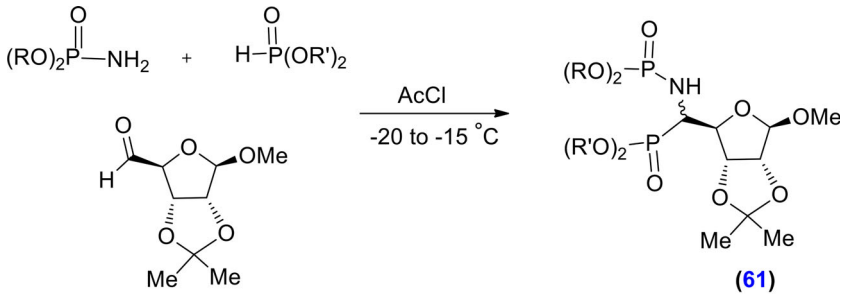
(58)

Ando et al.[93] furnished the synthesis of (*R*,*S*)- and (*S*,*S*)-α-aminophosphonates (**59, 60**) by one-pot three-component reaction of (*S*)-α-methylbenzylamine, benzaldehyde, octanal, and cyclohexanecarboxaldehyde with diphenyl phosphite by employing magnesium dodecyl sulfate as catalyst at room temperature, in moderate yield and diastereoisomeric ratio. Similar results were obtained when the reaction was carried out in the presence of Et_3N or sparteine.



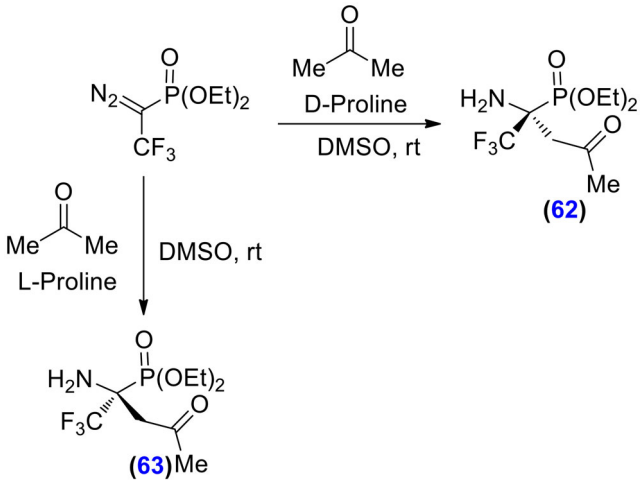
R= Ph, *n*-Oct, *c*-Hex

Miao et al.[94] described the one-pot reaction of di-*n*-propyl or diethyl phosphoramidate with methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside and dialkyl phosphites in the presence of acetyl chloride as dehydrating agent, to afford the methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides (**61**) in moderate yield and diastereoisomeric ratios.

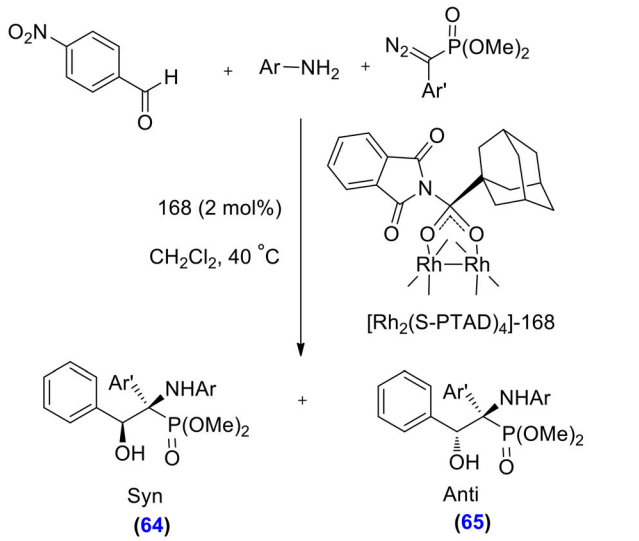


R = *n*-Pr, Et. R' = Me, Et, *n*-Pr. *i*-Pr, *n*-Bu.

Very recently, Onys'ko et al.[95] carried out the synthesis of both enantiomers of α-amino-α-trifluoromethyl-γ-oxobutanephosphonates (**62**, **63**) in 80% yield and >90% enantiomeric excess, based on the enantioselective proline-catalyzed reaction of α-iminotrifluoroethanephosphonate with acetone in DMSO at room temperature.



Zhou et al.[96] afforded the *syn*- (**64**) and *anti*-α-amino-β-hydroxyphosphonates (**65**) in 56-86% yield, with 76:24 to 90:10 *syn*/*anti*-ratio and 60-98% enantiomeric excess for the *syn*-derivatives by the three-component reaction of dimethyl α-diazo(-arylmethane)phosphonate with substituted anilines and 4-nitrobenzaldehyde in the presence of catalytic amounts of [Rh_2(S-PTAD)$_4$]-168 complex inCH_2Cl_2at 40 °C.

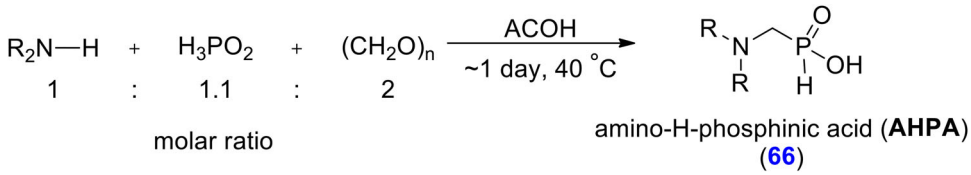


Ar = 2-MeC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 2,3-dihydro-inden-4-yl, 2-Br,4-ClC_6H_3, 2-naphthyl, 3-ClC_6H_4, 4-ClC_6H_4, 3-MeOC_6H_4, 2-FC_6H_4, 2-Br,4-FC_6H_3

Ar' = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4.

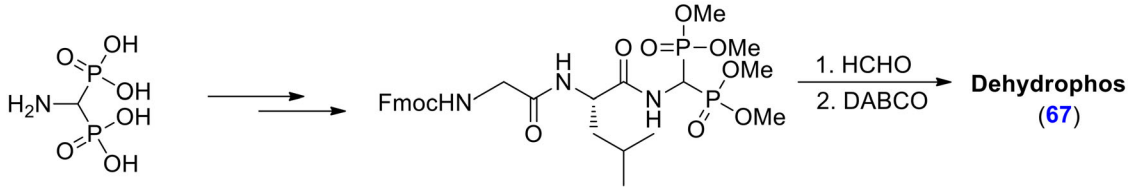
Phospha-Mannich reaction

Aminoalkanephosphorus acids are usually prepared by reaction of a precursor with a P(O)–H bond, an aldehyde and a primary/secondary amine. The most common P–H reagents for the synthesis of the aminoalkane-H-phosphinic acids are hypophosphorous acid, its esters or trivalent phosphines. However, employing a general procedure for their synthesis is a limiting factor. Urbanovsky et al.[97] employed unusual conditions of the phospha-Mannich reaction of H_3PO_2 (sometimes called Moedritzer-Irani-Redmore reaction), and the reactivity of H_3PO_2 as H–P precursor was tested for the synthesis of aminoalkanephosphinic acids.



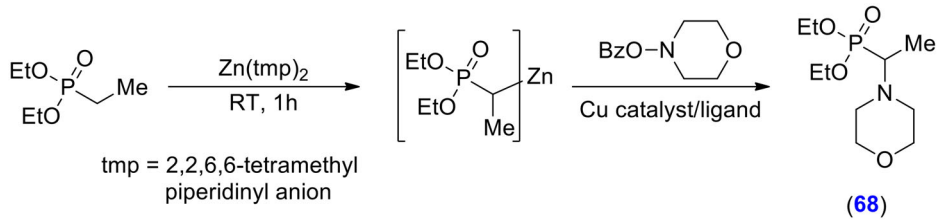
Catalytic hydrogenation of dehydroaminophosphonates

Methods based on conventional heating in organic solvents and with catalyst are still used for routine organic synthesis. Other thermal and non-thermal activation techniques are also considerably used. Cativiela et al.[98] have employed an efficient procedure for the synthesis of the vinyl phosphonate tripeptide dehydrophos. However, the efficiency of this method proceeds *via* the Horner-Wadsworth-Emmons reaction to yield a dehydro-aminophosphonate residue at the *C*-terminal position.



Electrophilic amination

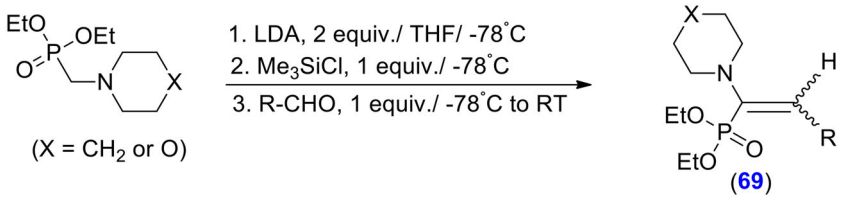
Taking the advantage of transition-metal-catalyzed couplings, Qiu Wang's research group[99] coupled the benefits of copper as catalyst for α-amination of phosphonates. They demonstrated this research output as a first example of CN bond formation which directly introduces acyclic and cyclic amines to the α-position of phosphonates in one step. The reaction has been proven to work successfully at room temperature with as little as 0.5 mol% of catalyst, and demonstrates the high efficiency on a broad substrate scope. This strategy was inspired by pioneering studies on the electrophilic amination of arylzinc reagents with hydroxylamines.



(68)

Addition of amines to enaminophosphonates

Although the addition of aldehyde and amines to phosphites is widely adopted to obtain phosphonates, simultaneously other conventional methods are also gaining consideration due to their great value for the synthesis of alkanephosphonates and phosphonic acids. N. Collignon *et al.*[100] described for the first time a valuable synthesis of α-piperidino- or α-morpholinoalkenylphosphonates, based on the Peterson olefination strategy. This methodology has been suitably improved for the preparation of a new series of α-piperidino or α-morpholino substituted phosphonic acids.

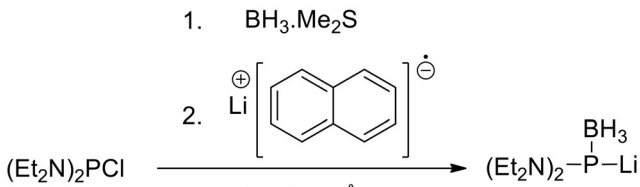


(69)

Matveeva et al.[101] have found out that the catalytic variant of the Kabachnik-Fields reaction sufficiently increases its synthetic potential. They demonstrated that recent improvements and developments with systematic search of (i) novel conditions (micro reactor), (ii) reaction without solvent and (iii) novel catalysts [$Mg(ClO_4)_2$, p-TsOH, $In(OTf)_3$-$MgSO_4$, CdI_2] under ultrasonic irradiation at room temperature exhibits a simple product isolation procedure and improves the yields and selectivity. Other advantages were the accelerated reaction rate, recovery and reuse with satisfactory yields, and the above method was eco-friendlier than the classical methods.

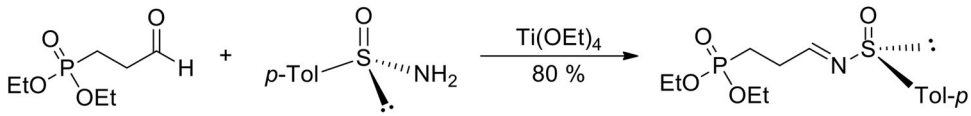
Mario et al. [102, 103,] have collected and published a review about the most relevant procedures reported up to now on the synthesis of quaternary α-aminophosphonic acids either in racemic or in enantiopure form in a multigram scale and were convinced that these synthetic moieties will be a fundamental key in the design of new peptides with improved pharmacological properties.

Addition of lithiated bis(diethylamino)phosphine borane complex to enantiopure sulfinimines is another example of usage of nucleophilic phosphorus reagents for the synthesis of α-aminophosphonic acids with high enantiomeric purities. The stereoselectivity of the addition was elucidated by suggesting a transition state model where steric approach control is an influential factor.[104]



(70)

Nevertheless, it is favorable to construct α-aminophosphonates by a one-pot method. i.e., via the Kabachnik-Fields reaction due to its simplicity and efficiency. Thus, it is still the most widely used method. In extending the above method, Mikolajczyk and Lyzwa[105] developed a new asymmetric synthetic methodology. They used, for the first time, organic sulfur reagents e. g. the enantiopure sulfinimines as chiral reagents for the synthesis of α- and *β*-aminophosphonic acids.



(71)

Conclusions

In this review article, α-aminophosphonates are reported to exhibit diverse applications ranging from biomedical to the development of new catalytic systems. An understanding of the structure function correlation in the α-aminophosphonate molecule is important for designing and finding new medications based on the knowledge of a biological target. The literature reveals that the Kabachnik-Fields reaction represents a really powerful green new eco-friendly process and tool for the preparation of α-aminophosphonates. Simultaneously, chiral functionalized α-aminophosphonates will remain the significant focus of chemical research. However, the challenges in building these α-aminophosphonates with fine tuning of physical, chemical and biological properties are diverse and require a multidisciplinary approach to reach full understanding of these molecules.

This review is meant to serve as a guide for researchers who are interested in the phosphorus chemistry area and are in particular, specialized in α-aminophosphonate chemistry. It will, furthermore, be a source of information, inspiration and encouragement for the scientific community who are already involved in the magnificent chemistry of phosphonates.

References

[1] Naydenova, E. D.; Todorov, P. T.; Mateeva, P. I.; Zamfirova, R. N.; Pavlov, N. D.; Todorov, S. B. Synthesis and Biological Activity of Novel Small Peptides with Aminophosphonates Moiety as NOP Receptor Ligands. *Amino Acids*. **2010**, *39*, 1537–1543. DOI: 10.1007/s00726-010-0624-1.

[2] Fields, S. C. Synthesis of Natural Products Containing a C-P Bond. *Tetrahedron* **1999**, *55*, 12237–12273. DOI: 10.1016/S0040-4020(99)00701-2.

[3] (a) Allen, M. C.; Fuhrer, 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. DOI: 10.1021/jm00127a041. (b) Giannousis P. P.; Bartlett P. A. Phosphorus Amino Acid Analogs as Inhibitors of Leucine Aminopeptidase. *J. Med. Chem*. **1987**, *30*, 1603–1609. 10.1021/jm00392a014.

[4] Atherton, F. R.; Hassall, C. H.; Lambert, R. W. Synthesis and Structure-Activity Relationships of Antibacterial Phosphonopeptides Incorporating (1-Aminoethyl)Phosphonic Acid and (Aminomethyl)Phosphonic Acid. J. Med. Chem. **1986**, *29*, 29–40. DOI: 10.1021/jm00151a005.

[5] (a) Haffmann, H.; Foerster, H. Darstellung von α-Aminophosphonsäureestern und verwandten Verbindungen. *Monatsh. Chem*. **1968**, 99, 380–388. DOI: 10.1007/BF00908943. (b) Hyun-Joon, H.; Gong-Sil, N. An Efficient Synthesis of Anilinobenzylphosphonates. *Synth. Commun*. **1992**, *22*, 1143–1148. DOI: 10.1080/00397919208021098.

[6] Gancarz, R.; Wieczorek, J. S. A Useful Method for the Preparation of 1-Aminoalkanephosphonic Acids. *Synthesis* **1977**, *1977*, 625–625. DOI: 10.1055/s-1977-24503.

[7] Seyferth, D.; Marmor, R. S.; Hilbert, P. Reactions of Dimethylphosphono-Substituted Diazoalkanes. $(MeO)_2P(O)CR$ Transfer to Olefins and 1,3-Dipolar Additions of $(MeO)_2P(O)C(N_2)R$. *J. Org. Chem*. **1971**, *36*, 1379–1386. DOI: 10.1021/jo00809a014.

[8] Worms, K. H.; Schmidt-Dunker, M.; Kosolapo, G. M.; Marier, L. *Organic Phosphorus Compounds*, John Wiley & Sons: New York, **1976**, p.1.

[9] Barycki, J.; Mastalerz, P.; Soroka, M. Simple Synthesis of 2-Aminoethylphosphonic Acid and Related Compounds. *Tetrahedron Lett* **1970**, *11*, 3147–3150. DOI: 10.1016/S0040-4039(00)99713-2.

[10] (a) Genet, J. P.; Uziel, J.; Port, M.; Touzin, A. M.; Roland, S.; Thorimbert S.; Tanier, S. A Practical Synthesis of α-Aminophosphonic Acids. *Tetrahedron Lett*. **1992**, 33, 77–80. DOI: 10.1016/S0040-4039(00)77677-5. (b) Qian, C.; Huang, T. One-Pot Synthesis of α-Aminophosphonates from Aldehydes Using Lanthanide Triflate as a Catalyst. *J. Org. Chem*. **1998**, 63, 4125–4128. DOI: 10.1021/jo971242t. (c) 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. DOI: 10.1021/ol990079g. (d) Manabe, K.; Kobayashi, S. Facile Synthesis of α-Aminophosphonates in Water Using a Lewis Acid–Surfactant-Combined Catalyst. *Chem. Commun*. **2000**, 2000, 669–670. DOI: 10.1039/B000319K. (e) Chanderasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. Three Component Coupling Catalyzed by $TaCl_5$–SiO_2: Synthesis of α-Aminophosphonates. *Tetrahedron Lett*. **2001**, 42, 5561–5563. DOI: 10.1016/S0040-4039(01)01053-X.

[11] (a) 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**, *2004*, 2692–2696. (b) Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F.; Tashrifi, Z. Efficient Synthesis of Secondary and Primary Dialkyl α-Aminophosphonates Catalyzed by Tetramethyl-tetra-3,4-pyridinoporphyrazinato Copper(II) Methyl Sulfate Under Solvent-free Conditions. *J. Porphyr. Phthalocyanines*. **2008**, *12*, 849–856. DOI: 10.1142/S1088424608000248. (c) Sobhani, S.; Safaei, E.; Asadi M.; Jalili, F. An Eco-friendly Procedure for the Efficient Synthesis of Dialkyl α-Aminophosphonates in Aqueous Media. *J. Organo met. Chem*., **2008**, *693*, 3313–3317. DOI: 10.1016/j.jorganchem.2008.07.037. (d) Sobhani S.; Tashrifi, Z. $Al(OTf)_3$ as an Efficient Catalyst for One-Pot Synthesis of Primary Diethyl 1-Aminophosphonates Under Solvent-Free Conditions. *Synth. Commun*. **2009**, *39*, 120–131. https://doi.org/10.1080/00397910802369695. DOI: 10.1055/s-2004-831251.

[12] Kaboudin, B. A Convenient Synthesis of 1-Aminophosphonates from 1-Hydroxyphosphonates. *Tetrahedron Lett* **2003**, *44*, 1051–1053. DOI: 10.1016/S0040-4039(02)02727-2.

[13] Tillu, V. H.; Dumbre, D. K.; Wakharkar, R. D.; Choudhary, V. R. One-Pot Three-Component Kabachnik–Fields Synthesis of α-Aminophosphonates Using H-Beta Zeolite Catalyst. *Tetrahedron Lett* **2011**, *52*, 863–866. DOI: 10.1016/j.tetlet.2010.11.105.

[14] Ranu, B. C.; Hajra, A. A Simple and Green Procedure for the Synthesis of α-Aminophosphonate by a One-Pot Three-Component Condensation of Carbonyl Compound, Amine and Diethyl Phosphite without Solvent and Catalyst. *Green Chem* **2002**, *4*, 551–554. DOI: 10.1039/B205747F.

[15] Zhan, Z. P.; Li, J. P. Bismuth(III) Chloride–Catalyzed Three-Component Coupling: Synthesis of α-Amino Phosphonates.

Synth. Commun **2005**, *35*, 2501–2508. DOI: 10.1080/00397910500212692.

[16] Sobhani, S.; Tashrifi, Z. One-Pot Synthesis of Primary 1-Aminophosphonates: Coupling Reaction of Carbonyl Compounds, Hexamethyldisilazane, and Diethyl Phosphite caTalyzed by $Al(OTf)_3$. *Heteroatom Chem.* **2009**, *20*, 109–115. DOI: 10.1002/hc.20517.

[17] 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. DOI: 10.1016/j.catcom.2008.02.011.

[18] Heydari, A.; Hamadi, H.; Pourayoubi, M. A New One-Pot Synthesis of α-Amino Phosphonates Catalyzed by $H_3PW_{12}O_{40}$. *Catal. Commun* **2007**, *8*, 1224–1226. DOI: 10.1016/j.catcom.2006.11.008.

[19] Kaboudin, B.; Zahedi, H. Calcium Chloride as an Efficient Lewis Base Catalyst for the One-Pot Synthesis of α-Aminophosphonic Esters. *Chem. Lett.* **2008**, *37*, 540–541. DOI: 10.1246/cl.2008.540.

[20] Tian, Y. P.; Xu, F.; Wang, Y.; Wang, J. J.; Li, H. L. PPh_3-Catalysed One-Pot Three-Component Syntheses of α-Aminophosphonates under Solvent-Free Conditions. *J. Chem. Res. (S)* **2009**, *2009*, 78–80. DOI: 10.3184/030823409X401097.

[21] Kassaee, M. Z.; Movahedi, F.; Masrouri, H. ZnO Nanoparticles as an Efficient Catalyst for the One-Pot Synthesis of α-Amino Phosphonates. *Synlett* **2009**, *2009*, 1326–1330. DOI: 10.1055/s-0028-1088135.

[22] Hosseini-Sarvari, M. TiO_2 as a New and Reusable Catalyst for One-Pot Three-Component Syntheses of α-Aminophosphonates in Solvent-Free Conditions. *Tetrahedron* **2008**, *64*, 5459–5466. DOI: 10.1016/j.tet.2008.04.016.

[23] Kaboudin, B.; Jafari, E. Hydrophosphorylation of IminesCatalyzed by Tosyl Chloride for the Synthesis of α-Aminophosphonates. *Synlett* **2008**, *2008*, 1837–1839. DOI: 10.1055/s-2008-1078509.

[24] Syamala, M. A Decade of Advances in Three-Component Reactions. *Org. Prep. Proced. Int* **2005**, *37*, 103–171. DOI: 10.1080/00304940509354882.

[25] Kabachnik, M. I.; Medved, T. Y. New Synthesis of Aminophosphonic Acids. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689–692.

[26] Fields, E. K. The Synthesis of Esters of Substituted Amino Phosphonic Acids. *J. Am. Chem. Soc.* **1952**, *74*, 1528–1531. DOI: 10.1021/ja01126a054.

[27] Pudovik, A. N. Addition of Dialkyl Phosphites to Imines. New Method of Synthesis of Esters of Amino Phosphonic Acids. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865–868.

[28] Cherkasov, R. A.; Galkin, V. I. The Kabachnik–Fields Reaction: Synthetic Potential and the Problem of the Mechanism. *Russ. Chem. Rev.* **1998**, *67*, 857–882. DOI: 10.1070/RC1998v067n10ABEH000421.

[29] Galkin, V. I.; Zvereva, E. R.; Sobanov, A. A.; Galkina, I. V.; Cherkasov, R. A. Kinetics and Mechanism of Kabachnik-Fields Reaction in Dialkylphosphite-Benzaldehyde-Aniline System. *Zhur. Obsch. Khim* **1993**, *63*, 2224–2227.

[30] Galkina, I. V.; Sobanov, A. A.; Galkin, V. I.; Cherkasov, R. A. Kinetics and Mechanism of the Kabachnik-Fields Reaction: IV. Salicyaldehyde in the Kabachnik-Fields Reaction. *Russ. J. Gen. Chem* **1998**, *68*, 1398–1401.

[31] Gancarz, R.; Gancarz, I. Failure of Aminophosphonate Synthesis Due to Facile Hydroxyphosphonate - Phosphate Rearrangement. *Tetrahedron Lett* **1993**, *34*, 145–148. DOI: 10.1016/S0040-4039(00)60079-5.

[32] Gancarz, R. Nucleophilic Addition to Carbonyl Compounds. Competition between Hard (Amine) and Soft (Phosphite) Nucleophile. *Tetrahedron* **1995**, *51*, 10627–10632. DOI: 10.1016/0040-4020(95)00634-K.

[33] Reddy, B. V. S.; Krishna, A. S.; Ganesh, A. V.; Kumar, G. G. K. S. N. Nano Fe_3O_4 as Magnetically Recyclable Catalyst for the Synthesis of α-Aminophosphonates in Solvent-Free Conditions. *Tetrahedron Lett* **2011**, *52*, 1359–1362. DOI: 10.1016/j.tetlet.2011.01.074.

[34] Disale, S. T.; Kale, S. R.; Kahandal, S. S.; Srinivasan, T. G.; Jayaram, R. V. Choline Chloride·$2ZnCl_2$ Ionic Liquid: An Efficient and Reusable Catalyst for the Solvent Free Kabachnik–Fields Reaction. *Tetrahedron Lett* **2012**, *53*, 2277–2279. DOI: 10.1016/j.tetlet.2012.02.054.

[35] Sheykhan, M.; Mohammadnejad, H.; Akbari, J.; Heydari, A. Superparamagnetic Magnesium Ferrite Nanoparticles: A Magnetically Reusable and Clean Heterogeneous Catalyst. *Tetrahedron Lett* **2012**, *53*, 2959–2964. DOI: 10.1016/j.tetlet.2012.03.069.

[36] Tang, J.; Wang, L.; Wang, W.; Zhang, L.; Wu, S.; Mao, D. A Facile Synthesis of α-Aminophosphonates Catalyzed by Ytterbium Perfluorooctanoate under Solvent-Free Conditions. *J. Fluorine Chem* **2011**, *132*, 102–106. DOI: 10.1016/j.jfluchem.2010.12.002.

[37] Zahouily, M.; Elmakssoudi, A.; Mezdar, A.; Rayadh, A.; Sebti, S. Natural Phosphate and Potassium Fluoride Doped Natural Phosphate Catalysed Simple One-Pot Synthesis of α-Aminophosphonates under Solvent-Free Conditions at Room Temperature. *Catal. Commun.* **2007**, *8*, 225–230. DOI: 10.1016/j.catcom.2006.06.017.

[38] Bhattacharya, A. K.; Rana, K. C. Amberlite-IR 120 Catalyzed Three-Component Synthesis of α-Amino Phosphonates in One-Pot. *Tetrahedron Lett* **2008**, *49*, 2598–2601. DOI: 10.1016/j.tetlet.2008.02.102.

[39] Patil, A. B.; Patil, D. S.; Bhanage, B. M. ZnO Nanoparticle by Solar Energy and Their Catalytic Application for α-Aminophosphonates Synthesis. *Mater. Lett.* **2012**, *86*, 50–53. DOI: 10.1016/j.matlet.2012.07.009.

[40] Subba Reddy, G.; Uma Maheswara Rao, K.; Syama Sundar, C.; Sudha, S. S.; Haritha, B.; Swapna, S.; Suresh Reddy, C. Neat Synthesis and Antioxidant Activity of α-Aminophosphonates. *Arab. J. Chem.* **2014**, *7*, 833–838. DOI: 10.1016/j.arabjc.2013.01.004.

[41] Khatri, C. K.; Satalkar, B. V.; Chaturbhuj, G. U. Sulfated Polyborate Catalyzed Kabachnik-Fields Reaction: An Efficient and Eco-Friendly Protocol for Synthesis of α-Aminophosphonates. *Tetrahedron Lett* **2017**, *58*, 694–698. DOI: 10.1016/j.tetlet.2017.01.022.

[42] Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. Three Component Coupling Catalyzed by $TaCl_5$–SiO_2: Synthesis of α-Aminophosphonates. *Tetrahedron Lett.* **2001**, *42*, 5561–5563. DOI: 10.1016/S0040-4039(01)01053-X.

[43] Heydari, A.; Zarei, M.; Alijanianzadeh, R.; Tavakol, H. One-Pot Synthesis of N-Trimethylsilyloxy-α-Aminophosphonates from Aldehydes Using Lithium Perchlorate/Diethyl Ether as a Catalyst. *Tetrahedron Lett.* **2001**, *42*, 3629–3631. DOI: 10.1016/S0040-4039(01)00233-7.

[44] Heydari, A.; Javidan, A.; Schaffie, M. Lithium Perchlorate/Diethyl Ether Catalyzed One-Pot Synthesis of α-Hydrazinophosphonates from Aldehydes by a Three-Component Reaction. *Tetrahedron Lett.* **2001**, *42*, 8071–8073. DOI: 10.1016/S0040-4039(01)01702-6.

[45] Azizi, N.; Saidi, M. R. Synthesis of Tertiary α-Aminophosphonate by One-Pot Three-Component Coupling Mediated by LPDE. *Tetrahedron* **2003**, *59*, 5329–5332. DOI: 10.1016/S0040-4020(03)00759-2.

[46] Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. K. $In(OTf)_3$ Catalysed Simple One-Pot Synthesis of α-Aminophosphonates. *J. Mol. Catal. A Chem.* **2004**, *210*, 53–57. DOI: 10.1016/j.molcata.2003.09.020.

[47] Azizi, N.; Rajabi, F.; Saidi, M. R. A Mild and Highly Efficient Protocol for the One-Pot Synthesis of Primary α-Aminophosphonates under Solvent-Free Conditions.

Tetrahedron Lett. **2004**, *45*, 9233–9236. DOI: 10.1016/j.tetlet.2004.10.092.

[48] Kaboudin, B.; Moradi, K. A Simple and Convenient Procedure for the Synthesis of 1-Aminophosphonates from Aromatic Aldehydes. *Tetrahedron Lett.* **2005**, *46*, 2989–2991. DOI: 10.1016/j.tetlet.2005.03.037.

[49] Heydari, A.; Arefi, A. One-Pot Three-Component Synthesis of α-Aminophosphonate Derivatives. *Catal. Commun.* **2007**, *8*, 1023–1026. DOI: 10.1016/j.catcom.2006.10.019.

[50] Ambica, S. K.; 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. DOI: 10.1016/j.tetlet.2008.02.047.

[51] Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F. An Eco-Friendly Procedure for the Efficient Synthesis of Dialkyl α-Aminophosphonates in Aqueous Media. *J. Oranomet. Chem.* **2008**, *693*, 3313–3317. DOI: 10.1016/j.jorganchem.2008.07.037.

[52] Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M. R.; Jafari, A. A.; Zare, H. R. Design and one-pot synthesis of alpha-aminophosphonates and bis(alpha-aminophosphonates) by iron(III) chloride and cytotoxic activity. Eur. J. Med. Chem. **2009**, *44*, 4266–4275. DOI: 10.1016/j.ejmech.2009.07.009.

[53] Vinu, A.; Kalita, P.; Balasubramanian, V. V.; Oveisi, H.; Selvan, T.; Mano, A.; Chari, M. A.; Reddy, B. V. S. Mesoporous Aluminosilicate Nanocage-Catalyzed Three-Component Coupling Reaction: An Expedient Synthesis of α-Aminophosphonates. *Tetrahedron Lett.* **2009**, *50*, 7132–7136. DOI: 10.1016/j.tetlet.2009.10.003.

[54] Thirumurugan, P.; Nandakumar, A.; Sudha Priya, N.; Muralidaran, D.; Perumal, P. T. $KHSO_4$-Mediated Synthesis of α-Aminophosphonates under a Neat Condition and Their ^{31}P NMR Chemical Shift Assignments. *Tetrahedron Lett.* **2010**, *51*, 5708–5712. DOI: 10.1016/j.tetlet.2010.08.066.

[55] Dake, S. A.; Raut, D. S.; Kharat, K. R.; Mhaske, R. S.; Deshmukh, S. U.; Pawar, R. P. Ionic Liquid Promoted Synthesis, Antibacterial and in Vitro Antiproliferative Activity of Novel α-Aminophosphonate Derivatives. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2527–2532. DOI: 10.1016/j.bmcl.2011.02.039.

[56] Borse, A. U.; Patil, N. L.; Patil, M. N.; Mali, R. S. Synthetic Utility of Kabachnik–Fields Reaction: A Convenient One-Pot Three-Component Synthesis of N-Phenyl Isoquinolone-1-Phosphonates. *Tetrahedron Lett.* **2012**, *53*, 6940–6942. DOI: 10.1016/j.tetlet.2012.10.030.

[57] Heo, Y.; Cho, D. H.; Mishra, M. K.; Jang, D. O. Efficient One-Pot Synthesis of α-Aminophosphonates from Aldehydes and Ketones Catalyzed by Ytterbium(III) Triflate. *Tetrahedron Lett.* **2012**, *53*, 3897–3899. DOI: 10.1016/j.tetlet.2012.05.068.

[58] Ali, N. S.; Zakir, S.; Patel, M.; Farooqui, M. Synthesis of New α aminophosphonate system bearing Indazole moiety and their biological activity . Eur. J. Med. Chem. **2012**, *50*, 39–43. DOI: 10.1016/j.ejmech.2012.01.024.

[59] Reddy, C. B.; Kumar, K. S.; Kumar, M. A.; Reddy, M. V. N.; Krishna, B. S.; Naveen, M.; Arunasree, M. K.; Reddy, C. S.; Raju, C. N.; Reddy, C. D. PEG-SO(3)H Catalyzed Synthesis and Cytotoxicity of α-Aminophosphonates. Eur. J. Med. Chem. **2012**, *47*, 553–559. DOI: 10.1016/j.ejmech.2011.11.026.

[60] Zhang, Y.; Zhu, C. Gold Complex-Catalyzed C-P Bond Formation by Kabachnik–Fields Reactions. *Catal. Commun.* **2012**, *28*, 134–137. DOI: 10.1016/j.catcom.2012.08.001.

[61] Bhattacharya, A. K.; Raut, D. S.; Rana, K. C.; Polanki, I. K.; Khan, M. S.; Iram, S. Diversity-Oriented Synthesis of α-Aminophosphonates: A New Class of Potential Anticancer Agents. Eur. J. Med. Chem. **2013**, *66*, 146–152. DOI: 10.1016/j.ejmech.2013.05.036.

[62] Reddy, P. S.; Reddy, P. V. G.; Reddy, S. M. Phosphomolybdic Acid Promoted Kabachnik–Fields Reaction: An Efficient One-Pot Synthesis of α-Aminophosphonates from 2-Cyclopropylpyrimidine-4-Carbaldehyde. *Tetrahedron Lett.* **2014**, *55*, 3336–3339. DOI: 10.1016/j.tetlet.2014.04.053.

[63] Suresh, M.; Kumar, A. S.; Kumar, A. A.; Lavanya, P. Efficient Organocatalytic Multicomponent Synthesis of (α-Aminoalkyl)Phosphonates. *Arab. J. Chem.* **2016**, *9*, 787–791. DOI: 10.1016/j.arabjc.2013.04.011.

[64] Jian-Yi, C.; Xiao-Yun, X.; Zi-Long, T.; Yu-Cheng, G.; De-Qing, S. Synthesis and Herbicidal Activity Evaluation of Novel α-Amino Phosphonate Derivatives Containing a Uracil Moiety. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1310–1313. DOI: 10.1016/j.bmcl.2016.01.010.

[65] Reddy, N. B.; Sundar, C. S.; Rani, C. R.; Rao, K. U. M.; Nayak, S. K.; Reddy, C. S. Triton X-100 Catalyzed Synthesis of α-Aminophosphonates. *Arab. J. Chem.* **2016**, *9*, S685–S690. DOI: 10.1016/j.arabjc.2011.07.025.

[66] Li, X. C.; Gong, S. S.; Zeng, D. Y.; You, Y. H.; Sun, Q. Highly Efficient Synthesis of α-Aminophosphonates Catalyzed by Hafnium(IV) Chloride. *Tetrahedron Lett* **2016**, *57*, 1782–1785. DOI: 10.1016/j.tetlet.2016.03.033.

[67] Reddy, P. S.; Reddy, M. V. K.; Reddy, P. V. G. Camphor-Derived Thioureas: Synthesis and Application in Asymmetric Kabachnik-Fields Reaction. *Chinese Chem. Lett.* **2016**, *27*, 943–947. DOI: 10.1016/j.cclet.2016.01.046.

[68] Reddy, M. V.; Dindulkar, S. D.; Jeong, Y. T. $BF_3{\cdot}SiO_2$-Catalyzed One-Pot Synthesis of α-Aminophosphonates in Ionic Liquid and Neat Conditions. *Tetrahedron Lett.* **2011**, *52*, 4764–4767. DOI: 10.1016/j.tetlet.2011.07.027.

[69] Jaiyeola, A. O.; Anand, K.; Kasumbwe, K.; Ramesh, M.; Gengan, R. M. Catalytic Synthesis of α-Amino Chromone Phosphonates and Their Antimicrobial, Toxicity and Potential HIV-1 RT Inhibitors Based on Silico Screening. *J. Photochem. Photobiol. B, Biol.* **2017**, *166*, 136–147. DOI: 10.1016/j.jphotobiol.2016.11.014.

[70] Kaboudin, B.; Karami, L.; Kato, J.; Aoyama, H.; Yokomatsu, T. A Catalyst-Free, Three-Component Decarboxylative Coupling of Amino Acids with Aldehydes and H-Dialkylphosphites for the Synthesis of α-Aminophosphonates. *Tetrahedron Lett.* **2013**, *54*, 4872–4875. DOI: 10.1016/j.tetlet.2013.06.129.

[71] Kobra, A.; Meghdad, K.; Akbar, H. A Catalyst-Free Synthesis of α-Aminophosphonates in Glycerol. *Tetrahedron Lett.* **2014**, *55*, 7236–7239. DOI: 10.1016/j.tetlet.2014.11.057.

[72] Wang, Q.; Yang, L.; Ding, H.; Chen, X.; Wang, H.; Tang, X. Synthesis, X-Ray Crystal Structure, DNA/Protein Binding and Cytotoxicity Studies of Five α-Aminophosphonate N-Derivatives. Bioorg. Chem. **2016**, *69*, 132–139. DOI: 10.1016/j.bioorg.2016.10.007.

[73] Fang, Z.; Yang, H.; Miao, Z.; Chen, R. Asymmetric Mannich-Type Synthesis of N-Phosphinyl α-Aminophosphonic Acid Monoesters. *HCA.* **2011**, *94*, 1586–1593. DOI: 10.1002/hlca.201100025.

[74] Yan-Chun, G.; Li, J.; Jiao-Li, M.; Zhi-Ran, Y.; Wang, H. W.; Wen-Juan, Z.; Xin-Cheng, L.; Yu-Fen, Z. Synthesis and Antitumor Activity of α-Aminophosphonate Derivatives Containing Thieno[2,3-d]Pyrimidines. *Chin. Chem. Lett.* **2015**, *26*, 755–758. DOI: 10.1016/j.cclet.2015.03.026.

[75] Hellal, A.; Chafaa, S.; Chafai, N.; Touafri, L. Synthesis, Antibacterial Screening and DFT Studies of Series of α-Amino-Phosphonates Derivatives from Aminophenols. *J. Mol. Struct.* **2017**, *1134*, 217–225. DOI: 10.1016/j.molstruc.2016.12.079.

[76] 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. DOI: 10.1016/j.bmcl.2005.12.041.

[77] Heydari, A.; Khaksar, S.; Tajbakhsh, M. Trifluoroethanol as a Metal-Free, Homogeneous and Recyclable Medium for the Efficient One-Pot Synthesis of α-Amino Nitriles and

α-Aminophosphonates. *Tetrahedron Lett.* **2009**, *50*, 77–80. DOI: 10.1016/j.tetlet.2008.10.106.

[78] Xia, M.; Lu, Y. D. Ultrasound-Assisted One-Pot Approach to α-Amino Phosphonates under Solvent-Free and Catalyst-Free Conditions. *Ultrason. Sonochem.* **2007**, *14*, 235–240. DOI: 10.1016/j.ultsonch.2006.04.006.

[79] Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. Solvent-free sonochemical preparation of alpha-aminophosphonates catalyzed by 1-hexanesulphonic acid sodium salt. Ultrason. Sonochem. **2010**, *17*, 760–763. DOI: 10.1016/j.ultsonch.2010.02.002.

[80] 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.

[81] Agawane, S. M.; Nagarkar, J. M. Nano Ceria Catalyzed Synthesis of α-Aminophosphonates under Ultrasonication. *Tetrahedron Lett.* **2011**, *52*, 3499–3504. DOI: 10.1016/j.tetlet.2011.04.112.

[82] Xu, W.; Zhang, S.; Yang, S.; Jin, L. H.; Bhadury, P. S.; Hu, D. Y.; Zhang, Y. Asymmetric Synthesis of Alpha-aminophosphonates Using the Inexpensive Chiral Catalyst 1,1'-binaphthol Phosphate. *Molecules* **2010**, *15*, 5782–5796. DOI: 10.3390/molecules15085782.

[83] Kaur, P.; Wever, W.; Rajale, T.; Li, G. Asymmetric Hydrophosphylation of Chiral N-Phosphonyl Imines Provides an Efficient Approach to Chiral α-amino phosphonates . *Chem. Biol. Drug Des.* **2010**, *76*, 314–319. DOI: 10.1111/j.1747-0285.2010.01013.x.

[84] Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. Catalytic Asymmetric Synthesis of Alpha Amino Phosphonates Using Lanthanoid-Potassium-BINOL Complexes. *J. Org. Chem.* **1995**, *60*, 6656–6657. DOI: 10.1021/jo00126a003.

[85] Arun, S.; Rajshekhar, A. U.; Vinod, K. S. Enantioselective Hydrophosphonylation of in Situ Generated N-Acyl Ketimines Catalyzed by BINOL-Derived Phosphoric Acid. *Org. Lett.* **2017**, *19*, 476–479. DOI: 10.1021/acs.orglett.6b03623.

[86] Cheng, X.; Goddard, R.; Buth, G.; List, B. Direct Catalytic Asymmetric three-component Kabachnik-Fields reaction. Angew. Chem. Int. Ed. Engl. **2008**, *47*, 5079–5081. DOI: 10.1002/anie.200801173.

[87] Wang, L.; Cui, S. M.; Meng, W.; Zhang, G. W.; Nie, J.; Ma, J. A. Asymmetric Synthesis of α-Aminophosphonates by Means of Direct Organocatalytic Three-Component Hydrophosphonylation. *Chin. Sci. Bull.* **2010**, *55*, 1729–1731. DOI: 10.1007/s11434-009-3743-x.

[88] Zhou, X.; Shang, D.; Zhang, Q.; Lin, L.; Liu, X.; Feng, X. Enantioselective Three-Component Kabachnik-Fields Reaction Catalyzed by Chiral Scandium(III)-N,N'-Dioxide Complexes. Org. Lett. **2009**, *11*, 1401–1404. DOI: 10.1021/ol9000813.

[89] Ohara, M.; Nakamura, S.; Shibata, N. Direct Enantioselective Three-Component Kabachnik–Fields Reaction Catalyzed by Chiral Bis(Imidazoline)-Zinc(II) Catalysts. *Adv. Synth. Catal.* **2011**, *353*, 3285–3289. DOI: 10.1002/adsc.201100482.

[90] Thorat, P. B.; Goswami, S. V.; Magar, R. L.; Patil, B. R.; Bhusare, S. R. An Efficient Organocatalysis: A One-Pot Highly Enantioselective Synthesis of α-Aminophosphonates. *Eur. J. Org. Chem.* **2013**, *2013*, 5509–5516. DOI: 10.1002/ejoc.201300494.

[91] Bedolla-Medrano, M.; Hernandez-Fernandez, E.; Ordonez, M. Phenylphosphonic Acid as Efficient and Recyclable Catalyst in the Synthesis of α-Aminophosphonates under Solvent-Free Conditions. *Synlett* **2014**, *25*, 1145–1149. DOI: 10.1055/s-0033-1341069.

[92] (a) Todorov, P. T.; Wesselinova, D. W.; Pavlov, N. D.; Martinez, J.; Calmes, M.; Naydenova, E. D. Cytotoxic Activity of New Racemic and Optically Active N-Phosphonoalkyl Bicyclic β-Amino Acids Against Human Malignant Cell Lines. *Amino Acids*. **2012**, 43, 1445–1450. DOI: 10.1007/s00726-012-1217-y. (b) Todorov, P. T.; Pavlov, N. D.; Shivachev, B. L.; Petrova, R. N.; Martinez, J.; Naydenova, E. D.; Calmes, M. *Heteroatom Chem.* **2012**, *23*, 123–130. DOI: 10.1002/hc.

[93] Ando, K.; Egami, T. Facile Synthesis of α-Aminophosphonates in Water by Kabachnik–Fields Reaction Using Magnesium Dodecyl Sulfate. *Heteroatom Chem.* **2011**, *22*, 358–362. DOI: 10.1002/hc.20689.

[94] Cui, Z.; Zhang, J.; Wang, F.; Wang, Y.; Miao, Z.; Chen, R. The Diastereoselective Synthesis of Methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-O-isopropylidene-beta-D-ribofuranosides. Carbohydr. Res. **2008**, *343*, 2530–2534. DOI: 10.1016/j.carres.2008.06.009.

[95] Rassukana, Y. V.; Yelenich, I. P.; Vlasenko, Y. G.; Onys'ko, P. P. Asymmetric Synthesis of Phosphonotrifluoroalanine Derivatives via Proline-Catalyzed Direct Enantioselective C-C Bond Formation Reactions of N-H Trifluoroacetimidoyl Phosphonate. *Tetrahedron: Asymmetry* **2014**, *25*, 1234–1238. DOI: 10.1016/j.tetasy.2014.07.007.

[96] Zhou, C. Y.; Wang, J. C.; Wei, J.; Xu, Z. J.; Guo, Z.; Low, K. H.; Che, C. M. Dirhodium Carboxylates Catalyzed Enantioselective Coupling Reactions of α-diazophosphonates, anilines, and electron-deficient aldehydes. Angew. Chem. Int. Ed. Engl. **2012**, *51*, 11376–11380. DOI: 10.1002/anie.201206551.

[97] Urbanovsky, P.; Kotek, J.; Cısarova, I.; Hermann, P. Selective and Clean Synthesis of Aminoalkyl-*H*-Phosphinic Acids from Hypophosphorous Acid by Phospha-Mannich Reaction. *RSC Adv.* **2020**, *10*, 21329–21349. DOI: 10.1039/d0ra03075a.

[98] Jiménez-Andreu, M. M.; Sayago, F. J.; Cativiela, C. An Improved Synthesis of the Antibiotic Dehydrophos. *Eur. J. Org. Chem.* **2018**, *2018*, 3965–3973. DOI: 10.1002/ejoc.201800689.

[99] McDonald, S. L.; Wang, Q. Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives. Angew. Chem. Int. Ed. Engl. **2014**, *53*, 1867–1871. DOI: 10.1002/anie.201308890.

[100] Dufrechou, S.; Collignon, N.; Combret, J. C.; Malhiac, C. Efficient Synthesis of α-Enaminophosphonates in the Series of Piperidine and Morpholine. Examples of Synthetic Applications. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *127*, 1–14. DOI: 10.1080/10426509708040491.

[101] Zefirov, N. S.; Matveeva, E. D. Catalytic Kabachnik-Fields Reaction: New Horizons for Old Reaction. *ARKIVOC* **2008**, *2008*, 1–17. DOI: 10.3998/ark.5550190.0009.101.

[102] Ordóñez, M.; Sayago, F. J.; Cativiela, C. Synthesis of Quaternary α-Aminophosphonic Acids. *Tetrahedron* **2012**, *68*, 6369–6412. DOI: 10.1016/j.tet.2012.05.008.

[103] Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. An Overview of Stereoselective Synthesis of α-Aminophosphonic Acids and Derivatives. *Tetrahedron* **2009**, *65*, 17–49. DOI: 10.1016/j.tet.2008.09.083.

[104] Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. A New Efficient Procedure for Asymmetric Synthesis of A-Aminophosphonic Acids via Addition of Lithiated Bis(Diethylamino)Phosphine Borane Complex to Enantiopure Sulfinimines. *Tetrahedron: Asymmetry* **2002**, *13*, 2571–2576. DOI: 10.1016/S0957-4166(02)00684-5.

[105] Mikolajczyk, M.; Lyzwa, P. Recent Progress in Asymmetric Synthesis of Aminophosphonic Acids Mediated by Chiral Sulfinyl Auxiliary. *Pure Appl. Chem.* **2017**, *89*, 357–365. DOI: 10.1515/pac-2016-1023.