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6 Synthesis of α-aminophosphonates by the Kabachnik–Fields reaction and by the Pudovik reaction

Abstract: α-Aminophosphonates are of significant importance due to their biological activity. The most widely applied synthetic routes towards α-aminophosphonates are the Kabachnik–Fields reaction involving the condensation of amines, oxo compounds and >P(O)H species, such as dialkyl phosphites, and the Pudovik reaction of imines and >P(O)H reagents. By the double Kabachnik–Fields reaction, bis(aminophosphonates) have also became available. This chapter summarizes the synthesis of α-aminophosphonates and related derivatives through the two main routes as described in the literature over the last five years.

Keywords: Kabachnik–Fields reaction, Pudovik reaction, α-aminophosphonates, bis(aminophosphonates).

6.1 Introduction

α-Aminophosphonic acids are considered as bioisosteres of the corresponding α-aminocarboxylic acids, in which the planar carboxylic group is replaced by a tetrahedral phosphonic acid functionality. Due to their versatile biological activity, they are important targets in biochemistry [1, 2], medicinal chemistry [3–6] and pesticide chemistry [7–9]. The synthesis and application of α-aminophosphonic acid derivatives attracted considerable interest, comprising more than one thousand five hundred papers since 1952 (Figure 6.1).

The most widely used synthetic routes to α-aminophosphonates are the Kabachnik–Fields condensation and the (aza-)Pudovik reaction. This chapter is aimed at giving insights into the synthesis of α-aminophosphonates and related derivatives surveying the literature data over the last five years.

6.2 Kabachnik–Fields Reaction

The Kabachnik–Fields (phospha-Mannich) reaction is a three-component condensation of a primary or secondary amine, a carbonyl compound (aldehyde or ketone) and a >P(O)H reagent, such as a dialkyl phosphite or a secondary phosphine oxide (Figure 6.2) [10–13].

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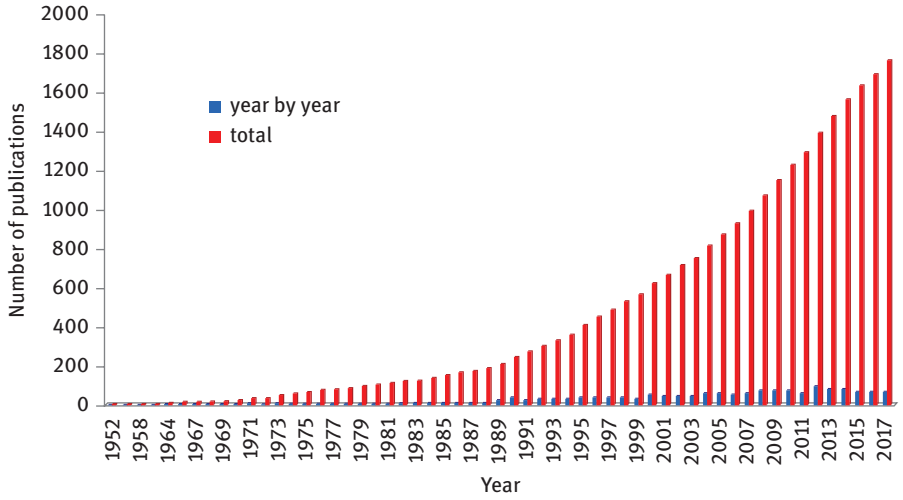


Figure 6.1: The number of publication on α-aminophosphonic acid derivatives (1952–2017). ScienceDirect keyword search on "α-aminophosphonic acid" and "α-aminophosphonate".

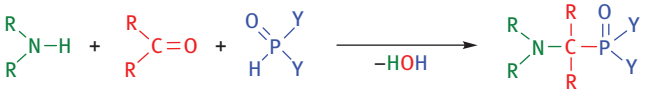


Figure 6.2: General scheme for the Kabachnik–Fields reaction.

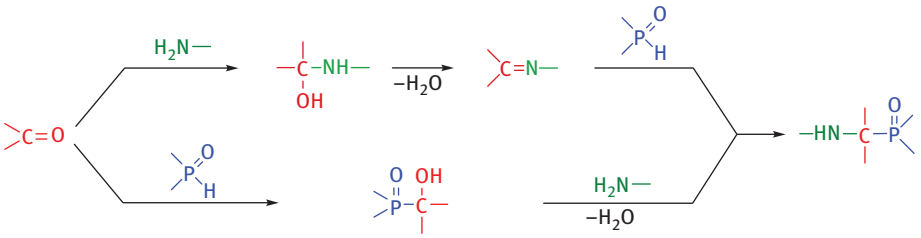


Figure 6.3: Two possible mechanistic pathways for the Kabachnik–Fields reaction.

In general, there are two possible reaction pathways for the Kabachnik–Fields reaction (Figure 6.3). One is when the carbonyl compound and the primary amine react with each other resulting in the formation of an imine (Schiff base) intermediate, and then the P-reagent is added on the C=N unit. According to the other route, the first step is the addition of dialkyl phosphites to the carbonyl group of the oxo component, to provide an α-hydroxyphosphonate, which undergoes substitution by the amine to furnish the α-aminophosphonate. On the basis of kinetic studies, it was concluded that the mechanism depends on the nature of the reactants [12–14].

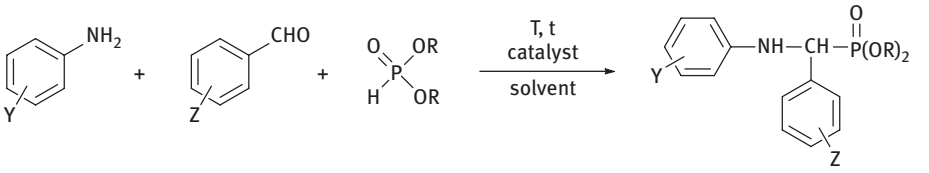
Kabachnik–Fields reactions may be accomplished in many variations. These condensations are usually carried out in the presence of various catalysts and/or solvents [13]. They can be carried out under green chemical conditions, including microwave (MW)-assisted synthesis, which are also of special interest [15].

6.2.1 Kabachnik–Fields Reactions in the Presence of Catalysts and Solvents

Most of the papers published in the field of Kabachnik–Fields reaction since 2002 suggest the use of special catalysts [16–25], such as metal triflates [17], lanthanide triflates [17, 18], gallium(III) iodide [19], bismuth(I) nitrate [20], magnesium perchlorate [21, 22], samarium(II) iodide [23], indium(III) chloride [24] and phthalocyanine–$AlCl_3$ complex [25] etc. in solvents or under neat conditions. According to the literature reports, catalytic approaches still dominated over the last five years (Table 6.1). The main goal is to find efficient, cost-effective, reusable and environmentally benign catalysts for the three-component synthesis of α-aminophosphonates. In the case of the condensation of aromatic amines, benzaldehyde derivatives and dialkyl phosphites, the use of triflates was still a common practice (Table 6.1, entries 1–3). In one case, the reaction was carried out with ytterbium triflate [$Yb(OTf)_3$] in water using polyoxyethanyl α-tocopheryl sebacate (PTS) as an amphiphilic species (Table 6.1, entry 1), while in another instance, copper triflate was applied with a fluorous bis(oxazoline) ligands using acetonitrile as the solvent (Table 6.1, entry 2). Pentafluorophenylammonium triflate (PFPAT) was also efficient as a new organocatalyst for the synthesis of α-aminophosphonates at room temperature (Table 6.1, entry 3). Various diethyl(3,5-dibromo-4-hydroxyphenylamino) methylphosphonates were synthesized in a household MW oven using cerium(III) chloride heptahydrate as the catalyst in THF (Table 6.1, entry 4). A series of α-aminophosphonates were prepared *via* a Kabachnik–Fields reaction catalyzed by a gold–bipyridine complex (Table 6.1, entry 5). The three-component condensation of anilines, benzaldehydes and diphenyl phosphite was elaborated in dichloromethane applying zinc(II) di(L-prolinate) as the catalyst (Table 6.1, entry 6). An efficient method has been developed for the synthesis of α-aminophosphonates using a heterogeneous, reusable silica-supported dodecatungstophosphoric acid (DTP/SiO_2) catalyst at room temperature (Table 6.1, entry 7). Polyaniline-methanesulfonic acid salt (PANI-MSA)-coated glass slide in hexane was also an effective catalyst in the reaction of various amines, aldehydes and dimethyl phosphite (Table 6.1, entry 8). A combination of [bmim][$AlCl_4$] ionic liquid and ultrasonic irradiation was used as an alternative to conventional acid catalysts in the Kabachnik–Fields reaction (Table 6.1, entry 9). The ultrasound-assisted synthesis of α-aminophosphonates is reviewed in detail by Bubun and Keglevich in Chapter 13. In another case, 1,4-diazabicyclo[2.2.2]octane hydrochloride

([H-DABCO]Cl) quaternary ammonium salt was applied as the catalyst in methanol (Table 6.1, entry 10). Finally, a nonionic surfactant (Tween-20) catalyzed process was also reported in aqueous media (Table 6.1, entry 11).

Table 6.1: Catalytic Kabachnik–Fields reactions using solvents.



Entry	Y	Z	R	Catalyst	Solvent	*T, t*	Yield (%)	Ref.
1	H, 4-Me, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 4-F, 4-NO_2	H, 4-Me, 4-MeO, 4-Cl, 2-NO_2, 4-NO_2	Et	$Yb(OTf)_3$ (1%)	PTS/H_2O	25 °C, 1 h	83–96	[26]
2	H, 4-Me, 4-MeO, 4-Cl, 4-NO_2	H, 4-Me, 4-MeO, 3-Cl, 4-Cl, 2-Br, 4-F, 3-NO_2, 4-NO_2, 3-CF_3, 4-CF_3, 4-NMe_2	Et	$Cu(OTF)_2$ (5%) with fluorous bis(oxazoline) ligands (5%)	DCM	25 °C, 6 h	73–94	[27]
3	H, 4-MeO, 4-HO, 4-Cl, 4-Br	H, 4-Cl, 4-Br	Me	$C_6F_5NH_3(OTf)$ (PFPAT) (10%)	ACN	25 °C, 1–2 h	85–95	[28]
4[a]	3,5-diBr-4-OH	4-MeO, 4-Cl, 4-HO, 3-NO_2, 4-NMe_2, 2,4-diCl, 2,4-diMeO	Et	$CeCl_3{\cdot}7H_2O$ (5%)	THF	490 W, 8–11 min	89–94	[29]
5	H, 4-Me, 4-MeO, 4-Cl	H, 4-Me, 4-MeO, 4-Cl, 4-Br, 4-NO_2	Et	$[AubpyCl_2]Cl$ (5%)	ACN	40 °C, 3–10 h	85–95	[30]
6	H, 4-Me, 2,6-diMe, 4-MeO, 4-Cl, 4-Br, 4-I, 4-F, 4-NO_2	H, 4-Me, 4-MeO, 4-Cl, 4-Br, 4-F, 3-NO_2, 3-HO, 4-CF_3, 4-NMe_2	Ph	Zn(L-Pro)$_2$ (10%)	DCM	25 °C, 20–60 min	87–98	[31]
7	H, 3-Cl, 4-Cl, 2,4,6-triMe, 4-MeO, 4-NO_2	H, 4-Me, 4-MeO, 2,5-diMeO, 4-Cl,	Me, Et, Bn	DTP/SiO_2 (20%)	ACN	25 °C, 1 h	93–98	[32]
8	H, 4-MeO, 4-Br, 4-NO_2	4-Me, 4-MeO, 4-Cl, 4-OH, 4-NO_2	Me	PANI-MSA-coated glass slide	Hexane	25 °C, 3 h	73–98	[33]

(continued)

Table 6.1: (Continued)

Entry	Y	Z	R	Catalyst	Solvent	*T*, *t*	Yield (%)	Ref.
9[b]	H, 4-Me	H, 2-Me, 4-MeO, 2-Cl, 3-NO_2, 4-NO_2	Me	[bmim][$AlCl_4$] (10%)	MeOH	25 °C, 5–10 min	87–93	[34]
10	H, 4-Me, 4-MeO, 4-F	H	Et	[H-DABCO]Cl (1 equiv.)	MeOH	25 °C, 10–30 min	90–93	[35]
11	H, 2-Me, 4-MeO, 4-Cl, 4-Br, 2-NO_2, 4-NO_2	6-Niroben-zo[*d*]-[1,3] dioxole-5-car-baldehyde	Et	Tween-20 (5%)	Water	60 °C, 25–60 min	82–91	[36]

[a]Under MW irradiation in a household MW oven. [b]Under ultrasonic irradiation.

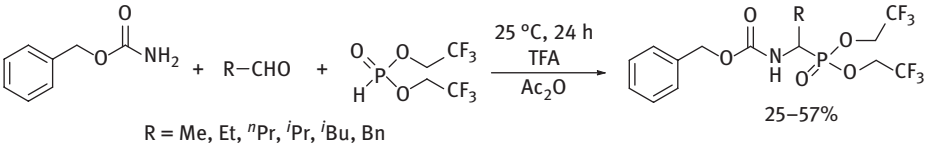


Figure 6.4: Synthesis of bis(trifluoroethyl) esters of α-aminophosphonic acids.

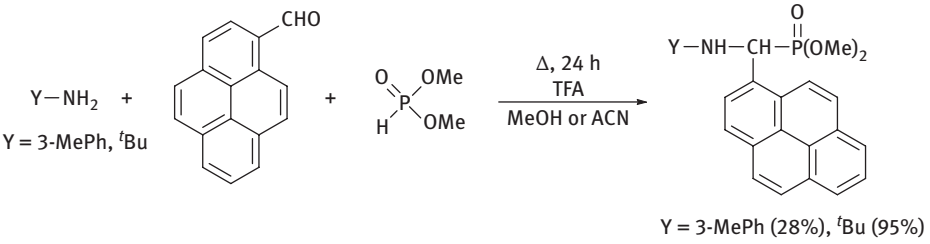


Figure 6.5: Synthesis of pyrene-derived α-aminophosphonates.

Bis(trifluoroethyl) esters of α-aminophosphonic acids were prepared as inhibitors of serine proteases by the reaction of benzyl carbamate, aldehydes and bis(2,2,2-trifluoroethyl) phosphite in the presence of trifluoroacetic acid (TFA) and acetic anhydride (Figure 6.4) [37].

The reaction of 3-methylaniline or *tert*-butylamine with pyrene-1-carboxaldehyde and dimethyl phosphite was also described in the presence of a catalytic amount of TFA (Figure 6.5) [38]. The pyrene-derived α-aminophosphonates obtained showed fluorescent properties.

2-Cyclopropylpyrimidin-4-yl-aryl- and 2-cyclopropylpyrimidin-4-yl-benzothiazole-derived α-aminophosphonates were obtained by the condensation of anilines or *N*-benzothiazole amines, 2-cyclopropylpyrimidin-4-carbaldehyde and dialkyl phosphites using phosphomolybdic acid ($H_3PMo_{12}O_{40}$) as the catalyst in dichloromethane (Figure 6.6) [39].

The three-component condensation of amines, 2-alkynylindole-3-carbaldehydes and dimethyl phosphite was carried out applying a catalytic amount of $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst (Figure 6.7) [40].

Another example for the $BF_3{\cdot}OEt_2$-mediated Kabachnik–Fields reaction involves the preparation of a series of α-aminophosphonates containing a pyrazole moiety (Figure 6.8) [41].

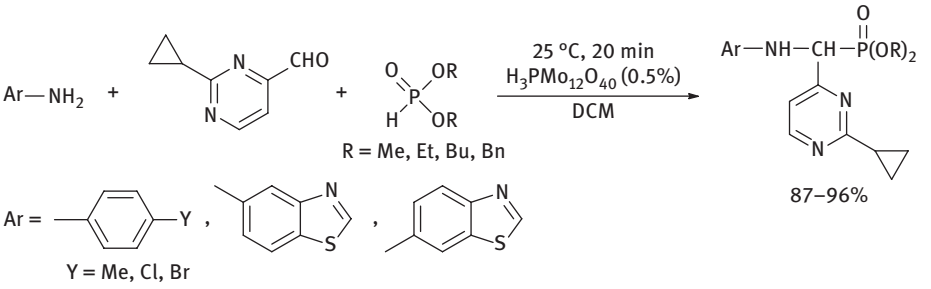


Figure 6.6: Kabachnik–Fields reaction of 2-cyclopropyl pyrimidine-4-carbaldehyde.

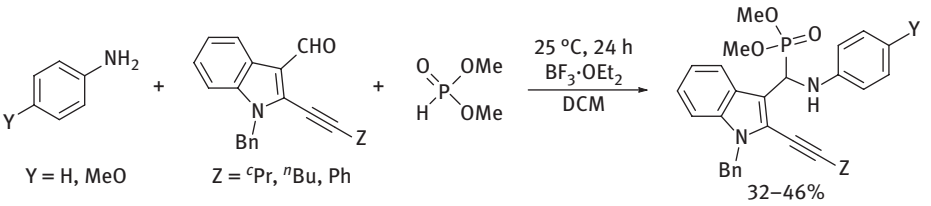


Figure 6.7: Kabachnik–Fields reaction of 2-alkynylindole-3-carbaldehydes.

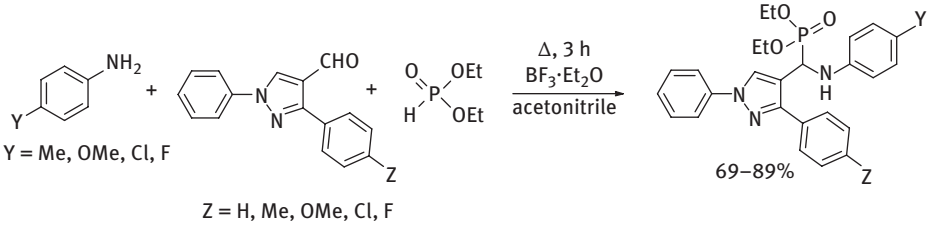
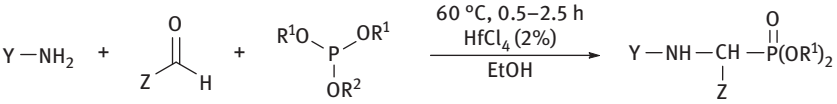


Figure 6.8: Synthesis of α-aminophosphonates with a pyrazole moiety.

In other instances, trialkyl phosphite was used instead of dialkyl phosphite as the P-component in the Kabachnik–Fields condensation. Only a few examples are introduced in the following paragraphs. A series of α-aminophosphonates were synthesized by the condensation of amines, aldehydes and trialkyl phosphites using hafnium(IV) chloride in ethanol (Figure 6.9) [42].

The synthesis of α-aminophosphonates with an isoxazole ring was accomplished using trialkyl phosphites in the presence of iron(III) chloride in THF (Figure 6.10) [43].

A comparative study was reported by our group, where the possibilities for the Kabachnik–Fields reaction of benzylamine, benzaldehyde and triethyl phosphite or diethyl phosphite were investigated in water (Figure 6.11) [44]. It was found that in the case of trialkyl phosphites, *p*-toluenesulfonic acid (PTSA) had to be used as the catalyst. On the other hand, the reaction could be performed without any catalyst, in a solvent-free manner when diethyl phosphite was the P component.



Y = Ph, 4-MeOPh, 4-NCPh, Bn, ^{c}Hex
Z = Ph, 4-MeOPh, ^{c}Hex, ^{s}Bu, pentyl, furyl
R^1 = Me, Et, Ph; R^2 = H or R^1

Figure 6.9: $HfCl_4$-catalyzed Kabachnik–Fields reaction with trialkyl phosphites.

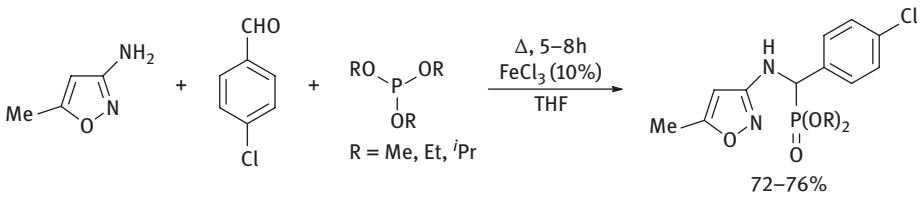


Figure 6.10: $FeCl_3$-catalyzed synthesis of α-aminophosphonates containing an isoxazole ring.

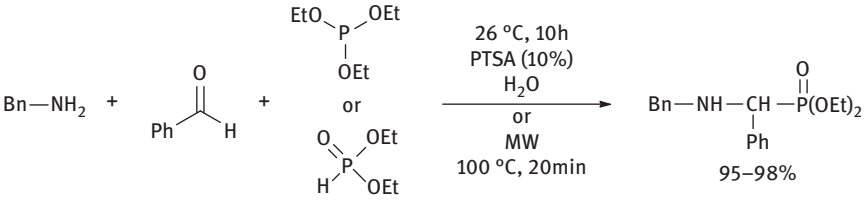
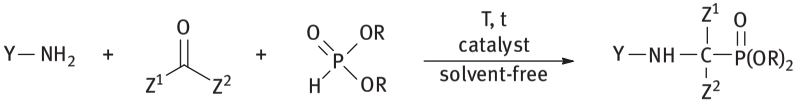


Figure 6.11: Kabachnik–Fields reaction with triethyl phosphite or diethyl phosphite.

6.2.2 Kabachnik–Fields Reactions in the Presence of Catalysts under Solvent-free Conditions

More examples from the literature cover catalytic Kabachnik–Fields reactions under solvent-free conditions (Table 6.2). A series of new fluorinated α-aminophosphonates was synthesized starting from fluorinated aniline derivatives, aldehydes and diethyl phosphite in the presence of $BF_3{\cdot}OEt_2$ (Table 6.2, entry 1). In most cases, metal-containing catalysts were applied in the solvent-free Kabachnik–Fields reactions. For example, the three-component reactions of various amines, aldehydes and dialkyl phophites were performed with zinc acetate dihydrate (Table 6.2, entry 2). In another instance, a series of α-aminophosphonates was prepared in the presence of cadmium perchlorate hydrate (Table 6.2, entry 3). Nickel(II) sulfate hexahydrate was an efficient and reusable catalyst for the synthesis of α-aminophosphonates under mild conditions (Table 6.2, entry 4). Micron-particulate aluminium nitride (AlN/Al) was also applied as a new heterogeneous catalyst in the Kabachnik–Fields condensation (Table 6.2, entry 5). Acid supported magnetite nanoparticles (Fe_3O_4) also acted as novel and effective catalysts for the solvent-free synthesis of *α*-aminophosphonates (Table 6.2, entries 6 and 7). In one case, dehydroascorbic acid (DHAA; Table 6.2, entry 6), while in another case, phosphotungstic acid (PTA) was the acid component of the catalyst (Table 6.2, entry 7). Several α-aminophosphonates were synthesized in MW-assisted reactions of 2-naphthyl- or 2-fluorenylamine, different aldehydes and dimethyl phosphite using a titanium dioxide-silica catalyst (Table 6.2, entry 8). Air-stable zirconocene bis(perfluorobutanesulfonate) was prepared and applied as a catalyst in the solvent-free Kabachnik–Fields reaction of amines, aldehydes/ketones and diethyl phosphite (Table 6.2, entry 9). A series of new pyrenyl-α-aminophosphonates was synthesized by the one-pot reaction of aryl/heteroaryl amines, pyrene aldehyde and diethyl phosphite in the presence of silica-supported polyacrylic acid (PAA; Table 6.2, entry 10). The preparation of quinoline-containing α-aminophosphonate derivatives was elaborated using a polyethyleneimine-grafted mesoporous nanomaterial as the catalyst (Table 6.2, entry 11). Acidic Amberlite-IR 120 resin was also an effective catalyst in the Kabachnik–Fields condensations, which were carried out in a household MW oven (Table 6.2, entry 12). Another acidic catalyst, such as triflic acid supported carbon was found to be suitable for the synthesis of various α-aminophosphonates (Table 6.2, entry 13). Phenylboronic acid-catalyzed Kabachnik–Fields reactions of benzyl amine, aliphatic or aromatic aldehydes and dimethyl phosphite were accomplished in the absence of a solvent (Table 6.2, entry 14). The condensation was extended to aliphatic and aromatic ketones (Table 6.2, entry 15). A facile method was developed for the synthesis of tertiary and quaternary α-aminophosphonates using phenylphosphonic acid as the catalyst (Table 6.2, entry 16). 2,3-Dihydro-1*H*-inden-5-amine and 2-aminofluorene were reacted with various aldehydes and dimethyl phosphite under MW conditions (Table 6.2, entries 17 and 18). In the first case, the condensations were catalyzed with molybdate sulfuric acid (MSA) (Table 6.2, entry 17), while in the latter

Table 6.2: Solvent-free Kabachnik–Fields reactions in the presence of catalysts.

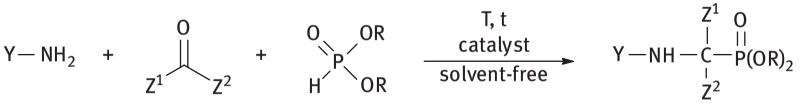


Entry	Y	Z^1	Z^2	R	Catalyst	*T, t*	Yield (%)	Ref.
1	4-FPh, 3,4-diFPh	4-FPh, 2-F-,4-ClPh	H	Et	$BF_3 \cdot Et_2O$	70 °C, 2 h	83–96	[45]
2	2,4-diClPh, 4-BrPh, 4-NO_2Ph	4-HOPh, 4-MeOPh	H	Me, Et, Bn	$Zn(OAc)_2 \cdot H_2O$ (12%)	50 °C, 15–22 min	85–94	[46]
3	Ph, 4-BrPh, 4-FPh, 4-NO_2Ph	Ph, 4-^{i}PrPh, 4-MeOPh, 4-EtOPh, 4-ClPh, 4-BrPh, 4-HOPh, 4-NO_2Ph	H	Me, Et	$Cd(ClO_4)_2 \cdot H_2O$ (5%)	25 or 40 °C, 10–360 min	52–98	[47]
4	Ph, 4-MePh, 4-CF_3Ph	Ph, 4-MeOPh, 4-ClPh, 4-NO_2Ph, 4-biphenyl, 3-furyl	H	Et	$NiSO_4 \cdot 6H_2O$ (5%)	25 °C, 10–20 min	92–98	[48]
5	4-FPh, 4-^{i}PrPh	Ph, 3,4-diMeOPh, 4-MeSPh, 4-HOPh, indole-3-carbaldehyde, fluorene-3-carbaldehyde	H	Et, ^{n}Bu	AlN/Al (5%)	50 °C, 1 h	84–94	[49]
6	Ph, 4-MePh, 4-BrPh	Ph, 4-MePh, 4-MeOPh, 4-ClPh, PhCH=CH, 2-thienyl	H	Me	DHAA–Fe_3O_4 (0.9%)	40 °C, 1–2 h	75–95	[50]
7	Ph, Bn	Ph, 2-MePh, 2-MeOPh, 4-MeOPh, 2-ClPh, 4-ClPh, 2-NO_2Ph, 4-NO_2Ph, 2-CF_3Ph	H	Me, Et	Fe_3O_4@SiO_2-PTA (5%)	25 °C, 3–6 h	72–97	[51]
8[a]	2-Naphthyl, 2-Fluorenyl	4-MePh, 4-HOPh, 4-MeOPh, 4-EtOPh, 4-ClPh 4-BrPh, 4-FPh, 4-NO_2Ph, Et, ^{n}Pr, ^{n}Bu	H	Me	TiO_2–SiO_2 (5%)	70 °C, 3–5 min	85–97	[52]
9	Ph, Bn, 4-MePh, 4-ClPh, 4-NO_2Ph, 4-CF_3Ph, 1-naphthyl, benzidinyl, 2-pyridinyl, 4-pyridinyl, cyclohexyl	Ph, 4-MePh, 4-MeOPh, 4-HOPh, 3-NO_2Ph, 2-CF_3Ph, 4-CF_3Ph, 4-ClPh, 2-BrPh, 4-BrPh, 2-FPh, ^{n}Pr, cyclohexanone	H, Me	Et	$[Cp_2Zr(OSO_2C_4F_9)_2 \cdot 2H_2O]$ (5%)	25 °C, 2.5–12 h	49–98	[53]

10	Ph, 4-MePh, 4-MeOPh, 4-HOPh, 3-ClPh, 4-ClPh, 4-FPh, 4-NO_2Ph, 4-pyridinyl, 6-methyl-2-pyridinyl, 3-isoxazolyl	1-Pyrenyl	H	Et	PAA-SiO_2 (30%)	70 °C, 90–130 min	81–96	[54]
11	Ph, 4-FPh, CH_2CH_2Ph	4-Quinoline-carboxaldehyde		Et, Ph	MCM-41@ PEI (20%)	50–80 °C, 5–6 h	86–91	[55]
12[a]	^{n}Pr, Bn, Ph, 2-HOPh, 4-HOPh, 2-MePh, 2,6-diMePh, 3-ClPh, 3-FPh	Piperonyl, H, 4-MePh, 2-MeOPh, 4-FPh, 3,4-diMeOPh, 3-NO_2Ph, 4-NO_2Ph	H	Et, ^{n}Bu, Ph, allyl	Amberlite-IR 120 (H^+) (10%)	900 W, 1–5 h	79–98	[56]
13	Ph, 4-BrPh, 3-ClPh, 4-ClPh, 3-NO_2Ph, 4-NO_2Ph	Ph, 3-MePh, 4-MePh, 4-^{i}PrPh, 4-MeOPh, 4-HOPh, 2,5-$(MeO)_2$Ph, 3,4-diHOPh, 4-ClPh, 4-FPh	H	Et	TfOH/C (10%)	25 °C, 1–9 h	85–98	[57]
14	Bn	^{i}Pr, ^{s}Bu, ^{t}Bu, 2-MeOPh, 4-MeOPh, 3,4-diMeOPh, 4-ClPh, 3-HOPh	H	Me	$PhB(OH)_2$ (10%)	50 °C, 15–45 min	62–93	[58]
15	Bn	Acetophenone, prophiophenone, acetone, diethyl ketone, methyl ethyl ketone, 1-indanone, 2-indanone, cyclohexanone		Me	$PhB(OH)_2$ (10%)	50 °C, 0.5–8 h	28–93	[58]
16	Bn	3-HOPh, 3,4-diHOPh, 2-MeOPh, 4-MeOPh, 4-ClPh, 4-CF_3Ph, 4-biphenyl, indole-3-yl, pyrrole-2-yl, 2-furyl, Me, Et, ^{n}Pr, ^{i}Pr, ^{i}Bu, ^{t}Bu	H, Me, Et	Me	$PhP(O)(OH)_2$ (10%)	50 °C, 25–100 min	47–98	[59]
17[a]	2,3-Dihydro-1*H*-indenyl	3-MePh, 4-MePh, 4-^{i}PrPh, 4-MeOPh, 4-EtOPh, 4-ClPh, 3-BrPh, 4-BrPh, 2-FPh, 4-FPh, 4-NO_2Ph	H	Me	MSA (5%)	60 °C, 4–10 min	90–97	[60]
18[a]	2-Fluorenyl	4-MePh, 4-MeOPh, 2-ClPh, 4-ClPh, 4-BrPh, 4-FPh, 2-NO_2Ph, 4-NO_2Ph, Et, ^{n}Pr, ^{i}Pr, ^{n}Bu, ^{c}Hex, piperonyl	H	Me	PS/PTSA (5%)	70 °C, 3–5 min	84–98	[61]

(continued)

Table 6.2: (Continued)



Entry	Y	Z^1	Z^2	R	Catalyst	*T, t*	Yield (%)	Ref.
19	Ph, Bn, 4-ClPh, 4-BrPh, 4-FPh	Ph, 4-MeOPh, 2-ClPh, 3-ClPh, 3-BrPh, 4-BrPh, 4-HOPh	H	Et	$C_5H_{14}ClNO \cdot 2ZnCl_2$ IL (15%)	25 °C, 30–120 min	70–98	[62]
20	Ph, 4-MePh, 4-NO_2Ph, ^{n}Pr, Bn	Ph, 4-Ph, 4-MeOPh, 4-HOPh, 4-NO_2Ph, 4-ClPh, 4-BrPh Terephthalaldehyde, 1- or 2-naphthaldehyde, furan-2-carbaldehyde, acetophenone, cyclohexanone	H	Et	MWCNT-[mpIm] HSO_4 (7%)	25 °C, 33–80 min	89–96	[63]
21	Ph, 4-ClPh	Ph, 4-MePh, 4-MeOPh, 3-ClPh, 4-ClPh, 3-NO_2Ph, 4-NO_2Ph	H	Et	Acidic ionic liquid (10%)	50 °C, 1–2.5 h	85–96	[64]
22	Bn, Ph, 2-MeOPh, 2-HOPh, 3-FPh	Ph, 4-MePh, 2-HOPh, 4-HOPh, 3-MeOPh, 4-MeOPh, 4-NO_2Ph 4-MeOPh, 5-HOPh	H	Et	Bakers' yeast, phosphate buffer (pH 7.0), D-glucose	25 °C, 36–48 h	55–83	[65]

[a]Under microwave irradiation in a household MW oven.

instance, polystyrene-supported PTSA was applied (Table 6.2, entry 18). Ionic liquids may also be important as catalysts in Kabachnik–Fields reactions. In one example, the condensations were performed using choline chloride·2$ZnCl_2$ ionic liquid (Table 6.2, entry 19). In the next two instances, the utilization of 1-methyl-3-(ethoxysilylpropyl)-imidazolium hydrogensulfate anchored on multiwalled carbon nanotube (MWCNT) and benzimidazolium-based dicationic acidic ionic liquid as catalysts was reported (Table 6.2, entries 20 and 21). A biocatalyst-, such as bakers' yeast-mediated synthesis of α-aminophosphonates was also described (Table 6.2, entry 22).

A SiO_2–$ZnBr_2$-catalyzed variation of the Kabachnik–Fields reaction of 4-(4-chlorophenoxy)aniline, various aldehydes and diethyl phosphite was developed (Figure 6.12) [66]. The condensations were carried out under conventional heating, as well as ultrasonic and MW irradiation. The latter one proved to be more efficient, than the others, and the corresponding α-aminophosphonates were obtained in yields of 93–98%.

A wide range of α-aminophosphonates containing a 1,3,4-thiadiazole moiety was prepared by the three-component condensation of 2-amino-5-ethyl-1,3,4-thiadiazole, aldehydes and diethyl phosphite (Figure 6.13) [67]. The reactions were performed in a household MW oven using phosphosulfonic acid, as a reusable heterogeneous solid acid catalyst.

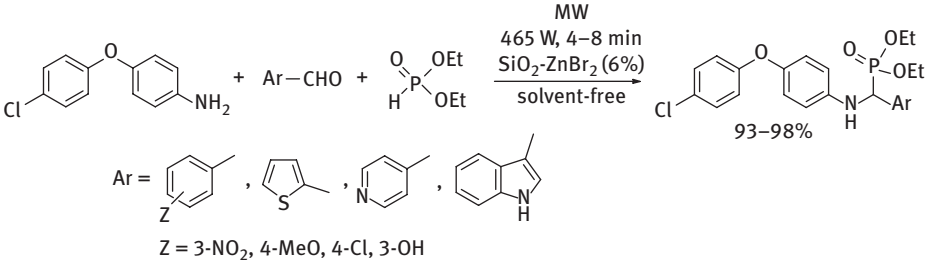


Figure 6.12: Kabachnik–Fields reaction of 4-(4-chlorophenoxy)aniline under MW conditions.

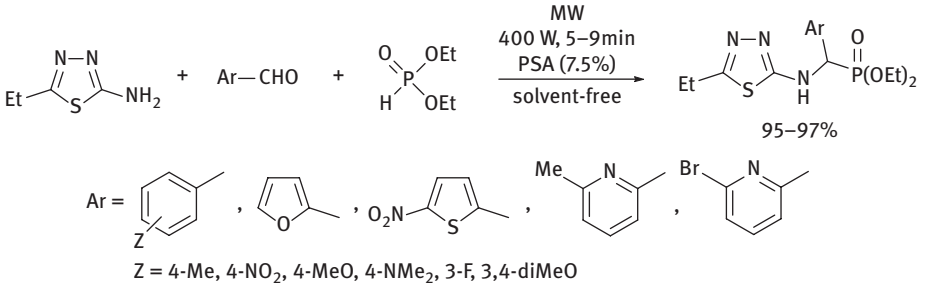


Figure 6.13: Synthesis of thiadiazolyl aminophosphonates under MW irradiation.

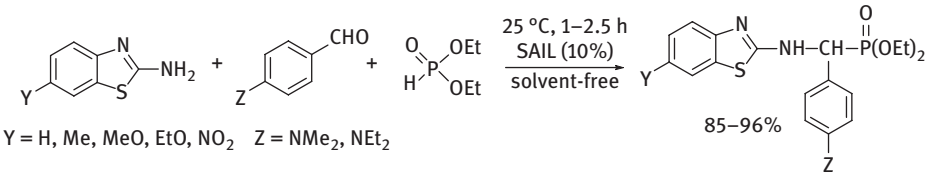


Figure 6.14: Kabachnik–Fields reaction of 2-aminobenzothiazoles in the presence of an acidic ionic liquid.

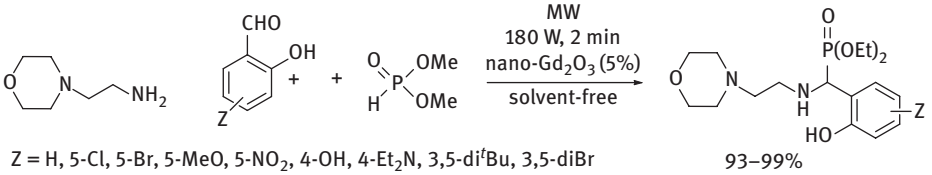


Figure 6.15: Nano-Gd_2O_3-catalyzed synthesis of α-aminophosphonates incorporating an *N*-morpholinoethyl moiety.

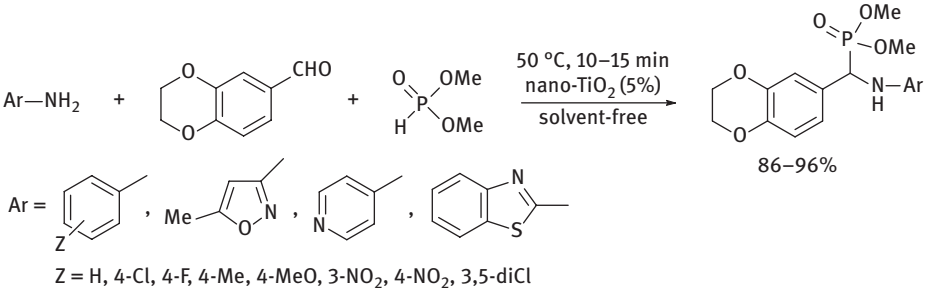


Figure 6.16: Synthesis of dimethyl (2,3-dihydrobenzodioxinyl)-(arylamino)-methylphosphonates.

A sulfonic acid-functionalized ionic liquid was synthesized and applied as the catalyst in the solvent-free synthesis of *N*-benzothiazolyl-α-aminophosphonates (Figure 6.14) [68].

2-Morpholinoethanamine was reacted with salicylaldehydes and dimethyl phosphite using gadolinium oxide nanopowder (nano-Gd_2O_3) under neat conditions (Figure 6.15) [69]. The condensations were performed in a household MW oven, and the corresponding α-aminophosphonates were obtained in yields of 93–99%.

The reaction of various amines, 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde and dimethyl phosphite was carried out in the presence of nano-TiO_2 at 50 °C for 10–15 min (Figure 6.16) [70].

L-Cysteine-functionalized magnetic nanoparticles were used as magnetic reusable catalysts in the synthesis of α-aminophosphonates incorporating benzimidazole, theophylline or adenine nucleobases (Figure 6.17) [71].

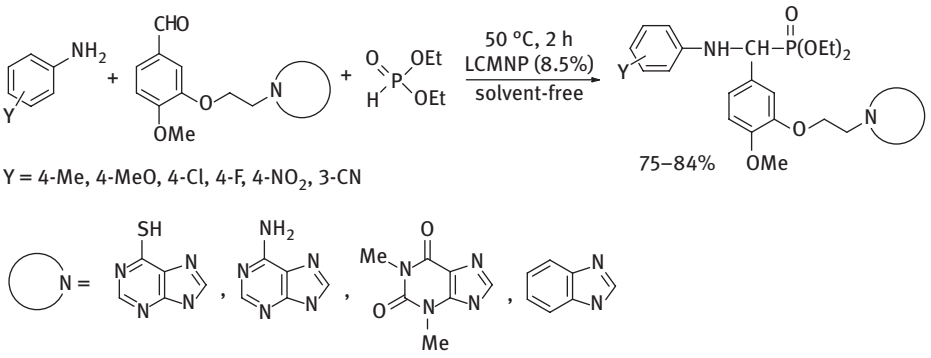


Figure 6.17: Synthesis of α-aminophosphonates containing a benzimidazole, theophylline or adenine moiety

6.2.3 Catalyst-free Kabachnik–Fields Reactions

Only a few examples have been reported on the catalyst-free Kabachnik–Fields condensations. A number of carbazole- and phenothiazine-based α-aminophosphonates were prepared by the reaction of aniline derivatives, bromo-9-ethyl-9*H*-carbazole-3-carbaldehyde or 10-ethyl-10*H*-phenothiazine-3-carbaldehyde and diethyl phosphite using polyethylene glycol (PEG) as a green reaction media (Figure 6.18) [72, 73].

An MW-assisted catalyst- and solvent-free Kabachnik–Fields reaction of amines, aldehydes and dimethyl phosphite was also described (Figure 6.19) [74]. The condensations were carried out in a multimode MW reactor at 80 °C, and the corresponding α-aminophosphonates were obtained in yields of 40–98%.

An eco-friendly accomplishment for the synthesis of various α-aminophosphonates and α-aminophosphine oxides was developed by the Keglevich group (Figure 6.20) [75].

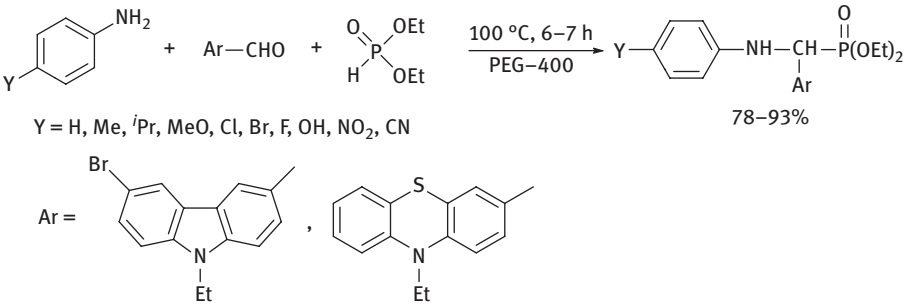


Figure 6.18: Synthesis of carbazole- and phenothiazine-based α-aminophosphonates.

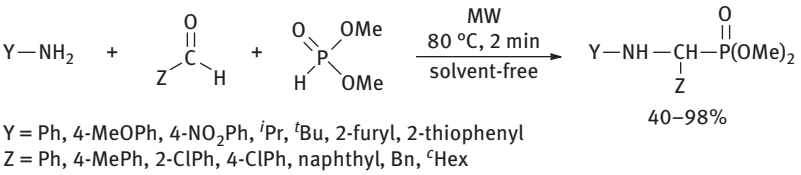


Figure 6.19: MW-assisted catalyst- and solvent-free Kabachnik–Fields reactions.

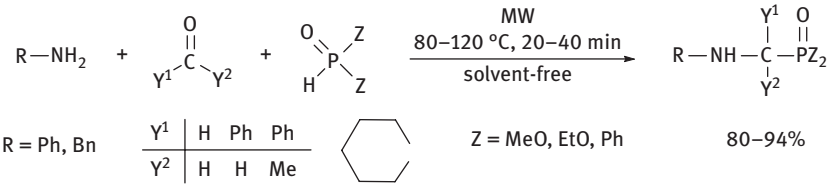


Figure 6.20: MW-assisted synthesis of α-aminophosphonates in the absence of catalyst and solvent.

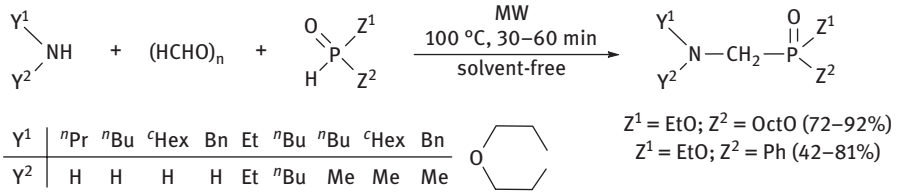


Figure 6.21: Green accomplishment of Kabachnik–Fields reactions with ethyl octyl phosphite and alkyl phenyl-*H*-phosphinates.

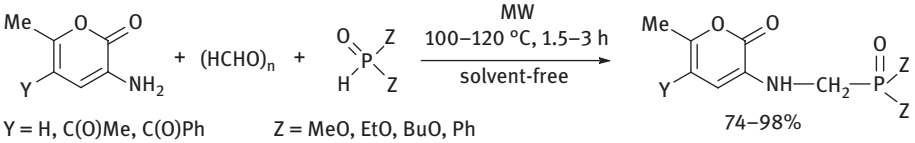


Figure 6.22: Kabachnik–Fields reaction of 3-amino-6-methyl-2*H*-pyran-2-ones under green conditions.

The MW-assisted Kabachnik–Fields reactions of primary or secondary amines, paraformaldehyde and ethyl octyl phosphite or alkyl phenyl-*H*-phosphinates were investigated by our research group (Figure 6.21) [76, 77].

A series of new *N*-(2*H*-pyranonyl)-α-aminophosphonates and α-aminophosphine oxides was obtained in high yields under catalyst-free MW conditions (Figure 6.22) [78]. When dialkyl phosphites were used, the condensations were carried out in the

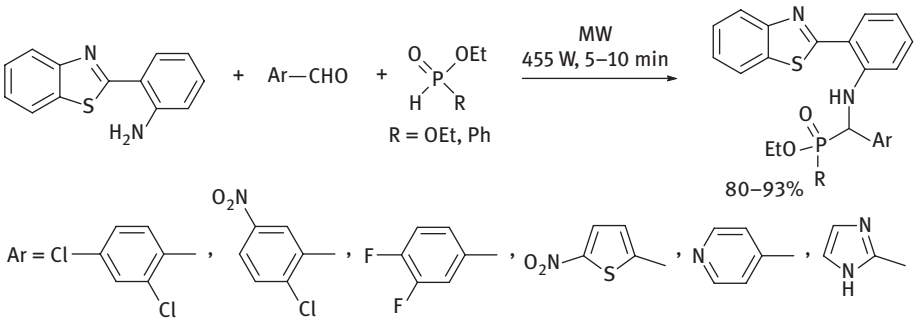


Figure 6.23: Kabachnik–Fields reaction of 2-(2-aminophenyl)benzothiazole.

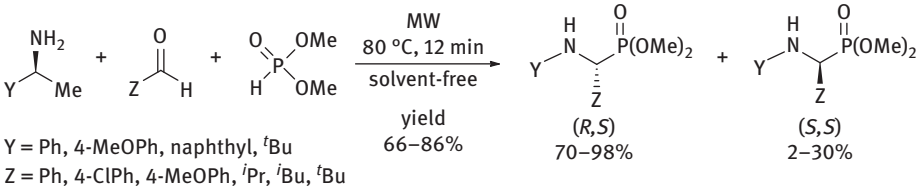


Figure 6.24: Diastereoselective synthesis of α-aminophosphonates.

absence of a solvent. On the other hand, acetonitrile had to be used when diphenyl phosphine oxide was the P component.

The Kabachnik–Fields reaction of 2-(2-aminophenyl)benzothiazole, aromatic or heteroaromatic aldehydes and diethyl phosphite or ethyl phenyl-*H*-phosphinate was performed in a household MW oven without any catalyst and solvent (Figure 6.23) [79].

Ordónez and co-workers reported a catalyst- and solvent-free MW-assisted, highly diastereoselective synthesis of α-aminophosphonates by the condensation of chiral amines, alkyl or aryl aldehydes and dimethyl phosphite (Figure 6.24) [80].

(*S*)-α-Phenylethylamine was applied as a chiral building block in MW-assisted Kabachnik–Fields condensations with paraformaldehyde and various >P(O)H reagents affording the formation of optically active α-aminophosphonate derivatives (Figure 6.25) [81].

A convenient approach was elaborated for the synthesis of novel heterocyclic α-aminophosphonates starting from primary amines, 2-hydroxybenzaldehyes or 2-hydroxyacetophenones and dialkyl phosphites (Figure 6.26) [82].

A wide range of α-ureidophosphonates was synthesized by the catalyst-free condensation of urea, benzaldehyde derivatives and diethyl phosphite in toluene (Figure 6.27) [83].

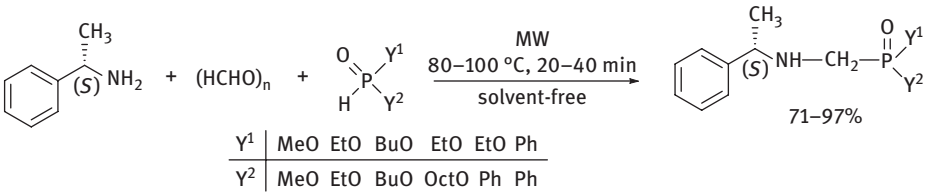


Figure 6.25: Synthesis of optically active α-aminophosphonate derivatives.

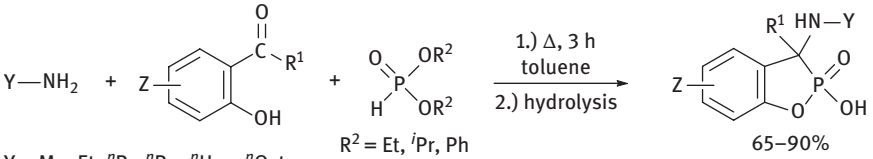


Figure 6.26: Synthesis of a dihydro-oxaphosphole oxide by the Kabachnik–Fields condensation followed by subsequent transformation.

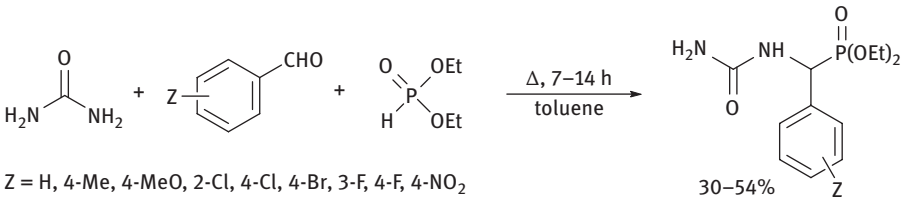


Figure 6.27: Synthesis of α-ureidophosphonates.

6.3 Double Kabachnik–Fields Reactions

In the double Kabachnik–Fields (bis(phospha-Mannich)) condensation, a primary amine reacts with 2 equivalents of a carbonyl compound (aldehyde or ketone) and with 2 equivalents of a P-reagent, such as dialkyl phosphite or secondary phosphine oxide (Figure 6.28). This reaction is an elegant synthetic route for the preparation of bis(α-aminophosphonates) and related derivatives.

According to the literature, double Kabachnik–Fields reactions are usually carried out in various solvents, without any catalyst [84–91]. Nowadays, green chemical approaches, such as the catalyst- and solvent-free MW-assisted syntheses, have also became more and more popular [77, 92–96].

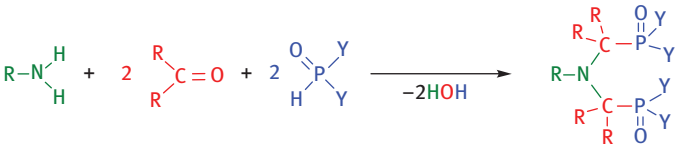
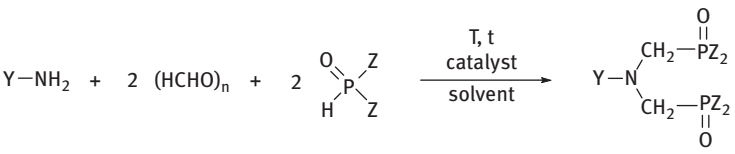


Figure 6.28: General scheme for the double Kabachnik–Fields reaction.

6.3.1 Double Kabachnik–Fields Reactions of Primary Amines

Most of the papers published in the field of double Kabachnik–Fields reaction deal with the condensation of various primary amines, 2 equivalents of formaldehyde or paraformaldehyde and the same amount of dialkyl phosphites or secondary phosphine oxides (Table 6.3). In two examples, acidic or basic catalyst was used (Table 6.3, entries 1 and 2). In one case, the three-component reaction was carried out in the presence of PTSA as the catalyst in toluene (Table 6.3, entry 1) [97]. In another instance, potassium carbonate was applied as the catalyst without any solvent (Table 6.3, entry 2) [98]. The catalyst-free reaction of benzylamine with 2 equivalents of paraformaldehyde and diethyl phosphite was carried out in D_2O (Table 6.3, entry 3) [84]. The catalyst-free double Kabachnik–Fields reactions were also performed using propargyl amine, formaldehyde or paraformaldehyde and dimethyl phosphite (Table 6.3, entry 4) [85, 86].

Table 6.3: Double Kabachnik–Fields reactions in the presence of catalysts and/or solvents.



Entry	Y	Z	Catalyst	Solvent	*T, t*	Yield (%)	Ref.
1	Bn	BuO	PTSA (15%)	Toluene	110 °C, 24 h	72	[97]
2	CH_2=$CHCH_2$, ^{n}Bu, Bn, ^{c}Hex	EtO	K_2CO_3 (1.4%)	–	100 °C, 4 h	78–84	[98]
3[a]	Bn	EtO	–	D_2O	0 °C → 110 °C, 72 h	57	[84]
4	HC≡CCH_2	MeO	–	THF	25 °C → 70 °C, 12 h	60/76	[85, 86]

[a]Deuterated paraformaldehyde $(DCDO)_n$ was applied.

The three-component reactions of propylamine or 4-aminopyridine with 2 equivalents of both the heterocyclic aldehydes and the diethyl phosphite were elaborated without any catalyst in toluene (Figure 6.29) [87]. The corresponding bis(aminophosphonates) were synthesized in 73–95% yields.

The MW-assisted catalyst- and solvent-free double Kabachnik–Fields condensation of primary amines, paraformaldehyde and various >P(O)H reagents, such as dialkyl phosphites, alkyl phenyl-*H*-phosphinates or oxaphosphorine oxide derivatives, was described by our research group (Figure 6.30) [77, 92, 93].

Amino acid derivatives may also be the starting materials in the Kabachnik–Fields reaction. The condensation of 4-(aminomethyl)benzoic acid, 2 equivalents of paraformaldehyde and the same amount of dimethyl phosphite was carried out in THF, and 4-[[bis[(dimethoxyphosphinyl)-methyl]-amino]-methyl]-benzoic acid was obtained in excellent yield (Figure 6.31) [88].

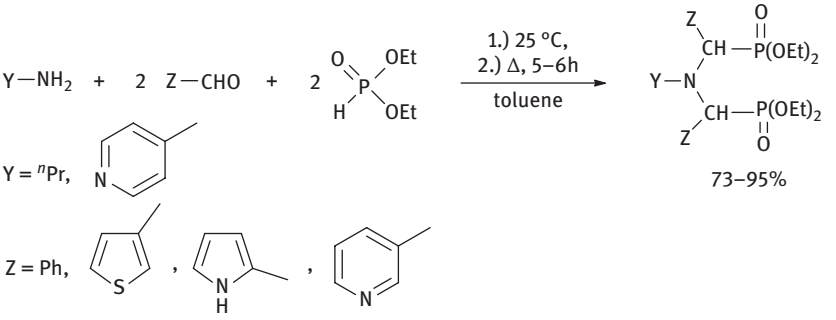


Figure 6.29: Double Kabachnik–Fields reaction of heterocyclic aldehydes.

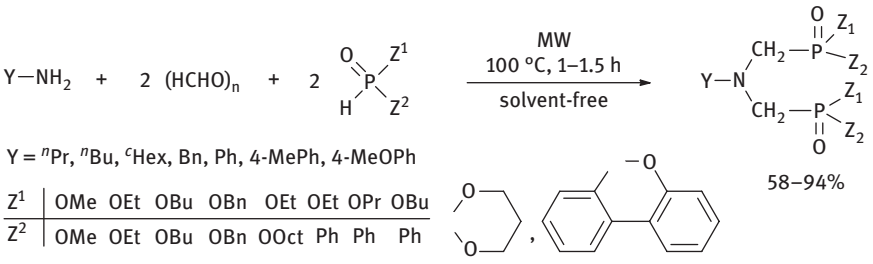


Figure 6.30: Catalyst- and solvent-free double Kabachnik–Fields reaction.

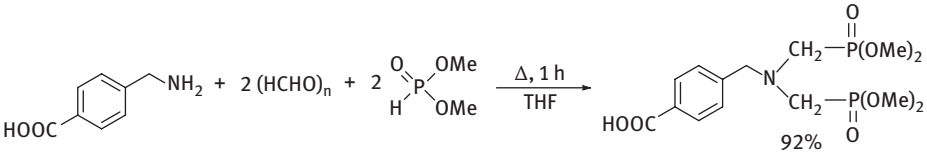
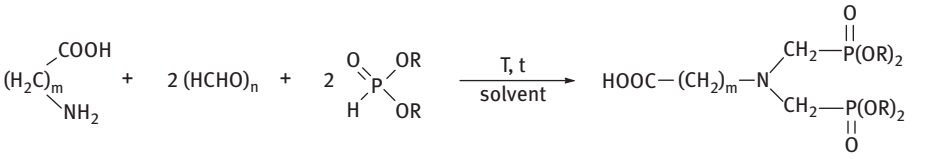


Figure 6.31: Kabachnik–Fields reaction using 4-(aminomethyl)benzoic acid as the starting material.

Table 6.4: Double Kabachnik–Fields reactions of long-chain amino acids.



Entry	m	R	Solvent	T, t	Yield (%)	Ref.
1	5, 10	Me	THF	66 °C, 2 h	92, 95	[88]
2	5, 10	Oct	Acetonitrile	82 °C, 3 h	81, 84	[89]

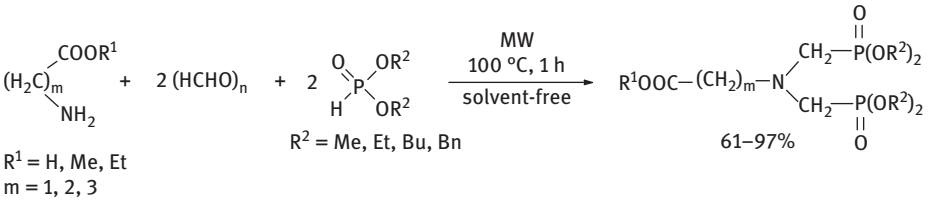


Figure 6.32: Kabchnik–Fields reactions of α-, β- and γ-amino acid derivatives under green conditions.

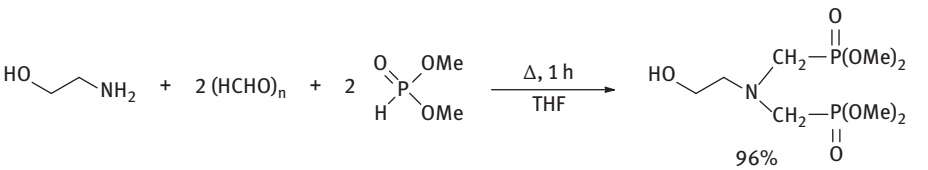


Figure 6.33: Double Kabachnik–Fields reaction of ethanolamine.

The reactions of long-chain amino acids with 2 equivalents of paraformaldehyde and dimethyl or dioctyl phosphite were also described (Table 6.4) [88, 89]. The condensations were performed in THF or in acetonitrile, and the corresponding bis(α-aminophosphonates) were obtained in 81–95% yields.

The catalyst- and solvent-free MW-assisted condensation of α-, β- and γ-amino acid derivatives with 2 equivalents of paraformaldehyde and 2 equivalents of dialkyl phosphites was studied in our group (Figure 6.32) [94, 95].

Ethanolamine was reacted with 2 equivalents of paraformaldehyde and 2 equivalents of dimethyl phosphite in THF, and the corresponding bis(α-aminophosphonate) was obtained in a yield of 96% (Figure 6.33) [88].

The double condensation of amino-terminated polyethylene glycol was accomplished with 2 equivalents of formalin and dimethyl phosphite in THF (Figure 6.34) [90].

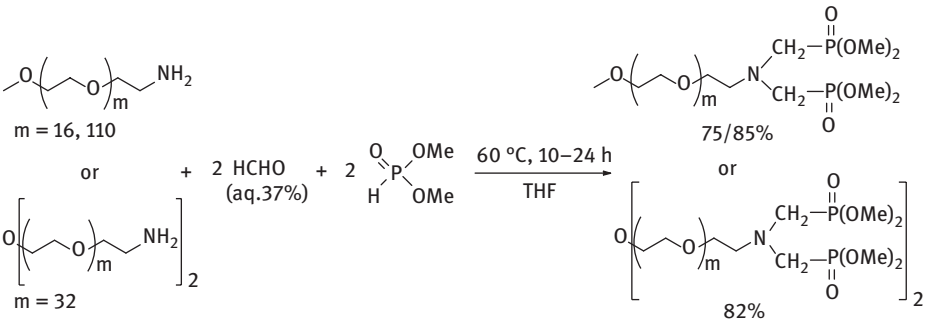


Figure 6.34: Preparation of bis(aminophosphonates) incorporating polyethylene glycol moiety.

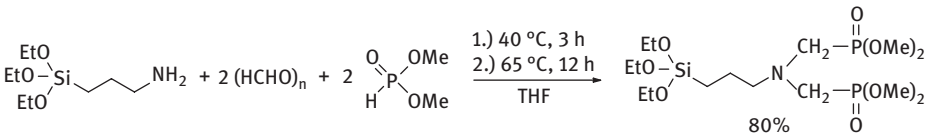


Figure 6.35: Synthesis of 3-(triethoxysilyl)propylazanediyl containing bis(aminophosphonate).

(3-Aminopropyl)triethoxysilane was also applied as the starting material in the double Kabachnik–Fields reaction, and the bis(aminophosphonate) obtained was applied as a novel flame retardant (Figure 6.35) [91].

6.3.2 Double Kabachnik–Fields Reactions of Diamines and Dialdehydes

According to the literature, there are several particular examples for the Kabachnik–Fields condensation of diamines and dialdehydes also affording bis(aminophosphonate) derivatives. Milen and co-workers studied the one-pot reaction of *p*-phenylenediamine, 2 equivalents of aromatic aldehydes and the same amount of diethyl phosphite in the presence of propylphosphonic anhydride (T3P®) yielding diamine bisphosphonate derivatives (Figure 6.36) [99].

The three-component condensation of *p*-phenylenediamine or benzidine, various aldehydes and diethyl phosphite was also performed using a benzimidazolium dicationic ionic liquid as the catalyst (Figure 6.37) [100]. The advantages of this method were the high yields and the reusability of the catalyst.

Cerium(III) chloride heptahydrate supported silica ($CeCl_3 \cdot 7H_2O$-SiO_2) was used as a catalyst for the double Kabachnik–Fields reaction of a 4,4'-sulfonyldianiline, aldehydes and diethyl phosphite (Figure 6.38) [101]. The condensation was carried out under conventional heating and MW irradiation. The latter method proved to be more efficient.

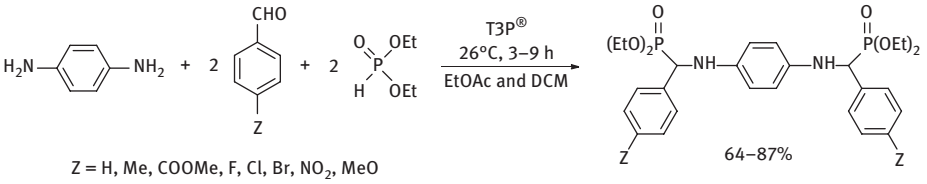


Figure 6.36: T3P®-catalyzed Kabachnik–Fields reaction of *p*-phenylenediamine.

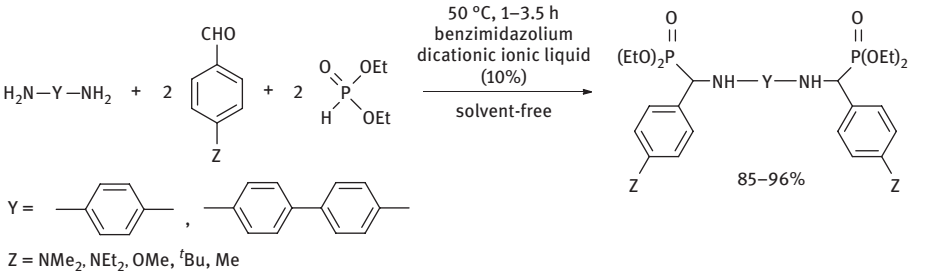


Figure 6.37: Condensation of diamines, aromatic aldehydes and diethyl phosphite.

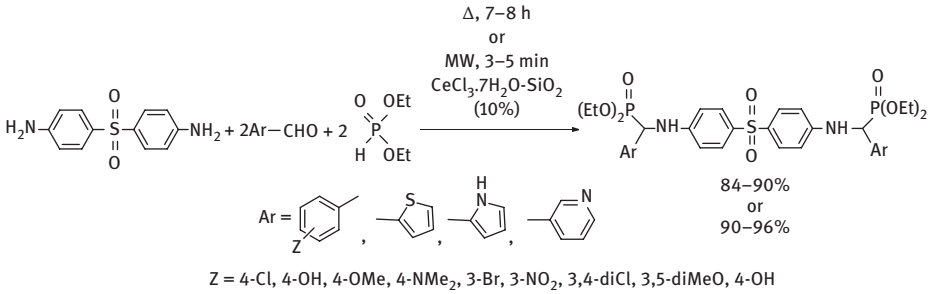


Figure 6.38: Synthesis of α-diaminophosphonates in the presence of $CeCl_3 \cdot 7H_2O$-SiO_2.

Diamines were also reacted with 2 equivalents of 9-anthracenecarboxaldehyde and the same amount of diethyl phosphite in benzene without the use of catalyst (Figure 6.39) [102].

PEG-600 in water, as a green reaction media, was used in the three-component condensation of 4,4′-dioxyaniline, 2 equivalents of aromatic aldehyde and 2 equivalents of diphenyl phosphite (Figure 6.40) [103].

The catalyst- and solvent-free condensation of 2,6-di(aminomethyl)pyridine with formaldehyde and diethyl phosphite was studied at 100 °C. The tetramethylphosphonic octaethyl ester was obtained in a yield of 60% (Figure 6.41) [104].

A solvent- and catalyst-free MW-assisted method was developed for the one-pot reaction of a dialdehyde, 2 equivalents of aromatic amines and 2 equivalents of diethyl- or dibutyl phosphite (Figure 6.42) [105].

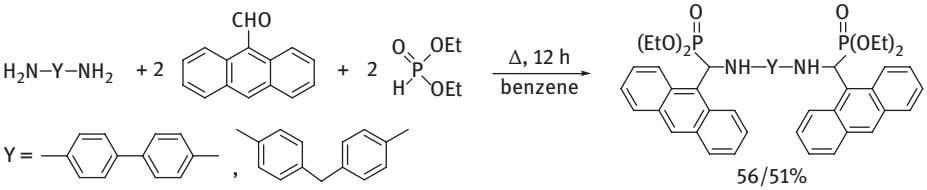


Figure 6.39: Kabachnik–Fields reaction using 9-anthracenecarboxaldehyde.

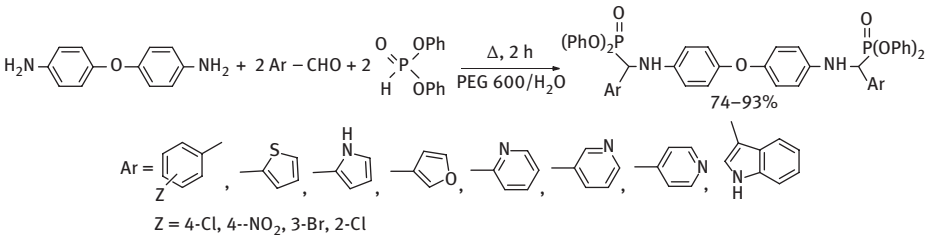


Figure 6.40: Double Kabachnik–Fields reaction applying PEG-600 in water.

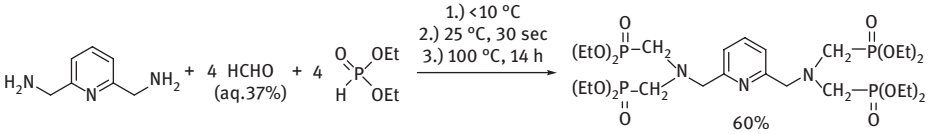


Figure 6.41: Catalyst- and solvent-free synthesis of a tetramethylphosphonic ethyl ester

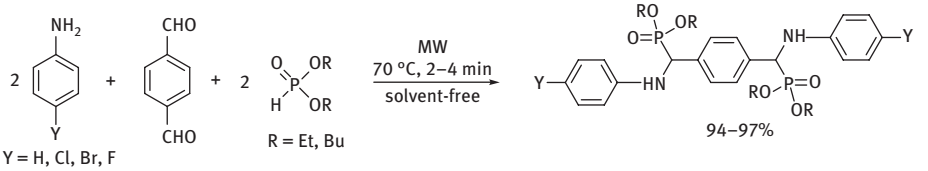
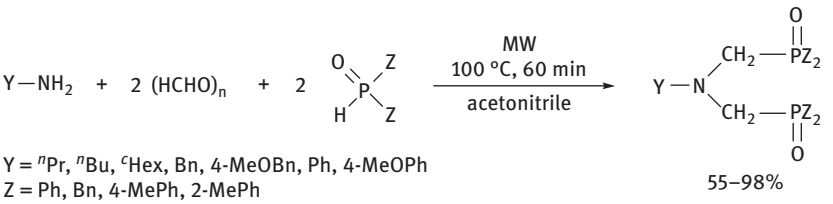


Figure 6.42: Synthesis of bis(α-aminophosphonates) under MW conditions.

6.3.3 An Insight into the Synthesis and Utilization of Bis(Aminophosphine Oxides)

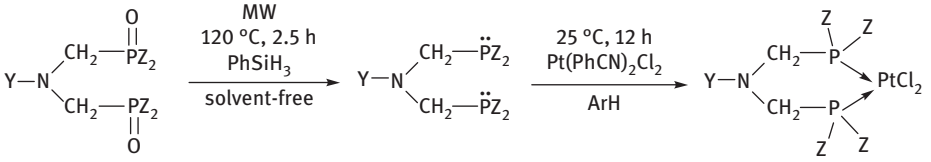
In our research group, the catalyst-free MW-assisted double Kabachnik–Fields reaction of primary amines, 2 equivalents of paraformaldehyde and the same amount of secondary phosphine oxides in acetonitrile was elaborated for the synthesis of bis(aminophosphine oxides) (Figure 6.43) [93, 96].

The bis(phosphinoylmethyl)amines were utilized as precursors of bidentate phosphine ligands [93, 96]. The bisphosphines obtained after double deoxygenation



Y = ^{n}Pr, ^{n}Bu, ^{c}Hex, Bn, 4-MeOBn, Ph, 4-MeOPh
Z = Ph, Bn, 4-MePh, 2-MePh

Figure 6.43: The MW-assisted synthesis of bis(aminophosphine oxides).



Y = ^{n}Bu, ^{c}Hex, Bn
Z = Ph, Bn, 4-MePh

Figure 6.44: Utilization of bis(phosphinoylmethyl)amines as precursors of bidentate P-ligands.

were converted to cyclic platinum complexes, which were tested as catalysts in the hydroformylation of styrene (Figure 6.44).

6.4 The Pudovik Reaction

The Pudovik (also known as aza-Pudovik) reaction of imines and >P(O)H reagents (such as dialkyl phosphites, alkyl phenyl-*H*-phosphinates or secondary phosphine oxides) represents a common synthetic route towards α-aminophosphonates, α-aminophosphinates and α-aminophosphine oxides [106]. In most cases, α-(aryl or hetaryl)-α-aminophosphonate derivatives were prepared by this reaction, starting from α-aryl or α-hetaryl imines, while aliphatic Schiff bases are used rather rarely [107, 108]. Asymmetric syntheses of α-aminophosphonate derivatives were also described applying chiral starting materials or chiral catalysts. The most recent developments of the Pudovik reaction are summarized in the following section.

6.4.1 Pudovik Reactions of α-aryl Imines

6.4.1.1 Pudovik Reactions in the Presence of Catalysts and Solvents

α-Aminophosphonates bearing an *N*-indazole moiety were prepared by the addition of diethyl phosphite on the C=N unit of *N*-indazole imines. The reactions were performed in ethanol with tetramethyl guanidine (TMG) as the catalyst (Figure 6.45) [109].

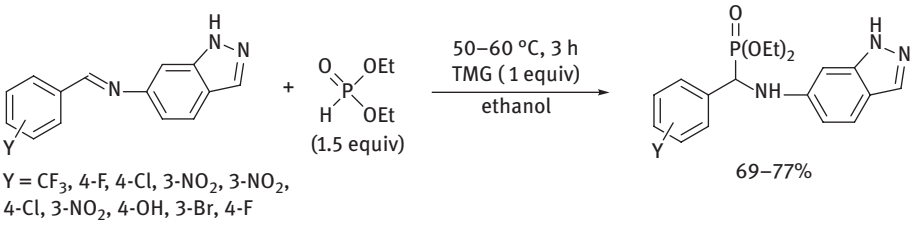


Figure 6.45: Addition of diethyl phosphite to *N*-indazole imines catalyzed by TMG.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was also checked as a catalyst in Pudovik reactions. The products were obtained in yields of 75–88%. The use of a large excess (4 equivalents) of both diethyl phosphite and DBU were necessary for the reaction completion at 60 °C after 24 h (Figure 6.46) [110].

New α-aminophosphonates were prepared by the reaction of an α-anthryl Schiff base with dimethyl phosphite in toluene applying CdI_2 as the catalyst. The product showed only weak genotoxic and cytotoxic activity in *in vivo* tests (Figure 6.47) [111].

A nucleophilic carbene, such as 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene was also applied as an organocatalyst in the Pudovik reaction of (*N*-benzilidene)butylamine and dimethyl phosphite in THF (Figure 6.48) [112].

A complex with Yb and Li central atoms was synthesized and used as a catalyst in the Pudovik reaction of aromatic imines. After a reaction at 40 °C for 6 h in acetonitrile, the target compounds were obtained in yields of 42–99% (Figure 6.49) [113].

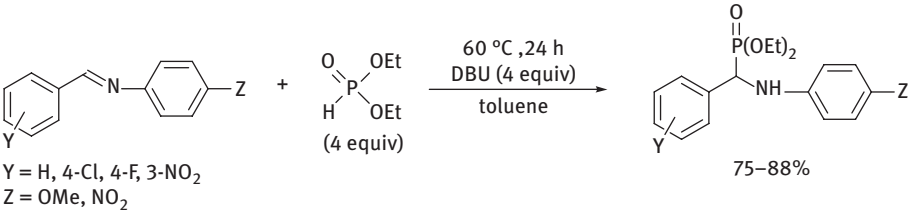


Figure 6.46: DBU-promoted synthesis of α-aminophosphonates.

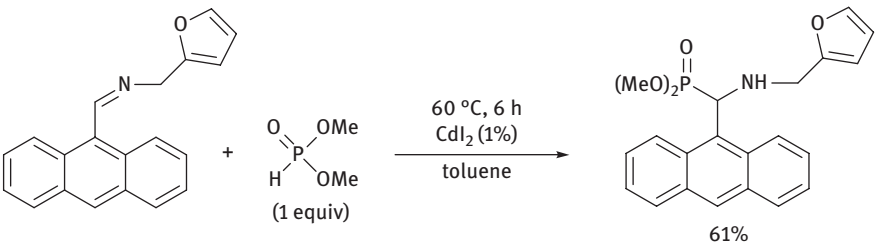


Figure 6.47: Pudovik reaction catalyzed by CdI_2.

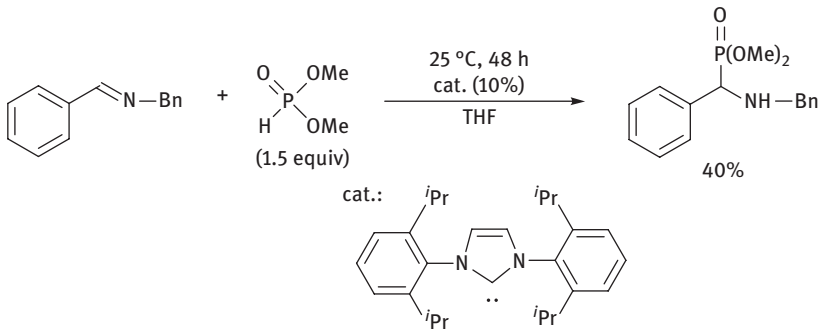


Figure 6.48: A nucleophilic carbene used as an organocatalyst in the Pudovik reaction.

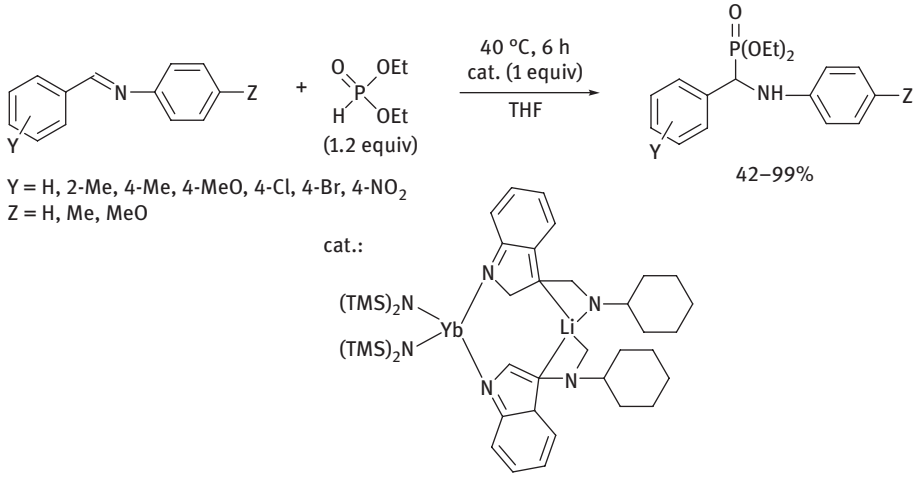


Figure 6.49: Pudovik reaction catalyzed by a Yb- and Li-containing complex.

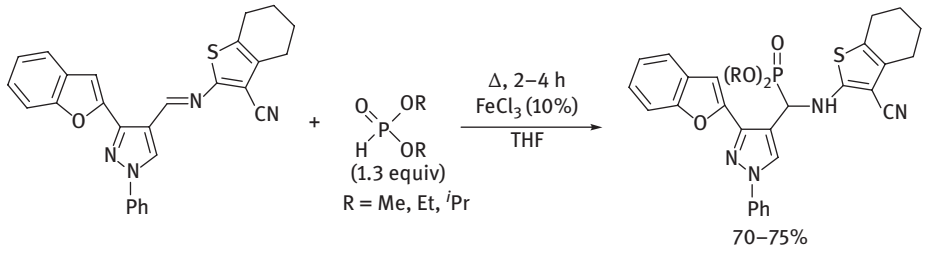


Figure 6.50: Hydrophosphonylation of a pyrazole-containing imine catalyzed by $FeCl_3$.

A pyrazole-containing Schiff base was converted to the corresponding α-aminophosphonates by hydrophosphonylations using dialkyl phosphites and $FeCl_3$ catalyst in THF. The target compounds were obtained in yields of 70–75% (Figure 6.50) [114].

TMG was a useful catalyst in the preparation of α-aminophosphonates with α-thiophene and *N*-carbazole moieties. The addition of dialkyl phosphites led to the products in yields of 78–86% (Figure 6.51) [115].

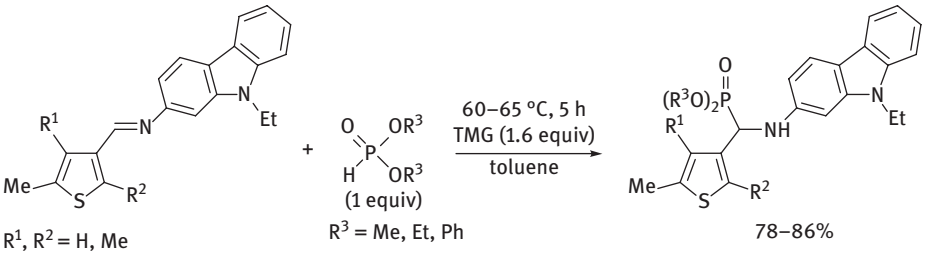


Figure 6.51: TMG-mediated Pudovik reaction of imines with α-thiophene and *N*-carbazole moieties.

6.4.1.2 Pudovik Reactions in the Presence of Catalysts under Solvent-free Conditions

The addition of dialkyl phosphites to the C=N double bond of imines derived from amlodipine was performed in the presence of $SnCl_2{\cdot}2H_2O$ as the catalyst. The ultrasound-mediated procedure was compared with a control experiment carried out using conventional heating. In the case of sonication, the reaction times of 4–6 h could be shortened to 20–24 min. The products showed antibacterial, antiviral and antifungal activities (Figure 6.52) [116].

MoO_2Cl_2 was also used as an efficient catalyst in the Pudovik reactions of aromatic Schiff bases. After 5–60 min of reaction times at 80 °C, the α-aminophosphonates were obtained in yields of 80–95% (Figure 6.53) [117].

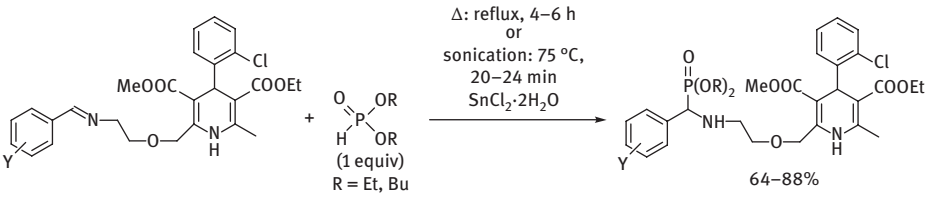


Figure 6.52: Addition of dialkyl phosphites to imines derived from amlodipine.

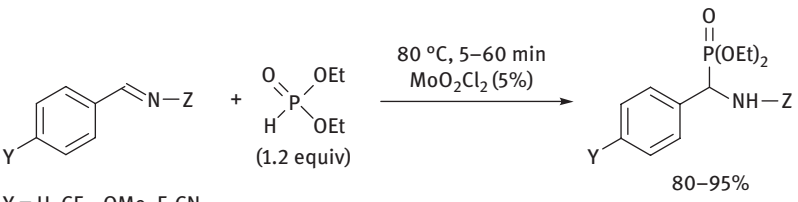
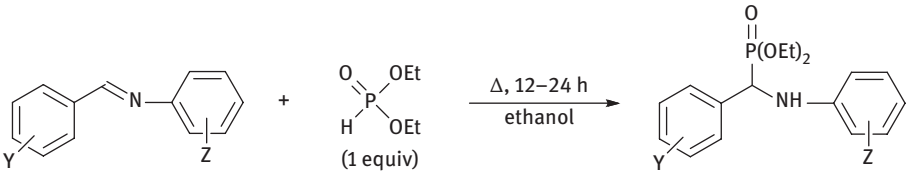


Figure 6.53: MoO_2Cl_2-catalyzed Pudovik reactions.

6.4.1.3 Catalyst-free Pudovik Reactions in Solvents

A number of α-aryl and *N*-aryl aminophosphonates were prepared by the reaction of the corresponding imines with diethyl phosphite in ethanol. Despite the rather long (12–24 h) reaction times, only moderate yields (30–64%) could be reached (Figure 6.54) [118, 119].

A fluorescent aminophosphonate library was synthesized by the Pudovik reaction. The Schiff bases incorporating potentially fluorescent groups were reacted with dibenzyl and diphenyl phosphites in THF (Figure 6.55) [120].



Y = H, 2-OMe, 2-OH, 4-Cl, 2-NO_2, 4-NO_2
Z = H, 2-Cl, 4-Cl, 2-Br, 4-NO_2,

Figure 6.54: Pudovik reaction of aromatic imines with diethyl phosphite.

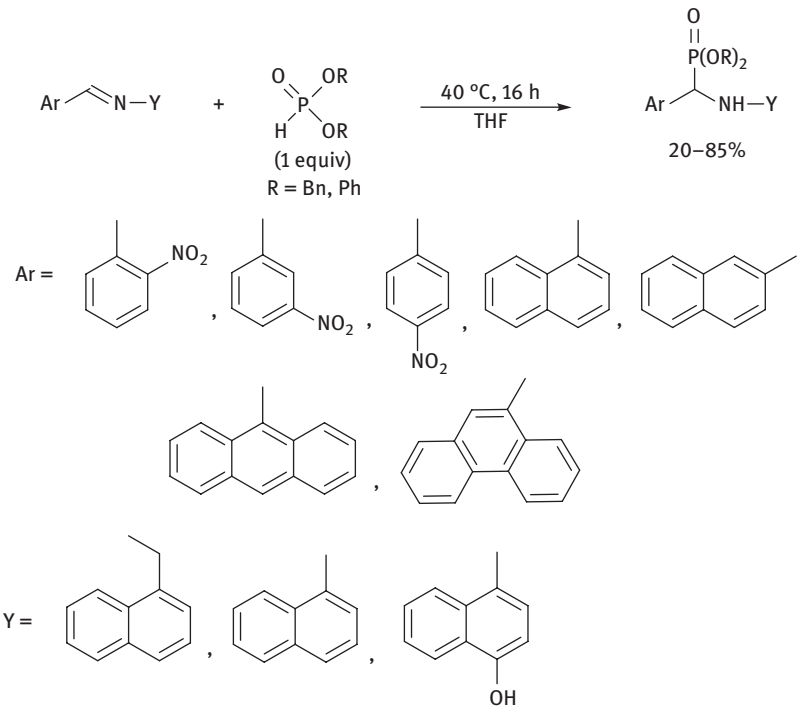


Figure 6.55: Synthesis of aminophosphonates with fluorescent properties.

Imines derived from anthracene carbaldehyde were reacted with dialkyl phosphites in refluxing diethyl ether or benzene. The α-anthryl-aminophosphonates were obtained in yields of 66–74% (Figure 6.56) [121].

Various P-reagents (diethyl phosphite, ethyl phenyl-*H*-phosphinate and diphenylphosphine oxide) were added to imines incorporating an α-imidazole ring in boiling toluene (Figure 6.57) [122].

Schiff bases, prepared from quinoline derivatives, also served as starting materials in Pudovik reactions. Completion of the addition of P-species on the C=N bond required 2 h in boiling toluene (Figure 6.58) [123].

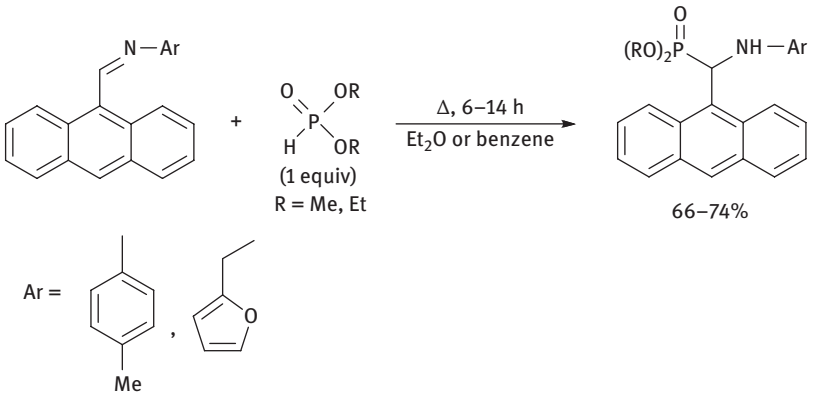


Figure 6.56: Pudovik reaction of anthryl-containing imines.

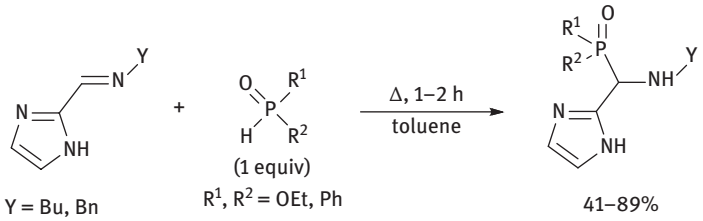


Figure 6.57: Addition of >P(O)H reagents to imines with an α-imidazole ring.

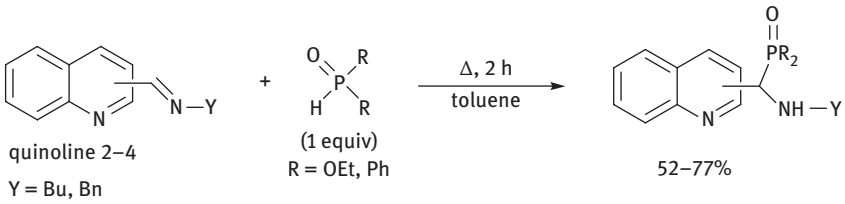


Figure 6.58: Preparation of quinoline-containing α-aminophosphonate derivatives.

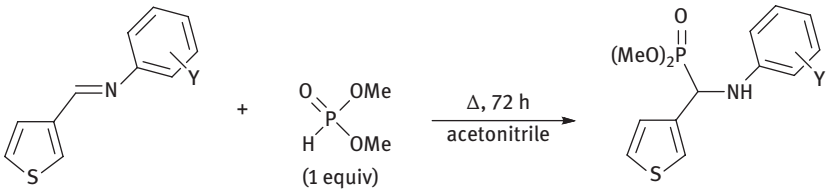


Figure 6.59: Pudovik reaction of imines with an α-thiophene ring.

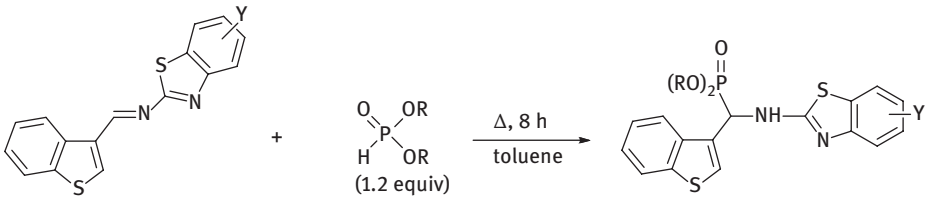


Figure 6.60: Imines with a benzothiazole ring as starting materials in the Pudovik reaction.

α-Thienyl-aminophosphonates were obtained by the Pudovik reaction of imines with α-thiophene ring and dimethyl phosphite. The components were refluxed in acetonitrile for a rather long (72 h) reaction time (Figure 6.59) [124].

Imines bearing a benzothiazole moiety were reacted with dialkyl phosphites or diphenyl phosphite in toluene at reflux temperature for 8 h (Figure 6.60) [125].

6.4.1.4 Catalyst- and Solvent-free Pudovik Reactions

The addition of >P(O)H reagents to α-aryl imines took place under MW-assisted solvent- and catalyst-free conditions at 80–100 °C to afford α-aminophosphonates and α-aminophosphine oxides in yields of 68–97% (Figure 6.61) [126].

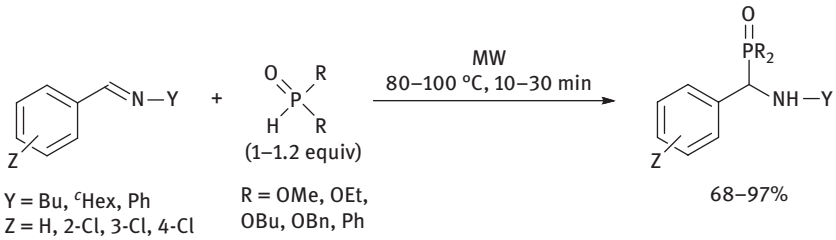


Figure 6.61: MW-assisted solvent- and catalyst-free Pudovik reaction of α-aryl imines.

Diethyl phosphite was added to a 2-hydroxyphenyl Schiff base; the reaction was carried out at 110 °C for 1 h. The corresponding 2-hydroxyphenyl α-aminophosphonate was reacted further without purification (Figure 6.62) [127].

In the synthesis of aminophosphonates containing an *N*-pyrazole moiety, unusually large excess (130 equivalents) of diethyl phosphite was applied. In fact, this method cannot be considered as a green procedure. The products showed satisfactory insecticidal activities in bioassay studies (Figure 6.63) [128].

An imine derived from furan-3-carbaldehyde and propargyl amine was converted to an aminophosphonate by a hydrophosphonylation reaction with dimethyl phosphite. The catalyst- and solvent-free addition was complete at 60 °C after 8 h (Figure 6.64) [129].

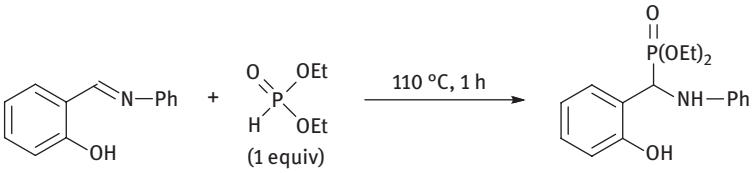


Figure 6.62: Synthesis of a 2-hydroxyphenyl α-aminophosphonate without catalyst and solvent.

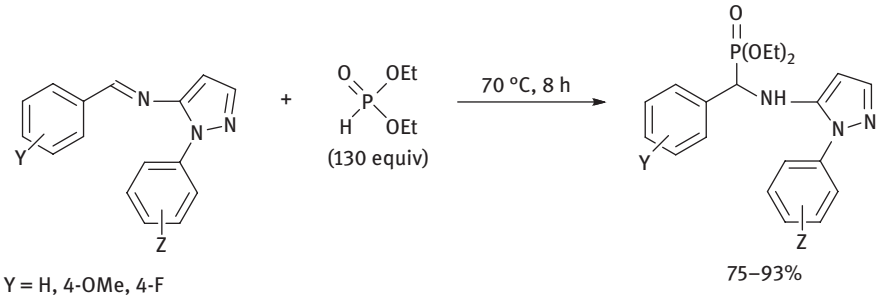


Figure 6.63: Preparation of *N*-pyrazol-containing α-aminophosphonates.

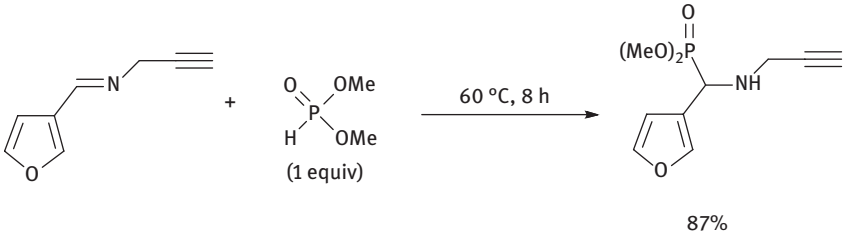


Figure 6.64: Pudovik reaction of an α-furyl *N*-propargyl imine.

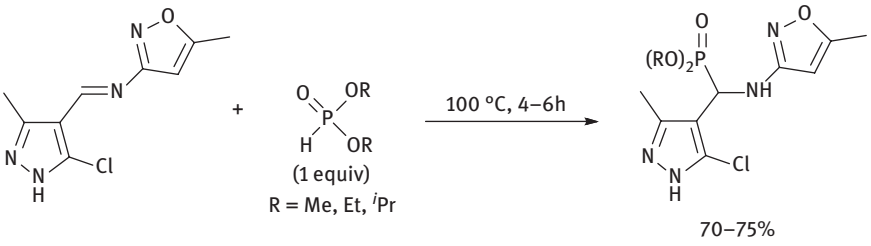


Figure 6.65: Addition of dialkyl phosphites to a Schiff base containing α-pyrazol and *N*-isoxazole moieties.

An α-pyrazol and *N*-isoxazole containing Schiff base was reacted with dialkyl phosphites at 100 °C for 4–6 h. The aminophosphonates were obtained in yields of 70–75% (Figure 6.65) [130].

6.4.2 Pudovik Reactions of α-aliphatic Imines

α-Fluoroalkyl-aminophosphonates were also synthesized *via* a Pudovik reaction. Schiff bases derived from fluoroalkyl aldehydes were reacted with diethyl phosphite in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane at room temperature (Figure 6.66) [131].

Pudovik reactions of α-aliphatic imines can also be catalyzed by MoO_2Cl_2. The reaction with diethyl phosphite was performed at 80 °C for 5–30 min. The desired α-aminophosphonates were obtained in yields of 95% (Figure 6.67) [117].

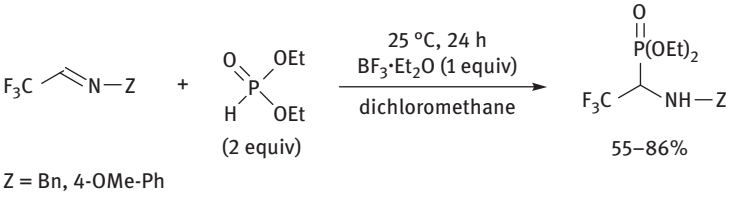


Figure 6.66: Synthesis of fluoroalkyl-aminophosphonates.

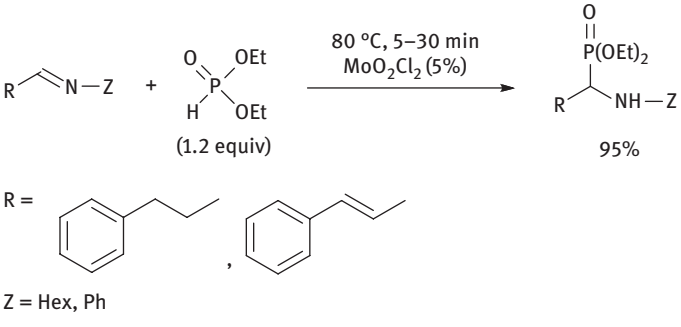


Figure 6.67: Pudovik reaction of α-aliphatic imines catalyzed by MoO_2Cl_2.

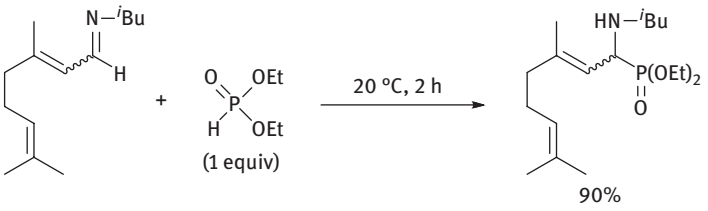


Figure 6.68: Pudovik reaction of a terpene-type imine.

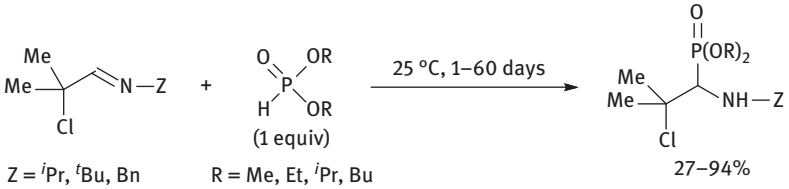


Figure 6.69: The hydrophosphonylation of (*N*-2-methyl-2-chloropropylidene)alkylamines with dialkyl phosphites.

A terpene-type Schiff base was converted to an α-aminophosphonate by reaction with diethyl phosphite at 20 °C for 2 h (Figure 6.68) [132].

The hydrophosphonylation of (*N*-2-methyl-2-chloropropylidene)alkylamines with dialkyl phosphites was performed at room temperature. Depending on the substituents, prolonged (60 days) reaction times were necessary in a few cases (Figure 6.69) [133].

N-Sulfonyl and *N*-carboxylic imine derivatives were also applied as starting materials in the Pudovik reaction to prepare the corresponding α-aminophosphonates [134–137].

6.4.3 Stereoselective Pudovik Reactions

A phosphoric acid with 1,1'-bi-2-naphthol (BINOL) moiety was applied as the catalyst in the asymmetric α,β-hydrophosphonylation of conjugated imines. The reactions were performed at room temperature for 24 h in xylene. The corresponding products were obtained in moderate yields (30–65%) and enantiomer excess values (8–62%; Figure 6.70) [138].

Another example for the asymmetric Pudovik reaction was carried out in the presence of chiral Ti-complexes. The additions needed rather long (20–30 h) reaction times at room temperature in toluene to afford the chiral aminophosphonates in good yields (82–92%) and high enantiomeric purities (92–98%; Figure 6.71) [139].

Chiral quinine derivatives were also utilized as catalysts in the asymmetric hydrophosphonylation of aromatic imines. The desired products were obtained in excellent yields (93–99%) and *ee* values (91–99%) after the reaction at room temperature for 12 h (Figure 6.72) [140].

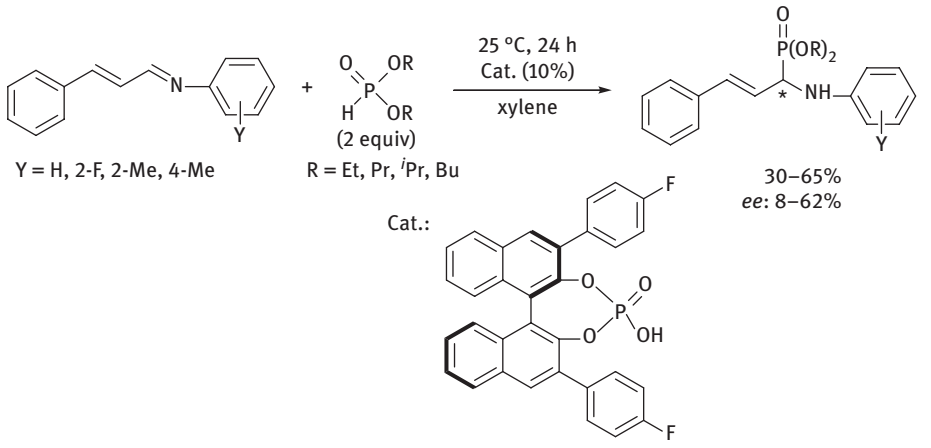


Figure 6.70: Asymmetric addition of dialkyl phosphites catalyzed by a chiral phosphoric acid derivative.

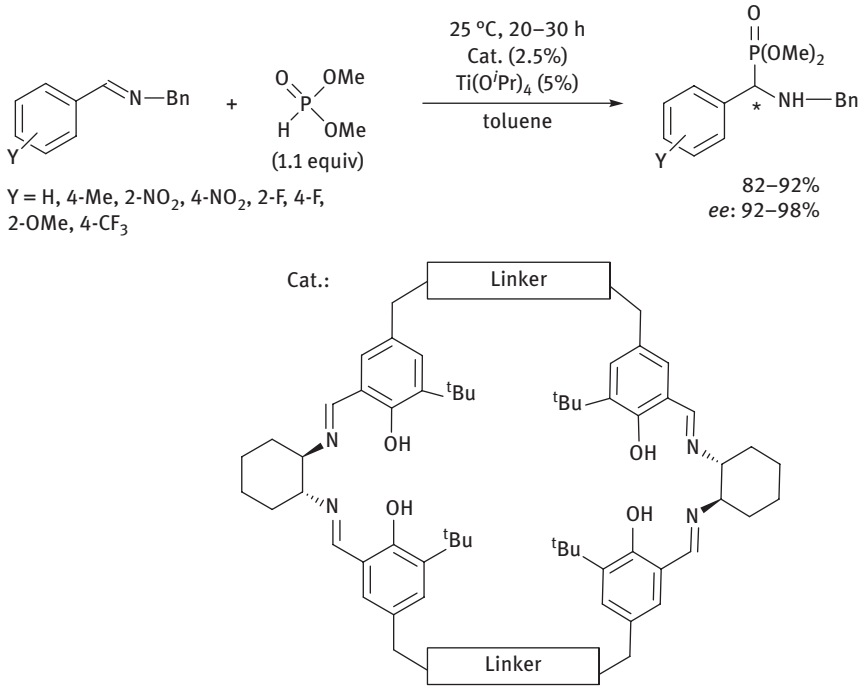


Figure 6.71: A Pudovik reaction catalyzed by chiral Ti-complexes.

In another case, (*R*)-menthyl-phenyl-*H*-phosphinate was added to the double bond of *O*-pivaloylated-D-galactosyl imines. In the presence of $BF_3 \cdot Et_2O$ in THF at room temperature, the addition afforded the desired products in yields of 45–88% and with *de* values of 75–90% (Figure 6.73) [141].

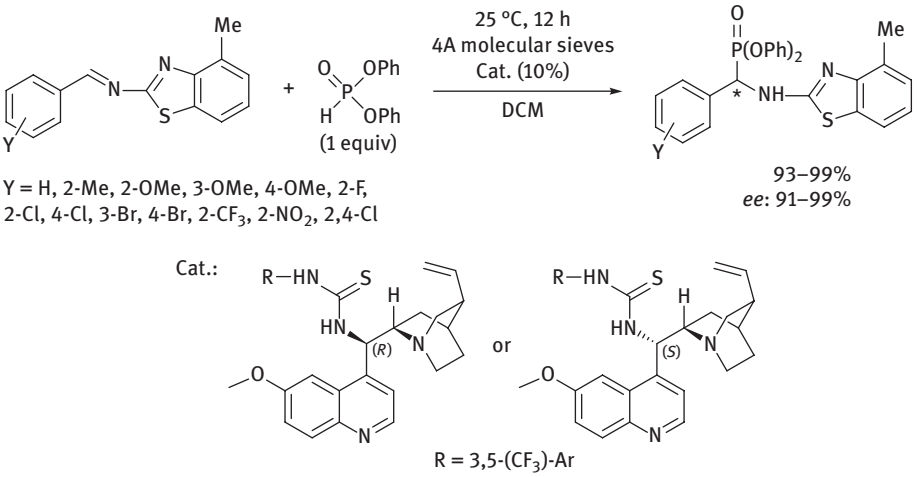


Figure 6.72: Asymmetric hydrophosphonylation of aromatic imines mediated by chiral quinine derivatives.

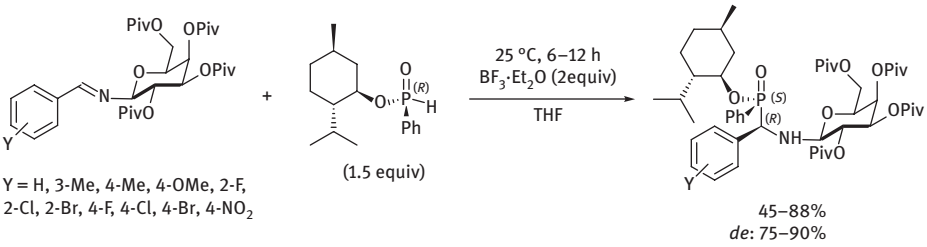


Figure 6.73: Diastereoselective hydrophosphonylation of *O*-pivaloylated-D-galactosyl imines by a chiral phosphinate.

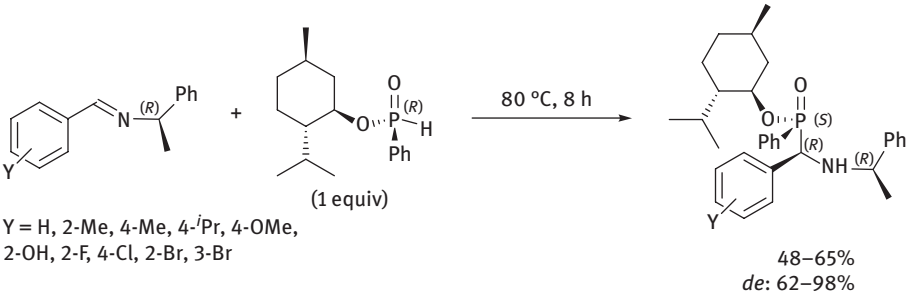


Figure 6.74: Reaction of optically pure chiral aromatic imines with (*R*)-menthyl-phenyl-*H*-phosphinate.

The reaction of the same chiral phosphinate with chiral aromatic imines led to one predominant diastereomer. After a reaction at 80 °C for 8 h, the products were obtained in yields of 48–65%. The diastereomer excess was 62–98% (Figure 6.74) [142].

6.5 Conclusion

In this chapter, the synthesis of α-aminophosphonates and related derivatives by the single and the double Kabachnik–Fields condensations, as well as by the Pudovik reaction was summarized. This field of organophosphorus chemistry has attracted much attention over the last five years. Although there is a wide variety of catalytic methods still being applied, the green accomplishments, such as the catalyst- and solvent-free reactions and the MW-assisted synthesis, come to the forefront of contemporary research.

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