Review

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Review

The Kabachnik–Fields Reaction: A Key Transformation in Organophosphorus Chemistry

Giovanni Ghigo [1]*, Sara Nicoletti [1] and Stefano Dughera [1]*

University of Turin. Department of Chemistry; giovanni.ghigo@unito.it; sara.nicoletti@edu.unito.it

* Correspondence: stefano.dughera@unito.it Tel.: (+ 39 11 6707823)

Abstract

The Kabachnik–Fields (KF) reaction is a versatile three-component condensation of amines, carbonyl compounds, and P–H reagents, enabling efficient synthesis of α-aminophosphonates—key bioactive and functional molecules. This review critically examines the literature of the last 25 years, with the exception of selected mechanistic studies, highlighting mechanistic insights. Advances in catalyst-free methodologies, sustainable synthetic approaches, Lewis and Brønsted acid catalysis are discussed, alongside developments in enantioselective KF reactions in the presence chiral metal complexes or organocatalysts.

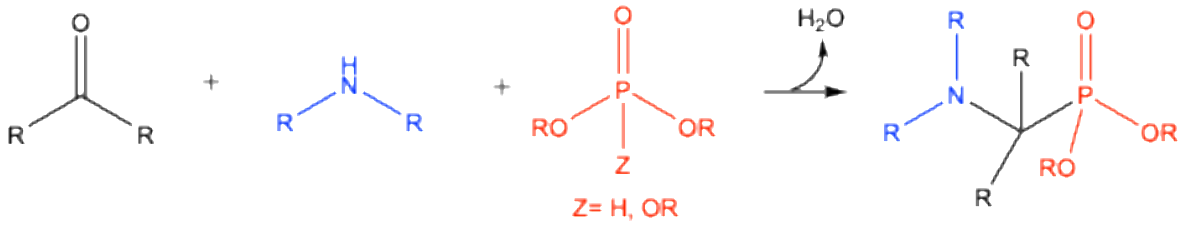
Keywords: Kabachnik–Fields reaction; multicomponent reactions; enantioselective synthesis

1. Introduction

During the early 1950s, the field of organophosphorus chemistry experienced significant expansion, particularly in the development of methods for C–P bond formation and the synthesis of P-substituted amino acid analogues. In this context, Kabachnik and Medved [1] reported in 1952 that dialkyl phosphites (or H-phosphonates) react, in the presence of an aldehyde (or ketone) and ammonia (or an amine), to afford α-aminophosphonic acids or their corresponding esters. Independently, in the same year, Fields [2] described a one-pot protocol for the reaction of dialkyl phosphites with aldehydes or ketones and amines, leading to the formation of α-amino phosphonate.

In the following decades, the reaction was systematically refined: mechanistic aspects were elucidated, the substrate scope was expanded to include a wide variety of carbonyl compounds, amines, and phosphorus reagents beyond simple dialkyl phosphites, and environmentally benign as well as catalytic versions were developed. [3-6]

The Kabachnik–Fields (KF) reaction—also referred to as the phospha-Mannich reaction—can thus be defined as a three-component condensation involving an amine, a carbonyl compound (aldehyde or ketone), and a P–H-containing reagent (typically a dialkyl o diaryl phosphite) to yield α-aminophosphonates or related derivatives. [4-7] Alternatively, trialkyl or triaryl phosphites have also been employed (Scheme 1).



Scheme 1. Kabachnik-Fields (KF) reaction.

These products are structural bioisosteres of α-aminoacids (Figure 1) and have attracted considerable attention due to their broad spectrum of biological activities [8,9], as well as their utility

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in the preparation of functionalized polymeric materials. [6] Moreover, α-aminophosphonates have been employed as bidentate ligands in platinum complexes. [10]

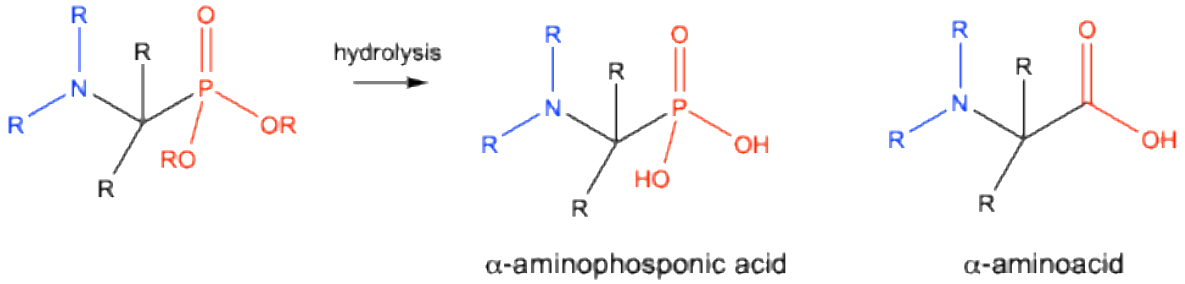

Figure 1. α-Aminophosphonates as bioisosters of α-aminoacids.

The KF reaction represents one of the earliest and most illustrative examples of a multicomponent reaction. Over time, it has evolved into a powerful and versatile tool for modern organic synthesis, particularly within phosphorus chemistry. Its ability to assemble the N–C–P framework in a convergent, single-step process offers significant advantages over conventional stepwise methodologies. The enduring appeal of the KF reaction lies in its operational simplicity, mild reaction conditions, and broad substrate tolerance.

The mechanistic complexity of the reaction, together with the multitude of factors influencing yield and stereochemical outcome, makes its practical implementation nontrivial. Consequently, mechanistic understanding, stereoselective control, and optimization of reaction conditions remain central topics of ongoing research.

2. Mechanistic Studies

Despite the apparent simplicity of the reactive system, the detailed mechanism of the Kabachnik–Fields reaction has long been the subject of debate. Available data have often been fragmentary and sometimes contradictory. Only in recent years, through kinetic studies and in-depth analyses, has it become possible to clarify many aspects and propose a more unified description of the process. Nevertheless, several fundamental points remain unresolved.

The main challenge in elucidating the Kabachnik–Fields mechanism lies in determining the precise sequence of elementary steps. The process is inherently multistep and complex, involving parallel and intersecting pathways that yield different intermediates (Scheme 2). The dominant pathway depends on the nature of the reactants (amine, carbonyl compound, and phosphite) as well as the reaction conditions (solvent, catalyst, and temperature). The two main competing—or potentially complementary—pathways are as follows:

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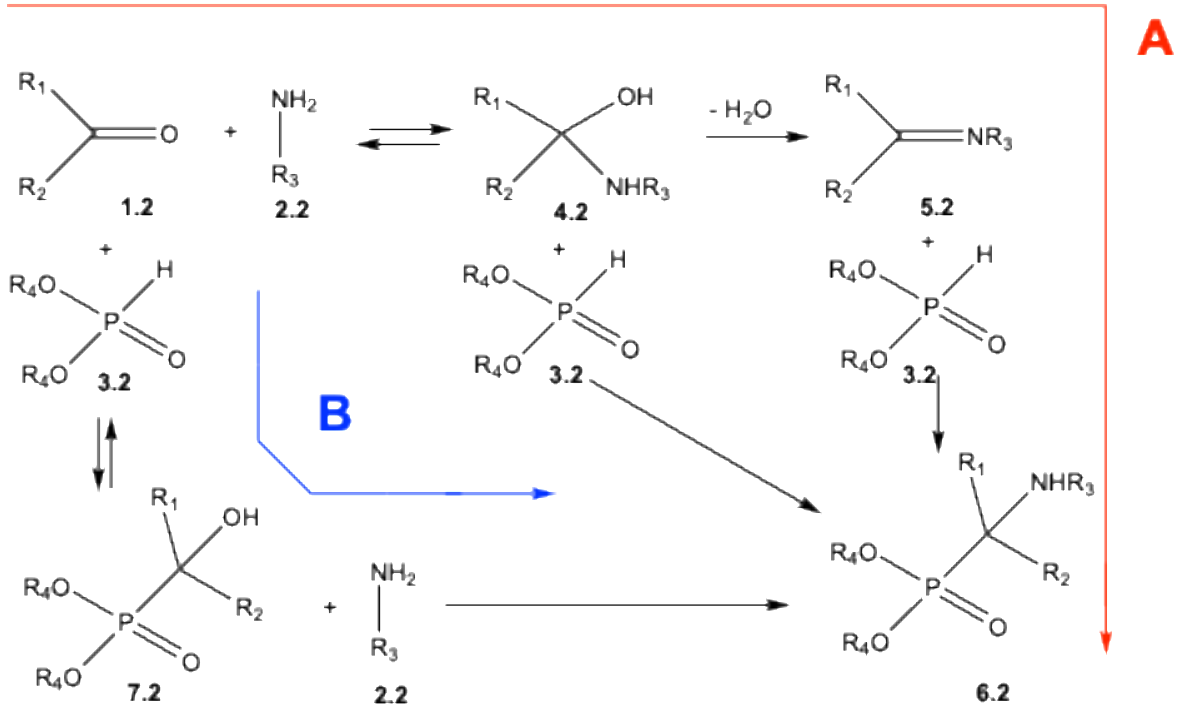

Scheme 2. Mechanisms of KF reaction.

Pathway A. This pathway was proposed by Fields in 1952. [2] Here, an imine (Schiff base, **5.2**) formed through condensation of the carbonyl compound **1.2** with a primary amine **2.2** to give the α-amino alcohol intermediate **4.2**, followed by water elimination. Because imine formation is reversible, removal of the generated water drives the equilibrium toward product formation. The subsequent addition of a dialkyl phosphite **3.2** to the C=N double bond (the Pudovik reaction, first described in 1952 [11]) yields the α-aminophosphonate **6.2**.

The condensation of aniline, benzaldehyde, and a dialkyl phosphite was shown to follow this mechanism [7,12] as UV spectroscopic studies of the reaction kinetics indicated that imine formation is the fastest reaction in the system. Similar results were obtained with various substituted benzaldehydes, where the "imine" pathway was consistently preferred. More recently, Gabor [8] confirmed the same conclusion in the solvent-free reaction of aniline, benzaldehyde, and diethyl phosphite, where imine **5.2** formed rapidly and in larger amounts than the hydroxyphosphonate **7.2**.

Dimukhametov [13] also demonstrated that only the imine mechanism operates in the system involving dimethylphosphite, benzaldehyde, and (R,S)-1-phenylethanamine and Matveeva and Zefirov confirmed that condensation of cyclohexylamine, benzaldehyde, and dialkyl phosphite follows Pathway A [14].

FT-IR and computational studies by Keglevich [15] indicated that, before condensation between aniline and benzaldehyde, a hydrogen bond forms between the P=O group of the phosphite and the N–H group of the amine (cyclohexylamine), modulating the reactivity of the reagents. These experiments and calculations support Pathway A as the most likely route. Keglevich once again reached the same conclusion through in situ FT-IR studies of the KF reaction between benzaldehyde, N-propylamine, and diethyl phosphite at 80°C in acetonitrile. [16]

More recently, Mu [17] used DFT calculations to study the reaction between benzaldehyde, aniline, and diphenyl phosphine oxide in a deep eutectic solvent (DES), confirming that the reaction proceeds via Pathway A.

Pathway B. This alternative pathway involves initial formation of an α-hydroxyphosphonate **7.2** via Abramov addition of the phosphite to the carbonyl compound. [18] The resulting hydroxyphosphonate **7.2** can then undergo nucleophilic substitution by the amine to form α-

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aminophosphonate **6.2**. This mechanism was first proposed by Kabachnik and Medved by analogy with reactions described by Rodionov and Strecker. [1,19]

It was also suggested by Cherkasov and Galkin in reactions of the more nucleophilic cyclohexylamine with benzaldehyde and a dialkyl phosphite.[7,20] Here, too, a preliminary interaction is observed before phosphite addition, likely involving a hydrogen bond between the P(O)H group of the phosphite and the amine nitrogen.

However, Matveeva and Zefirov [14] found no experimental evidence for the formation of hydroxyphosphonate **7.2**; when independently prepared, **7**.2 did not yield amination products upon reaction with cyclohexylamine. In 1993, Gancarz [21] demonstrated the reversibility of hydroxyphosphonate **7.2** formation. It was experimentally confirmed that this intermediate—derived from both aliphatic and aromatic aldehydes or ketones—can decompose back into the starting carbonyl compound and phosphite in the presence of primary or tertiary amines (e.g., butylamine, triethylamine). Subsequent ^{31}P NMR studies also confirmed that hydroxyphosphonates **7** decompose into the original hydrophosphoryl and carbonyl compounds in the presence of amines.[22]

In some cases, formation of hydroxyphosphonates **7.2** from aromatic ketones is irreversible, but the intermediate then converts irreversibly to phosphates, terminating productive pathways.[21,23]

The nature of the hydrophosphoryl compound is also important; replacing alkoxy groups with alkyl groups (e.g., dialkyl phosphites → dialkyl phosphinites) can result in unproductive formation of stable hydroxyphosphonate **7.2**, as in the reaction of dibutylphosphinous acid ($Bu_{22}PHO$) with salicylaldehyde. [7]

It has been proposed that Pathway B is effective only in the presence of sufficiently basic amines (pKa > 6), whereas the imine pathway predominates with less basic amines (pKa < 6). This correlation is supported by ^{31}P-NMR data, showing that the phosphite chemical shift (δ ^{31}P) increases with amine basicity. [7]

Thus, the reversibility of the Abramov reaction suggests that α-hydroxyphosphonates **7**, when formed under Kabachnik–Fields conditions, do not necessarily imply that product formation proceeds via the hydroxyphosphonate pathway; they may instead serve as transient reservoirs of the carbonyl compound.

Fields[2] also considered a Mannich-type mechanism in which the α-amino alcohol **4.2** reacts with the hydrophosphoryl **3** to generate α-aminophosphonate (pathway **4.2**+ **3.2** → **6.2** in Scheme 2), but this route has not been further discussed in the literature.

Kinetic studies indicate that the Kabachnik–Fields reaction is often third-order overall (first-order in each reagent), although the precise mechanism depends on the relative nucleophilicities of the reactants. According to HSAB (Hard and Soft Acids and Bases) theory, competition between the amine (a hard nucleophile) and the phosphite (a soft nucleophile) for the electrophilic carbonyl center determines which pathway is favored.[24]

For example, with softer carbonyl compounds such as benzaldehyde, phosphite addition is preferred, while with harder carbonyls (e.g., ketones), condensation with the amine predominates.

It should be noted that the reaction might not proceed through a fully isolable intermediate but could involve a concerted or partially concerted process, in which the amine, aldehyde, and phosphite interact simultaneously in a multistep transition state.[25]

As discussed extensively in the following sections, the Kabachnik–Fields reaction can be performed in the presence of both Brønsted and Lewis acid catalysts. In most cases, the mechanism proceeds through **pathway A** (Scheme 1), in which the acid catalyst first activates the carbonyl compound **1.2** thereby promoting imine formation, and subsequently activates imine **5.2,** facilitating the nucleophilic attack of the phosphite **3.2**.

On this ground, Halasz, Delogu, Braga, and Colacino [26] investigated the mechanochemical KF reaction under ball-milling conditions, with ZrO_2 acting as a recyclable heterogeneous Lewis catalyst. In situ Raman studies confirmed that the reaction proceeds via an imine intermediate **5**, which forms rapidly and then slowly converts to the α-aminophosphonate.

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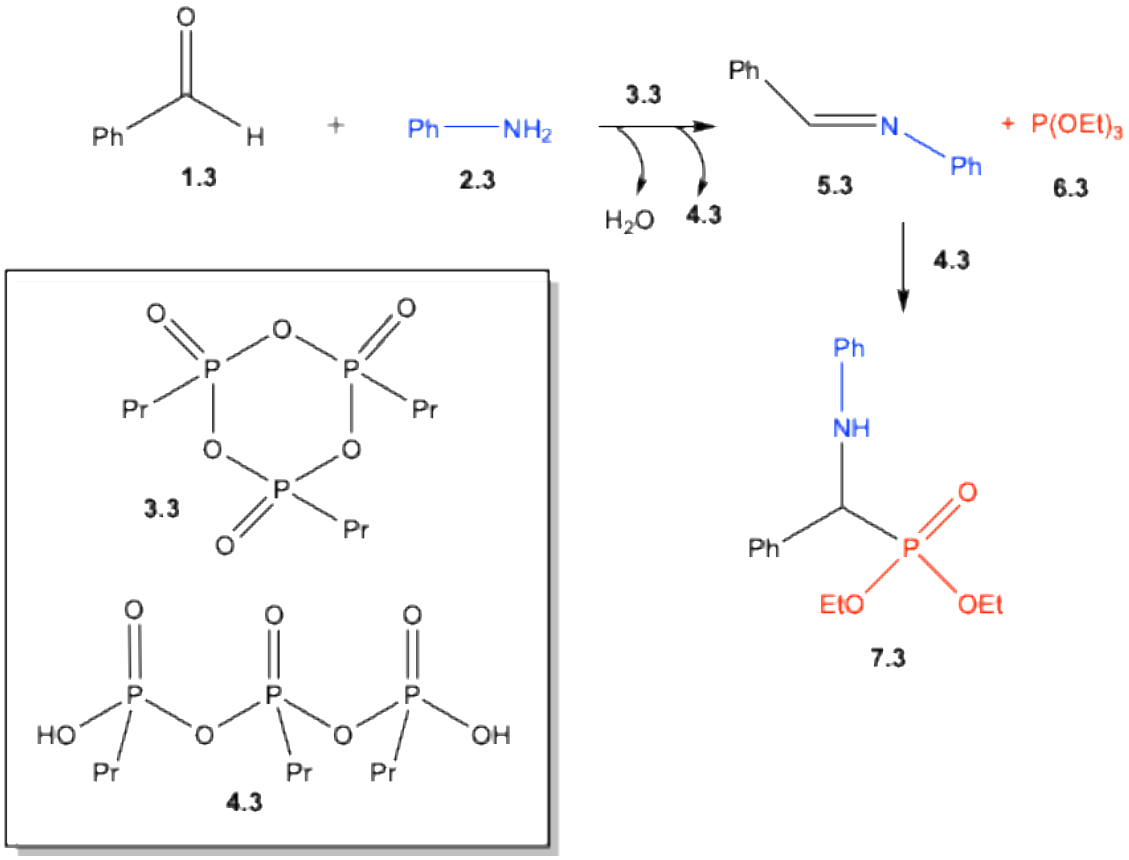
Keglevich[27] used propanephosphonic acid anhydride (**3.3**) as a catalyst, which promotes both the condensation of aldehyde **1.3** and amine **2.3** to form the imine **5.3**. The acid by-product **4.3** then catalyzes the subsequent nucleophilic addition of triethyl phosphite (**6.3**) to **5.3**. The resulting phosphonium intermediate, undergoes an Arbuzov-type rearrangement to yield the α-aminophosphonate **7.3** (Scheme 3).



Scheme 3. KF reactions catalyzed by propanephosphonic acid anhydride.

Indium salts as Lewis acids have also been employed to catalyze both imine formation and phosphine oxide addition according to the Pathway A of Scheme 2. [28]

As an alternative to the ionic mechanisms described above, a radical pathway was proposed by Rit. [29] As illustrated in Scheme 4, this KF reaction was carried out with $AgSBF_6$ as catalyst which interacts with dimethyl phosphite (**3.4**) to form phosphorus radicals **5.4**. Reaction of **5.4** with pre-formed imine **4.4** generates radical **6.4** which ultimately affords α-aminophosphonate **7.4**.

Control experiments performed in the presence of radical scavengers suppressed the reaction, supporting the proposed radical pathway.

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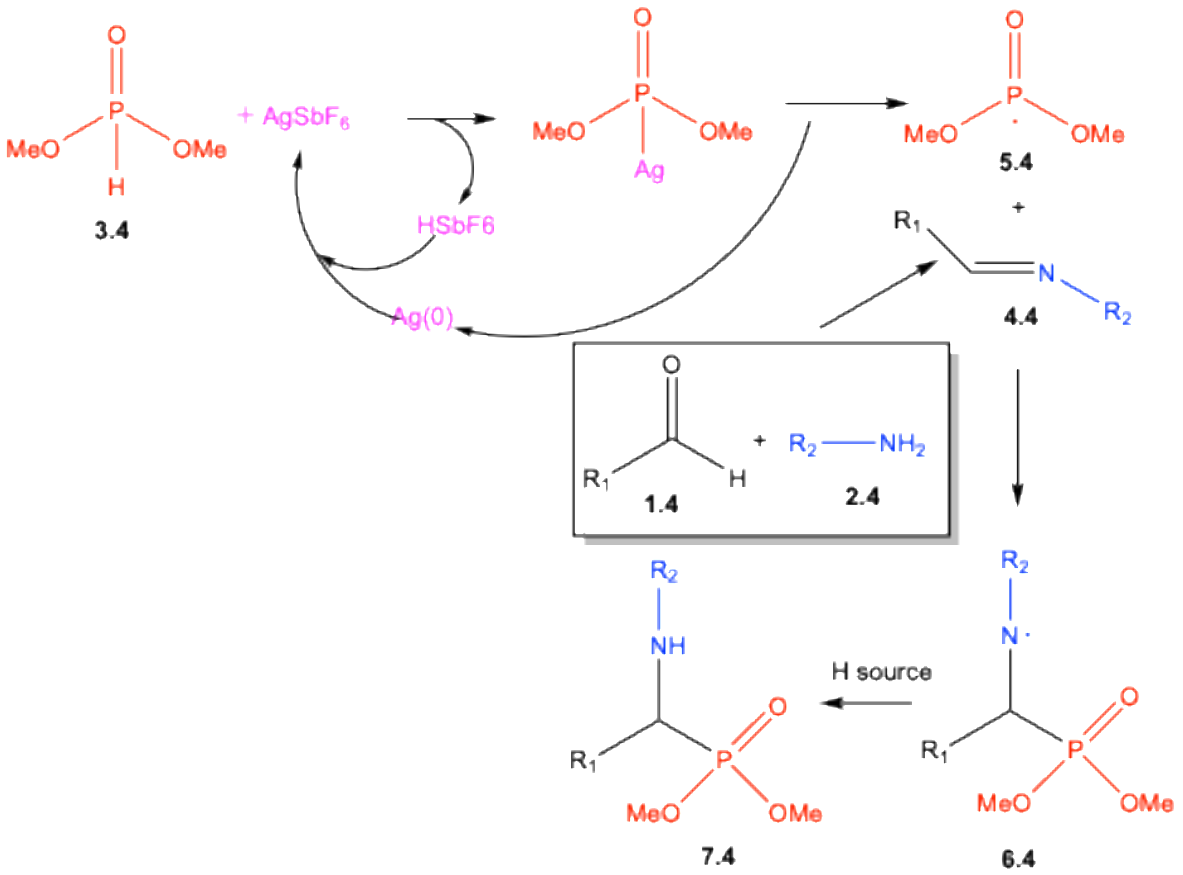

Scheme 4. Radical pathway.

It is therefore reasonable to conclude that the operative mechanism depends on the specific reaction components. Nonetheless, the imine pathway appears to be more general and widely applicable than the route involving an α-hydroxyphosphonate intermediate. As illustrated in Scheme 2, regenerated phosphite and carbonyl compound from hydroxyphosphonate decomposition can re-enter the reaction via the imine pathway.

In light of these findings, it is evident that the mechanistic course and efficiency of the Kabachnik–Fields reaction are highly dependent on the intrinsic properties of each reaction partner.

3. Catalyst-Free Kabachnik–Fields Reactions

Typically, Kabachnik–Fields (KF) reactions employ a wide range of catalysts (see Sections 4-6) to accelerate the transformation and improve yields. However, there is increasing interest in carrying out these reactions without added catalysts, motivated by green chemistry principles aimed at reducing cost and toxicity, simplifying the workup, and minimizing environmental impact. Several studies have demonstrated that good yields can be obtained even under catalyst- and solvent-free conditions.

Recently, Milen [8] reported a green and efficient method for synthesizing α-aminophosphonates **4.5**, **6.5** via the KF reaction—combining carbonyl compounds **1.5**, amines **2.5**, and phosphites **3.5**, **5.5** (aliphatic or aromatic)—without any solvent or catalyst, and at room temperature. High to excellent yields (up to 97%) were obtained with a wide range of aromatic aldehydes and aniline derivatives, while aliphatic aldehydes and amines gave lower yields and required longer reaction times. The method scaled well, maintaining yields above 80% in larger batches (Scheme 5).

Similarly, Alavi [30] described a green, solvent- and catalyst-free one-pot synthesis of α-aminophosphonates **6.5** under mild conditions. Reactions between a broad range of dialkyl

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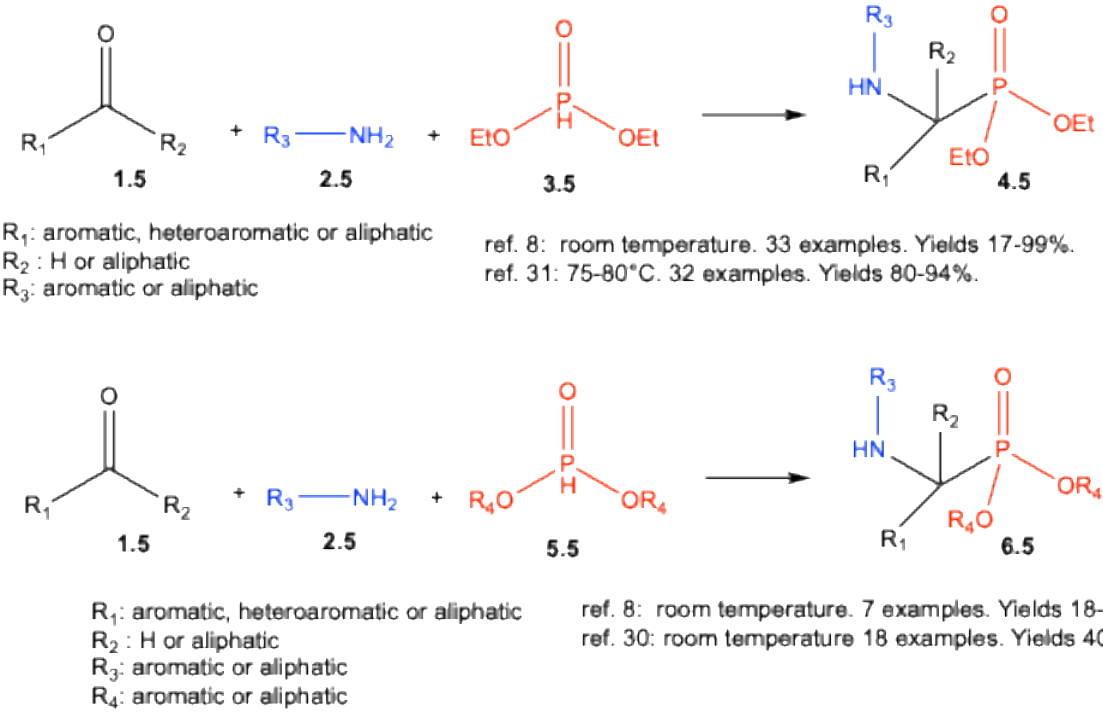
phosphites **5.5**, aldehydes **1.5** and amines **2.5** proceeded at room temperature with yields up to 95%. Notably, the dialkyl phosphite **6.5** acts as a self-catalyst via its trivalent tautomeric form, eliminating the need for an external catalyst (Scheme 5).

Ranu [31] proposed a simple, general, efficient, and environmentally friendly method for synthesizing *α*-aminophosphonates **4.5** through a solvent- and catalyst-free, one-pot, three-component condensation of various carbonyl compounds **1.5**, aliphatic or aromatic amines **2.5**, and diethyl phosphite **3.5** (Scheme 5).



Scheme 5. Solvent and catalyst-free KF reactions.

Ghahremanzadeh [32] reported a one-pot, four-component KF-type reaction involving ninhydrin (**1.6**), o-phenylenediamines **3.6**, aniline derivatives **2.6**, and dialkyl or diaryl phosphites **4.6** under solvent- and catalyst-free conditions. Target products **5.6** were obtained in high yields; the workup was straightforward with minimal purification required (Scheme 6).

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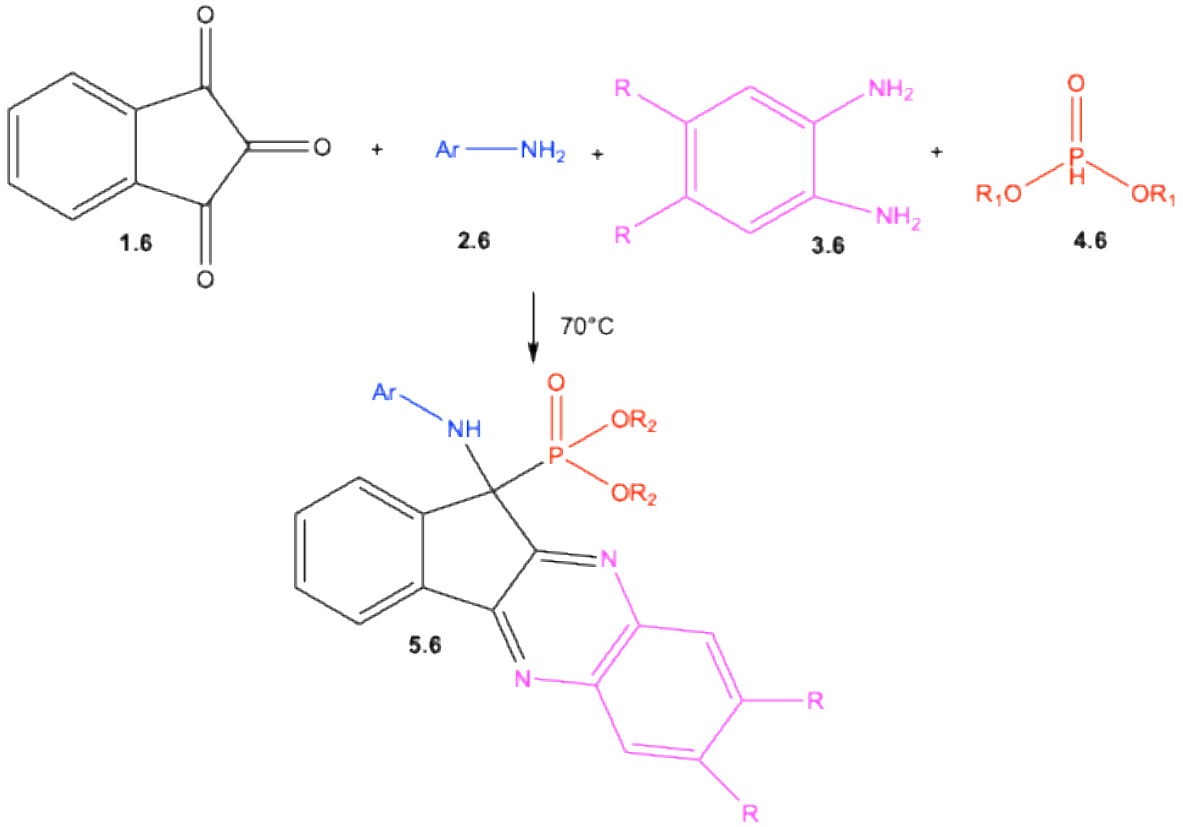
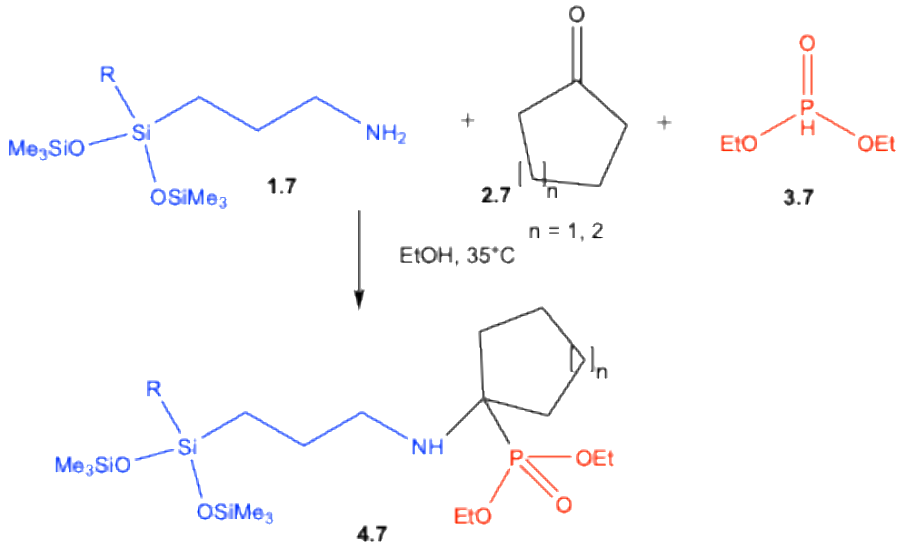


Scheme 6. One-pot four component KF reaction.

Lu [33] developed a method for synthesizing phosphonate-containing siloxanes **4.7** via a KF reaction under mild, catalyst-free conditions, using 3-aminopropylsilanes **1.7**, cyclic ketones **2.7** and diethyl phosphite (**3.7**), achieving high yields (Scheme 7).



Scheme 7. Synthesis of phosphonate-containing siloxanes **4.7.**

Naveen [34] achieved good yields of α-aminophosphonates **4.8** by simply heating mixtures of substituted anilines **2.8**, substituted benzaldehydes **1.8** and diethyl phosphite (**3.8**) in acetonitrile at

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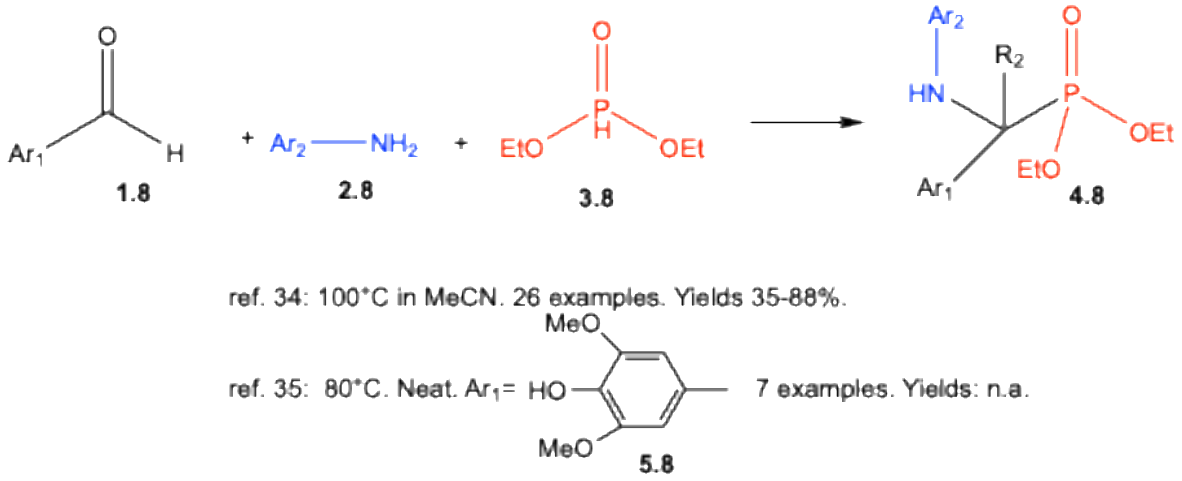
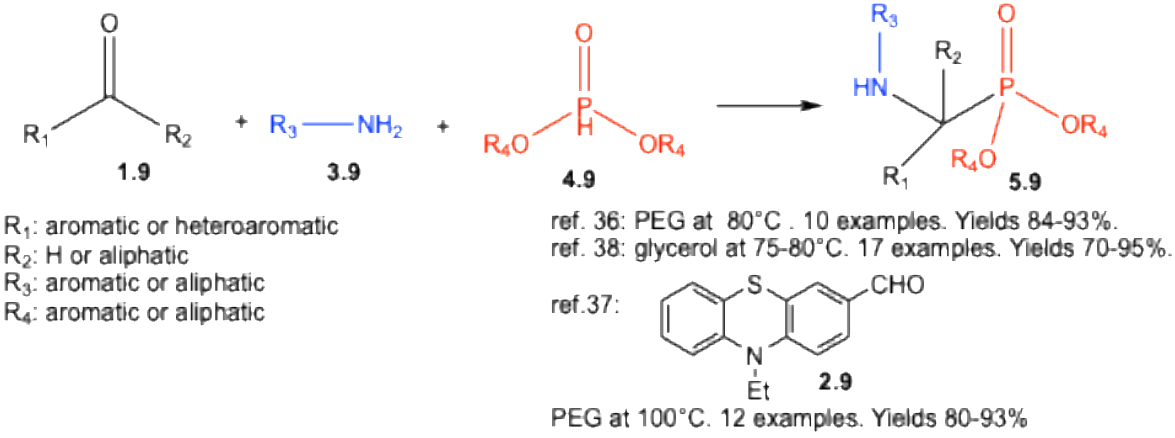
100 °C. Tang [35] synthesized seven novel syringaldehyde α-aminophosphonate derivatives **4.8** by mixing and heating syringaldehyde (**5.8**) with various aryl amines and diethyl phosphite (**3.8**) at 80 °C in a one-pot, solvent- and catalyst-free reaction (Scheme 8).



Scheme 8. Catalyst-free KF reactions.

Revaprasadu [36] and Kumar [37] demonstrated that polyethylene glycol (PEG) serves as a green reaction medium for KF reactions. Using PEG, a variety of α-aminophosphonates **5.9** were synthesized in good yields from various aldehydes **1.9** or **2.9**, amines **3.9**, and diphenyl- or diethylphosphite **4.9**. Heydari [38] developed a convenient KF protocol in glycerol using aromatic and heteroaromatic aldehydes **1.9** or ketones **1.9**, aliphatic or aromatic amines **3.9**, and dimethyl, diethyl, or diphenyl phosphites **4.9** (Scheme 9).



Scheme 9. KF reactions in green solvents.

The adaptation of KF reactions to deep eutectic solvents (DESs) or ionic liquids represents a significant advance in sustainable synthesis, combining efficiency, selectivity, and environmental compatibility (Scheme 10).

Panda [39] reported that a DES composed of choline chloride (ChCl) and urea (1:2) provides an efficient, cost-effective, reusable, and environmentally benign medium for catalyst-free KF reactions. In this system, ChCl–urea (1:2) functions both as a solvent and as an effective catalyst. Using this protocol, a number of α-aminophosphonates derivatives **5.10** were obtained in excellent yields with short reaction times and good functional group tolerance.

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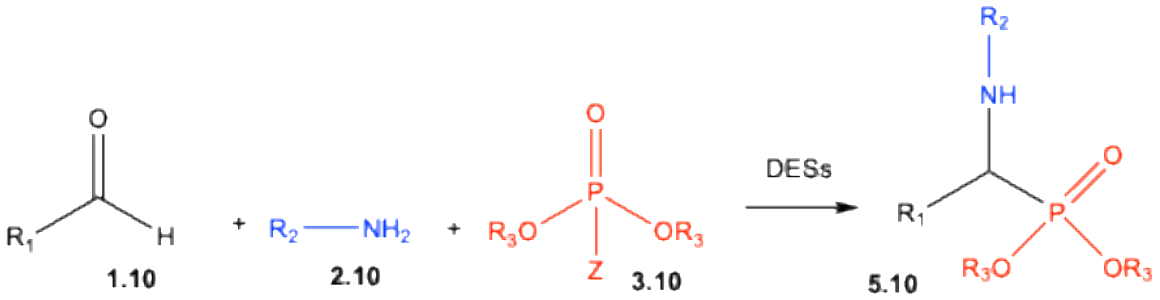
Similarly, Sreekumar [40] tested six different DESs and demonstrated that a DES formed from $ZrOCl_2 \cdot 8H_2O$ and urea (1:5) is an excellent medium and catalyst for the rapid synthesis of α-aminophosphonates **5.10**. The method was successfully applied to 21 different derivatives.

Azizi [41] employed a polymeric DES composed of polyvinylpyrrolidone and $ZnCl_2$. KF reactions of aromatic or heteroaromatic aldehydes **1.10**, aromatic or aliphatic amines **2.10**, and trimethyl phosphite (**4.10**) afforded α-aminophosphonates **5.10** in good yields.

Cheraiet [42] carried out KF reactions in a natural deep eutectic solvent (NaDES) consisting of betaine and lactic acid (1:2) for reactions of aromatic aldehydes **1.10** and amines **2.10** with triethyl phosphite **4.10**.

It must be stressed that the reactions carried out in DESs follow mechanism described in pathway A (Scheme 2). Once the imine is formed, the DES facilitates the nucleophilic attack of the phosphite.

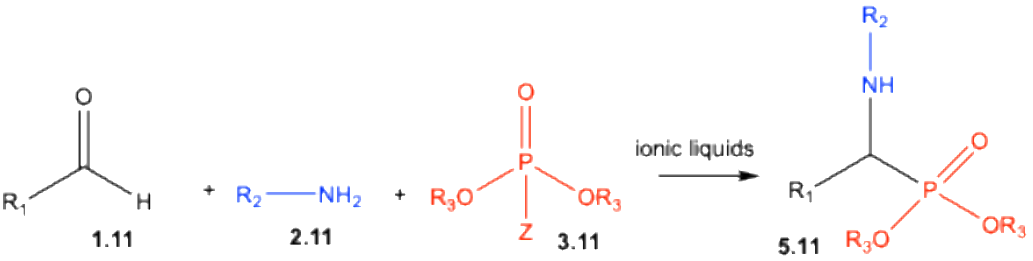


R_1: aromatic, heteroaromatic or aliphatic
R_2: aromatic or aliphatic
R_3: aromatic or aliphatic
Z: H or OR_3 as $P(OR_3)$ **4.10**

ref.39: choline chloride/urea 1:2. 60°C. 43 examples. Yields: 84-92%
ref.40: $ZrOCl_2.8H_2O$/urea 1:5. Room temperature. 50 examples. Yields: 64-98%
ref.41: polyvinylpyrrolidone/n$ZnCl_2$. Room temperature. 21 examples. Yields: 88-98%
ref.42: betaineCl/lactic acid 1:2. Room temperature. 12 examples. Yields: 45-96%

Scheme 10. KF reactions in DESs.

Regarding ionic liquids (Scheme 11), Henderson [43] found that solvate ionic liquids are excellent media for KF reactions. Reactions of various aromatic aldehydes **1.11** with aniline **2.11** or aromatic diamines and diphenyl phosphite **3.11** gave α-aminophosphonates **5.11** in short reaction times with good yields. Fang [44] also reported efficient synthesis of α-aminophosphonates **5.11** using dicationic ionic liquids as solvents with aromatic or heteroaromatic aldehydes **1.11**, aromatic amines **2.11**, and trimethyl phosphite **4.11**.



R_1: aromatic
R_2: aromatic or aliphatic
R_3: aromatic or aliphatic
Z: H or OR_3 as $P(OMe)_3$ **4.11**

ref.43: solvate ionic liquids. Room temperature. 26 examples. Yields: 25-96%
ref.44: dicationic ionic liquids. Room temperature. 15 examples. Yields: 84-96%

Scheme 11. KF reactions in ionic liquids.

The introduction of microwave technology into KF reactions represents a major advance in α-aminophosphonate synthesis, enhancing efficiency, speed, and sustainability. Keglevich and co-

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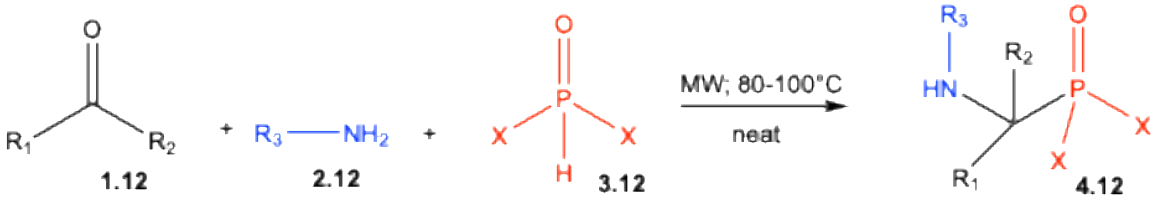
workers [45-53] extensively studied this approach, demonstrating that solvent- and catalyst-free microwave-assisted KF reactions achieve high yields, short reaction times, and broad substrate scope (Schemes 12-14).

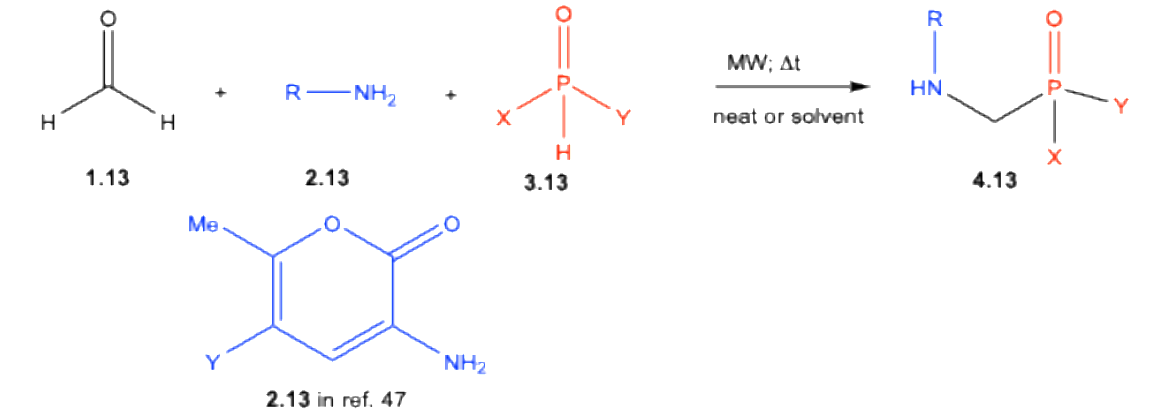


1.12 + 2.12 + 3.12 → 4.12

R_1: H, Ph, Me
R_2: H, Me
R_3: Ph, Bn
X: MeO, EtO, Ph

ref.45: 17 examples. Yields: 80-94%

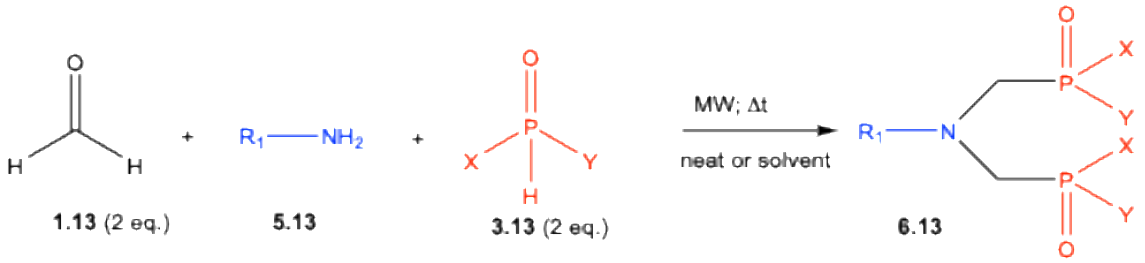
Scheme 12. Microwaves assisted KF reactions.



1.13 + 2.13 + 3.13 → 4.13

2.13 in ref. 47

R: aliphatic, aromatic or amino acid (amino ester) derivatives
X, Y: Oaryl, Oalkyl, alkyl, aryl.
Ref. 46: 18 examples. Yields 80-94%. Ref. 48: 9 examples. Yields 61-98%. Ref. 49: 10 examples. Yields 72-92%
Ref. 50: 12 examples. Yields 42-70%. Ref. 51: 12 examples. Yields 88-96%. Ref 52: 6 examples. Yields 95-98%



1.13 (2 eq.) + **5.13** + **3.13** (2 eq.) → **6.13**

R_1: aliphatic, aromatic, amino ester derivatives. X: Oaliphatic, Oaromatic. Y: Oaliphatic, Oaromatic, Ph
Ref. 47: 20 examples. Yields: 55-98%

Scheme 13. Microwaves assisted KF reactions of formaldehyde or para formaldehyde.

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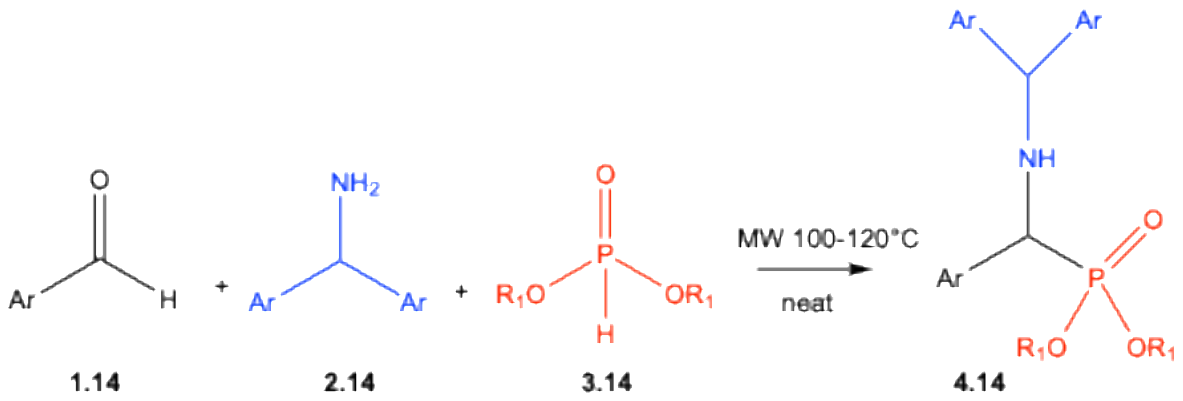
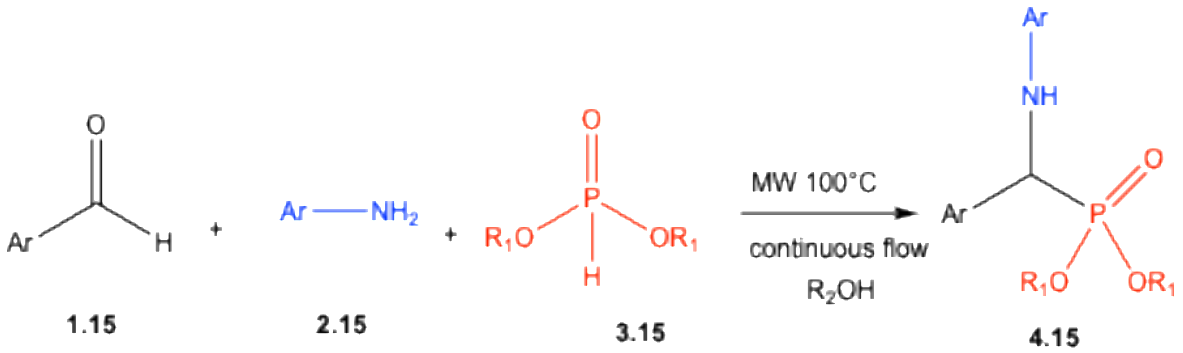


R_1 : aliphatic. ref.53. 8 examples. Yields: 68-88%

Scheme 14. Microwaves assisted KF reactions of hindered amines **2.14.**

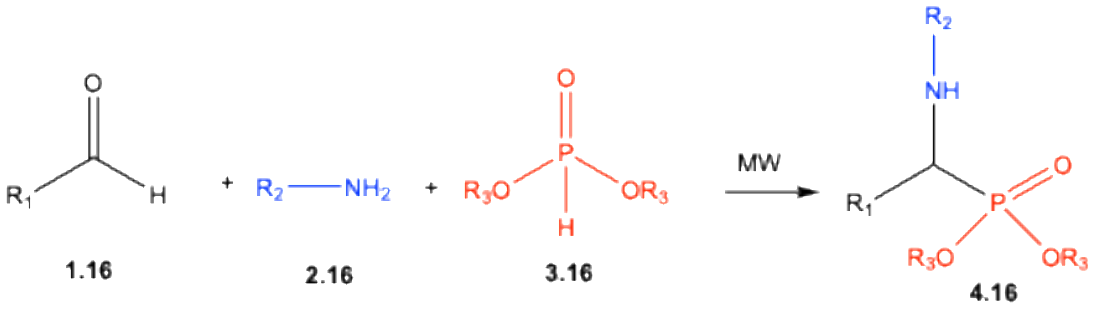
Interestingly, Keglevich and Balint [54] reported that a continuous-flow reactor combined with microwave heating enabled catalyst-free formation of α-aryl-α-aminophosphonates **4.15** from aromatic aldehydes **1.15**, primary aromatic amines **2.15** and phosphites **3.15** in alcoholic solvents, achieving excellent yields. Reaction times were shorter than in batch processes, and lower reagent excesses were required (Scheme 15).



R_1,R_2 : aliphatic. ref. 54. 13 examples. Yields: 90-95%

Scheme 15. Microwaves assisted KF reactions of in a continuous flow reactor.

Also Mu [55] and Lopez Cortina [56] developed microwave-assisted, catalyst- and solvent-free KF reactions for synthesizing several α-aminophosphonates **4.16**. Reactions were highly efficient (2–10 minutes), economical and environmentally friendly (Scheme 16).



ref. 55. R_1: aliphatic; aromatic. R_2: aliphatic, aromatic. R_3: Me. 80°C, neat . 24 examples. Yields: 40-97%
ref. 56. R_1: aromatic. R_2: aromatic. R_3: Ph. 80°C, EtOH. 14 examples. Yields: 11-87%

Scheme 16. Enviromentally friendly microwaves assisted KF reactions.

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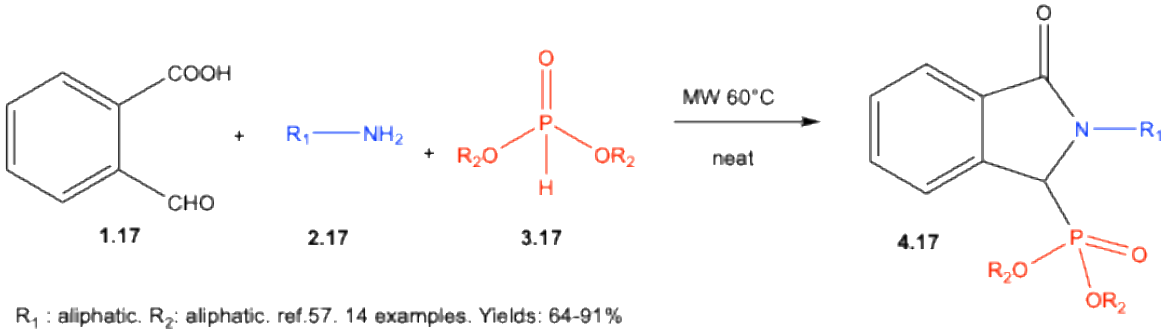
Finally, Balint [57] synthesized isoindolin-1-one-3-phosphonates **4.17** via a microwave-assisted protocol, reacting 2-formylbenzoic acid (**1.17**), aliphatic primary amines **2.17**, and various dialkyl phosphites **3.17**. Both batch and continuous-flow reactions were optimized with respect to temperature, reaction time, and molar ratios of starting materials (Scheme 17).



Scheme 17. Synthesis of isoindolin-1-one-3-phosphonates.

In recent decades, sonochemistry—the application of high-frequency ultrasound (20 kHz–10 MHz) to accelerate chemical transformations—has emerged as a powerful tool for improving the efficiency and sustainability of multicomponent reactions such as KF condensation. Zhang [58] and Singh [59] developed efficient, environmentally friendly procedures for α-aminophosphonates **5.18** via one-pot three-component reactions of aldehydes **1.18**, amines **2.18**, and diethyl phosphite (**3.18**) or triethyl phosphite (**4.18**) in water-ethyl lactate or under neat conditions at room temperature using ultrasonic irradiation (Scheme 18).

K'tir [60] prepared novel α-aminophosphonates containing 1,2,3-oxathiazolidine-2,2-dioxide scaffold **9.18** via KF reactions of β-amino alcohols **7.18**, benzaldehyde (**6.18**) and triethyl phosphite (**4.18**) under ultrasonic conditions (Scheme 18).

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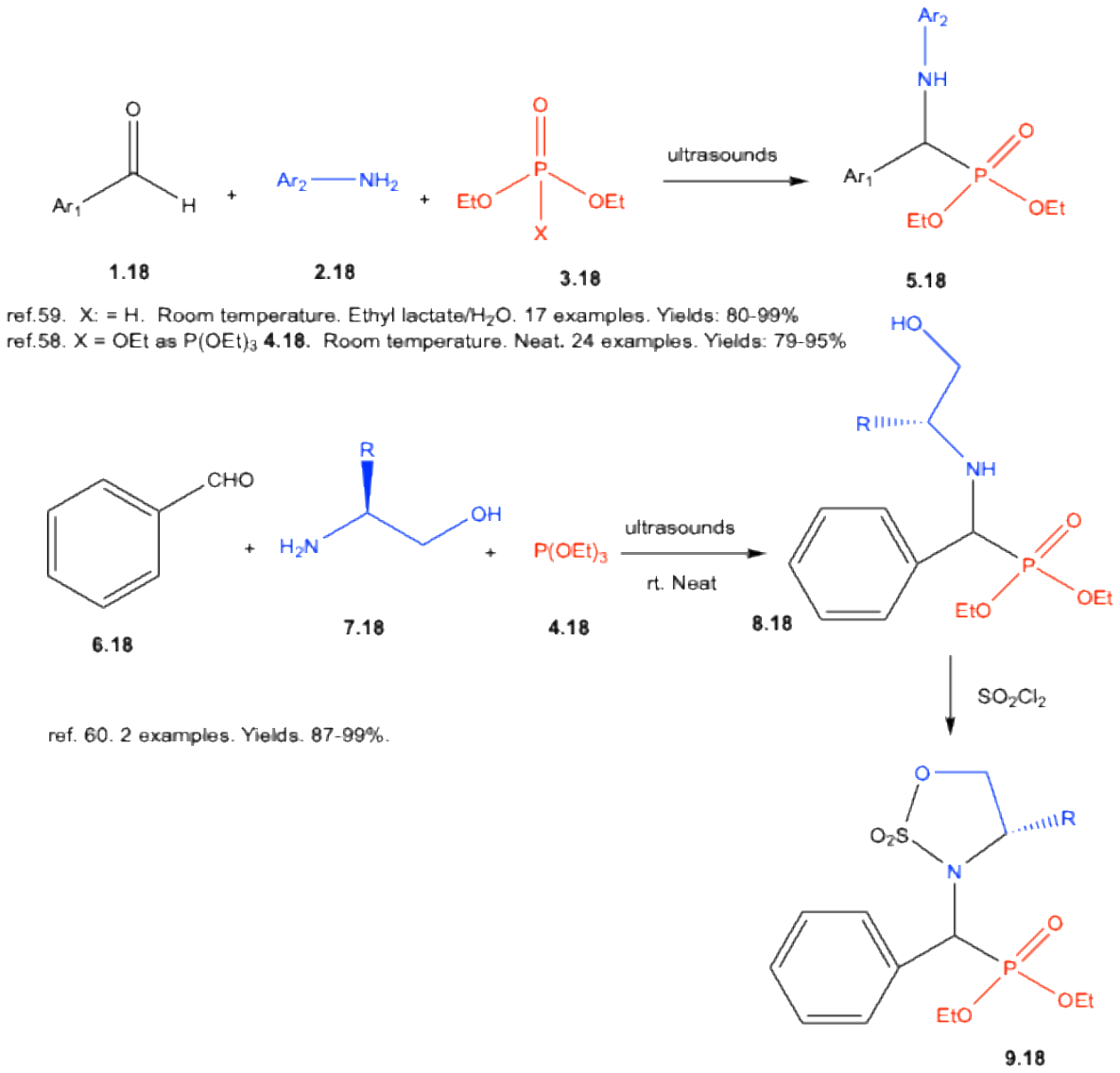
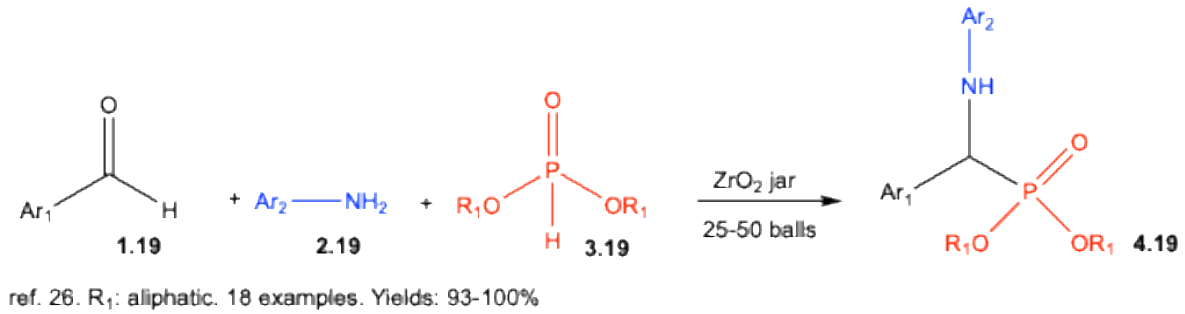


Scheme 18. Ultrasounds assisted KF reactions.

Mechanochemistry [26] has also proven valuable for preparing *α*-aminophosphonate derivatives **4.19** in high yields with complete selectivity, often surpassing comparable solution-phase methods. These reactions proceed without external catalysts, possibly via metal-mediated surface processes, with zirconium oxide commonly used as the milling medium (Scheme 19).



Scheme 19. Mechanochemistry assisted KF reactions.

4. Lewis Acid-Catalyzed Kabachnik–Fields Reactions

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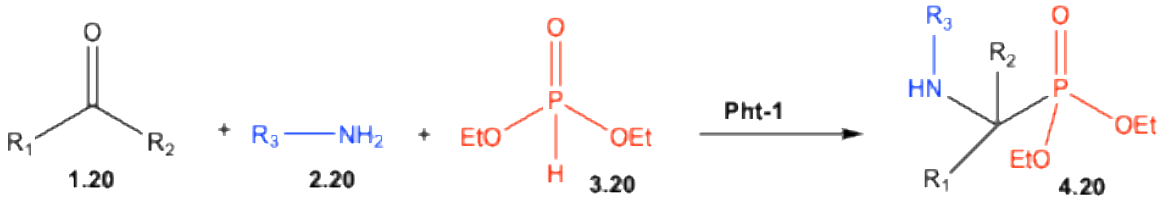
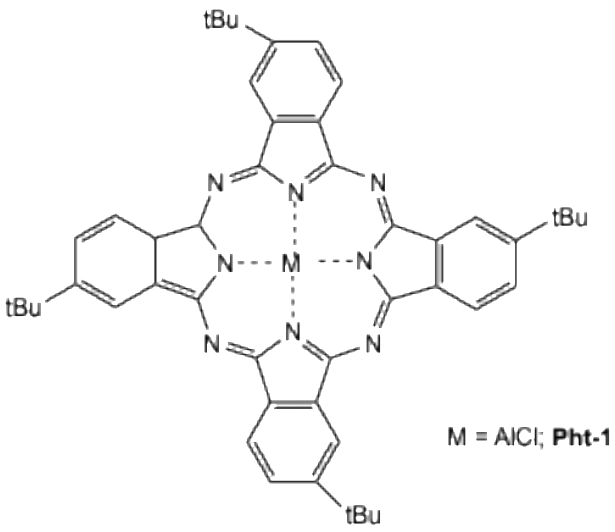
The use of Lewis acids as catalysts in KF reactions has emerged as an effective strategy to enhance the of α-aminophosphonate synthesis. By activating the carbonyl group of aldehydes and ketones, these catalysts promote both imine formation and the subsequent addition of phosphites, enabling the reactions to proceed under milder conditions, with shorter reaction times and generally high yields. The wide variety of available Lewis acids offers remarkable versatility, allowing the method to be applied to aromatic, aliphatic, heterocyclic, and even sterically hindered substrates.

Studies by Zefirov [61] in 2003 and Podrugina [62] in 2018 demonstrated that ketones **1.20**—including cyclic, sterically hindered, and cage ketones —react efficiently with diethylphosphite (**3.20**) and amines **2.20** (benzylamine or ammonia) in the presence of a tetra- t -butyl-substituted phthalocyanine–AlCl complex **Pht-1**, yielding α-aminophosphonates **4.20** in satisfactory yields (Scheme 20).



R_1: aliphatic or aromatic. R_2: aliphatic. R_1 and R_2: in a cycle. R_3: Bn or H.
Ref. 61. 22 examples. Yields: 18-98%. Ref. 62. 7 examples. Yield: 15-98%.



Scheme 20. KF reactions catalyzed by phthalocyanine–AlCl complex.

Popowycz [63] reported the synthesis of furan-based α-aminophosphonates **4.21** under environmentally benign conditions using iodine as a non-metal Lewis catalyst and 2-MeTHF as solvent. The reactions, involving 5-hydroxymethylfurfural **1.21**, various aliphatic or aromatic amines **2.21**, and dialkyl phosphites **3.21**, proceeded smoothly to give good yields of **4.21** (Scheme 20). Similarly, Cirandur [64] employed silica-supported iodine as a Lewis acid catalyst for microwave-assisted KF reactions, producing α-furfuryl-2-alkylaminophosphonates **7.21** from various aromatic aldehydes **5.21**, furfurylamine **6.21** and dialkylphosphites **3.21** in a green chemistry approach (Scheme 20). Iodine, acting as Lewis acids, activate the carbonyl group of aldehydes, accelerating imine formation and subsequent phosphite addition

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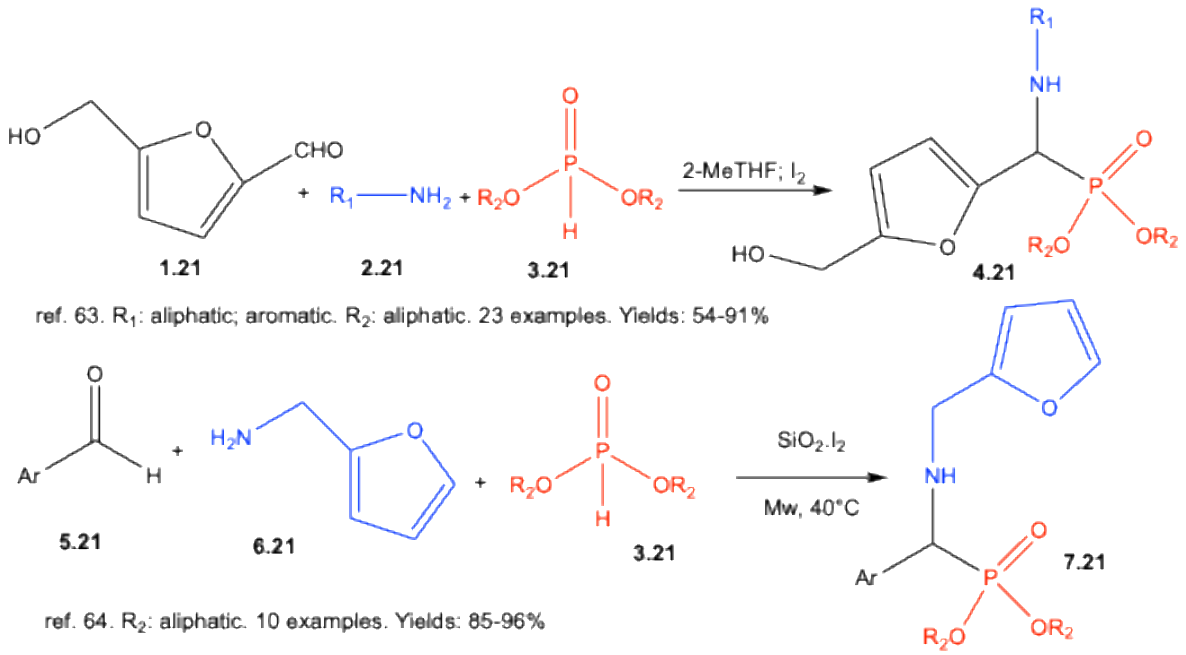
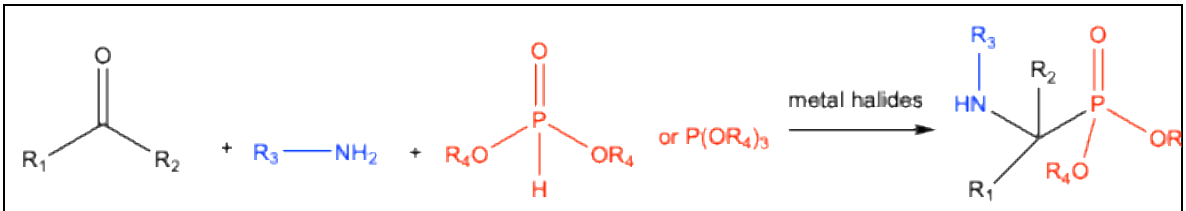


Scheme 21. Iodine catalyzed KF reactions.

A large number of metal halides have been reported as effective catalysts in KF reactions (Table 1; entries 1-13): $CeCl_3 \cdot 7H_2O$ [65], $FeCl_3$ [66], $AlCl_3$ [67], $SbCl_3$ adsorbed on Al_2O_3 [68], $TaCl_5$ adsorbed on SiO_2 [69], $BiCl_3$ [70], $ZrOCl_2 \cdot 8H_2O$ [71], $LiClO_4$ [72], $NbCl_5$ [73], $HfCl_4$ [74], $InCl_3$ [75], $LaCl_3 \cdot 7H_2O$ [76], and $LaCl_3 \cdot 7H_2O$ supported on SiO_2 [77].

Table 1. Metal halides catalyzed KF reactions.



Entry	Aldehydes or Ketones	Amines	Phosphites	Catalyst	Yields	Ref.
1	Aromatic Cyclohexanone	Aromatic	Diethyl	$CeCl_3.7H_2O$	21 examples: 87-95%	65
2	Aromatic	Aromatic	Diethyl	$FeCl_3$	9 examples: 87-95%	66
3	Aromatic Heteroaromatic Aliphatic	Aromatic Heteroaromatic Aliphatic	Trimethyl	$AlCl_3$ or $ZrCl_4$	11 examples: 66.87%	67
4	Aromatic	Aromatic, Heteroaromatic, Aliphatic	Dimethyl Diethyl	$SbCl_3$ on SiO_2	26 examples: 49-92%	68

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5	Aromatic Heteroaromatic Aliphatic Acetophenone	Aromatic	Diethyl	$TaCl_5$ on SiO_2	18 examples: 81-94%	69
6	Aromatic Aliphatic Cyclic ketones	Aromatic Aliphatic	Dimethyl Diethyl	$BiCl_3$	18 examples: 70-95%	70
7	Aromatic Heteroaromatic Aliphatic Cyclohexanone	Aromatic Heteroaromatic Aliphatic	Dimethyl Diethyl	$ZrOCl_2{\cdot}8H_2O$	56 examples: 70-96%	71
8	Aromatic	$(Me_3Si)_2NH$	Trimethyl Triethyl	$LiClO_4$	9 examples: 82-92%	72
9	Aromatic	Aromatic	Diethyl	$NbCl_5$	19 examples: 87-95%	73
10	Aromatic Aliphatic	Aromatic Aliphatic	Dimethyl Diethyl Trimethyl Triethyl	$HfCl_4$	23 examples: 82-98%	74
11	Ferrocene 2-carboxaldehyde	Aromatic	Diethyl Diphenyl	$InCl_3$	8 examples: 88-95%	75
12	Aromatic	Aromatic	Dimethyl	$LaCl_3{\cdot}7H_2O$	10 examples: 60-96%	76
13	Aromatic	Derivatives of benzothiazole or thiadiazole	Diethyl	$LaCl_3{\cdot}7H_2O$ on SiO_2	32 examples: 87-97%	77

Metal triflates provide an alternative catalytic strategy, offering a balance of activity, versatility, and, in some cases, environmental compatibility (Table 2; entries 1-6). E.g., lanthanide triflates in ionic liquids [78], $Cu(OTf)_2$ with trimethylphosphite [79], $In(OTf)_3$ [80], $Zn(OTf)_2$ [81], and $Fe(OTf)_3$ [82] have been successfully applied.

Ewies [82], in particular, achieved an high-yield synthesis of α-aminophosphonate oxadiazoles from 1,3,4-oxadiazole acetohydrazide derivatives (Table 2; entry 5. Figure 2), aldehydes, and diethylphosphite. Bismuth nitrate pentahydrate (Table 2; entry 7) has also been employed as a mild and effective catalyst [83].

Table 2. Metal triflates or nitrates catalyzed KF reactions.

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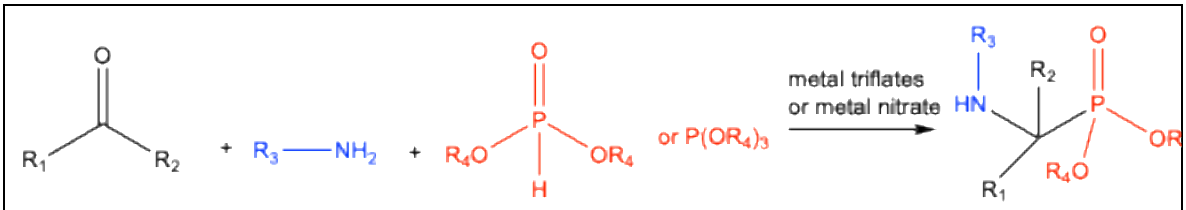

Entry	Aldehydes or Ketones	Amines	Phosphites	Catalyst	Yields	Ref.
1	Aromatic	Aniline	Diethyl Triethyl	Lanthanides triflates	23 examples: 18-99%	78
2	Aromatic Aliphatic	Aromatic Aliphatic	Trimethyl	$Cu(OTf)_2$	11 examples: 57-97%	79
3	Aromatic Aliphatic Cyclohexanone	Aromatic Aliphatic	Diethyl	$In(OTf)_3$	21 examples: 16-99%	80
4	Aromatic Aliphatic	Aromatic, Aliphatic	Dimethyl Diethyl	$Zn(OTf)_2$	20 examples: 72-93%	81
5	Aromatic Heteroaromatic	**Figure 2**	Diethyl	$Fe(OTf)_3$	13 examples: 65-73%	82
6	Aromatic	Heteroaromatic	Diethyl Diphenyl	**Figure 3**	18 examples: 86-97%	28
7	Aromatic Aliphatic	Aromatic	Diethyl	$Bi(NO_3)_3.5H_2O$	18 examples: 80-95%	83

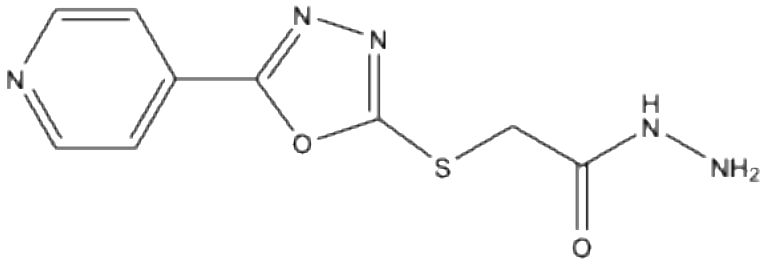

Figure 2. 1,3,4-oxadiazole acetohydrazide derivative (Table 2; entry 5).

More recently, Gupta [28] demonstrated that KF reactions of various aldehydes, amines, and diphenyl phosphite catalyzed by indium complexes give α-aminophosphonates in good yields. (Table 2; entry 6)

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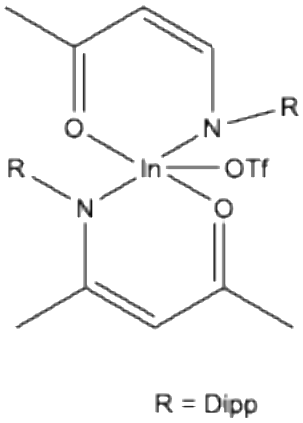

Figure 3. Indium complex as a catalyst (Table 2; entry 6).

Clays have also been used as Lewis acid catalysts (Scheme 22); e.g., Yadav [84] performed microwave-assisted, solvent-free three-component condensations using montmorillonite KSF.

Fernandes [85] reported that chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium [$CpRu(PPh_3)_2Cl$], recoverable and reusable for at least 12 cycles, efficiently catalyzes the direct aminophosphonylation of aldehydes under solvent-free conditions. Reactions of various aromatic and heteroaromatic aldehydes **5.22** with aromatic amines **6.22** and diethylphosphite (**3.22**) afforded α-aminophosphonates **7.22** in good to excellent yields, with high chemoselectivity and tolerance for multiple functional groups.

Adimule [86] designed an environmentally friendly copper(II)-β-cyclodextrin catalyst, enabling one-pot, solvent-free synthesis of α-aminophosphonates **9.22** from aromatic aldehydes **5.22**, aromatic or aliphatic amines **2.22** and triethyl phosphite (**8.22**) and proposed a plausible reaction mechanism.

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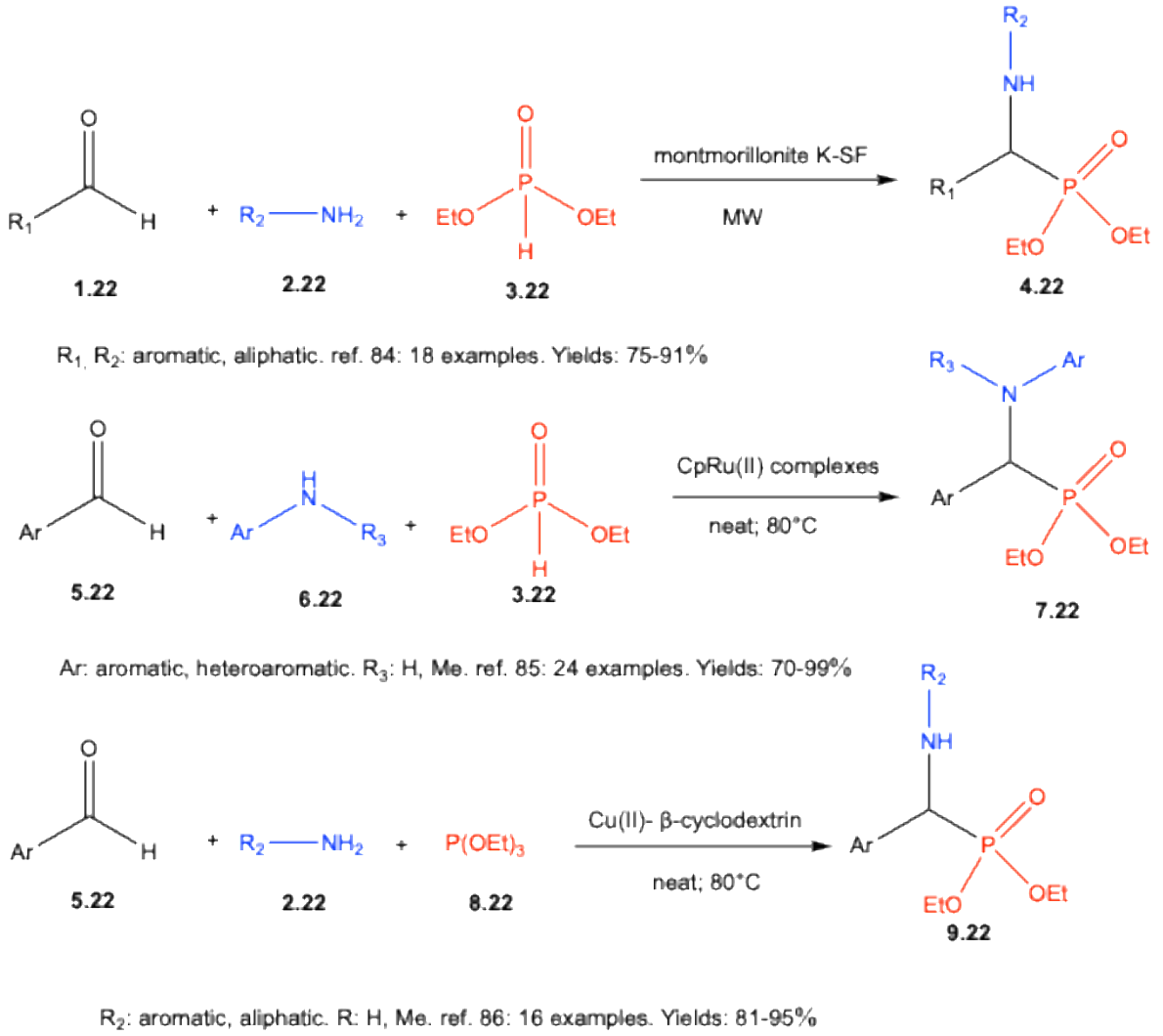

Scheme 22. Lewis acids as heterogeneous catalysyts for KF reactions.

5. Brønsted Acid-Catalyzed Kabachnik–Fields Reactions

Brønsted acid catalysis represents an effective and environmentally friendly strategy for the KF reaction (Table 3). This approach simplifies reaction setups, aligns with green chemistry principles, enhances reaction rates and yields, and eliminates the need for heavy metal catalysts. Mechanistically, Brønsted acids activate the carbonyl or iminium intermediates via protonation or hydrogen bonding, facilitating the addition of phosphites and improving overall reaction efficiency.

p-Toluenesulfonic acid (PTSA) has proven to be a practical and versatile Brønsted acid catalyst for the K–F reaction. Its application often improves reaction yields, accelerates reaction rates, and simplifies operational procedures when conditions are properly optimized. Kaboudin [87] demonstrated that aromatic aldehydes, ammonia, and diethyl phosphite could be efficiently converted to 1-aminoalkylphosphonates using PTSA (Table 3; entry 1). Cherkasov [88,89] further showed that formaldehyde reacts with aliphatic, aromatic, and heteroaromatic amines in the presence of PTSA to afford α-amino phosphonates. Interestingly, in the presence of chiral phosphites and chiral amines optical actives α-amino phosphonates were obtained (Table 3; entries 2, 3).

Amines containing acetal groups were also successfully employed (Table 3; entries 4,5). The resulting α-amino phosphonates were reacted with phenols in order to obtain polyphenols, containing aminophosphonate moiety [90,91]. Wu [9] reported a three-component reaction of substituted salicylaldehydes, aromatic amines, and triphenyl phosphite catalyzed by PTSA, producing various α-amino phosphonates in good yields (Table 3; entry 6).

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Venkatanarayana [92] synthesized a series of novel α-aminophosphonates from fluoro-substituted benzaldehydes, substituted amines, and diethyl phosphonate using a catalytic amount of methanesulfonic acid (Table 3; entry 7). Desai [93] identified sulfamic acid as an effective room-temperature catalyst for the three-component condensation of aldehydes, amines, and diethyl phosphite (Table 3; entry 8).

Akiyama [94] explored reactions of diverse aldehydes—including aromatic, heteroaromatic, aliphatic, and α,β-unsaturated—with 4-methoxyaniline and diethyl phosphite under solvent-free conditions catalyzed by trifluoroacetic acid (CF_3COOH), obtaining excellent yields of the corresponding α-amino phosphonates (Table 3; entry 9). Bommena [95] developed a solvent-free protocol employing (bromodimethyl)sulfonium bromide, where the active HBr catalyst was generated in situ. Aromatic or α,β-unsaturated aldehydes, aromatic or aliphatic amines, and dimethyl phosphite were successfully used (Table 3; entry 10).

Kasana [96] reported that tartaric acid (10 mol%) catalyzes the reaction of triethyl phosphite with in situ-generated imines from aromatic aldehydes and aromatic amines, yielding α-aminophosphonates in good yields (Table 3; entry 11).

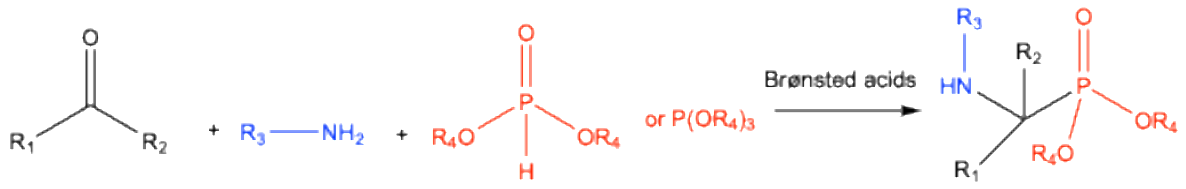
Ordóñez [97,98] developed mild one-pot, three-component methods for synthesizing α-aminophosphonates by reacting benzylamine with dimethyl phosphite and various aldehydes or ketones using phenylboronic or phenylphosphonic acid as catalysts under solvent-free conditions at 50 °C (Table 3; entries 12,13).

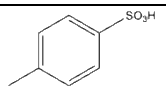
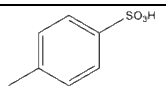
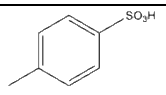
Hellal [99] described an aqueous, one-pot procedure using citric, malic, tartaric, or oxalic acids as catalysts for reactions of aromatic aldehydes, aminophenols, and dialkyl phosphites, achieving high yields (Table 3; entry 14).

Reddy [100] synthesized 2-cyclopropylpyrimidin-4-yl-aryl/benzothiazole α-aminophosphonates through a simple three-component condensation of 2-cyclopropylpyrimidin-4-carbaldehyde, various anilines or benzothiazole amines, and different phosphites. Phosphomolybdic acid ($H_3PMo_{12}O_{40}$) in dichloromethane at room temperature served as the catalyst, giving good to excellent yields with short reaction times (Table 3; entry 15).

Recently, Chavan [101] introduced N-(1-hydroxybutan-2-yl)-4-nitrobenzene sulfonamide (Figure 4) as a novel Brønsted acid catalyst for KF reactions of aromatic aldehydes, aromatic amines, and diethyl phosphite, yielding α-amino phosphonates efficiently (Table 3; entry 16)

Table 3. Brønsted Acid catalyzed KF reactions.



Entry	Aldehydes or Ketones	Amines	Phosphites	Catalyst	Yields	Ref.
1	Aromatic	NH_4OH	Diethyl		9 examples: 53-81%	87
2	HCHO	Aromatic Aliphatic	Aromatic Aliphatic		8 examples: 51-95%	88
3	HCHO	2-Aminopyridine or 2-Phenylethan-1-amine	Didecyl or Decyl phenyl		2 examples: 94%	89

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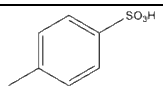
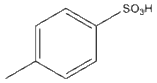
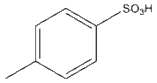
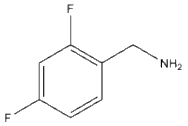
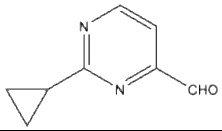
4	HCHO	aminoacetaldehyde dimethylacetal	Dihexyl		1 example: 91%	90
5	HCHO	aminoaaldehyde dimethylacetals	Aliphatic		8 examples: Yields n.a.	91
6	Salicylaldehydes	Aromatic	Triphenyl		12 examples: 82-94%	9
7	Aromatic		Diethyl	$MeSO_3H$	7 examples: 75-92%	92
8	Aromatic	Aromatic Aliphatic	Diethyl	Sulfamic acid	17 examples: 81-100%	93
9	Aromatic Heteroaromatic	p-Anisidine	Diethyl	CF_3COOH	9 examples: 87-95%	94
10	Aromatic Aliphatic	Aromatic	Trimethyl	$Me_2S^+Br\ Br^-$	14 examples: 87-95%	95
11	Aromatic	Aromatic	Triethyl	Tartaric acid	12 examples: 65-89%	96
12	Aromatic Aliphatic Cyclic Ketones Aliphatic Ketones	Benzylamine	Dimethyl	Phenyl boronic acid	22 examples: 28-93%	97
13	Aromatic Aliphatic Aliphatic Ketones	Benzylamine	Dimethyl	Phenyl phosphonic acid	20 examples: 47-98%	98
14	Aromatic	Aromatic	Diethyl	Citric acid Malic acid Tartaric acid Oxalic acid	84 examples: 54-95%	99
15		Aromatic Heteroaromatic	Aliphatic Diphenyl	$H_3PMo_{12}O_{40}$	14 examples: 89-96%	100
16	Aromatic Heteroaromatic Aliphatic	Aromatic	Diethyl	Figure 4	26 examples: 87-96%	101

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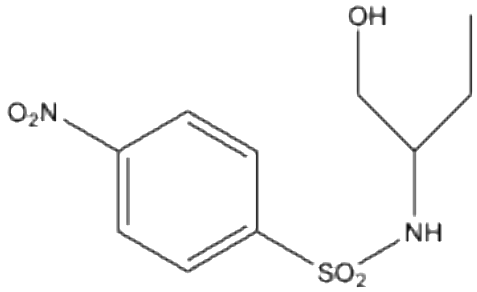

Figure 4. N-(1-hydroxybutan-2-yl)-4-nitrobenzene sulfonamide (Table 3; entry 16).

Also heterogeneous Brønsted acid catalysts have gained attention due to their reusability and high efficiency (Table 4).

Chaturbhuj [102] introduced an efficient, solvent-free protocol for the three-component KF reaction of aldehydes, amines, and diethyl phosphite using sulfated polyborate as a catalyst, giving α-amino phosphonates in good yields. Interestingly, sulfated polyborate acted as both a Lewis and Brønsted acid and could be recovered and reused up to four times without significant loss of catalytic activity (Table 4; entry 1).

Maghsoodlou [103] employed silica sulfuric acid for one-pot synthesis of α-amino phosphonates from aromatic aldehydes, aniline, and trialkyl phosphite (Table 4; entry 2). Zhang [104] developed a bio-supported xanthan sulfuric acid catalyst for solvent-free reactions of aromatic and heteroaromatic aldehydes, aromatic amines, and diethyl phosphite, which could be recovered and reused multiple times (Table 4; entry 3).

Sobhani [105] reported phosphoric acid supported on silica-coated magnetic nanoparticles (γ-Fe_2O_3@SiO_2-PA) as a magnetically recoverable catalyst for aqueous K–F reactions of aldehydes or ketones, aromatic amines, and triethyl phosphite. The catalyst was recovered and reused at least five times without significant activity loss (Table 4; entry 4). Heydari [106] used dehydroascorbic acid-capped magnetite (DHAA-Fe_3O_4) for the one-pot synthesis of α-aminonitriles and α-aminophosphonates from various aromatic and heteroaromatic aldehydes, aromatic amines, and dimethyl phosphite (Table 4; entry 5).

Gangireddy [107] demonstrated that polystyrene-supported PTSA (PS/PTSA) is an efficient heterogeneous catalyst under microwave irradiation in solvent-free conditions, providing good yields and recyclability (Table 4; entry 6). Cirandur [108] synthesized thiazolyl α-aminophosphonate derivatives via a one-pot K–F reaction using β-cyclodextrin-supported sulfonic acid (β-CD-SO_3H) as a reusable heterogeneous catalyst (Table 4; entry 7).

Reddy [109] reported polyethylene glycol sulfonic acid (PEG-SO_3H) as an effective catalyst for reactions of 4-(pyridin-4-yl)benzaldehyde, triethyl phosphite, and various aromatic or aliphatic amines, giving α-aminophosphonates in high yields (Table 4; entry 8).

Zeolites have also been employed as heterogeneous catalysts. Choudhary [110] showed that H-beta zeolite is reusable for K–F reactions of carbonyl compounds, primary aliphatic or aromatic amines, and methyl, ethyl or benzyldiphosphite (Table 4; entry 9).

Ghosh [111] utilized humic acid as a catalyst for reactions of various aromatic aldehydes and amines with diethyl phosphite, yielding α-aminophosphonates efficiently (Table 4; entry 10).

Kanade [112] found that as-synthesized N-TiO_2 exhibits significantly higher catalytic activity than commercial TiO_2 for synthesizing α-amino phosphonates under microwave irradiation, due to the presence of strong Brønsted acid sites on the porous nanorod surface (Table 4; entry 11). Servari [113] reported that commercially available TiO_2 efficiently catalyzes one-pot, solvent-free reactions of aromatic amines, aldehydes or ketones, and dialkyl phosphites, giving α-aminophosphonates in high yields and short times, with excellent catalyst recyclability (Table 4; entry 12).

Table 4. Brønsted Acid as heterogeneous catalysts for KF reactions.

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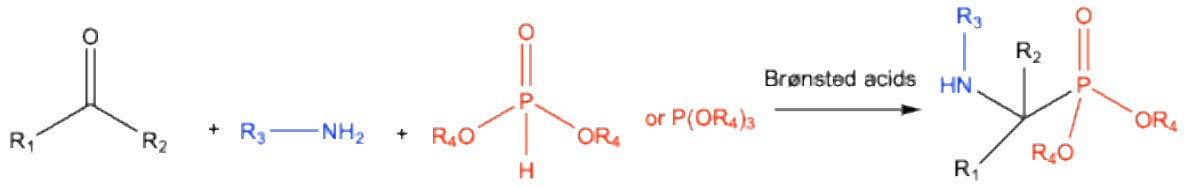
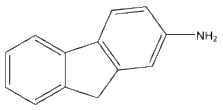
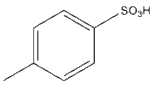
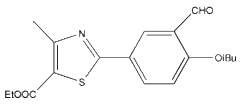
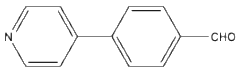
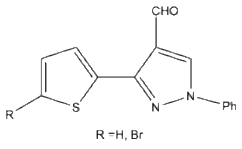


Entry	Aldehydes or Ketones	Amines	Phosphites	Catalyst	Yields	Ref.
1	Aromatic	Aromatic	Diethyl	Sulfated polyborate	20 examples: 90-98%	102
2	Aromatic	Aniline	Dimethyl Diethyl	Silica sulfuric acid	11 examples: 80-95%	103
3	Aromatic Heteroaromatic	Aromatic	Diethyl	Xanthan sulfuric acid	32 examples: 88-95%	104
4	Aromatic Aliphatic Cyclohexanone	Aromatic Aliphatic	Triethyl	Phosphoric acid on γ-Fe_2O_3@SiO_2	16 example: 82-95%	105
5	Aromatic Heteroaromatic Aliphatic Cyclohexanone	Aromatic Aliphatic	Methyl	DHAA-Fe_3O_4	10 examples: 75-95%	106
6	Aromatic Aliphatic		Diethyl	polystyrene-supported 	18 examples: Yields: n.a	107
7		Aromatic	Diethyl	β-cyclodextrin-supported sulfonic acid	10 examples: 91-96%	108
8		Aromatic Heteroaromatic	Triethyl	polyethylene glycol sulfonic acid	10 examples: 82-96%	109
9	Aromatic Heteroaromatic Aliphatic Acetophenone	Aromatic Aliphatic	Dialkyl	H-beta zeolite	15 examples: 76-93%	110
10	Aromatic Heteroaromatic	Aromatic Aliphatic	Diethyl	Humic acid	25 examples: 78-93%	111
11		Aromatic	Triethyl	N-TiO_2	11 examples: 71-95%	112
12	Aromatic Heteroaromatic	Aromatic Aliphatic	Diethyl	TiO_2	36 examples: 50-98%	113

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	Aliphatic Cyclohexanone Acetophenone					

6. Other Catalysts for Kabachnik–Fields Reactions

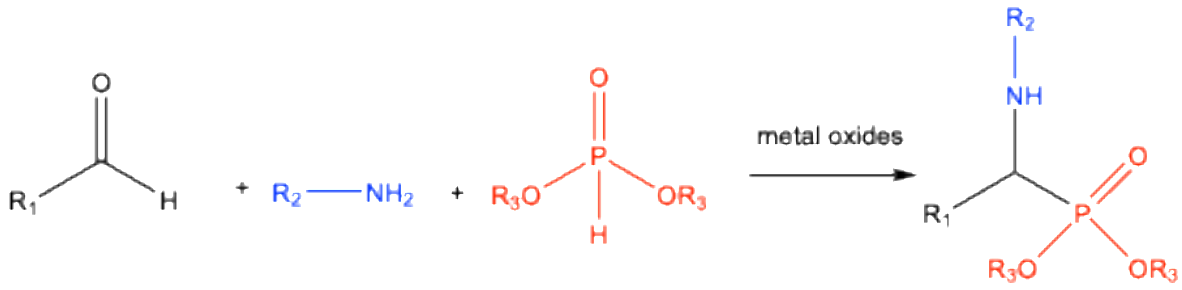
Traditionally, Kabachnik–Fields (KF) reactions are catalyzed by Brønsted acids or Lewis acids. Recently, however, research has increasingly focused on non-conventional catalysts that do not fit neatly into the Brønsted/Lewis classification.

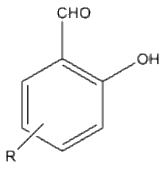
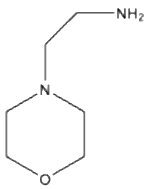
Metal oxides (Table 5) have emerged as particularly effective catalysts due to the synergistic interplay of their surface acidic and basic sites. E.g., Agawane [114] demonstrated that recyclable CeO_2 nanoparticles efficiently catalyze the condensation of aromatic and heteroaromatic aldehydes with aromatic amines and triethyl phosphite under ultrasound irradiation and solvent-free conditions, affording α-aminophosphonates in high yields (Table 5; entry 1). Similarly, Reddy [115] reported a one-pot, three-component reaction using nano-Gd_2O_3 as a catalyst under microwave irradiation. This method enabled the synthesis of various α-aminophosphonates from 2-morpholinoethanamine, dimethyl phosphite, and salicylaldehydes with excellent efficiency (Table 5; entry 2).

Expanding the range of catalytic systems, Reddy [116] developed a solvent-free approach employing a CuO–Au nanocatalyst to promote the reaction of 2-aminophenol with substituted aromatic aldehydes and dimethyl phosphite at 60 °C (Table 5; entry 3). Ummad [117] further illustrated the potential of heterogeneous catalysis by synthesizing a TiO_2-supported ZnO (TiO_2–ZnO) catalyst, achieving excellent yields of α-aminophosphonates from 2,4-difluorobenzylamine, aldehydes, and diethyl phosphite, along with a proposed reaction mechanism (Table 5; entry 4).

Bifunctional solid catalysts have also been explored. Ramanathan [118] utilized niobium pentoxide to catalyze the KF reaction between aromatic aldehydes, aromatic amines, and triethyl phosphite, yielding α-aminophosphonates in good yields (Table 5; entry 5).

Table 5. Metal oxides catalyzed KF reactions.



Entry	Aldehydes	Amines	Phosphites	Catalyst	Yields	Ref.
1	Aromatic Heteroaromatic	Aromatic Heteroaromatic Aliphatic	Diethyl	Nano CeO_2	16 examples: 67-99%	114
2			Dimethyl	Nano Gd_2O_3	10 examples: Yields: n.a	115
3	Aromatic	2-aminophenol	Dimethyl	Nano CuO-Au	10 examples:	116

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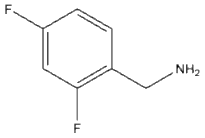
					87-96%	
4	Aromatic		Diethyl	TiO_2-ZnO	12 examples: 91-95%	117
5	Aromatic Aliphatic	Aromatic Heteroaromatic	Diethyl	Nb_2O_5	43 examples: 40-97%	118

As already reported in section 2, Keglevich [27] and Balint [119] showed that propylphosphonic anhydride (**4.23**) acted as an effective condensing agent facilitating KF reactions with various aldehydes **1.23**, aniline **2.23** and dialkyl phosphites **3.23** to afford α-aminophosphonates, including α-amino(2-alkynylphenyl)methylphosphonates **5.23** (Scheme 23) [119]. Moreover, CuCl-catalyzed reactions of 2-alkynylbenzaldehydes, aniline, and dialkyl phosphites were shown to efficiently produce 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates **6.23** via intramolecular nucleophilic attack and subsequent ring closure.

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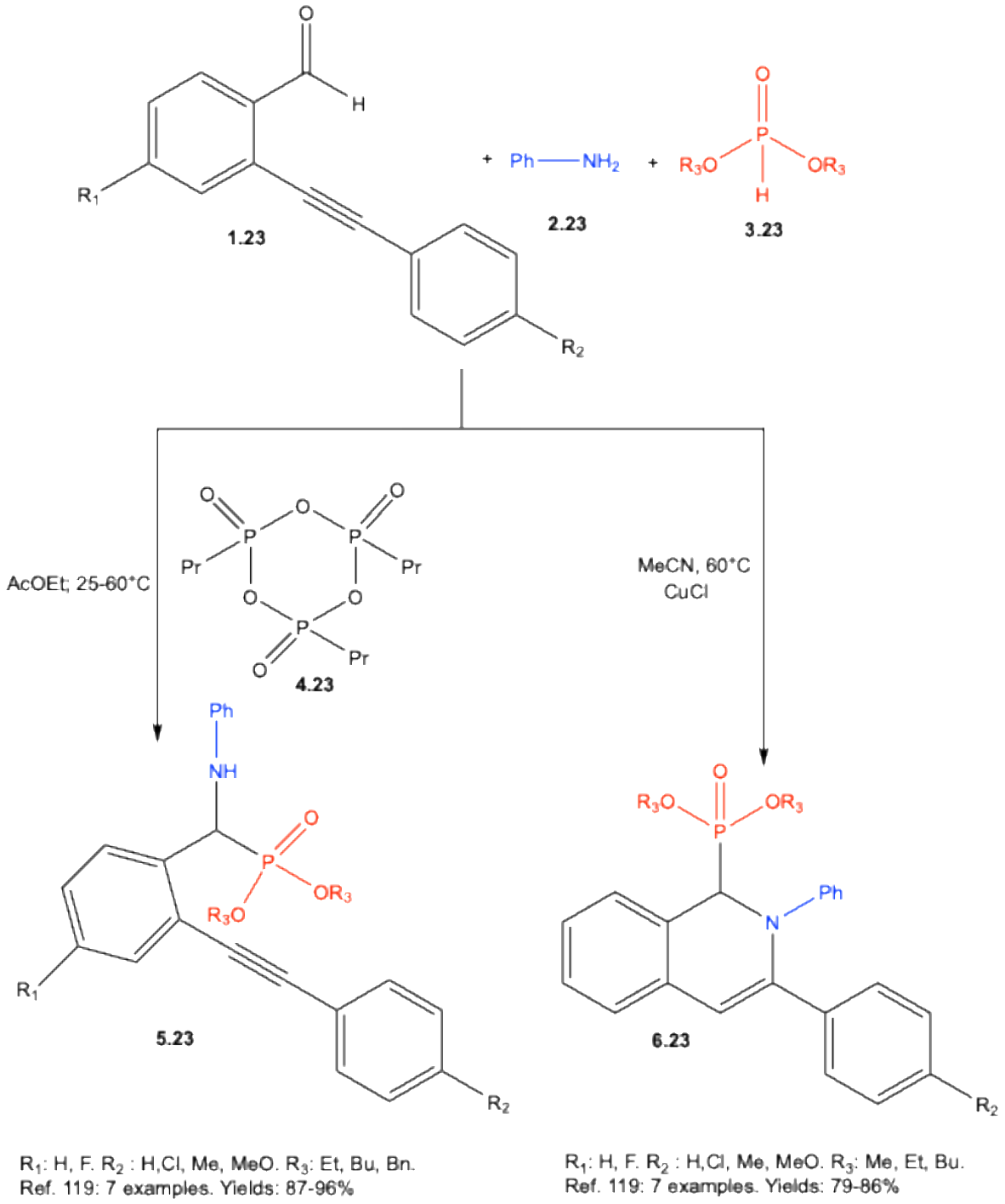

Scheme 23. Synthesis of α-amino(2-alkynylphenyl)methylphosphonates) or 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates.

Magnesium dodecyl sulfate has been reported as a green and readily available catalyst. Ando [120] demonstrated that it can catalyze the three-component reaction of aromatic or aliphatic aldehydes **1.24** with amines **2.24** and triethyl or diphenyl phosphite (**3.24**) in water at room temperature, producing α-aminophosphonates in high yields (Scheme 24)

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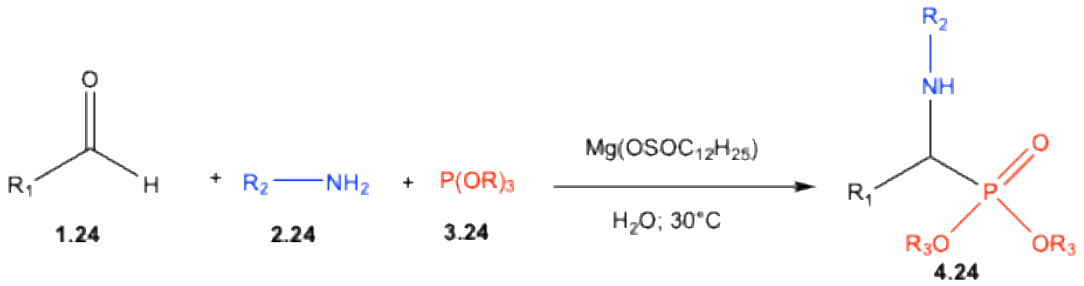
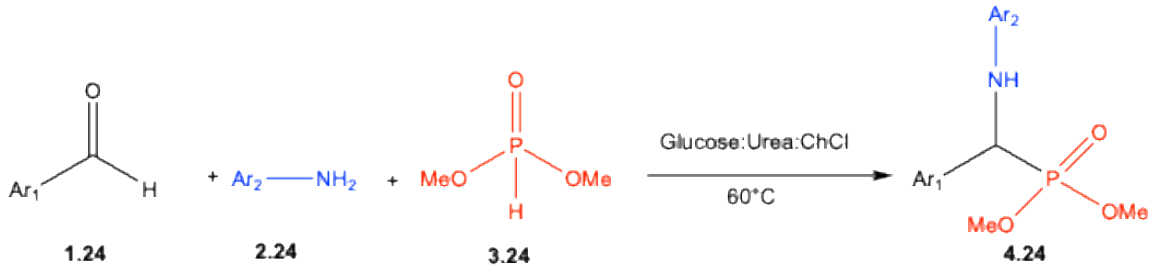


R1: aromatic, aliphatic R2 : aromatic, aliphatic. R3: Et, Ph. Ref. 120: 20 examples. Yields: 29-87%

Scheme 24. Magnesium dodecyl sulfate catalyzed KF reactions.

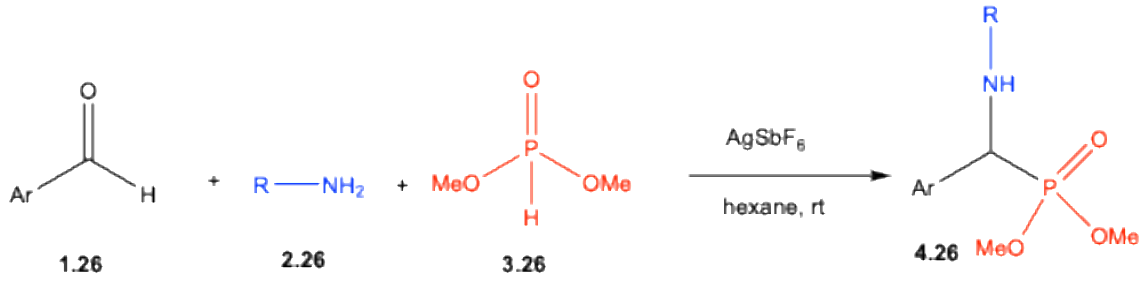
Very recently (2025), Letcy [121] showed that the KF reaction can proceed efficiently in a glucose–urea–choline chloride as a low-melting mixture, which acts both as solvent and catalyst, yielding α-aminophosphonates **4.25** from aromatic aldehydes **1.25** and amines **2.25** (Scheme 25).



Ref. 124: 9 examples. Yields: 73-97%

Scheme 25. KF reactions in a low-melting mixture.

As already reported in Section **2,** Rit [29] developed a solvent-, ligand-, and base-free protocol using $AgSbF_6$ as a catalyst, producing α-aminophosphonates **4.26**, including biologically relevant derivatives, through a radical mechanism (Scheme 26).



R: aromatic, aliphatic. Ref. 29: 26 examples. Yields: 75-95%

Scheme 26. $AgSbF_6$ catalyzed KF reactions.

7. Enantioselective Kabachnik–Fields Reactions

Optically active α-aminophosphonates are highly valuable compounds, both as intermediates in organic synthesis and for their broad applications in biological, pharmaceutical, and materials sciences [122,123]. Examples of biologically relevant α-aminophosphonic acids and esters are shown in Figure 5, including compounds of medical and agrochemical interest such as the antibacterial agent alafosfalin (**1.5**), and phospholeucine (**2.5**), a potent leucine aminopeptidase inhibitor. Phospholeucine is also a structural component in enzyme inhibitors **3.5**. Other notable examples include the natural phosphotyrosine tripeptide K-26 (**4.5**), an ACE inhibitor, and dufulin (**5.5**), widely used in China to combat viral diseases in crops.

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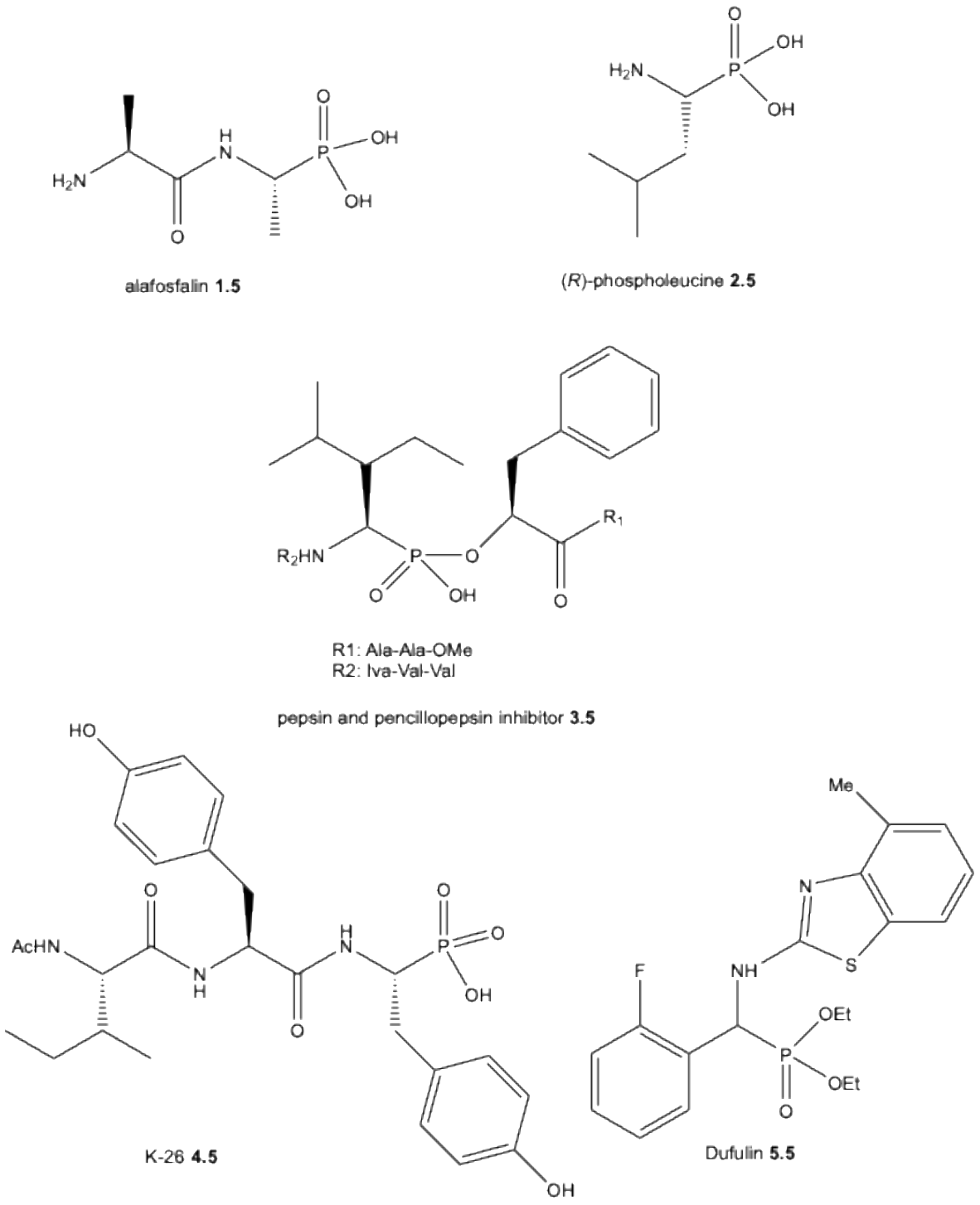

Figure 5. Optically active α-aminophosphonates.

The biological activity of α-aminophosphonates is strongly dependent on the absolute configuration of the α-carbon attached to phosphorus. For example**, 1.5** shows significant differences in activity between its isomers, and the (S)-enantiomer of phospholeucine **2.5** is 103 times less active than the (R)-enantiomer. Therefore, enantioselective synthesis of α-aminophosphonates remains a central goal, prompting the development of catalysts capable of inducing chirality during the formation of the α-stereogenic center.

Key strategies include the use of Lewis acid–based chiral metal complexes or chiral Brønsted acid organocatalysts, such as BINOL-derived phosphoric acids.

7.1. Lewis Acid–Catalyzed Reactions

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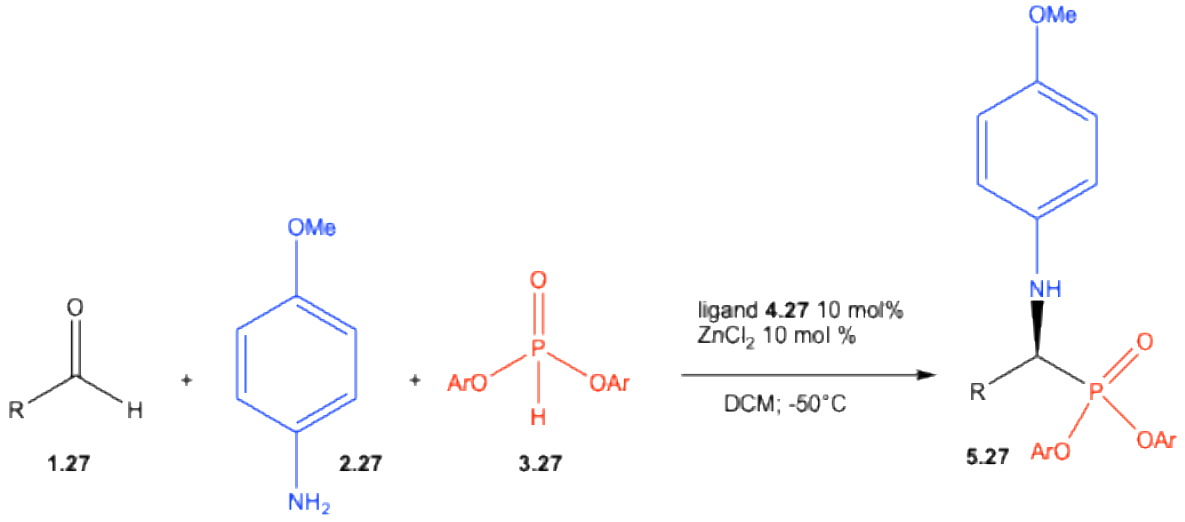
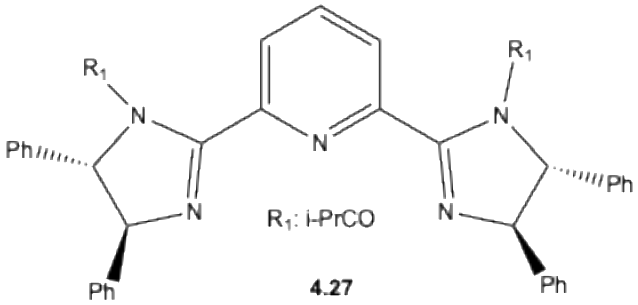
Chiral metal catalysts have significantly advanced enantioselective Kabachnik–Fields reactions. Nakamura (Scheme 27) [124] reported that a zinc(II)–bis(imidazoline) **4.27** complex can catalyze the three-component reaction of aromatic or aliphatic aldehydes **1.27**, 4-methoxyaniline (**2.27**) and aryl phosphites **3.27**, delivering α-aminophosphonates **5.27** in excellent yields (up to 99%) and good enantioselectivity (up to 93% ee). The detailed reaction mechanism remains unclear. However, authors proposed that the in situ formed imines coordinated to the chiral Zn(II) catalyst in an equatorial position to minimize the steric repulsion from bis(imidazoline). Coordination of the phosphite **3.27** oxygen to Zn(II) following by the deprotonation of phosphite generates the nucleophilic phosphonate, which then attacks the coordinated imine whitin the chiral enviroment to afford **5.27**.



R_1, R_2: aromatic, aliphatic. Ar: Ph or 2-MeOPh. ref. 124: 17 examples. Yields: 82-99%. Ee: 31-93%



Scheme 27. Enantioselective KF reaction catalyzed by zinc(II)–bis(imidazoline) complex.

Wulff [125] developed a chiral catalyst zirconium-based prepared from 7,7′- di-t-butyl VANOL ligand (**6.28**), N-methylimidazole (**5.28**) and zirconium tetraisopropoxide (**4.28**). This catalyst exhibited optimal performance in the presence of 10 mol% of benzoic acid.It enabled good enantioselectivities not only with aromatic aldehydes **1.28** but also with aliphatic ones **1.28** overcoming a long-standing challenge in asymmetric reactions of aliphatic aldehydes (Scheme 28).

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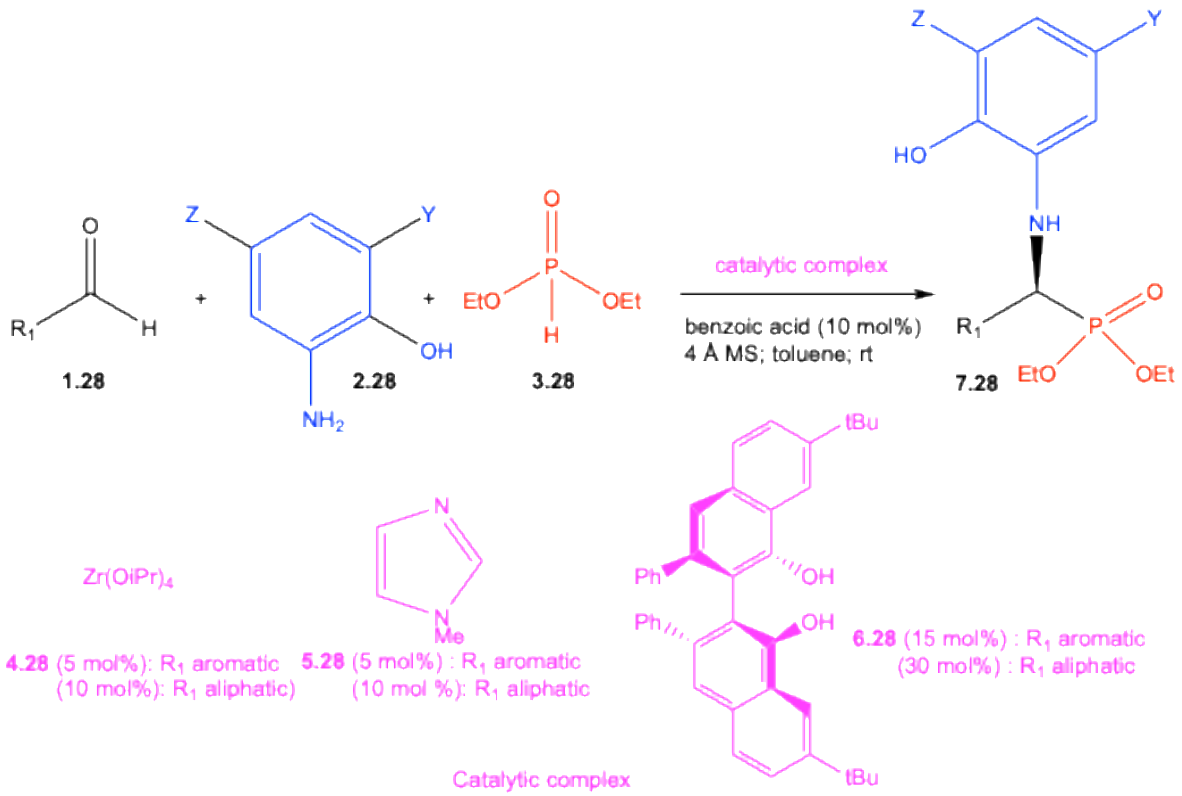

Scheme 28. Enantioselective KF reaction catalyzed by zirconium complex.

Chiral thiourea organocatalysts offered an alternative approach. Bis-thioureas derived from (1R,3S)-camphoric acid **4.29**, synthesized by Reddy [126], catalyzed the Kabachnik–Fields reaction with aldehyde **1.29**, yielding modest enantioselectivities of 14–35% ee (Scheme 29).

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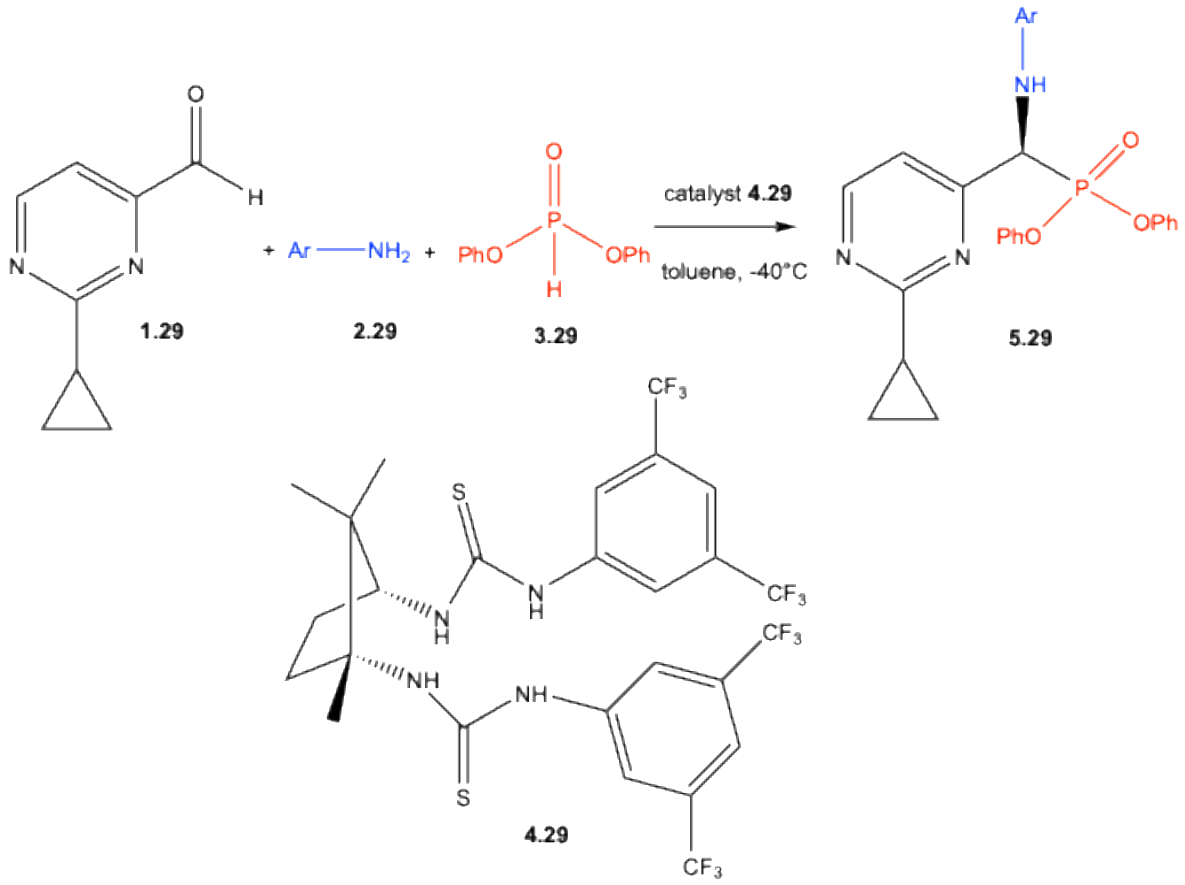

Scheme 29. Enantioselective KF reaction catalyzed by bis-thioureas derived **4.29.**

Katsuki [127] reported a highly enantioselective aluminum–salalen complex **4.30**, whose "cis-β-like" configuration creates a well-defined chiral environment around the metal center. This enables asymmetric hydrophosphonylation of aldehydes **1.30** (or aldimines) with dimethyl phosphite (**3.30**), producing α-aminophosphonates **5.30** in satisfactory yields and up to 94% ee (Scheme 30).

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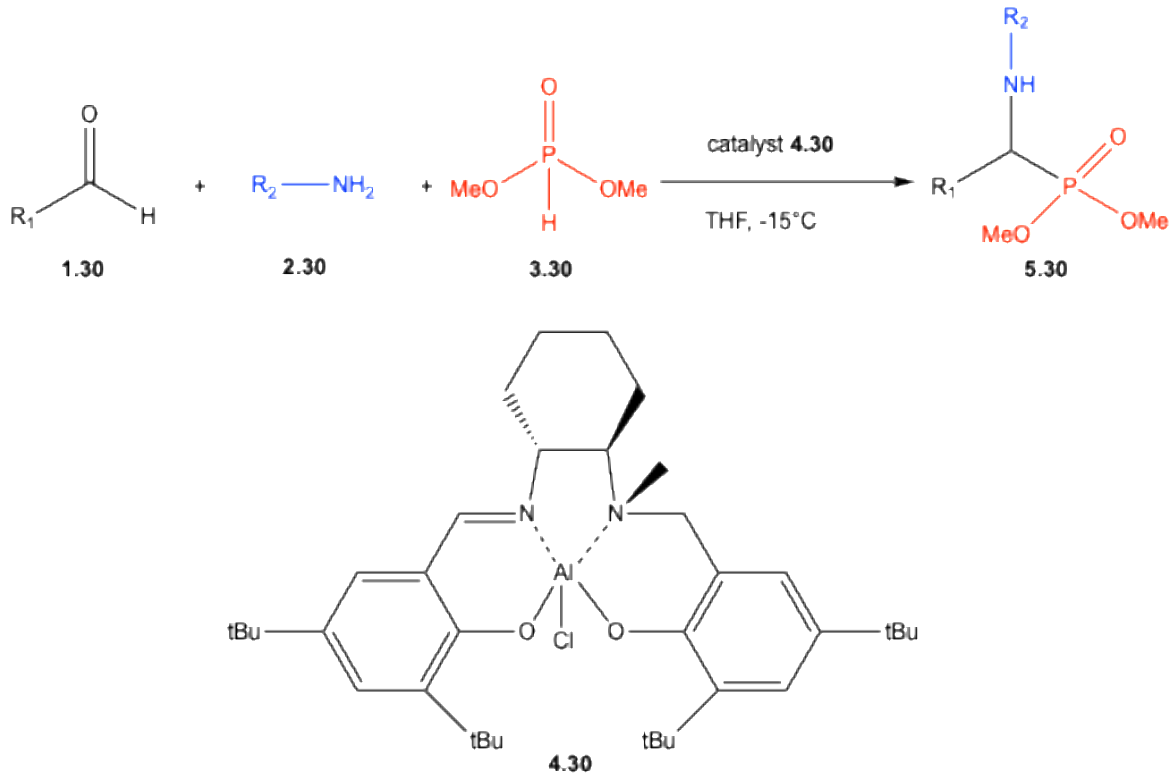

R1: aliphatic. R2: aromatic or aliphatic ref.127: 6 examples. Yields: 28-92%. Ee 15-94%

Scheme 30. Enantioselective KF reaction catalyzed by aluminum–salalen complex **4.30.**

Feng [128] described a one-pot enantioselective synthesis using a chiral Sc(III)–N,N′-dioxide complex **4.31**. Reactions of aromatic aldehydes **1.31**, 2-aminophenol (**2.31**) and diphenyl phosphite (**3.31**) afforded α-aminophosphonates **4.31** in high yields and up to 87% ee within short reaction times. The enhanced reactivity was attributed to bidentate coordination of the Sc(III) complex, stabilizing the transition state and promoting chiral induction (Scheme 31).

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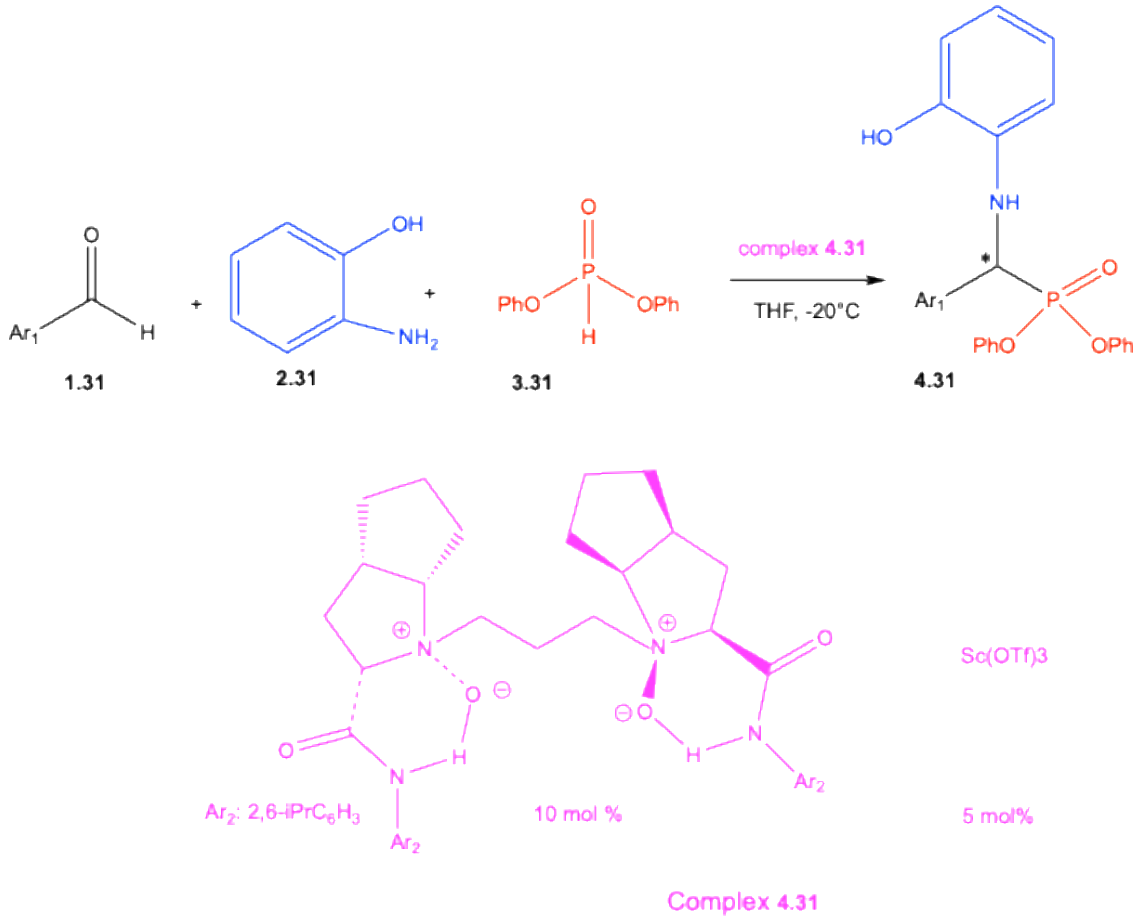

ref.128: 13 examples. Yields: 73-96%. Ee 80-87%

Scheme 31. Enantioselective KF reaction catalyzed by Sc(III)–N,N′-dioxide complex **4.31.**

7.2. Brønsted Acid–Catalyzed Reactions

Chiral Brønsted acids, particularly BINOL-derived phosphoric acids, have emerged as effective alternatives to metal catalysts in enantioselective Kabachnik–Fields reactions. These catalysts activate in situ generated imines and provide a chiral environment that governs the approach of the phosphorus nucleophile, favoring selective formation of a single enantiomer.

List [129] achieved high enantioselectivity using a chiral phosphoric acid **4.32**, reacting racemic branched aldehydes **1.32** with p-anisidine (**2.32**) to give aminophosphonic esters **5.32** with high diastereo- and enantioselectivity through dynamic kinetic resolution (Scheme 32).

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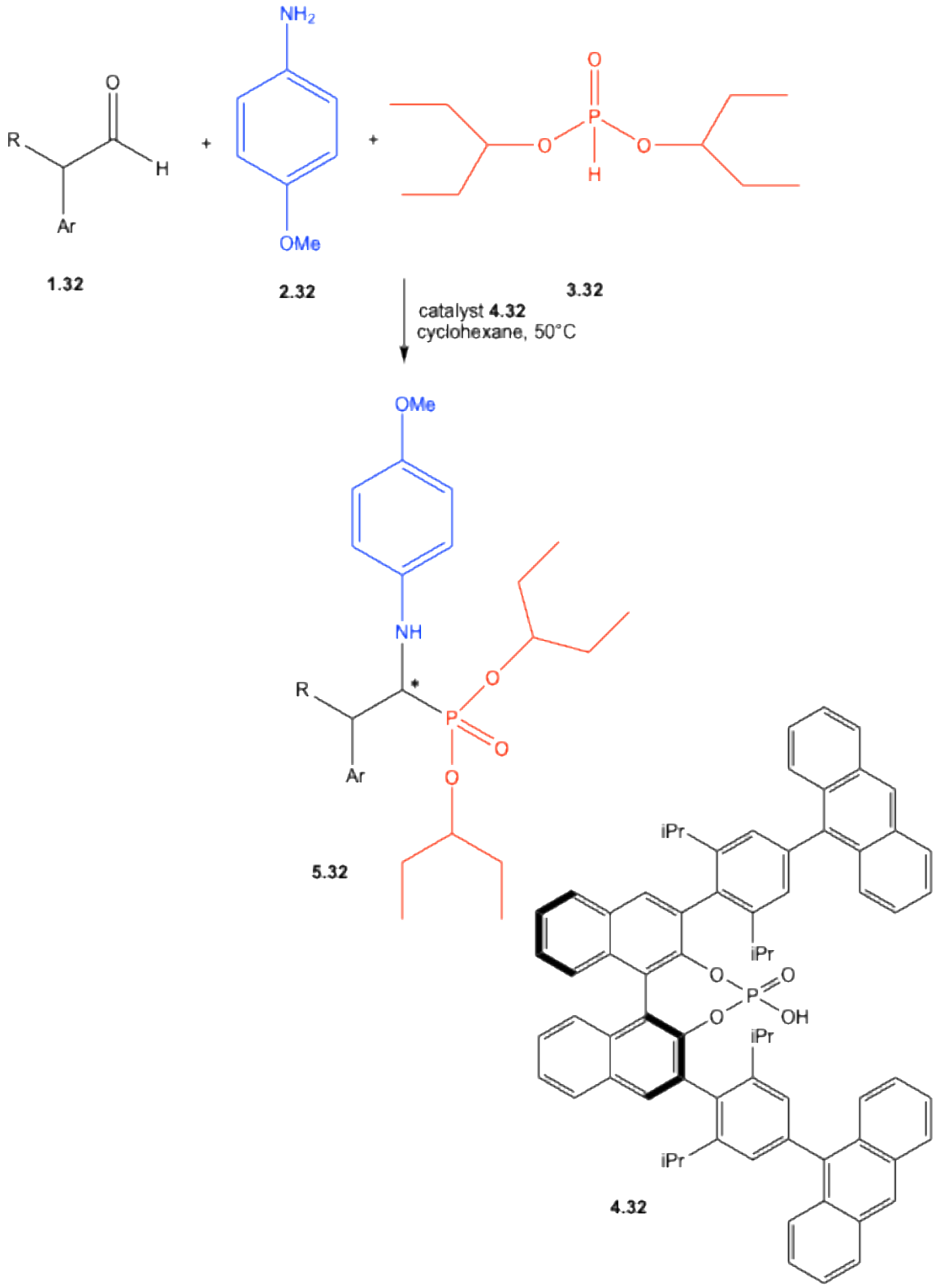

R: cyclopentyl, aliphatic. Ar: aromatic , heteroaromatic ref.129: 15 examples. Yields: 61-86%.
Dr value: between 3:2 and 28:1. Er value: between 51:49 and 95:5

Scheme 32. Stereoselective KF reaction catalyzed by chiral phosphoric acid **4.32.**

Ma [130] demonstrated that bulky substituents at the 3,3′-positions of BINOL (catalyst **4.33**) enhance chiral induction, and that solvent choice and molecular sieves improve ee. Moderate enantioselectivities (55–87% ee) and good yields (62–91%) were obtained (Scheme 33).

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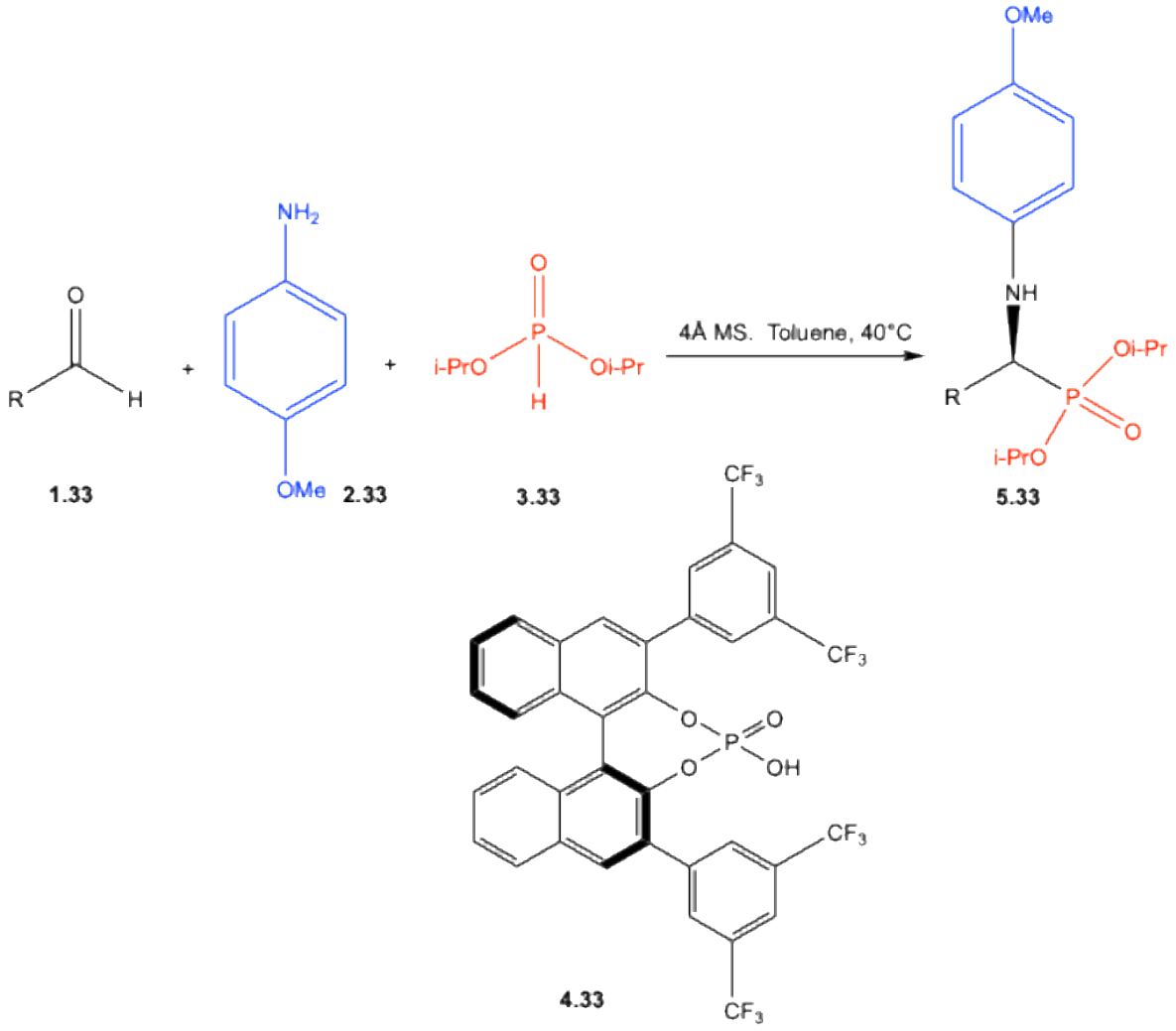

Scheme 33. Enantioselective KF reaction catalyzed by chiral phosphoric acid **4.33.**

A silver–spirocyclic phosphate complex **4.34**, formed in situ from silver carbonate and a chiral phosphoric acid [131], catalyzed an enantioselective three-component reaction of 2-alkynylbenzaldehydes **1.34**, aromatic amines **2.34** , and dimethylphosphite **3.34**, producing chiral C1-phosphonylated 1,2-dihydroisoquinolines **5.34** in up to 99% yield and 94% ee. Mechanistic studies revealed that silver activates the alkyne–imine system allowing a 6-endo-dig cyclization, while the chiral phosphate controls stereochemistry through ion-pair interactions.

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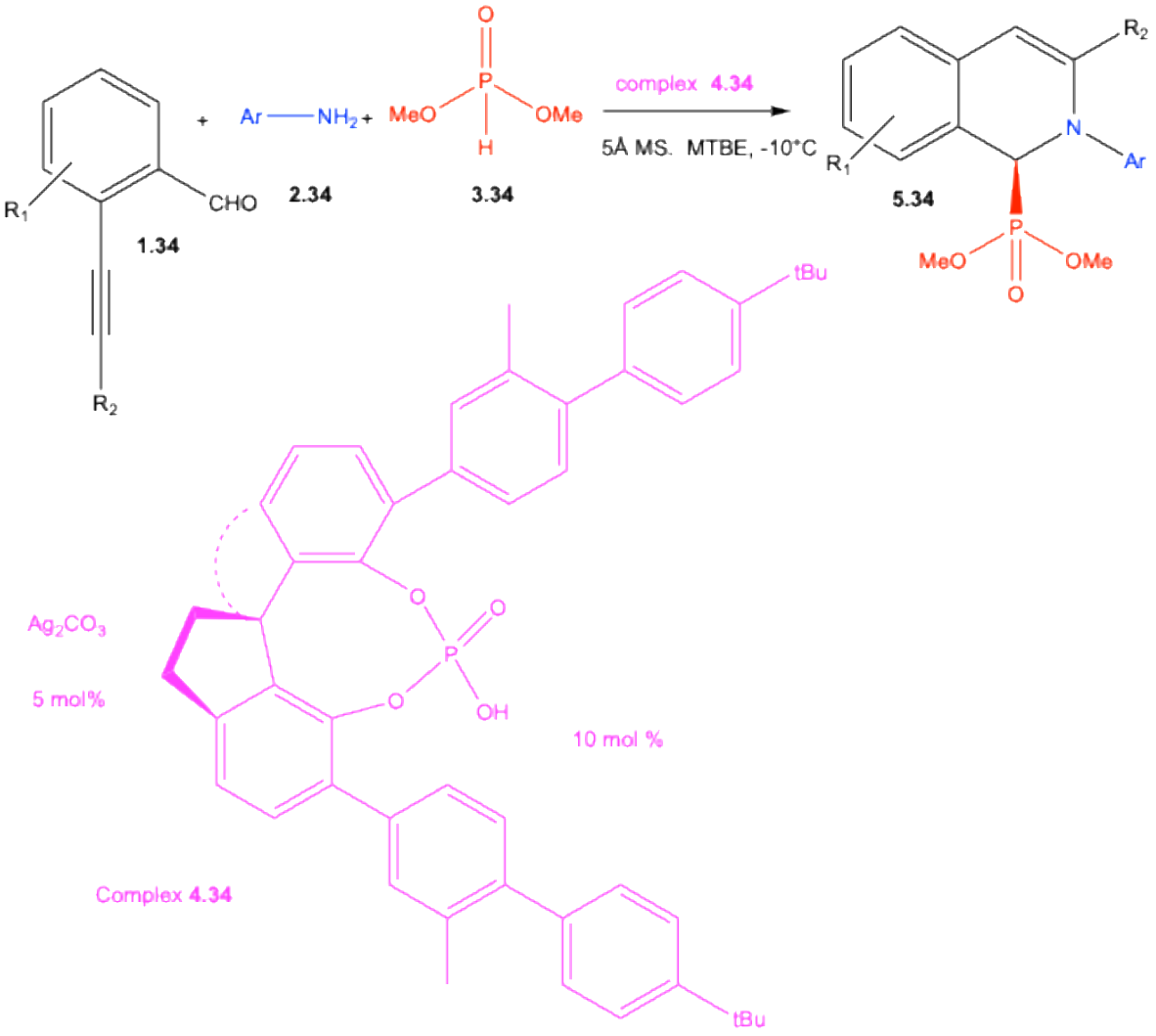

Scheme 34. Enantioselective KF reaction catalyzed by complex **4.34**.

Brønsted-assisted organocatalysis has also been explored [132], using pyrrolidine derivatives **4.35** with acetic acid as co-catalyst. This strategy enables the formation of α-aminophosphonate **5.35** under mild conditions within 24 hours, achieving yields of 71–90% and up to 91% ee (Scheme 35).

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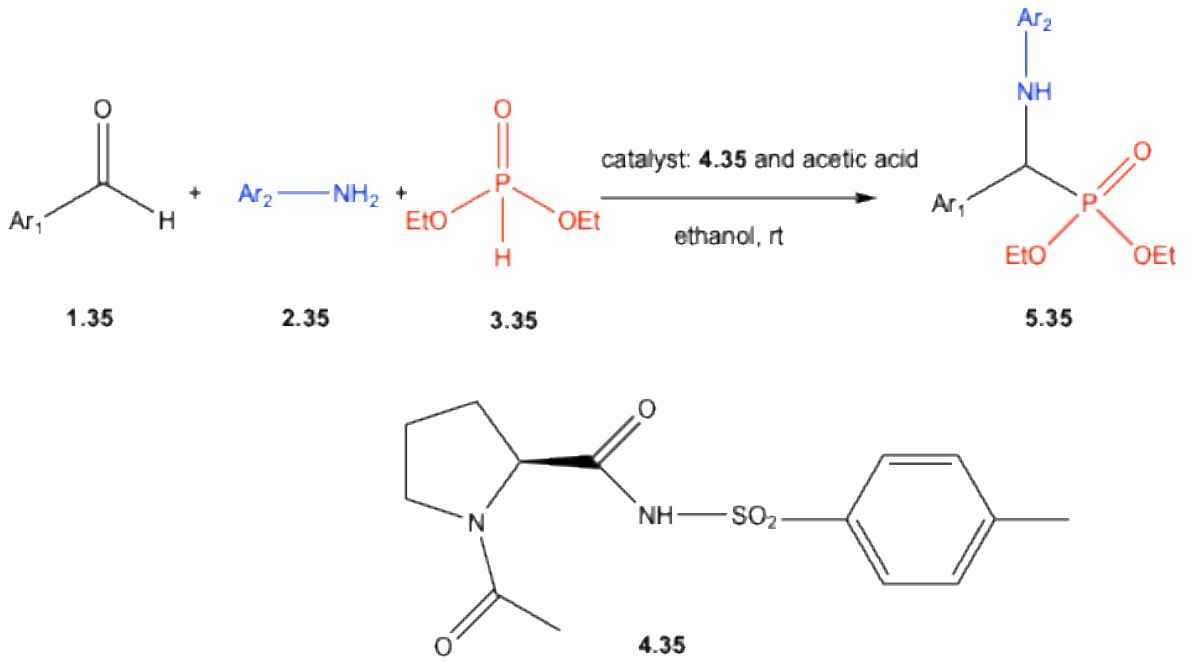
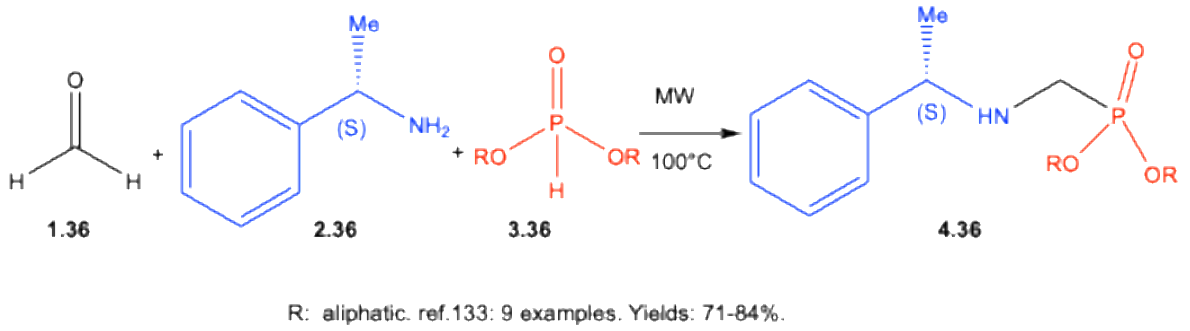


Scheme 35. Enantioselective KF reaction catalyzed by pyrrolidine derivative and acetic acid.

7.3. Enantioselective Synthesis Without Chiral Catalysts

Catalyst-free KF reactions generally yield racemic α-aminophosphonates. However, if one of the starting materials is optically active, enantioenriched products can be obtained. E.g., (S)-α-phenylethylamine (**2.36**) reacts with paraformaldehyde (**1.36**) and various phosphites (**3.36**) under microwave irradiation to give optically active α-aminophosphonates (**4.36**) [133].



Scheme 36. Synthesis of enantioenriched **4.36.**

Ordóñez [134] developed a general method for highly diastereoselective α-aminophosphonate **4.37** or **5.37** synthesis under solvent- and catalyst-free conditions. Aldehyde **1.37** reacted with various chiral amines **2.36** and dimethyl phosphite **3.37**. The nucleophilic attack of dimethyl phosphite tautomer **8.37** occurring preferentially at the Re face of intermediate **7.37**. (Scheme 37).

Dimukhametov [13] reported comparable results using benzaldehyde and S- or R-1-phenyl-1-ethylamine.

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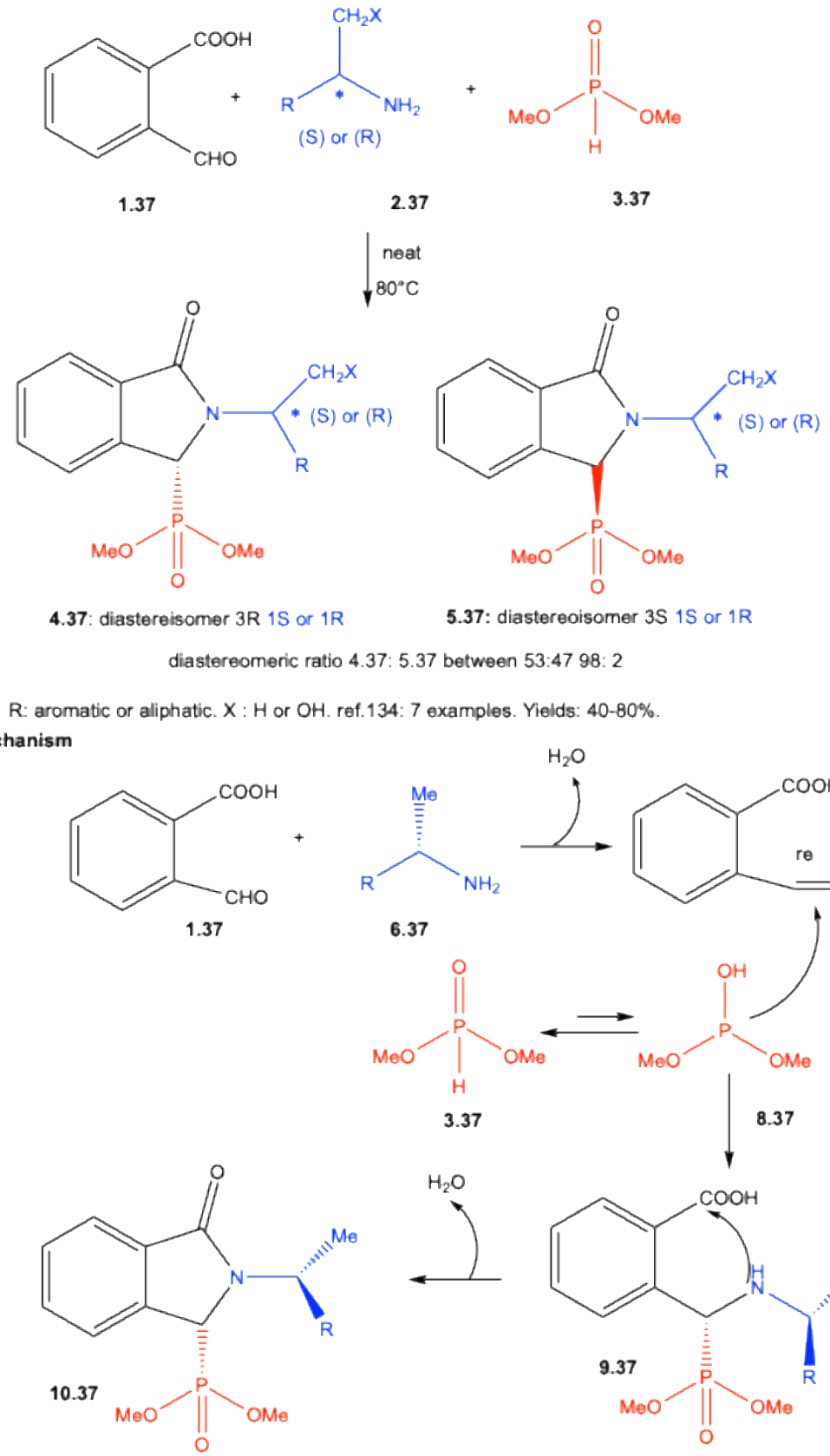

Scheme 37. Diastereoselective KF reactio.

8. Derivatives of *α*-Aminophosphonates

α-Aminophosphonates are versatile precursors of heterocyclic structures, such as isoindolines **5.38** or **6.38**. Ordóñez [135, 136] first prepared N-substituted dimethyl 3-oxoisoindolin-1-

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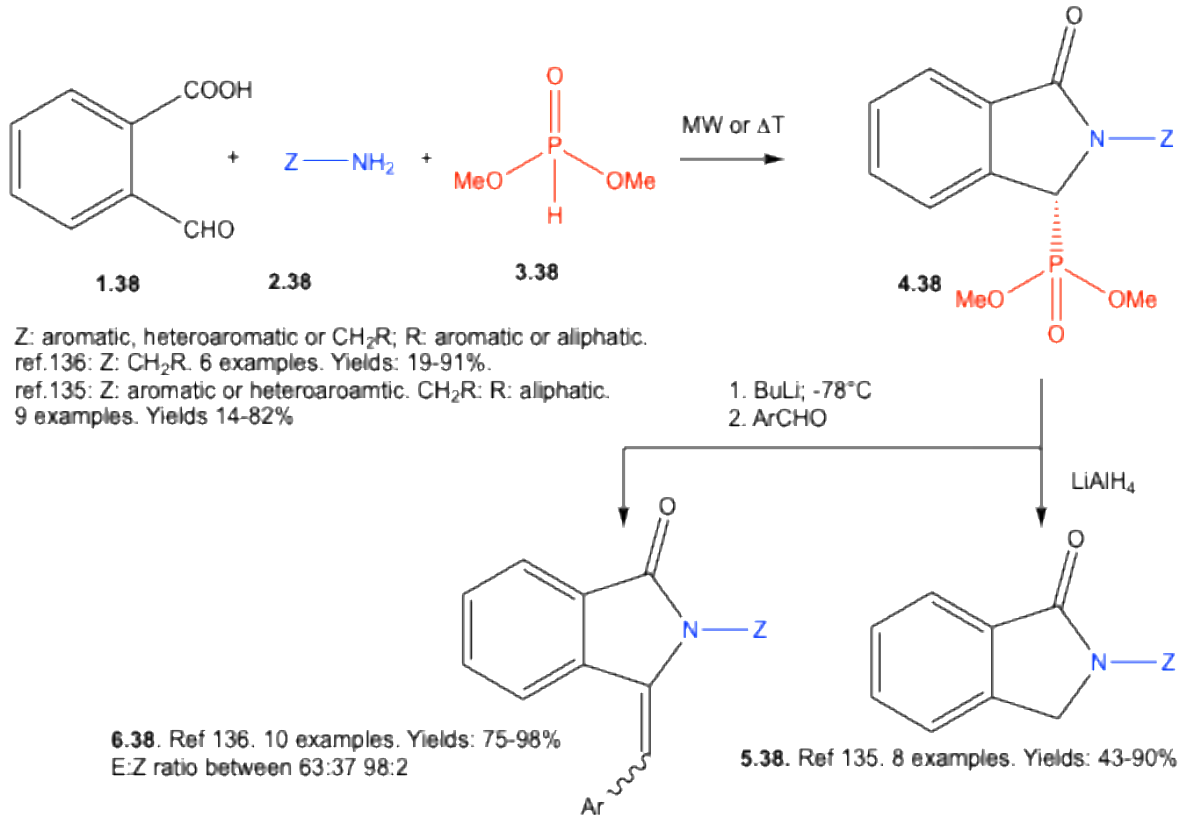
ylphosphonates **4.38** through a one-pot reaction of 2-formylbenzoic acid (**1.38**) with amines **2.38** and dimethyl phosphite 3.38 followed by intramolecular cyclization.These intermediates **4.38** can be efficiently converted into N-substituted isoindolin-1-ones **5.38** using lithium aluminum hydride. Alternatively [136], the Horner reaction enables their transformation into 3-(arylmethylene)isoindolin-1-ones **6.38**.



Scheme 38. Derivatives of α-aminophosphonates.

9. Conclusions

The Kabachnik–Fields reaction remains a robust and adaptable method for accessing α-aminophosphonates. Current mechanistic evidence supports the predominance of the imine–pathway, with alternative routes influenced by substrate and reaction conditions. Recent developments have significantly improved the sustainability and efficiency of the process, particularly through catalyst-free protocols, green solvents, and non-conventional activation techniques such as microwave irradiation, ultrasound, and mechanochemistry.

Lewis and Brønsted acid catalysis, has expanded substrate scope and provided operationally simple, high-yielding procedures. Advances in asymmetric variants now enable the synthesis of optically active α-aminophosphonates although further improvements in generality are still needed.

Overall, the Kabachnik–Fields reaction continues to evolve as a key transformation in organophosphorus chemistry, combining broad applicability with growing compatibility to modern, sustainable synthetic strategies.

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