The Kabachnik-Fields reaction by mechanochemistry: new horizons from old methods

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ABSTRACT. α-Aminophosphonates are an important class of biologically active compounds, attracting considerable attention in medicinal chemistry, by inhibiting enzymes involved in amino acid metabolism. Herein, the Kabachnik-Fields domino reaction was investigated by mechanochemistry for the first-time preparation of α-aminophosphonate derivatives in high yields and with full selectivity, outperforming comparable solution procedures. The reaction is a Lewis acid-catalysed process occurring however without the addition of any external catalyst, but occurring on the surface of the zirconium oxide used as the milling media. The mechanism of the mechanochemical reaction was also investigated by *in situ* Raman spectroscopy, the kinetic behavior was disclosed. The solid-state structures of two representative compounds have been determined by single-crystal X-ray diffractions.

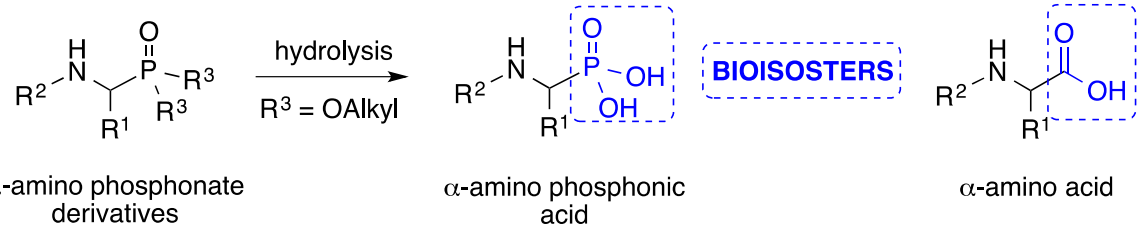
INTRODUCTION

One-pot synthetic strategies such as tandem, domino or cascade,[1,2] and multicomponent reactions[3] have been recognized as process with minimal waste generation. These synthetic strategies '*benign by design'*, are usually characterized by high atom economy and avoid the isolation of the reaction intermediates and synthetic pathways involving protection/deprotection steps. In combination with enabling technologies,[4] they become powerful tool to address the quest of sustainable organic synthesis.[5] In this regard, mechanochemistry[6-9] plays a central role, by improving the efficiency of a process and its ecological foot-print.

We previously reported the mechanochemical preparation of *N*- and *C*-functionalized amino acid derivatives,[10-11] and used them as building blocks to access biologically active compounds[12-

[15] and highly relevant active pharmaceutical ingredients[16] (API). Wishing to broaden the knowledge in this area of investigation, we turned our attention to the mechanochemical preparation of α-aminophosphonic acids and their corresponding esters,[17-18] which are structural *P*-analogues of α-amino acids.

They present an amino phosphonate framework P(O)-C-N and are bioisosters of the carboxyl unit[19] (Scheme 1).

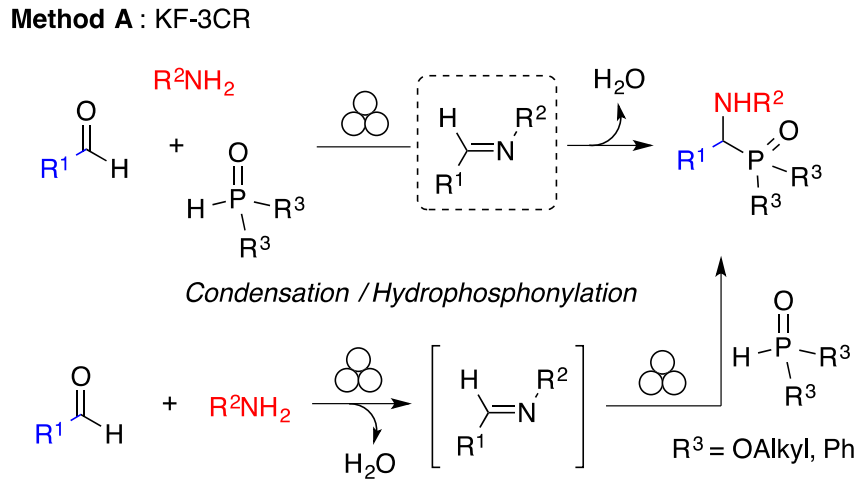


Scheme 1. Bioisosterism of α-aminophosphonate derivatives.

Indeed, the tetrahedral structure of the phosphonyl group acts as stable mimics of '*tetrahedral carbon intermediate*' (synthetic equivalent of 'transition state' analogue),[20] inhibiting enzymes or receptors to which natural aminoacids normally bind.[21] As a consequence, these family of compounds display diverse biological activities, raising growing interest in medicinal and pharmaceutical science applications.[22]

A unique method to build the amino phosphonate framework P(O)-C-N[22-27] relies on the three-component domino Kabachnik-Fields reaction (KF-3CR).[28-30] Also referred to as phospha-Mannich, the reaction involves a hydrophosphoryl compound (*e.g.*, dialkyl phosphite or secondary phosphine oxide), a carbonyl compound (aldehyde or ketone) and a primary or a

secondary amine, resulting in the formation of α-aminophosphonates (R^3 = OAlkyl) or α-aminophosphine oxides (R^3 = Ph) (Method A, Scheme 2).



Scheme 2. General approaches for the preparation of α-aminophosphonic acid derivatives. The mechanochemical activation[31] is also included here as an alternative to solution-based procedures.

The reaction is really attractive and presents several advantages: a) the cheapness and availability of reactants, b) its broad scope enabling to introduce '*all-in-one*' C-, N- and P-modifications on the α–amino phosphonate backbone, c) its importance from the point of view of sustainability, intrinsically displaying high atom economy and d) straightforward access to biologically relevant compounds.

In solution, the KF-3CR is flanked by an alternative synthetic pathway where the three-component domino reaction is divided into two distinct steps (Pudovik reaction)[32] involving the

formation of the intermediate Schiff base (*step 1*) followed by the addition of the 'P-nucleophile' to the C=N bond (*step 2*) (Method B, Scheme 2).

However, the outcome of the reaction occurring *via* these two different synthetic pathways is strongly influenced by the nature of the substrates and the solvent used.

Novel reaction conditions based on activation by alternative energy inputs in "batch" (microwaves,[21, 33] ultrasounds[34]) or under continuous flow,[35-36] with sustainable solvents[37] or solvent-free[24] (including manual grinding in a mortar),[38] catalyzed or not, were explored to improve the selectivity, the reaction efficiency, and the environmental footprint of KF-3CR compared to the conventional methods in solution.[17, 24, 26]

To our surprise, no reports deal with the use of mechanochemical procedures for the preparation of α-aminophosphonic acid derivatives and more generally for the formation of C(sp^3)-phosphorus bonds, while only one account describes the metal-catalyzed C(sp^2)-phosphorus bond formation in a ball-mill.[39]

By virtue of the high synthetic potential displayed by the KF-3CR, the activation by ball-milling becomes particularly appealing. We report herein the unprecedented mechanochemical preparation of several new α-aminophosphonate derivatives accessed straightforwardly, selectively and in very high yields. The use of any organic solvent (including during the work-up) or added catalyst was avoided and there was no need of post-reactional treatments. For the first time, the mechanism of the mechanochemically-activated KF-3CR was disclosed by *in situ* monitoring by Raman spectroscopy[40-41] and kinetic features of the mechanochemical process were examined by a mathematical model, allowing to describe the chemical changes under mechanical stress.[42-43] To complete the study, the solid-state characterization of two representative compounds was carried out also in order to compare the structural and crystal

packing features of the compounds obtained mechanochemically with those of analogous compounds obtained by conventional solution methods.

RESULTS AND DISCUSSION

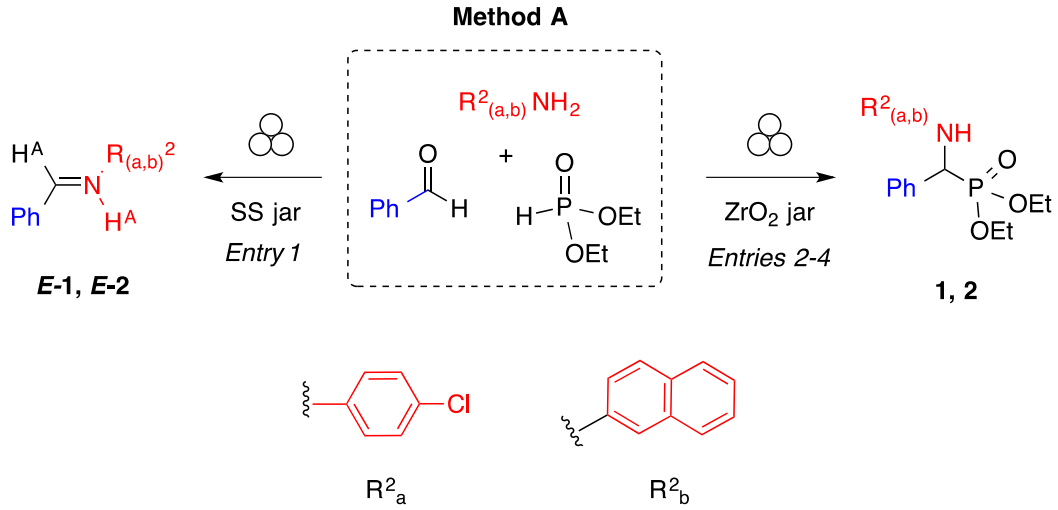
Optimization of reaction conditions. The mechanochemical preparation of α-aminophosphonates (R^3 = OAlkyl) and α-aminophosphine oxides (R^3 = Ph) was investigated according the two main pathways mentioned above: the Kabachnik-Fields reaction[28-29] (Method A) and its *one-pot*/two-step modification, known as Pudovik reaction[32] (Method B) (Scheme 2).

To optimize the reaction conditions and the mechanochemical parameters, two benchmark reactions, run in parallel in a planetary ball-mill, were selected. Two different amines (*p*-chloro aniline and 2-naphtylamine) were reacted with benzaldehyde and diethyl phosphite (R^3 = OEt), and a selection of data is reported in Table 1.

Parameters such as rotation frequency (up to 800 rpm), milling time, material of jars and balls (stainless steel or zirconium oxide), number of milling balls (25 or 50), mode of operation (cycled or continuous), in neat conditions or using liquid-assisted grinding[44] (LAG) procedures, were investigated together with the relative stoichiometry of the reactants.

The first trials were performed in a 12 mL stainless steel jar with 25 balls (5 mm diameter, total weight m^{tot} = 12.7 g) milling stoichiometric amount of the reactants at 450 rpm during cycled milling (Table 1, entries 1a and 1b). Monitoring the reaction by both ^{1}H NMR and ^{31}P NMR revealed that the conversion was not complete after the first milling cycle (2h), with 33% of residual aldehyde still present in the crude, together with the corresponding *E*-imines. Even by extending the milling time for further two hours, the corresponding α-aminophosphonic acid diethyl esters **1** and **2** were not formed even in traces.

Table 1. Selected data for the screening of the reaction and milling conditions for the preparation of α-aminophosphonates **1** and **2**.[a]



Entry	$R^2_{(a,b)}NH_2$	$H(O)P(OEt)_2$ (equiv)	LAG	Jar/Ball[a] #	t(h)/rpm	Conv. (%)	Product / Yield (%)
1a	R^2_a	1.0	-	SS[a] / 25	4[b] / 450	100	***E*-1**[c] / 99
1b	R^2_b					100	***E*-2**[c] / 98
2a	R^2_a	1.0	-	ZrO_2 / 25	4[b] / 450	73[d]	**1** / n.i.[e]
2b	R^2_b		-			35[d]	**2** / n.i.[e]
3a	R^2_a	1.0	EtOH[f]	ZrO_2 / 50	6 / 600	71[d,g]	**1** / n.i.[e]
3b	R^2_b					66[d,g]	**2** / n.i.[e]
4a	R^2_a	1.5	-	ZrO_2 / 50	6 / 600	100	**1** / 98
4b	R^2_b		-			100	**2** / 98

[a] Reaction scale: 1.5 mmol in 12 mL jar, SS = Stainless steel, Ball # = number of 5 mm ∅ balls; [b] cycled milling (2 cycles of 2 hours each) with *ex situ* analyses in between; [c] Only the *E*-isomer is formed. The *E*-geometry was assigned on the basis of previous reports for $H^AC{=}N$ proton: for ***E*-1**[45] δ(ppm): 8.44 ppm, for ***E*-2**[46-47] δ(ppm): 8.60 ppm; [d] The conversion was determined by comparing the ^1H NMR area of residual $H^AC{=}N$ proton of the Schiff base to the area of $P\text{-}CH^A$ proton in the final compound; [e] n.i. = not isolated (some reactants and/or imine were still present in the crude); [f] Liquid Assisted Grinding conditions (LAG) using EtOH (100 μL, η = 0.17), with η value[44] defined as the volume of the solvent (in μL) / the sample weight (in mg).

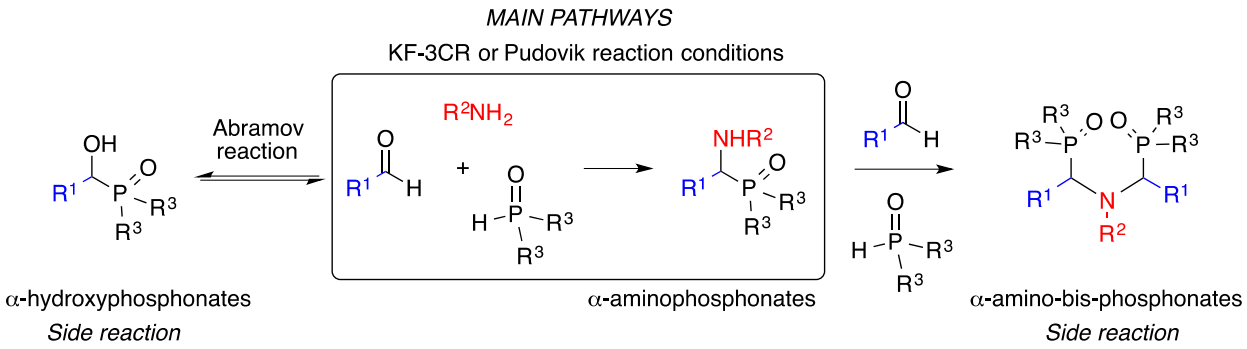
However, ^{31}P NMR analyses of the crude mixtures after 4 hour milling indicated the presence of unreacted diethylphosphite [δ(ppm): 7.34 ppm in $CDCl_3$] while ^{1}H NMR spectra clearly showed the full conversion of benzaldehyde and the amine, in favor of the selective and almost quantitative formation of the corresponding *E*-imines ***E*-1**[45] and ***E*-2**[46-47] (Table 1, entries 1a and 1b respectively). The recovery of pure solid *E*-imines ***E*-1** and ***E*-2** was straightforward: water was added directly into the jar, followed by the filtration of the precipitate and drying *under vacuo* over $MgSO_4$, while the unreacted liquid diethylphosphite and/or its hydrolysed counterpart were easily eliminated in the water phase.

Speculating that the jar material could somehow influence the mechanochemical reactivity of the system[48-52] by promoting the addition of the 'P-nucleophile' to the C=N bond, further tests were performed (entries 2-4). While keeping the same chemical, technological and process parameters, zirconium oxide jars and balls (5 mm diameter, total weight m^{tot} = 10.2 g) were used instead of stainless steel grinding jars. In this case, even if the kinetic energy delivered to the system was lower (m^{tot} = 10.2 g for ZrO_2 *vs* m^{tot} = 12.7 g for stainless steel, 5 mm diameter balls) and full conversion of the reactants could not be achieved, the addition of diethylphosphite to the C=N bond of the transient imine took place, leading to the corresponding α-aminophosphonic acid diethyl esters **1** and **2** (entry 2).

Further on, the mechanical energy transferred to the mixture was tuned by applying different combinations of rotation speed/number of balls, while the reaction conditions were adjusted by increasing the relative stoichiometry of diethylphosphite (entries 3 and 4). Indeed, when using a stoichiometric amount of the reactants, full conversion was usually not achieved (entries 2 and 3). This was probably due to the partial hydrolysis of the diethyl phosphite in the presence of water[28] generated *in situ* during the condensation step leading to the intermediate imine.

Better results were obtained with a continuous milling mode in zirconium oxide jars (at 600 rpm for 6 h), doubling the number of balls with (50 balls, m^{tot} = 20.5 g) and using 1.5 equivalent of diethylphosphite (entry 4). As per the imines ***E*-1** and ***E*-2**, also α-aminophosphonates **1** and **2** were recovered pure and in high 98% yield by simply adding water to the crude mixture and applying the same work-up procedures described so far. With the exception of water, generated during the condensation step, no other by-products were formed and the precipitation/filtration work-up allowed the elimination of residual diethyl phosphite derivatives.

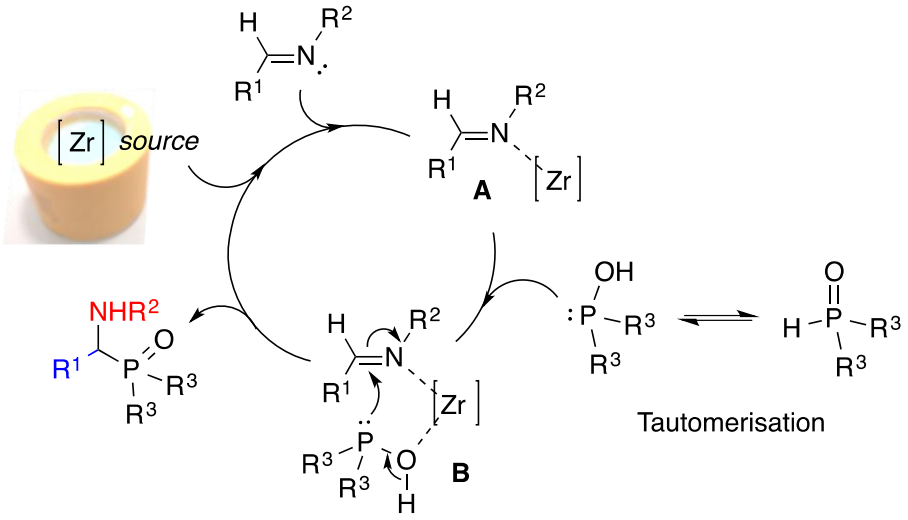
Similar conversions and yields were obtained by increasing the milling speed up to 800 rpm for a shorter reaction time (4 hours milling, under continuous milling mode), while LAG conditions with EtOH (entry 3) were detrimental. ^{1}H NMR, ^{31}P NMR and GC-MS analyses of the crude showed the presence of α-hydroxyphosphonate by-products,[17, 53] due the competitive Abramov addition[54] of the 'P-nucleophile' directly to the C=O carbonyl bond of the starting aldehyde (Scheme 3).



Scheme 3. Main side reactions occurring during the preparation of α-aminophosphonates.[17, 53]

These results showed that the hardness and density of the material could influence the activation process *via* surface-mediated phenomena involving the jar material (and the reactants),

by promoting the addition of diethyl phosphite to the C=N bond of the transient imine (Scheme 4).



Scheme 4. Plausible mechanism for the Zr-catalysed synthesis of α-aminophosphonates by mechanochemistry.

It is known that in solution, Lewis acids are effective catalysts for the Pudovik reaction, promoting the nucleophilic addition of phosphites to imines.[55-56] The preparation of α-aminophosphonates was also described in the presence of Zr-based catalysts at room temperature: in solution (*e.g.* with $ZrCl_4$),[57] solvent-free [*e.g.* with $Cp_2Zr(OSO_2C_4F_9)_2 \cdot 2H_2O$,[58] $ZrOCl_2 \cdot 8H_2O$ or $ZrO(ClO_4)_2 \cdot 6H_2O$[59]] or by grinding over Zr-supported pillared clay.[38]

Based on all these findings, zirconium oxide jars (and balls) may play a double role, acting at the same time as '*Zr source*' equivalent and Lewis catalyst: a) by generating *in situ* a more electrophilic C=N bond leading to an activated intermediate **A** by coordination between the nitrogen atom of the imine with the '*Zr source*' equivalent, and b) by exerting a template effect

placing close together the diethyl phosphite and the activated imine **A** (intermediate **B**), thus facilitating the addition reaction yielding to α-aminophosphonate (Scheme 4).

Commercially available milling media based on zirconium oxide have never been explored as heterogeneous and 'recyclable' 'catalyst' in any metal-mediated mechanochemical transformation described in the literature,[60] outperforms in comparison with stainless steel jars and complement the previous findings making use of manufactured on purpose copper-,[49-50] nickel-[51] and palladium-[52] milling media to catalyze '*click*' [3+2], [2+2+2+2] cycloaddition, and Suzuki-Miyaura reactions respectively.

To explain the role played by the 'Zr-based milling media, the mechanochemical Pudovik reaction (Method B, Scheme 1) was investigated using as starting materials *E*-imines having different electronic properties. We speculated that the addition of diethylphosphite to the C=N bond would have been successful with electron-rich imines, where the increased density on the nitrogen atom may favor the coordination with the ZrO_2 Lewis acid.

Unexpectedly, step 2 of Pudovik reaction was unsuccessful when diethyl phosphite was milled with both electron-poor benzylidene(4-chlorophenyl)amine ***E*-1** (from entry 1a) or electron-rich benzylidene(naphthalen-2-yl)amine ***E*-2** (from entry 1b), in the optimized conditions already disclosed (milling time was 4 h in this case) only traces of corresponding α-aminophosphonates were detected in the ^{1}H NMR of the crude, the main product being always the unreacted starting *E*-imines, with no *E/Z* isomerization reaction detected even in traces.

These preliminary findings shed light on the differences between solution *vs* mechanochemical methods to access α-aminophosphonates.[60] In solution, their preparation is preferably carried out by Pudovik method, involving a Lewis acid as catalysts, to promote the addition of diethylphosphite to C=N bond. However, the use of Lewis catalysts is not always effective for

solution-based Kabachnik-Field process. Even if this domino reaction involves the formation of an intermediate imine, the Lewis acid can be deactivated by nitrogen-containing compounds (the starting amine) or by the presence of water,[22] formed *in situ* during the reaction process. This is particularly true especially for moisture-sensitive catalysts (*e.g.* $ZrCl_4$[57]), even if dehydrating agents or water-stable catalysts such as rare earth metal triflates can be used as alternatives.

These limitations impact negatively on the use of KF-3CR in solution, limiting the choice of possible catalysts and reducing the environmental footprint of the reaction [*e.g.* generating more (toxic) waste]. These problems are overcome when performing the KF-3CR by mechanochemistry, resulting fully effective in our conditions.

Therefore, ball-milling the reactants in ZrO_2 jars represents a sustainable alternative to classic heterogenous catalysis making use of Lewis acids in solution (water-sensitive or not), the '*Zr source*' being indefinitely recyclable and not producing any metal-waste, expanding the reactivity windows for heterogeneous KF-3CR. In this regard, zirconium-mediated synthesis of imine cannot be excluded,[58] the process occurring on the jar/balls surface.

Among the advantages, zirconium oxide milling media benefit of the advantages of Zr(IV) derivatives, displaying a limited redox character,[61] low toxicity,[62] and acting as adhesion promoters in the presence of oxygenated species (including carbonyl groups).

Synthesis of a library of α-aminophosphonate derivatives. Once the optimized mechanochemical conditions were disclosed for KF-3CR method (Table 1, entry 4), a library of α-aminophosphonate derivatives **1-16** was prepared. The reaction were fully selective and excellent isolated yields were obtained whatever were the arylamine/arylaldehyde/P-nucleophile combination [P-nucleophiles: $P(O)H(OEt)_2$, $P(O)H(O^iPr)_2$ and $P(O)H(Ph)_2$] (Figure 1).[63] The α-aminophosphonates **1-11** and α-aminophosphine oxides **12-16** herein prepared, present *N*-, *C*-

and *P*-modifications and they were easily recovered by precipitation in water/filtration as previously described. The process was characterized by the absence of any side reaction (Scheme 3), including the Abramov pathway to α-hydroxyphosphonates or their rearrangement to phosphates and their amine-promoted decomposition. This greatly simplified the work-up procedures, making the mechanochemical Kabachnik-Fields reaction particularly straightforward compared to solution-based procedures.

Mechanochemical activation was particularly outperforming to prepare α-aminophosphine oxides **12-16**. Generally speaking, the preparation of this class of compounds is usually poorly investigated in solution. Their preparation usually requires the use of a large excess of amine, high temperature and long reaction times,[21] with a negative consequence also on the stability of diphenylphosphine oxide reactants, generating the corresponding oxidized diphenylphosphinic acid by-product. In this regard, a chromatographic purification of the final α-aminophosphine oxides is required, detrimental from the point of view of the ecological footprint of the intrinsically sustainable process.

Worth of note is that the reactivity of the KF-3CR by mechanochemistry was influenced by the nature of the P-nucleophile used. As a general trend, the preparation of diethyl esters of α-aminophosphonates required 4 h milling in the optimized reaction and process conditions (see Supporting Information), while 6 h milling was needed to achieve full conversion of the starting reagents (*e.g.* compounds **1** and **2** ***vs.*** compounds **11** and **10** respectively**)**, when increasing the branching at the alkyl chain of the P-nucleophile [P-nucleophiles: $P(O)H(OEt)_2$ or $P(O)H(Ph)_2$ *vs* $P(O)H(O^iPr)_2$]. The same trend was also verified in the case of α-aminophosphine oxides **12** and **13,** prepared faster (in 4h reaction) compared to their respective di-*iso*-propyl counterparts **11** and **10** (requiring 6 hours and less energetic conditions).[64]

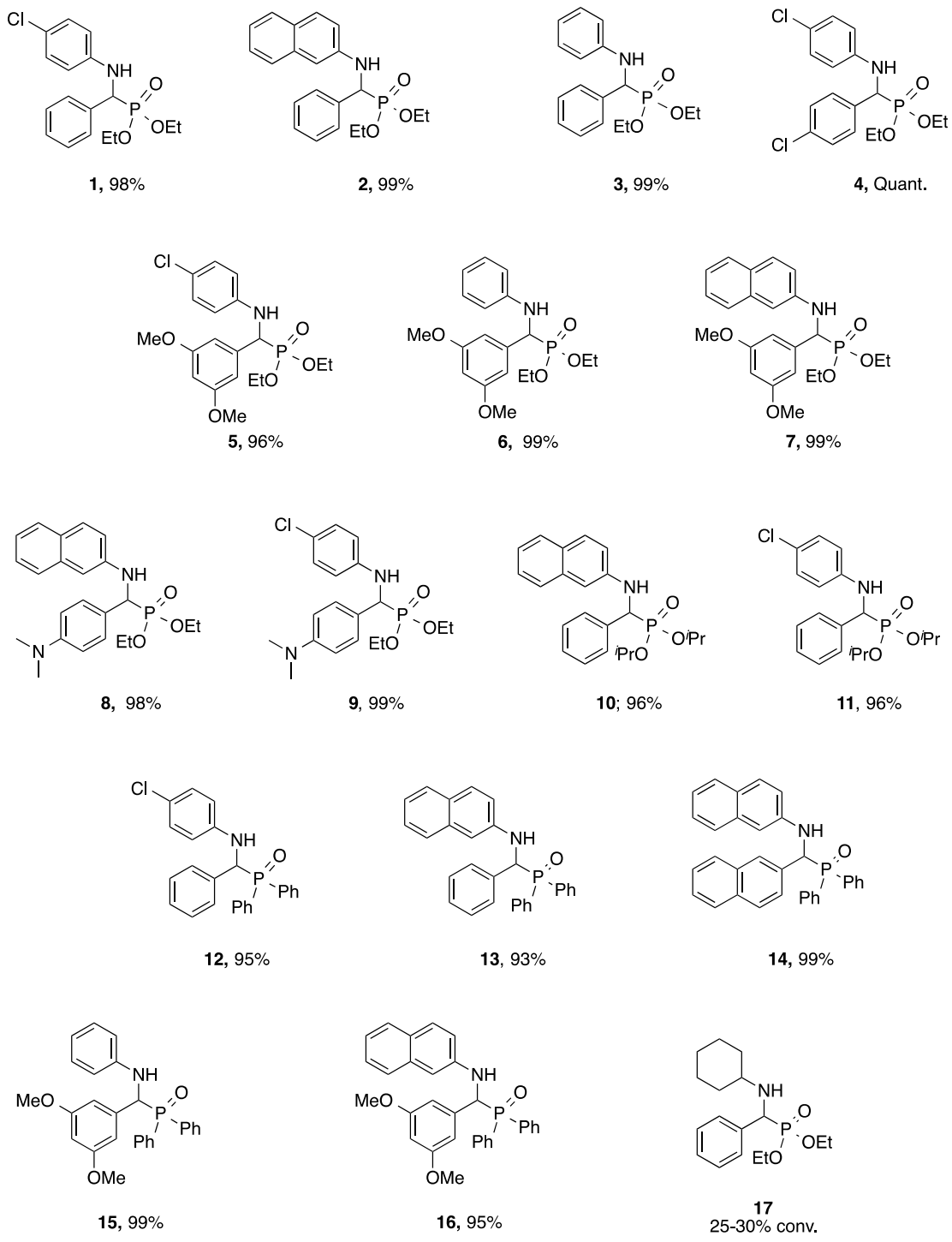


Figure 1. Library of α-aminophosphonate derivatives prepared by ball-milling.

On the basis of this finding, by grouping the α-aminophosphonate derivatives in the series having the same combination aldehyde/amine, but different P-nucleophiles (*e.g.* compounds in the Group I: **1**, **11**-**12**, Group II: **2**, **10**, **13**, Group III: **6** and **15**, Group IV: **7** and **16**) a reactivity trend can be disclosed, independently on the physical state of each reactant (liquid or low melting solid). The reactivity and reaction kinetics decreased in the order $P(O)H(Ph)_2$ > $P(O)H(OEt)_2$ > $P(O)H(O^iPr)_2$. Steric hindrance was ruled out as the possible reason of slower kinetics observed when increasing the branching at the alkyl, during the addition reaction of the P-nucleophile to the C=N bond, being mechanochemical activation able to challenge the reactivity of hindered substrates.[11, 65]

The possible explanation could rely on the slower kinetic of tautomerisation of $P(O)H(O^iPr)_2$ compared to $P(O)H(OEt)_2$, in the absence of a suitable proton carrier (usually the solvent). DFT studies demonstrated that the intramolecular proton transfer pathway is disfavored for the high activation barriers.[66-67] In this regard, the tautomeric equilibrium can possibly occur on the jar surface, mediated by the ZrO_2. These results clearly strengthen the previous observations, by confirming that the reactivity trend for KF-3CR by mechanochemistry is quite different from solution-based procedures, mainly favoring Pudovik method to prepare α-aminophosphonate derivatives. Additionally, being the solubility problems ruled out by mechanochemistry, the imine formation is not the rate determining step for KF-3CR during milling. Thus, the reactivity trends exclusively depend on the intrinsic nucleophilic character of the phosphorus derivatives (and their respective tautomerisation kinetics) and its resistance to hydrolysis. Because diphenylphosphine oxide $P(O)H(Ph)_2$ is not sensitive to the hydrolysis, a stoichiometric amount can be used compared to $P(O)H(OEt)_2$ and $P(O)H(O^iPr)_2$ (1.5 equiv were required).

The preparation of α-aminophosphonates **8** and **9,** involving the electron-rich 4-*N,N*-dimethylbenzaldehyde as starting material, occurred by one-pot/two step Pudovik method, however, the preparation of the corresponding α-aminophosphonates from electron-poor 4-nitrobenzaldehyde proved to be unsuccessful. These opposite outcomes suggested that the electronic nature of the intermediate imine can drive a switch of reactivity. Indeed, the increased electron-density on the nitrogen atom of the imine may favor the coordination with the ZrO_2 Lewis acid promoting the addition of the P-nucleophile across the C=N bond of the transient imine, while the reaction failed with the electron poor substrates (Scheme 4).

Additional results supporting the experimental evidence already disclosed regarding the postulated influence of surface-mediated process by alternative '*Zr-sources'* was obtained by repeating the reactions in stainless steel jars, in the same reaction conditions (Table 1 entry 4 and Supporting Information). The reactions were substrate-dependent and a residual amount of aldehyde was always detected by ^{1}H NMR analyses of the crude mixtures.

Another set of experiments was performed to demonstrate the beneficial effect played by mechanochemical activation for KF-3CR in comparison with solution-based procedures requiring thermal activation. It is generally demonstrated that under thermal heating the reaction is very slow or did not proceed at all, without a catalyst. The only exceptions relies on solvent-free procedures under microwaves[24, 68] (heating up to 120°C) or activated by indirect sonication[34] (with no control of the temperature). Therefore, the preparation of α-aminophosphonate **2** and α-aminophosphine oxide **13** (Tables S1 and S2)[64] was investigated in a sealed pyrex tube in solution or neat, at room temperature or upon heating up to 70°C. Even if good conversions were achieved in some cases after 5 h (in THF, CH_3CN and in neat conditions), the conversion of the starting reactants was never complete, residual imine was still present and post-reactional

treatments were always necessary (liquid-liquid extraction and purification by chromatography), negatively impacting on the ecological footprint of the process.

These results clearly demonstrated that thermal activation alone was not enough for achieving full conversions and high yields and alternative energy inputs based on tribochemical processes, such as ultrasounds[34, 69] and mechanochemistry, were more effective and allowed to solve the drawbacks experimented upon thermal activation. They have in common similar activation effects,[70-71] providing unusual reaction conditions and prohibitive activation barriers compared with the traditional thermal activation methods.

The ball milling procedure for Kabachnik-Fields reaction outperformed with respect to solution procedures: a) avoiding the use of additives and hazardous solvents, a large excess of phosphorus nucleophile and stoichiometric amounts of (toxic and non-recyclable) catalysts (*reagent and solvent economy*), b) not requiring chromatographic purifications and avoiding large amount of (toxic) waste generally associated with by-product formation, work-up and product isolation, not requiring chromatographic purifications, c) avoiding any heating (*energy economy*); d) simplifying the catalytic system (the jar can be used ideally for infinite reactions) making also thermally reluctant reactions possible, e) providing high selectivity and clean reaction profiles, reducing the environmental footprint of the process (*waste economy*), f) reaction times are reduced (*time economy*) and g) allowing to access selectively and high yield α-aminophosphonate derivatives by KF-3CR, usually low yielding in solution, and preferably prepared by the step-wise two-component process Pudovik reaction. Therefore, KF-3CR in solution usually considered not selective or low yielding compared to the preferably step-wise two-component process (Pudovik reaction),[17] results particularly effective under milling conditions.

The KF-3CR using aliphatic amines. The preparation of α-aminophosphonates from aliphatic amines deserves a separate discussion. Actually, the mechanochemical KF-3CR developed from aromatic amines seems to be not as effective when cyclohexylamine was used. The KF-3CR to α-aminophosphonate **17** in the conditions previously developed (Table 1, entry 4) was low yielding and not selective (Figure 1). ^{1}H NMR and ^{31}P NMR analyses of the crude indicated that the α-aminophosphonate **17** was formed, but the Abramov product α-hydroxyphosphonate product was the major compound (α-NH_2/α-OH ratio 0.6 : 1), with still 14% residual amount of imine (Table 2, entry 1). The preparation of diethyl α-cyclohexylamino-4-benzylphosphonate **17** was also carried out by *one-pot*/two step Pudovik reaction conditions were also tested to access diethyl α-cyclohexylamino-4-benzylphosphonate **17** (Table 2, entry 2).

Table 2. Investigation of the selectivity for mechanochemical KF-3CR with cyclohexylamine.

Entry	Method	R^1CHO	R^2NH_2	α-OH/ α-NH_2 (%)[a,b,c]	^{31}P NMR δ(ppm)[d]	
					α-OH	α-NH_2
1	A	Ph-	C_6H_{11}-	60 / 40	21.3[72]	24.2[73]
2	B	Ph-	C_6H_{11}-	64 / 36	21.3[72]	24.2[73]
3	A	4-NO_2-C_6H_4-	C_6H_{11}-	0 / 100	/[e,72]	24.9[e]
4	A	4-Cl-C_6H_4-	C_6H_{11}-	41 / 59	20.7[72, 74]	23.6[75]

[a] α-OH = α-hydroxyphosphonate, α-NH_2 = α-aminophosphonate; [b] The ratio was determined by ^{1}H NMR and ^{31}P NMR of the crude mixture; [d] $CDCl_3$ was used; [e] The value was attributed by comparing the chemical shift with that one reported for diethyl [hydroxy(4-nitrophenyl)methyl]phosphonate: ^{31}P NMR ($CDCl_3$) δ(ppm): 19.9.[72]

^{1}H NMR and GC/MS analyses confirmed that the formation of imine (*step 1*) is the bottleneck of this synthesis (30% conversion after one hour milling at 600 rpm). After the addition of

diethylphosphite (*step 2*), the compounds were milled for further 4h in the same conditions. Besides, the reaction was not selective and a mixture composed by 64% in favor of α-hydroxyphosphonate was formed (α-OH/α-NH_2 ratio was 1.81 : 1), due to the competitive P-addition of diethylphosphite to the C=O group of the residual benzaldehyde, instead of the C=N group of the newly formed intermediate imine.

Therefore, for both mechanochemically-activated KF-3CR and Pudovik reaction, the results suggest that slow kinetics characterize the formation of the imine when cyclohexylamine and benzaldehyde are used, favoring the competitive Abramov side-reaction. Worth of note, when aromatic amine was used instead of aliphatic cyclohexyl amine (*e.g.* α-aminophosphonate **3** *vs* α-aminophosphonate **17**), the α-hydroxyphosphonate was never observed, even in traces (Figure 1). This is in perfect agreement with the outcomes observed in solution, where the 'switch' of the selectivity depended on the easiness of imine formation.

To further confirm this trend for the mechanically-activated KF-3CR, cyclohexylamine was reacted with two aldehydes having electron withdrawing substituents (*e.g.* 4-nitrobenzaldehyde and 4-chlorobenzaldehyde) in the presence of diethylphosphite (Table 2, entries 3 and 4). The mixture was milled during 4 h at 600 rpm in ZrO_2 grinding media, as previously described (Table 1, entry 4). With the more electrophilic 4-nitrobenzaldehyde, the conversion of both aldehyde and cyclohexylamine to 4-nitrobenzylidene(cyclohexyl)amine was complete and the corresponding α-aminophosphonate was formed together with 27% of α-hydroxyphosphonate, as assessed by ^{1}H NMR analyses of the crude (Table 2, entry 3). In the case of 4-chlorobenzaldehyde, this trend was also confirmed (Table 2, entry 4), however, a residual 30% of imine was still present in the crude after 4 h milling. These data clearly show that with cyclohexylamine, the rate for imine formation depended on the nature of carbonyl compound,

with faster kinetics for electron-withdrawing substituents. This influenced also the reaction pathway driving the selectivity switch between KF-3CR *vs* Abramov reaction, under a preferred thermodynamic control towards the formation of the α-aminophosphonate in the presence of electrophilic aldehydes. In comparison, with aromatic amines, the mechanochemical activation drives the selectivity exclusively towards the 'imine pathway', with no formation of α-hydroxyphosphonate, whatever is the combination amine/aldehyde involved (Figure 1).

Several other process conditions in a vibratory ball-mill operating at 30 *Hz* were explored for accessing diethyl α-cyclohexylamino-benzylphosphonate **17** (*e.g.* Teflon or PMMA jars, stainless steel or ZrO_2 balls and use of additives). As a general trend, ^{1}H NMR analyses of the crude revealed, in all cases, that: a) the conversion of benzylidene(cyclohexyl)amine was incomplete even after 18 h milling, and b) the Abramov reaction pathway leading to the corresponding diethyl [hydroxy(phenyl)methyl]phosphonate was always favored.

Taking into account the reversibility of Abramov reaction in solution,[76] the preparation of α-[cyclohexylamino-(phenyl)methyl]phosphonate **17** was attempted by milling diethyl [hydroxy(phenyl)methyl]phosphonate with a two-fold excess of cyclohexylamine. The reaction was carried out at 30 *Hz* for 4.5 h in a Teflon jar (14 mL) with 1 zirconium oxide ball (8 mm diameter). However, in these conditions, no reaction occurred, ruling out that Abramov reaction could also lead to Kabachnik-Fields product **17**.

Investigation of the KF-3CR by in situ Raman spectroscopy. The study was also focused on the investigation of the KF-3CR mechanism occurring during mechanochemical activation. The reaction was monitored by *in situ* Raman spectroscopy.[41]

Attempts to perform reaction monitoring by *in situ* Raman spectroscopy were hindered by high luminescence of almost all reaction mixtures which either obscured the Raman scattering

signal from the sample or saturated the detector, even at low incident laser power, rendering any measurements impossible. *In situ* reaction monitoring was successful only for experiments where *N,N*-dimethylaminobenzaldehyde (dmab) and *p*-chloroaniline (pClan), both solids at ambient conditions, were milled in the presence of diethylphosphite – a reaction yielding the α-aminophosphonate **9**. Milling of the three reactants usually resulted in sticky reaction mixtures leading to uneven mixing and possibly a complete loss of the Raman scattering signal if the mixture got stuck in the corner of the PMMA reaction vessel. Therefore, we have attempted using NaCl as an additive to keep the mixture in the form of a free-flowing powder. Even if the conversion of the reactants was not complete, Raman spectra could be collected (Figure 2). The *in situ* monitoring, with the time resolution of 10 s, revealed rapid loss (within first 3-4 spectra corresponding to *ca.* 30-40 seconds of milling) of the C=O stretching band of the dmab at 1659 cm^{-1} and a subsequent slower formation of the corresponding Schiff base, via an intermediate. The Schiff base results from the reaction of the dmab and pClan, and is evidenced by the emergence of a set of bands positioned around 1600 cm^{-1} and a band at 983 cm^{-1} (Figure 2). Subsequent *ex situ* ^{1}H NMR analysis of the crude reaction mixture confirmed that the conversion of the reactants and the Schiff base to the target α-aminophosphonate **9** was not complete. The conversions were determined by comparing the ^{1}H NMR relative ratio of the integrals associated to the signals of: a) the CH=O proton of the starting dmab (singlet at 9.73 ppm in $CDCl_3$, 24% of the crude mixture), b) the CH=N proton (singlet at 8.27 ppm, 35% of the crude mixture) of the corresponding Schiff base and c) the P-CH-NH proton (doublet at 4.58 ppm, 41% of the crude mixture) in the α-aminophosphonate **9**.

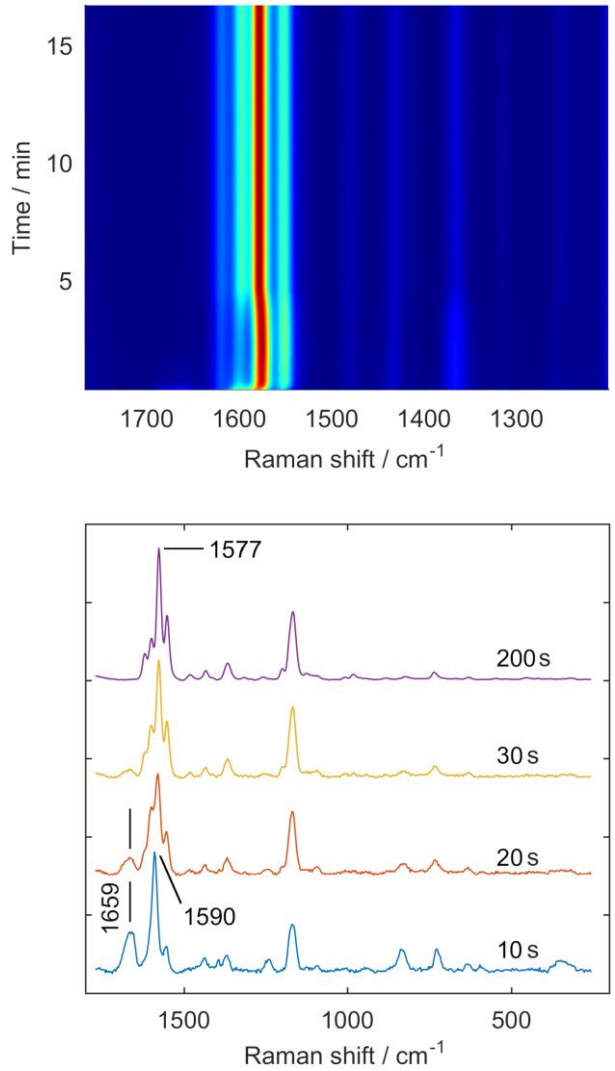


Figure 2. a) 2D plot of milling experiment for the formation of α-aminophosphonate **9** in the presence of NaCl. b) Normalised Raman spectra after 10, 20, 30 and 200 seconds.

However, from the *in situ* Raman spectra, the presence of the α-aminophosphonate **9** could not be evidenced and only the Schiff base was observed. This is likely due to its dominant contribution to Raman scattering where the scattering signal from other species is of significantly lower intensity. To verify that the *in situ* collected final Raman spectrum for the preparation of α-aminophosphonate **9** corresponds to the Schiff base spectrum, we have conducted *in situ* reaction monitoring of the preparation of the pure Schiff base (Figure 3). Virtually identical

spectra in these two experiments confirm the previous assumption, but importantly, also that the Schiff base is formed as an intermediate in the KF-3CR reaction (Figure 4).

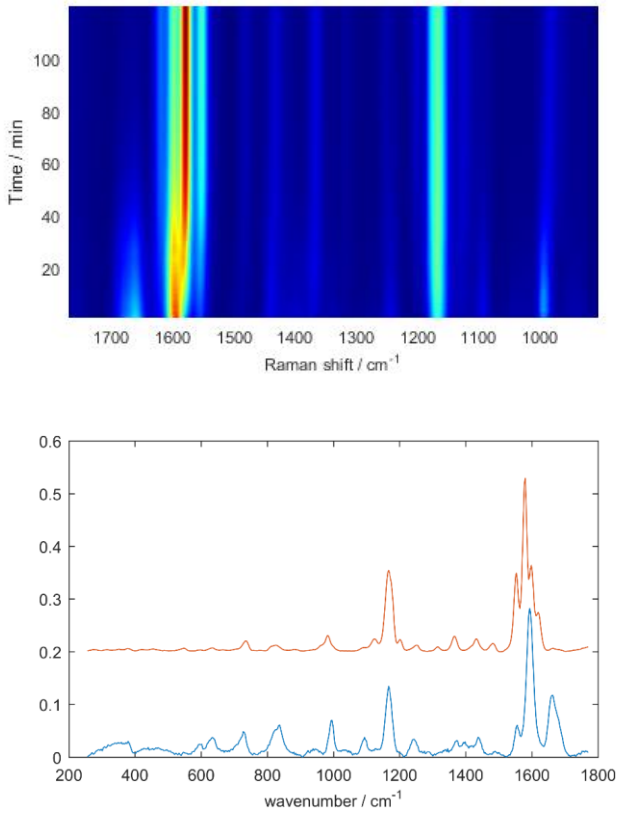


Figure 3. a) 2D plot milling of dmab and pClan in the presence of Na_2SO_4. B) Normalised Raman spectra after 20 seconds and 2 hours of milling.

Noteworthy, in the milling conditions used, the *in situ* Raman spectra of the KF-3CR reaction showed the presence of a stable Schiff base, which translates in a very slow Pudovik reaction or its full inhibition. This is in accordance with the observation that stainless steel milling media prevented the KF-3CR product formation. Observation of the product in our case by *ex situ* NMR analysis could have been the result of the reaction advancing after cessation of milling and before the *ex situ* analysis, upon aging the sample overnight.

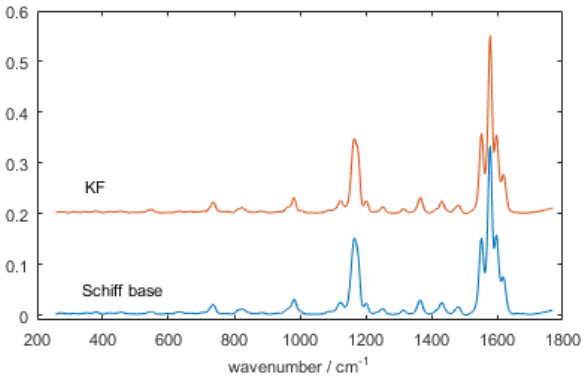


Figure 4. Comparison of final Raman spectra for the KF-3CR (orange line) and the corresponding Schiff base prepared separately upon milling of dmab and pClan (blue line).

Interestingly, reaction toward Schiff base formation during the KF-3CR is extremely fast as evidenced from the loss of the aldehyde band within two minutes of milling. However, in the absence of diethylphosphite (*i.e.* Method B, Scheme 1 for the first step of the Pudovik reaction targeting the Schiff base preparation), the conversion of the starting dmba is two orders of magnitude slower, with the aldehyde C=O stretching vanishing after 2 hours of milling. This may suggest a catalytic role played by the diethylphosphite for the Schiff base formation. This investigation was not pursued further as it lays outside the scope of this work.

The KF-3CR leading to the α-aminophosphonate **9** can nevertheless be driven to completion carrying out the reaction in a Teflon jar (instead of a PMMA jar) and milling the mixture during 16 hours, without the use of milling additives. Unfortunately, the Raman *in situ* monitoring can be carried out only in translucent PMMA vessels. White Teflon does not permit the incident Raman laser light to penetrate the reaction vessel walls. Worth of note is the increased reactivity observed when stainless steel balls where replaced by one ZrO_2 ball (8 mm diameter, weight of the ball m = 1.6 g). In this case, the reaction went to completion after 5

hours, confirming that the milling media acted as the necessary 'Zr source' to promote efficiently the Pudovik reaction.

Kinetics for KF-3CR. Starting from the Raman data collected *in situ* for the preparation of the α-aminophosphonate **9**, the kinetic behavior under mechanochemical processing for the KF-3CR was also disclosed. Quantitative analysis of Raman spectra allowed evaluating changes in mole fractions of reactants and the Schiff base product. The KF-3CR product was not observed in the *in situ* Raman spectra being obscured by the dominant scattering contribution from the Schiff base.

The results are shown in Figure 5, where the mole fractions of reactants, intermediate and the Schiff base are plotted as a function of time. Reactants undergo an immediate and relatively fast monotonic decrease associated with a corresponding increase of the intermediate.

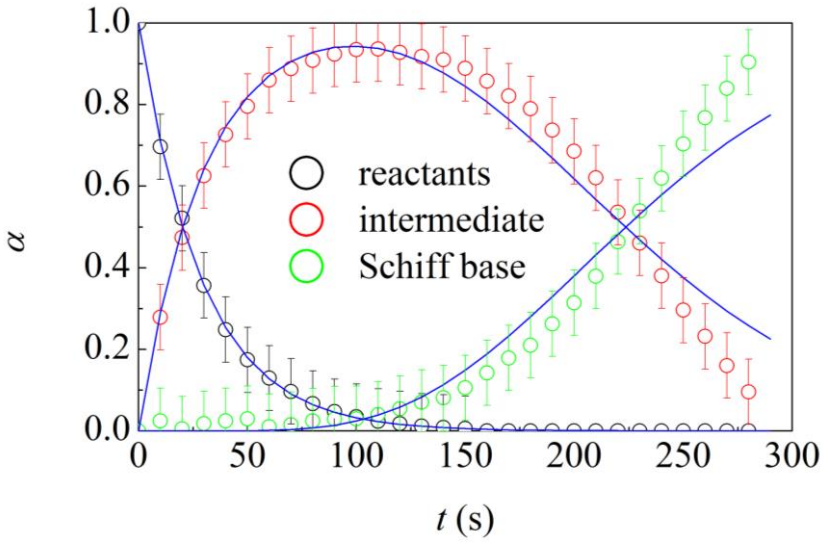


Figure 5. Reaction profile for Schiff base formation in the KF-3CR reaction leading to the α-aminophosphonate **9**. Best-fitted kinetic curves are shown.

Although very small amounts of Schiff base are detected since the very beginning of the mechanical processing, it is only after about 80 s that its mole fraction starts increasing. After about 300 s, the mole fraction of Schiff base reaches the value of about 0.9.

The kinetics behavior has been tentatively rationalized using a simplified kinetic model. Described in detail in a recent publication,[42] the model accounts for the statistical nature of the mechanical processing of powder by ball milling. Specifically, it combines the statistical nature with the chemical conversion activated by individual impacts, thus providing a set of kinetic equations that can be used to best-fit the experimental points. In the present case, the reactant dataset can be satisfactorily best-fitted by the simple exponential equation 1:

$$\alpha_r = \exp(-kt) \tag{1}$$

where α_r is the volume fraction of reactants, k is the apparent reaction rate and t is time. Specifically, k measures the volume fraction of powder that is processed effectively per unit time.[42] The intermediate volume fraction can be described by the equation 2:

$$\alpha_i = \left[kt + \frac{(kt)^2}{2!} + \frac{(kt)^3}{3!} + \frac{(kt)^4}{4!} + \frac{(kt)^5}{5!} + \frac{(kt)^6}{6!} + \frac{(kt)^7}{7!}\right]\exp(-kt) \tag{2}$$

while the Schiff base product volume fraction can be expressed as:

$$\alpha_p = 1 - \alpha_r - \alpha_i \tag{3}$$

In the absence of more accurate information on the microscopic processes taking place on the microscopic scale during individual impacts, the interpretation of experimental data can be only phenomenological. In this respect, Eqs. 1 and 3 indicate that at least one impact is needed to activate the transformation of reactants into the intermediate, whereas eight impacts are required

to form the Schiff base. Accordingly, the intermediate exhibits a considerable persistence under the mechanical processing conditions compared with reactants.

To a first approximation, the kinetic data can be best-fitted using a single value of the apparent rate constant k, equal to about 0.0343 s^{-1}. The use of a single k represents the best choice under the present experimental circumstances, which do not allow obtaining independent information on local processes occurring on the molecular scale. Even so, the k value allows estimating the amount of reactants and intermediates involved in effective compression events during individual impacts.

Taking into account that the total mass of powders inside the reactor is approximately 680 mg, the amount of material effectively processed per unit time is equal to about 23 mg. If we assume that the frequency of impacts is approximately 120 Hz, which is reasonable based on the use of a single ball and a reactor swing frequency of 30 Hz, we can expect that the mass of material compressed critically during each impact is around 0.2 mg.

Therefore, our experimental findings and the interpretation we give based on the kinetic analysis confirm that only a very small fraction of the material inside the reactor is effectively processed during individual impacts. Discovering what happens to powders on the microscopic scale remains one of the most ambitious objectives in the field of mechanochemistry and a necessary step to further progress on the way to practical application of mechanochemical methods.

*Solid-state characterization of α-aryl-α-aminophosphonate **1** and **11**.* Among the compounds reported in this work compounds **1** and **11** (Figure 1) have been chosen as representative examples of the 'diethylphosphonte' and of the 'diisopropylphosphonate' groups to illustrate the principal molecular and crystal structure features as determined by single-crystal X-ray

diffraction.[64] Correspondence between the structures of the compounds in the bulk materials resulting from the mechanosyntheses and those of the single crystals obtained from solution was verified by comparing[64] experimental powder diffraction patterns measured on polycrystalline samples of **1** and **11** with the diffractograms calculated on the basis of the single crystal structures described in the following.

The molecular diagrams together with the labelling schemes are shown in Figure 6. **1** and **11** share the fundamental structural unit of α-aryl-α-aminophosphonates and crystallize as racemic crystals with molecules organized in centrosymmetric hydrogen bonded dimers (vide infra) in the space groups $P2_1/c$ and in P-1 for **1** and **11**, respectively.

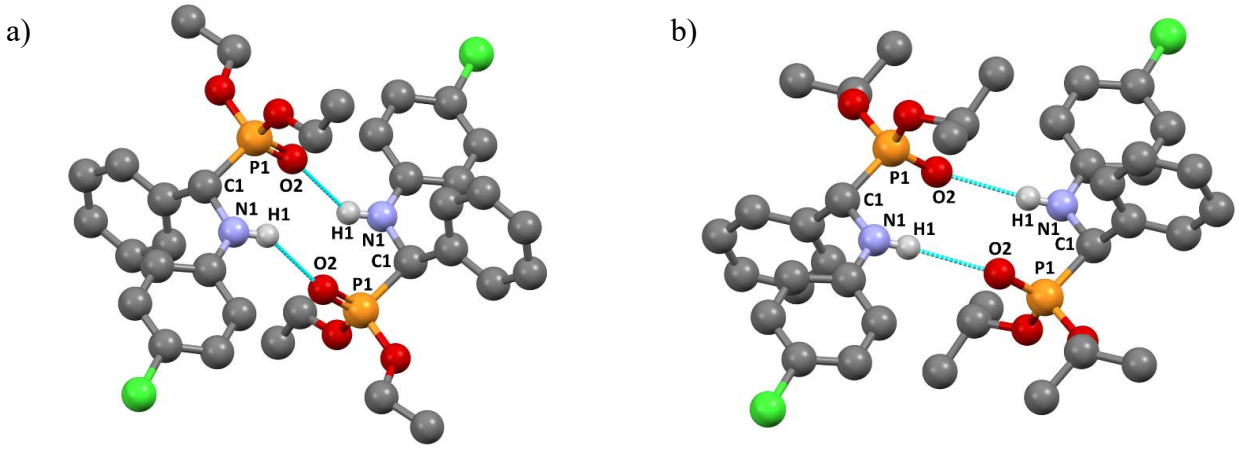
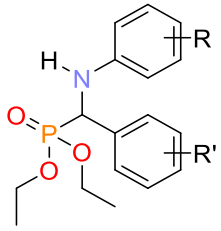
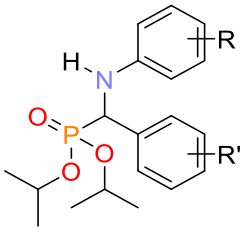


Figure 6. The molecular structures of **1** (a) and **11** (b) showing the labelling schemes of aminophosphonate groups and the hydrogen bonded rings formed by pairs of molecules in the crystals. H_{CH} hydrogen atoms omitted for clarity.

The hydrogen bonded rings formed by pairs of molecules in **1** and **11** can be described in graph set notation[77] as $^2_2R(10)$, *viz*. ten member rings with two hydrogen bonding N-H donors and two acceptor P=O groups. There is a noticeable difference in hydrogen bond length within

the two ring systems with $N_{NH}\cdots O_{PO}$ of 2.943(5) and of 3.116(6) Å in **1** and **11**, respectively. Such a difference can be ascribed to the larger steric demand of the isopropyl group in **11** with respect to the small ethyl groups in **1** hindering a closer approach in the former ring. A similar effect has been observed in a number of other cases and is substantiated by the comparison with other diethyl and diisopropyl aminophosphonates forming $^{2}_{2}R(10)$ rings extracted from the CSD[78] and shown in Table 3.

Table 3. Comparison of hydrogen bonded dimers $N_{NH}\cdots O_{PO}$ distance of diethyl and diisopropyl aminophosphonates.

		
CSD Refcode –	DEABPH[79] – 2.957	RAFFAH[80] – 3.070
$N_{NH}\cdots O_{PO}$ bond length, Å	LUPHAG[81] – 2.958	XUXJAC[82] – 3.079
	PESKAC[83] – 2.904	XUXJEG[82] – 3.066

It is interesting to note that the crystal structures of **1** and **11** (see Figure 7 for views of the packings) although obtained by mechanochemical methods as described herein present the same hydrogen bonded dimers as observed in many related compounds obtained by more conventional methods. For example, a similar hydrogen bonded ring is present in compound **3** whose structure had been previously determined by others (DEABPH[79]) and obtained first by a conventional solution method[84-85] and later via an unconventional procedure (MW)[86] and also by

us (see Figure 1). As a matter of fact, all compounds listed in Table 3 share with **1** and **11** the same fundamental $^{2}_{2}$R(10) hydrogen bonding motif. While this is not surprising *per se*, it is interesting to speculate on the fact that different processes, whether via solution or mechanochemistry, terminate with the same molecular recognition outcome.

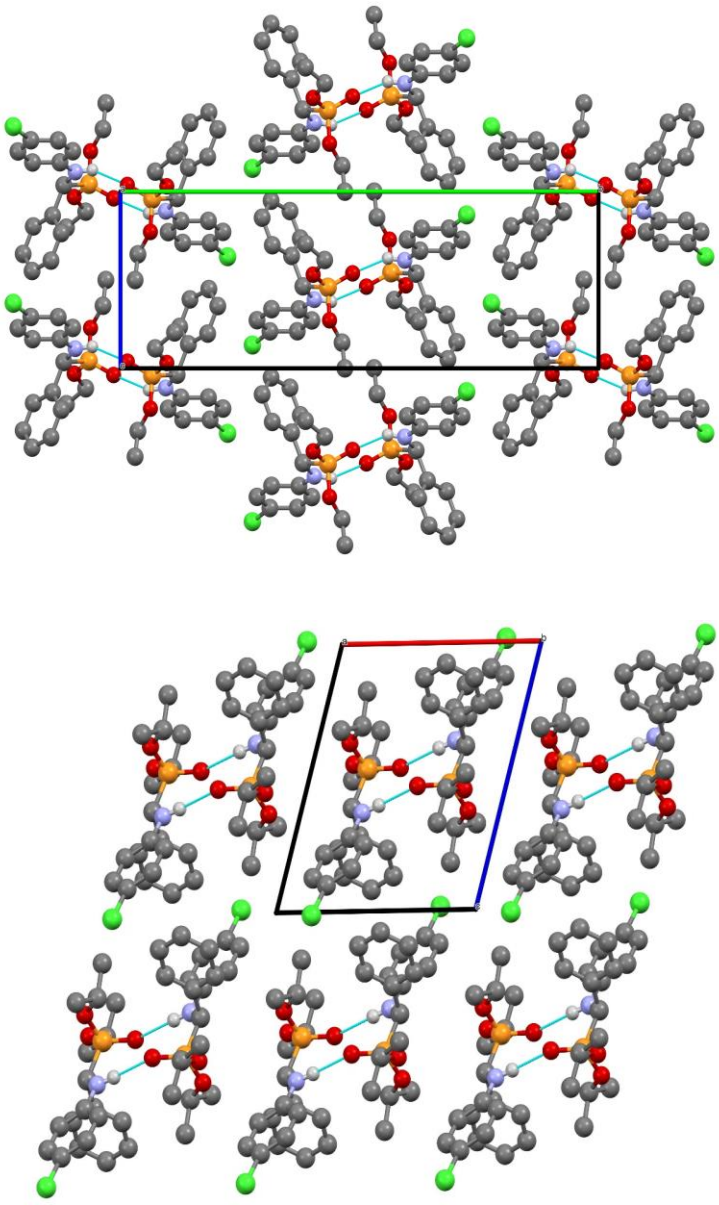


Figure 7. Crystal packing of **1** (top) viewed along the crystallographic *bc*-plane, and of **11** (bottom) viewed along the crystallographic *ac*-plane. H_{CH} have been omitted for the sake of clarity.

This consideration lends further support to the idea that molecules, even complex molecules such as those discussed herein, have great mobility also in solid-solid or solid-liquid mixtures and that the crystal nucleation stage follows exactly the same selection rules as in solution, leading in all these cases to crystals built around the same supramolecular dimers.

Finally, one may wonder why, in analogy with the crystal structures of carboxylic acids, the alternative "catemer" type arrangement, *i.e.* the extended one-dimensional hydrogen bonded polymer,[87] with no ring formation is not adopted in crystals of the aminophosphonates discussed here. The alternative "catemer" type hydrogen bonded polymer has been observed, for example, in the crystal of the phosphonate *diethyl(((4-methylphenyl)amino)(4-nitrophenyl) methyl)phosphonate* (KANWEE[88]), see Figure 8.

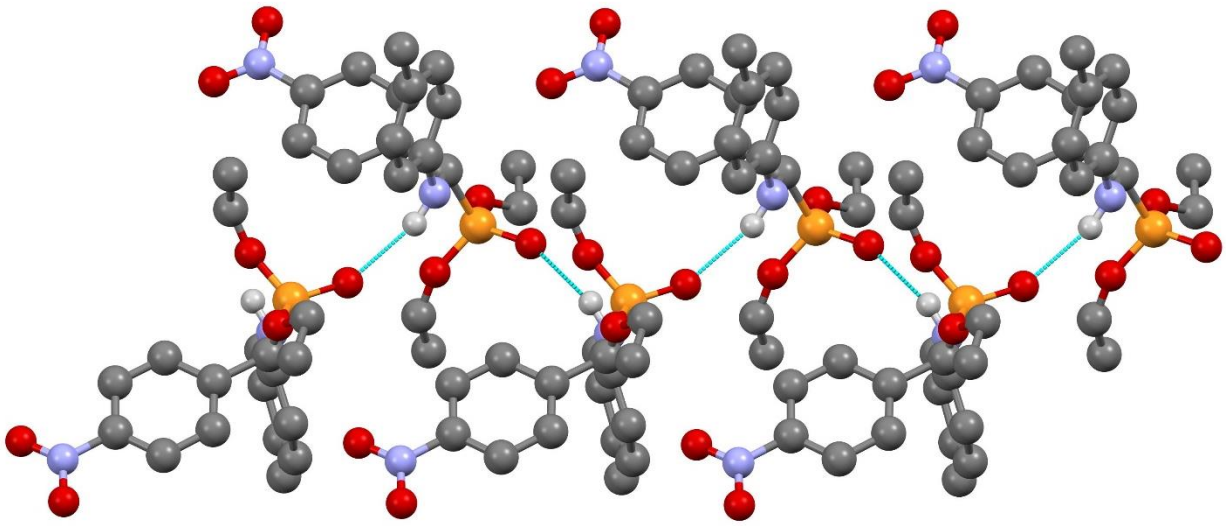


Figure 8. The "catemer" type hydrogen bonded network in crystalline *diethyl(((4-methylphenyl)amino)(4-nitrophenyl)methyl)phosphonate* KANWEE.[88] H_{CH} have been omitted for the sake of clarity.

The reason for the structural preference is not easily rationalized, although one may observe that the catemer type packing is not compatible with the formation of centrosymmetric molecular pairs which, as discussed above, are likely to aggregate prior to crystal nucleation stage, whether in solution or in the condensed phase. The existence of polymorphic modifications of the crystals of the species discussed herein cannot be ruled out and deserves an *ad hoc* investigation.

CONCLUSIONS

KF-3CR reaction, already synthetically powerful, become operationally simple, fully selective and sustainable when milling conditions were used. It was demonstrated that the reaction was promoted by surface-mediated interactions of the reactants and intermediates involving the zirconium oxide jar (and balls). The mechanochemical procedure allowed a fully selective transformation (by-products are avoided) and the final α-aminophosphonates were easily recovered by precipitation in water and not a drop of organic solvent was used for both synthesis and work-up. Additionally, the formation of phosphorus-carbon bonds by Kabachnik-Fields reaction under ball-milling conditions outperform compared to solution-based procedures and allowed a straightforward access to α-aminophosphonates and less common α-aminophosphine oxides having structural diversity and complexity. The preparation of compounds potentially endowed with biological activities, contributes to the advancement of a recent area of investigation referred to as *"medicinal mechanochemistry"*.[16, 89] In this regard, in view of the potential pharmaceutical applications of new active compounds, the evergreen topic of solid-state characterization merged with mechanochemical procedures for their preparation is more than ever of actuality, in view of the discovery of novel pharmaceutical polymorphs.[90]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, ^{1}H, ^{13}C, ^{31}P spectral data of compounds **1-17**. Structural and PXRD data for compounds **1** and **11**.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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GRAPHICAL ABSTRACT