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## RESEARCH ARTICLE

## Ball-Milling Assisted Synthesis of Monofluoroalkenes

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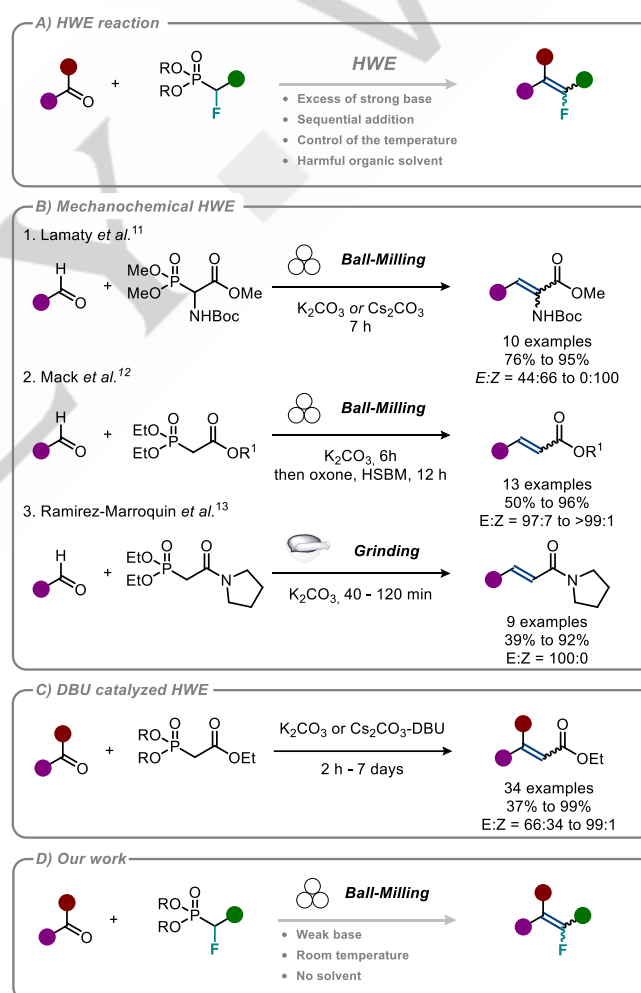
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**Abstract:** A solvent-free synthesis of valuable monofluoroalkenes was developed under ball-milling agitation. The use of 1.0 equivalent of carbonyl substrates and 1.1 equivalent of fluorophosphonoacetate derivatives with a weak inorganic base enabled the formation of the desired products after 30 min of reaction under sustainable conditions with minimized synthetic waste. No sequential addition of base, fluorophosphonate, and carbonyl substrates was needed, and the desired products were obtained with high purity only after a simple filtration. The protocol showed general efficiency and tolerance to a large panel of carbonyl substrates including aldehydes and ketones, as well as fluorophosphonoacetate derivatives with moderate stereoselectivities and yields ranging from 21 % to 99 % (48 examples).

## Introduction

Owing to its intrinsic properties, the fluorine atom plays a crucial role in modulating the physicochemical properties of organic molecules, enhancing their metabolic stability and lipophilicity.<sup>1</sup> As a consequence, organofluorine chemistry has undergone rapid expansion over the years, with about 30 to 40% of agrochemicals and 20% of commercially available pharmaceuticals containing at least one fluorine atom in their structure.<sup>2</sup> Among fluorinated compounds, the fluorine-substituted alkenes are of prime importance in medicinal chemistry.<sup>3</sup> Indeed, the fluoroalkene moiety is known as an isosteric and isoelectronic mimic of an amide linkage with substantially enhanced stability. In addition, fluoroalkenes are configurationally more stable than the amide bonds.<sup>4</sup> Therefore, fluoroalkenes have been explored as peptide bond bioisosteres to overcome poor metabolic stability and low membrane permeability of peptides.<sup>5</sup> As part of the multitude of synthetic strategies developed for the formation of monofluoroalkenes such as electrophilic and nucleophilic fluorination, reduction of terminal difluoroalkenes, and the Julia-Kocienski transformation,<sup>6</sup> the Horner-Wadsworth-Emmons (HWE) olefination has been successfully applied over the years for the one-step formation of



**Scheme 1.** State of the art and present work.

monofluoroalkene derivatives from readily available carbonyl compounds (Scheme 1A).<sup>7</sup> While this synthetic methodology has proven to be a powerful tool for obtaining fine fluoroalkene chemicals, there are some disadvantages to using such a transformation. Indeed, in most cases, an excess of strong bases

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such as sodium hydride or butyllithium must be used leading to the need for sequential addition of reactants. Specifically, the fluorophosphonoacetate must be added first with the strong base followed by addition of the carbonyl compounds after a certain amount of time. In addition, the use of a strong base such as butyllithium requires, on the one hand, careful control of the temperature of the reaction below 0 °C during the deprotonation step, and on the other hand, the use of potentially harmful organic solvents, which are mostly tetrahydrofuran and *N,N*-dimethylformamide. Therefore, the development of more practical and efficient protocols with a particular focus on sustainability is in high demand. Mechanochemistry, a technology known for centuries,<sup>8</sup> is re-emerging as a powerful synthetic tool in organic synthesis.<sup>9</sup> Mechanochemical synthesis using ball-milling agitation enables the avoidance of potentially harmful organic solvents in reactions toward the development of more practical processes with high sustainability metrics. In addition, shorter reaction times, no need for external heating, and improved or novel chemical selectivities are key benefits provided by mechanosynthesis.<sup>10</sup> In 2010, Lamaty's group utilized ball-milling technology for the synthesis of Boc-protected unsaturated amino esters through an innovative mechanochemical olefination under mild conditions starting from aldehydes (Scheme 1B).<sup>11</sup> Seven hours of reaction were required to fully consume the aldehydes. Ketones were reported to be non-reactive. Shortly afterward, Mack *et al.* reported a solid-state HWE transformation to obtain the desired product after 6 hours of reaction followed by 12 hours of mechanochemical Oxone oxidation of the excess of starting aldehydes (Scheme 1B).<sup>12</sup> This reaction was also limited to the use of aldehydes as starting carbonyl compounds. More recently, Ramirez-Marroquin and co-workers described the formation of  $\alpha,\beta$ -unsaturated amide derivatives in good yields, from a key  $\beta$ -amidophosphonate and aldehydes (Scheme 1B).<sup>13</sup> However, manual grinding in 10-minute intervals in a porcelain mortar and pestle for a total grinding time of 40 to 120 min was required. Later, the same research group reported a solvent-free mechanochemical synthesis of phosphonocinnamic esters using potassium *tert*-butoxide as a base through a 5-minute mortar and pestle grinding.<sup>14</sup> Ando's group reported a solvent-free HWE reaction (Scheme 1C).<sup>15</sup> A mixture of DBU<sub>cat.</sub> with K<sub>2</sub>CO<sub>3</sub> enabled the formation of the desired olefins with good yields after 2 to 24 hours of reaction. Ketone derivatives also reacted, albeit with a longer reaction time. Interestingly, no mechanochemical activation was needed. In addition, very recently, Templ and Schnürch reported that a high-energy ball-milling process enabled a 30-second Wittig olefination reaction allowing the formation of alkenes in moderate to high yields.<sup>16</sup> Stabilized ylides were used to obtain the corresponding alkenes in a short reaction time *via* the HWE reaction. While these reported works have initiated the development of more sustainable olefination reactions under solvent-free conditions, to the best of our knowledge, the synthesis of added-value monofluoroalkenes through a solvent-free HWE process has not yet been reported. Hence, as part of our program dedicated to the development of more sustainable access to valuable organofluorine compounds, we sought to establish a solvent-free methodology for the synthesis of monofluoroalkenes. Particular attention was given to

developing the most practical process, ensuring a short reaction time, a broad reaction scope applicable to both aldehydes and ketones, and avoiding time- and cost-consuming purification steps (Scheme 1D).

## Results and Discussion

At the outset of our investigation, benzaldehyde **1a** and commercially available triethyl 2-fluoro-2-phosphonoacetate **2a** were used as model substrates (Table 1, entry 1). Initially, cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>) was tested as a weak base mixing at a frequency of 18 Hz for 120 minutes with two 7.5 mm stainless-steel balls in a 5 mL stainless-steel jar. The desired product **3a** was obtained with complete conversion and an excellent 99% <sup>19</sup>F NMR yield. Interestingly, the *Z* isomer was obtained as a major product with a *E:Z* ratio of 1:1.7.

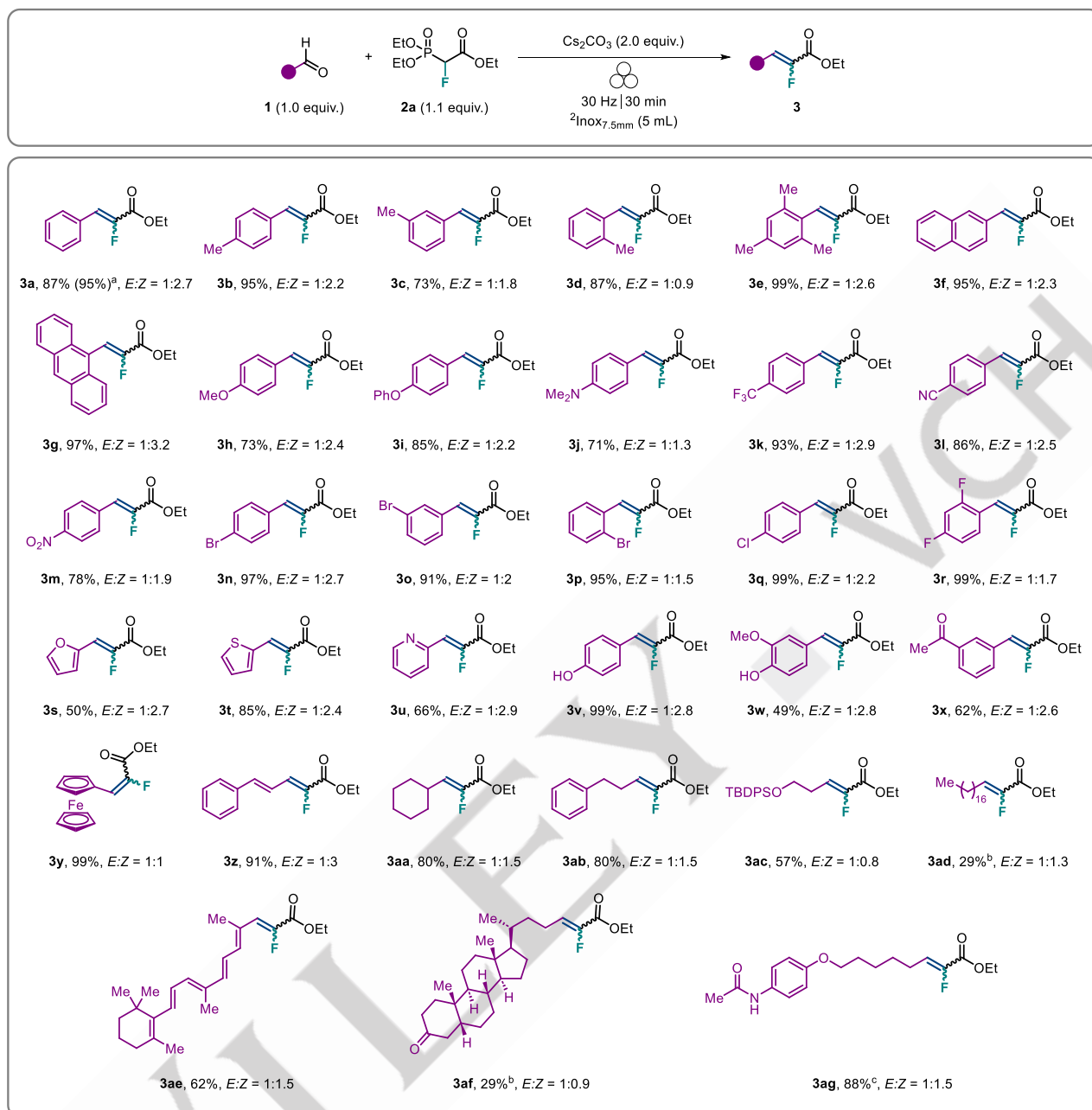
**Table 1.** Optimization of the mechanochemical formation of monofluoroalkene.



Entry	Variation from standard conditions	Yield (%) <sup>[a]</sup>	<i>E:Z</i> <sup>[b]</sup>
1	none	99	1:1.7
2	K <sub>2</sub> CO <sub>3</sub> (2.0 equiv.)	91	1:0.7
3	Na <sub>2</sub> CO <sub>3</sub> (2.0 equiv.)	69	1:0.3
4	Li <sub>2</sub> CO <sub>3</sub> (2.0 equiv.)	3	1:0.3
5	<sup>t</sup> BuOK (2.0 equiv.)	35	1:1.3
6	KOH (2.0 equiv.)	91	1:1.3
7	CsOH (2.0 equiv.) <sup>[c]</sup>	18	1:11.7
8	CsOH (2.0 equiv.) <sup>[d]</sup>	26	1:3.5
9	NEt <sub>3</sub> (2.0 equiv.)	31	1:0.3
10	1 stainless steel balls of 7.5 mm	58	1:1.6
11	30 min of reaction and 30 Hz of mixing	88	1:2
12	1.0 equiv. of <b>1a</b> and 1.1 equiv. of <b>2a</b>	(87) <sup>[f]</sup>	1:2.7

[a] <sup>19</sup>F NMR Yield using trifluoromethylbenzene as internal standard. [b] *E:Z* ratio determined by <sup>19</sup>F NMR. [c] CsOH in aqueous solution (50 w%). [d] CsOH monohydrate. [e] reaction was performed under a mixing frequency of 30 Hz for 30 min. [f] isolated yield

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**Scheme 2.** Scope of aldehydes. Indicated yields are isolated yields. [a] reaction performed on a 5 mmol scale. [b] 180 min of reaction. [c]  $^{19}\text{F}$  NMR yield using trifluoromethylbenzene as an internal standard

It is worth noting that compared to non-fluorinated phosphonates, which usually lead to *E*-alkenes, the major drawback of the HWE reaction for the production of fluoroalkenes is the lack of stereoselectivity; therefore, our low *E:Z* ratio is quite typical.<sup>7</sup> Nevertheless, aiming to increase the *E:Z* ratio, we tested several bases (entries 2 to 8). The use of  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ , and  $\text{Li}_2\text{CO}_3$  had a negative impact on the reaction yield, dropping down from 91% to 3%  $^{19}\text{F}$  NMR yield, respectively. However, the *E*-isomer was obtained as the major product, albeit with a low selectivity.  $\text{Cs}_2\text{CO}_3$  was then replaced by hydroxide bases (entries 5 to 8). Neither  $^t\text{BuOK}$  nor  $\text{KOH}$  had a significant impact on the reaction selectivity. However, when using an aqueous solution of  $\text{CsOH}$  (entry 7), **3a** was obtained with an excellent *E:Z* ratio of 1:11.7, albeit in a low 18%  $^{19}\text{F}$  NMR yield. Decreasing the amount of

water lowered the stereoselectivity but enabled a slight increase in the reaction efficiency (entry 8), showcasing a real impact of  $\text{H}_2\text{O}$  in our transformation. Different amounts of water were then added to the optimal conditions to study the influence on the stereoselectivity. The *E:Z* ratio was not significantly affected when going from 10 to 250  $\mu\text{L}$  of water, while the reaction yield started to decrease (see Table S-1). The weak organic base, triethylamine, was studied but did not result in any increase in efficiency and stereoselectivity (entry 9). Reducing the number of stainless-steel balls led to lower efficiency (entry 10). In order to increase the practicability of our reaction process, we sought to reduce reaction time. Increasing the mixing frequency to 30 Hz allowed us to reduce reaction time to 30 minutes (entry 11). A slight increase in the stereoselectivity was also observed. Then,

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to avoid chromatography purification, 1.0 equivalent of **1a** was reacted with 1.1 equivalent of **2a** (entry 12). Pleasingly, the desired product **3a** was isolated through simple filtration in an excellent 87% isolated yield. Additionally, an increased stereoselectivity was observed with a *E:Z* ratio of 1:2.7. It is worth mentioning that a reactivity test in DCM was performed to exclude reactivity upon solvent addition (see SI, section 5.d.).

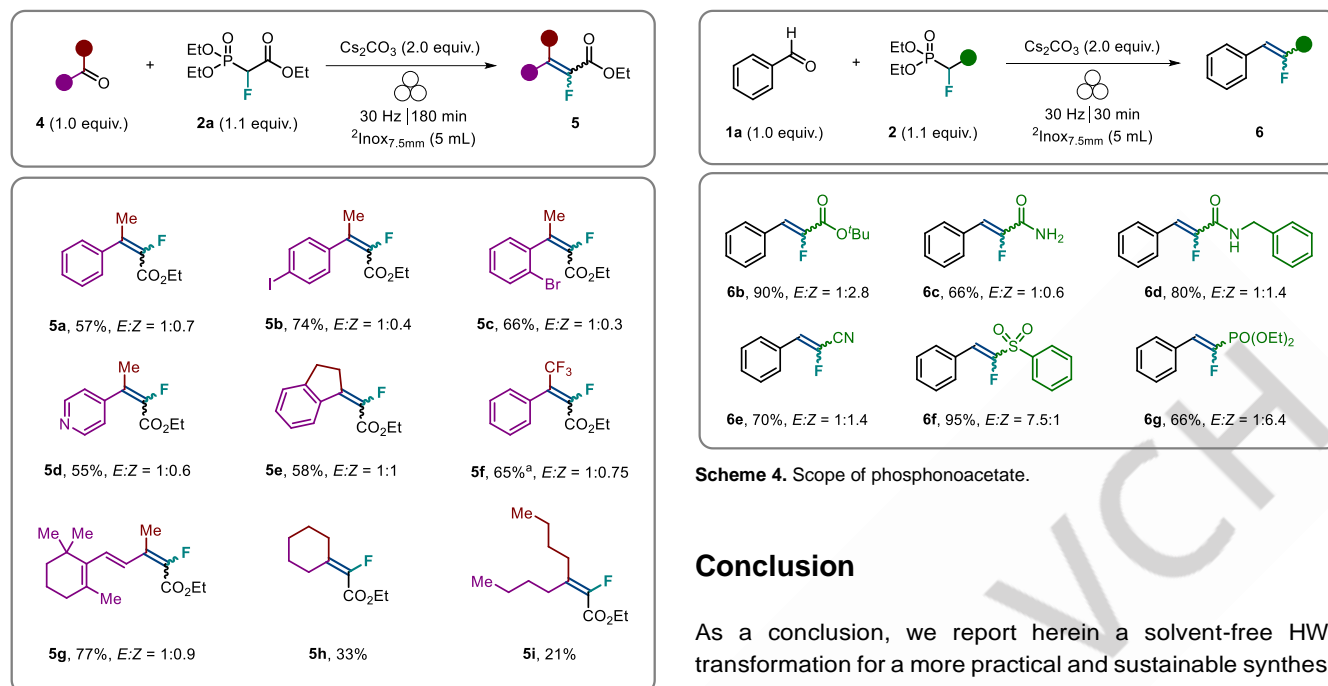
Having delineated the optimal reaction conditions (Table 1, entry 12), the scope of this ball-milling-assisted synthesis of monofluoroalkenes was investigated. A range of aldehydes was first studied (Scheme 2).

While the reactions were performed on a 1 mmol scale, a test on a 5 mmol scale of the model substrate (benzaldehyde **1a**) showcased that the scale of the reaction can be increased with even better reactivity, reaching 95% yield. The reaction efficiency was not affected by the substitution pattern. Aldehydes bearing a methyl group at the *para*-, *meta*- or *ortho*-position afforded the desired products in good to excellent yields (**3b-d**), showcasing no impact of steric hindrance on the reaction yield. However, the presence of the *o*-methyl substituent lowered the stereoselectivity of the reaction, affording the desired product in a 1:0.9 *E:Z* ratio. In addition, 2,4,6-trimethylbenzaldehyde proceeded well producing **3e** in quantitative yield. Aldehydes derived from naphthalene and anthracene were also efficient substrates, leading to the formation of interesting polyaromatic fluoroalkenes in excellent yields (**3f** and **g**) with a similar stereoselectivity. Our ball-milling-assisted olefination was fully tolerant to various functional groups. Good yields were obtained by reacting either aromatic aldehydes with electron-donating substituents (**3h-j**) or electron-withdrawing groups (**3k-m**), including valuable post-functionalizable cyano or nitro moieties. Nitrogen-containing functions such as amine (**3j**) or nitro (**3m**) led to the formation of the desired product with lower stereoselectivities. Halogen atoms were well tolerated under our solvent-free conditions, as benzaldehydes substituted by a *para*-, *meta*- or *ortho*-bromine (**1n-p**), chlorine (**1q**), and fluorine (**1r**) gave the corresponding products (**3n-r**) with excellent yields, enabling opportunities for further transformations. As we already mentioned, steric hindrance did not impact the reaction outcome, including reaction yield and stereoselectivity. Heteroaryl aldehydes were also tested in our reaction conditions. While furan-2-carbaldehyde afforded the desired product **3s** in a decent 50% yield, the reaction of thiophene and pyridine derived aldehydes enabled the formation of valuable heteroaromatic molecules in good yields (**3t** and **3u**). Free alcohol-containing aldehydes were efficiently used, as 4-hydroxybenzaldehyde and vanillin enabled the formation of products (**3v** and **3w**), with similar *E:Z* ratios albeit in a lower yield regarding vanillin substrate. In addition, the use of 3-acetylbenzaldehyde showcased a full regioselectivity towards aldehyde compared to ketone (**3x**). Interestingly, ferrocenecarboxaldehyde afforded product **3y** in an excellent yield, but with no stereoselectivity. Moreover, fluorinated diene **3z**, a potential versatile product in organic synthesis, was synthesized in a high yield and a good 1:3 *E:Z* ratio. Finally, aliphatic aldehydes were also reacted with good

efficiency, but with lower stereoselectivities (**3aa** to **3ad**). Interestingly, aldehyde **1ad**, derived from natural stearic acid, could be employed as a starting carbonyl compound. To further demonstrate the robustness of our ball-milling olefination strategy, we decided to evaluate more complex aldehydes such as retinal (**1ae**), a polyene chromophore, an aldehyde derived from lithocolic acid (**1af**), a bile acid, and an aldehyde derived from paracetamol (**1ag**). All these substrates were suitable, yielding monofluorinated alkenes, with an extended reaction time for **3af**. **3ag** could not be isolated from the remaining starting phosphonoacetate; nevertheless, <sup>19</sup>F QNMR indicated an excellent 88% yield. Interestingly, in 2015, Yi's group reported a deacylation reaction of  $\alpha$ -fluoro- $\beta$ -keto esters under mild conditions in acetonitrile (MeCN).<sup>17</sup> After 8 or 12 hours of reaction, several monofluorinated alkenes were obtained. However, ketones were not depicted as reactive substrates under these reaction conditions. Therefore, ketones **4** were then studied under our solvent-free reaction conditions to synthesize interesting tetra-substituted fluoroalkenes (Scheme 3). Ketone substrates being less reactive than aldehydes, longer reaction times were needed for the complete conversion of starting material **4**. Initially, acetophenone was tested in our reaction conditions enabling the formation of the desired olefin **5a** with a good yield. Halogen-substituted acetophenones (**4b,c**) were also efficient substrates in our transformation leading to better yields and stereoselectivities than acetophenone, despite the additional steric hindrance induced by the *ortho*-bromine substituent (**5c**). Heteroaryl and cyclic acetophenones (**4d** and **4e**) were also reacted under the optimal reaction conditions and were found to be efficient substrates. Interestingly, 2,2,2-trifluoroacetophenone afforded a tetra-substituted olefin **5f** bearing both a trifluoromethyl moiety and a fluorine atom in only 30 minutes of reaction. Our process also enabled the use of natural ketone as  $\beta$ -ionone (**4g**), an important fragrance used in perfumery, furnishing the corresponding product **5g** with a good 77% yield. Aliphatic ketones proved to be reactive substrates under the standard conditions (**5h** and **5i**), although with lower yields compared to aromatic and conjugated substrates. Interestingly, ketones **4** predominantly produced *E*-isomers, while reverse stereoselectivities were observed with aldehyde derivatives (Scheme 2). The major isomer was determined by HOESY NMR experiments (see SI). It should be noted that the products were isolated *via* simple purification, with the exception of **5a**, which was purified using classical column chromatography.

A set of fluorophosphonoacetate (**2**) derivatives was then tested to enhance the efficiency of the reaction and broaden the scope of fluoroalkenes (Scheme 4). Ethyl diethyl phosphonofluoroacetate was initially replaced by *tert*-butyl diethyl phosphonofluoroacetate resulting in the formation of the desired product **6b** in high yield, without any influence of the *tert*-butyl group on stereoselectivity. Pleasingly, our reaction

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**Scheme 3.** Study of ketones as starting carbonyl substrates. [a] 30 min of reaction.

conditions proved to be efficient with non-substituted (**2c**) and *N*-benzylamide diethyl (**2d**) as shown by the good yields obtained for products **6c** and **6e**. Interestingly, the use of **2c** led to the formation of *E* isomer as the major product while the *Z* isomer was obtained as the major compound when starting from the fluorophosphonoacetate **2d**. Diethyl cyanofluoromethylphosphonate **2e** was tested and demonstrated good efficiency, affording a valuable gem-cyanofluoroalkene **6e**. This type of product can be further transformed into aldehydes or amines, with subsequent utilization in peptidomimetics synthesis. Finally, the ( $\alpha$ -fluoro)vinyl sulfone **6f** and ( $\alpha$ -fluoro)vinyl diethyl phosphonate **6g**, which is a phosphate mimic, were efficiently synthesized with good yields from the corresponding phosphonofluoroacetate (**2f** and **2g**). Interestingly, in these two cases, good stereoselectivities were obtained in favor of the *Z* isomer, with *E:Z* ratios of 7.5:1 and 1:6.4, respectively.

**Scheme 4.** Scope of phosphonoacetate.

## Conclusion

As a conclusion, we report herein a solvent-free HWE transformation for a more practical and sustainable synthesis of valuable monofluoroalkenes at room temperature, using a weak base in a short reaction time. The mild reaction conditions provided the corresponding fluoroalkenes with yields up to 99% (48 examples). Indeed, the developed method was applicable to a wide range of aromatic and aliphatic aldehydes with a broad functional group tolerance. Notably, less reactive ketones were able to form tetra-substituted monofluorinated alkenes with good yields, which had not yet been reported in a mechanochemical setup. In addition, the reaction conditions proved to be tolerant to a large variety of fluorophosphonates such as amide, cyano, nitro, sulfone, and phosphonate derivatives, enabling potent further transformations toward added-value fluorinated chemicals, such as peptidomimetics. Interestingly, aldehydes predominantly produced the *Z*-isomers, while in the case of ketones, the *E*-isomers were the major products. However, explaining and increasing the *E:Z* stereoselectivity is still under study and will be reported in due course.

## Supporting Information

The data supporting this article can be found in the supporting information

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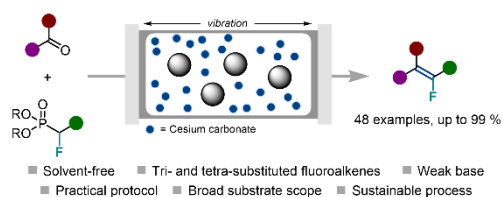
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**Keywords:** Fluoroalkene • Horner-Wadsworth-Emmons reaction • Ball-Milling • Synthetic methodology • Sustainable chemistry

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## RESEARCH ARTICLE

## Entry for the Table of Contents



A mechanochemical Horner-Wadsworth-Emmons reaction enabled the formation of monofluoroalkenes with yields up to 99%. The solid-state reaction condition allowed the formation of a broad scope of trisubstituted and tetrasubstituted fluorinated alkenes (48 examples) with the use of a weak base and a short reaction time from aldehydes or ketones. Moreover, the reaction conditions proved to be broadly applicable to various fluorophosphonoacetates, providing access to valuable fluorinated compounds.