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Sustainability and efficiency assessment of lignin-derived phenolic synthons' allylation: in solution versus ball-milling

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Abstract

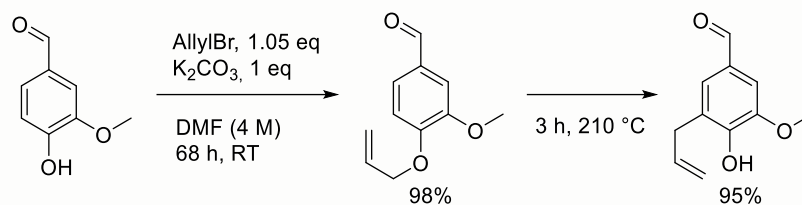
Allylation of phenols, a widely used reaction in multistep synthetic pathways, was herein investigated using mechanochemistry. This synthesis was first optimized on vanillin by varying key parameters including both chemical (e.g., stoichiometry, reaction time, liquid additive) and mechanical (e.g., rotational speed, material, size and number of beads) conditions, leading to the isolation of allylated vanillin at the gram scale in excellent yield (95%). The optimized procedure was also successfully implemented to another bio-based phenol of interest, ethyl ferulate (92% isolated yield). The environmental impact of these procedures was compared with more classical in-solution protocols by calculating *E* factors, clearly indicating the superiority of the ball-milling approach over the solution-based procedures. Thus, the present work demonstrates that mechanochemistry is a versatile, efficient and waste-less method for the allylation of biobased phenols such as vanillin and ethyl ferulate.

Introduction

Composed of *p*-hydroxyphenylpropanoids units, lignins are a natural and abundant polyphenolic resource that is gaining more and more interest and value in the chemical industry. Indeed, lignins can be used as macromolecular polyols¹ or (bio)-catalytically depolymerized to prepare monophenolics such as vanillin, syringaldehyde, or 4-hydroxyphenyl ethanol.² Among the various phenolics that can be readily obtained from lignins, vanillin is probably the most promising, by being mainly produced from the hydrolysis-oxidation of lignosulfonate coming from paper industries. In order to meet the world demand of vanillin, 15% of the general production comes from this lignosulfonate revalorization which would have been burned instead.^{3, 4, 5} These renewable phenolics constitute a great source of valuable synthons for the production of bio-based alternatives to petroleum-based phenolic/aromatic bioactive compounds – such as antioxidants,⁶ UV filters,^{7–13} monomers and corresponding polymers.³

Allylation is an easy and quick reaction to functionalize hydroxylic group with a reactive and versatile double bond, which is widely used in multistep synthetic pathways. The first group who applied allylation on vanillin was Ayer *et al* in 1991 (Scheme 1, first step), to synthesize a molecule inhibiting the growth of pathogens.¹⁴ Then, Detterbeck *et al.* used it in order to create hydroxylated arylidihydrobenzofuran systems as key structures to obtain natural compounds.¹⁵ Later on, Breloy *et al.*, who aimed to develop a green vanillin-based photoinitiator for free-radical polymerization of acrylated monomer, performed vanillin allylation to avoid radical side reaction on phenols during

polymerization.¹⁶ Still in the polymer field, Han *et al.* carried out the allylation of vanillin to ease the curing of a phthalonitrile resin.¹⁷ Willing to enhance the bioactivity of vanillin-based chalcones, Sharma *et al.* also implemented this allylation step.¹⁸ It is noteworthy to mention that some researchers, such as Yu *et al.*, took advantage of the resulting allyloxy group to perform Claisen rearrangement (Scheme 1, second step).¹⁹



Scheme 1: Allylation in solution¹⁴ followed by Claisen rearrangement¹⁹

Generally, allylation of vanillin is carried out in solution in organic solvents, such as DMF, acetone or ethanol, in the presence of potassium carbonate as a base. Although these reaction conditions allow the isolation of allylated vanillin in high yields, they also present some drawbacks such as the toxicity and the quantities of the solvent used,²⁰ long reaction times or the need to perform the reaction at relatively high temperature (such as in refluxing EtOH or acetone). Due to the critical importance of vanillin and other renewable phenolic compounds (*e.g.*, ethyl ferulate) as well as their allylated counterpart, the development of efficient and sustainable allylation conditions is of high interest.

Based on previous successes in the field, we therefore envisaged using mechanochemistry to produce allylated phenols.²¹⁻²³ Mechanochemistry can be defined as the field of science that studies chemical transformations facilitated by mechanical energy.²⁴ It has been demonstrated in many cases that mechanochemistry allows the development of more efficient and sustainable alternatives to the processes classically performed in solution.²⁵ Mechanochemical allylation of vanillin was therefore attempted by milling vanillin with K_2CO_3 and allyl bromide.

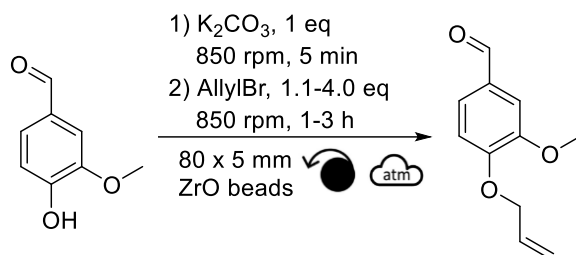
Results and discussion

I) Mechanochemical allylation of vanillin

a. Optimization of reaction conditions by ball milling

At first, 143.7 mg of vanillin were reacted with 130.6 mg of K_2CO_3 (1.0 eq) in a 20 mL reactor made of zirconium oxide (noted ZrO) containing 80 beads of the same material (5 mm diameter). After 5 min milling at 850 rpm at room temperature, 90.4 μ L of allyl bromide (1.1 eq) were added to the reactor and the reaction mixture was agitated at 850 rpm. After 1 h of milling, an HPLC analysis of the crude revealed that ~37% of vanillin was allylated (Table 1, entry 1).

Table 1: Optimization of the chemical parameters for the allylation of vanillin



Entry ^a	Allyl bromide equivalents	Reaction time (h)	Conversion ^b (%)
1	1.1	1	37 ± 8
2	1.5	1	36 ± 4
3	4.0	1	28 ± 4
4	1.1	3	40 ± 5
5	1.5	3	40 ± 1
6	4.0	3	38 ± 1

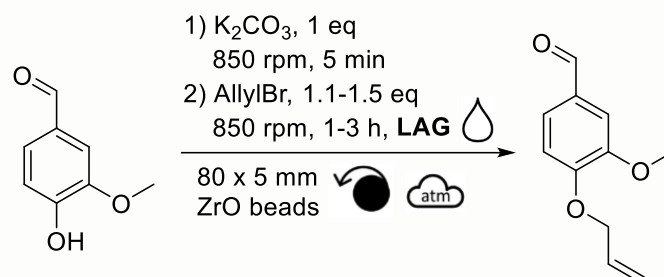
^a Vanillin: K₂CO₃ 1:1, 20 mL ZrO reactor, 80 ZrO beads (32 g, d = 5 mm), rotational speed: 850 rpm, total mass of reagents : 400 mg. Symbols utilized in this scheme are those proposed by Michalchuk *et al.*²⁴ Their signification is explained in the SI. ^b Estimated by calculating the HPLC surface area ratio of the peaks corresponding to the allylated vanillin over vanillin. Conversions are presented as an average of three samples taken at three different spots of the reaction mixture. The standard deviation therefore represents the homogeneity of the distribution of the reactants and products in the reaction mixture.

Here, the number of parameters that could be optimized being quite large (mechanical parameters adding to the chemical ones), performing a Design of Experiments (DoE) and Response Surface Methodology (RSM) was not adapted.²⁶ It was thus decided to implement classic One Variable At a Time approach (OVAT) to optimize the mechanochemical allylation of vanillin. Before studying and optimizing the mechanical parameters, it was decided to first investigate the chemical parameters and more specifically, the reaction time and the excess of allyl bromide, which is a liquid at ambient temperature (Table 1). Indeed, it is widely known in mechanochemistry that adding small amounts of a liquid can dramatically influence the course of the reaction. This technique, called Liquid-Assisted Grinding (LAG), often enables to increase homogeneity of the reaction mixture but also to accelerate and control selectivity of a reaction.²⁷⁻²⁹ To quantify LAG solvent added in the bulk, the η value was defined in the literature as the liquid volume added per total mass of reagents.³⁰ In this work, η will be calculated based on the total mass of the following reagents: phenol, potassium carbonate and allyl bromide.

In our case, it was expected that allyl bromide could both play the role of a reactant and of a beneficial liquid additive. Therefore, the quantity of allyl bromide was increased to 1.5 and 4.0 equivalents (Table 1, entries 2 and 3). Counterintuitively, increasing the equivalents of allyl bromide did not favor the conversion of vanillin. On the opposite, conversion dropped down to ~28% when using 4.0 equivalents of allyl bromide (Table 1, entry 3). Similar tendency was observed when the reaction time was raised to 3 hours (Table 1, entries 4-6). This confirmed the deleterious effect of allyl bromide as a liquid additive was stronger than the positive effect that would have been expected from increasing the excess of this reactant. Additionally, increasing the reaction time did not significantly improve the conversion, whatever the excess of allyl bromide used (Table 1, entries 4-6). Finding a suitable liquid additive was thus the next step of this study. Ten polar aprotic solvents and EtOH, which is a commonly used solvent for allylation, were then tested as liquid additives,

regardless of their toxicity: acetone, EtOAc, anisole, dimethylcarbonate, DMF, DMSO, diethyl malonate, acetonitrile, cyrene® and γ -valerolactone (Table 2). Vanillin and K_2CO_3 were first milled for 5 min before allyl bromide and the liquid additive were added and milled.

Table 2: Liquid additive screening for the mechanical allylation of vanillin



Entry ^a	Liquid additive ^b	η (μ L/mg)	Allyl bromide equivalents	Reaction time (h)	Conversion ^c (%)
1	EtOH	0.2	1.1	1	27 \pm 8
2	Acetone	0.2	1.1	1	40 \pm 2
3	EtOAc	0.2	1.1	1	33 \pm 2
4	Anisole	0.2	1.1	1	26 \pm 3
5	Dimethylcarbonate	0.2	1.1	1	33 \pm 4
6	DMF	0.2	1.1	1	79 \pm 2
7	DMSO	0.2	1.1	1	14 \pm 1
8	Diethylmalonate	0.2	1.1	1	12 \pm 2
9	Acetonitrile	0.2	1.1	1	28 \pm 8
10	Cyrene®	0.2	1.1	1	21 \pm 3
11	γ -valerolactone	0.2	1.1	1	35 \pm 1
12	DMF	0.1	1.1	1	48 \pm 4
13	DMF	0.2	1.5	3	98 \pm 0

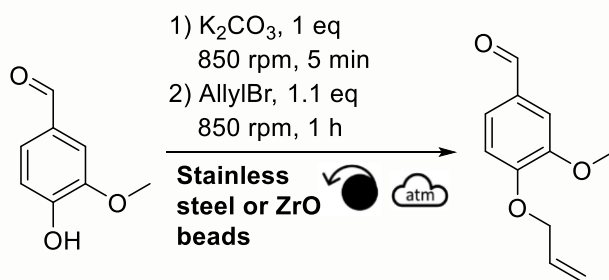
^a Vanillin: K_2CO_3 1:1, 20 mL ZrO reactor, 80 ZrO beads (32 g, $d = 5$ mm), rotational speed: 850 rpm, total mass of reagents : 400 mg. Symbols utilized in this scheme are those proposed by Michalchuk *et al.*²⁴ Their signification is explained in the SI. ^b All liquid additive were utilised in quantities corresponding to $\eta = 0.2 \mu$ L/mg. η is defined as the volume of liquid additive over the total mass of reactants.³⁰ ^c Estimated by calculating the HPLC surface area ratio of the peaks corresponding to the allylated vanillin over vanillin. Conversions are presented as an average of three samples taken at three different spots of the reaction mixture. The standard deviation therefore represents the homogeneity of the distribution of the reactants and products in the reaction mixture.

Among the different LAG tested, DMF allowed for the highest conversion (79%, Table 2, entry 6) while the use of diethyl malonate and DMSO provided the lowest (12% and 14%, respectively, Table 2, entries 7 & 8). DMF is a widespread and efficient solvent for many chemical processes, yet its toxicity is an incentive to the development of safer and more sustainable alternatives.³¹⁻³³ Among the solvents commonly recognized as more sustainable (*i.e.*, ethanol, acetone, EtOAc, anisole, dimethylcarbonate),³⁴ conversions unfortunately did not exceed 40% (Table 2, entries 1 to 5). Conversions obtained with other alternative solvents (acetonitrile, cyrene® and γ -valerolactone) did not provide better results (Table 2, entries 9 to 11). Of note, the low conversion in the case of cyrene® could be explained by its capacity to undergo K_2CO_3 -mediated deprotonation and subsequent homo-oligomerization through Michael-addition, aldol condensation or allylation.³⁵ Well-aware that DMF is not the ideal liquid additive because of its reproductive toxicity, reducing its concentration from 0.2 μ L/mg to 0.1 μ L/mg was attempted (Table 2, entry 12). Unfortunately, this resulted in a decrease in conversion from 79% to 48% (Table 2, entries 6 vs 12). By combining the

forementioned optimized parameters (*i.e.*, 1.5 eq. of allyl bromide and 0.2 μ l of DMF as LAG), while increasing the milling time to 3 hours, the conversion reached 98% (Table 2, entry 13).

In parallel with the optimization of the chemical parameters, the influence of the mechanical parameters on the conversion was studied: quantity, diameter and material of beads (Table 3), as well as rotational speed (Table 4). Indeed, such parameters will influence on the energy transferred to the reaction mixture, and hence on the course of the reaction. In total, three diameters and two materials were tested (*i.e.*, 3, 5 or 10 mm diameter beads made of ZrO or stainless steel) (Table 3). As a reminder, using 5 mm ZrO beads without any liquid additive provided allylated vanillin with a conversion of \sim 37% after 1 h of milling (Table 1, entry 1). Changing the material of the beads and reactor to stainless steel, while keeping other parameters constant, slightly reduced the conversion to 32% (Table 3, entry 1). Using larger stainless steel beads (10 mm diameter) also reduced the conversion (to 20%, Table 3, entry 2), yet smaller 3 mm beads increased the conversion (to 40%, Table 3, entry 3). The same tendency was observed with ZrO beads: conversion decreased to 23% with 10 mm diameter beads (Table 3, entry 4 compared to Table 1, entry 1) and increased to 42% with 3 mm diameter beads (Table 3, entry 5 compared to Table 1, entry 1).

Table 3: Influence of size and number of beads for the mechanical allylation of vanillin



Entry	Bead and reactor material ^a	Bead diameter (mm)	Conversion ^b (%)
1	Stainless steel	5	32 \pm 3
2	Stainless steel	10	20 \pm 1
3	Stainless steel	3	40 \pm 1
4	ZrO	10	23 \pm 3
5	ZrO	3	42 \pm 3

^a Vanillin:K₂CO₃:allyl bromide 1:1:1.1, reaction time: 1 h, rotational speed: 850 rpm. For each material, the total weight of beads was kept constant (32g for ZrO beads, 40g for stainless steel ones) and the 20 mL reactor was made of the same material than the beads (ZrO or stainless steel). Symbols utilized in this scheme are those proposed by Michalchuk *et al.*²⁴ Their signification is explained in the SI. ^b Estimated by calculating the HPLC surface area ratio of the peaks corresponding to the allylated vanillin over vanillin. Conversions are presented as an average of three samples taken at three different spots of the reaction mixture. The standard deviation therefore represents the homogeneity of the distribution of the reactants and products in the reaction mixture.

Another parameter allowing to easily modulate the induced mechanical energy is the rotational speed. Without any liquid additive, lowering the frequency to 600 rpm decreased the conversion down to 19% (Table 4, entry 1 vs \sim 37% in Table 1 entry 1). Adding DMF as a liquid additive (η = 0.2 μ L/mg) and increasing the excess of allyl bromide to 1.5 equivalents led to a better conversion of 55% (Table 4, entry 2). Yet, the highest conversion (93%) was obtained when running the reaction with a rotational speed of 850 rpm, the maximal acceptable rotational speed for our equipment (Table 4, entry 3). The latter results showed that lowering this parameter did not improve the conversion of vanillin toward allylated vanillin.

Table 4: Influence of the rotational speed on the allylation of vanillin by planetary ball milling

Entry ^a	LAG	Allyl bromide equivalents	Speed (rpm)	Conversion ^b (%)
1	No LAG	1.1	600	19 ± 2
2	DMF $\eta = 0.2^c$	1.5	600	55 ± 5
3	DMF $\eta = 0.2^c$	1.5	850	93 ± 2

^a Vanillin:K₂CO₃ 1:1, reaction time: 1 h, 20 mL ZrO reactor, 80 ZrO beads (32 g, d = 5 mm). ^b Estimated by calculating the HPLC surface area ratio of the peaks corresponding to the allylated vanillin over vanillin. Conversions are presented as an average of three samples taken at three different spots of the reaction mixture. The standard deviation therefore represents the homogeneity of the distribution of the reactants and products in the reaction mixture. ^c η is defined as the volume of liquid additive over the total mass of reactants.³⁰ It is expressed in $\mu\text{L}/\text{mg}$.

After having varied the different parameters of the reaction individually from each other (stoichiometry, reaction time, material of reactors, quantity, material and size of beads, as well as rotational speed), the allylation was performed using the optimal conditions (*i.e.*, 1.5 eq of allyl bromide, DMF $\eta = 0.2 \mu\text{L}/\text{mg}$, 20 mL ZrO reactor, 32 g of 3 mm ZrO beads, 3 h, 850 rpm) leading to a quantitative conversion of vanillin. After treatment of the crude solid obtained, 87% of pure allylated vanillin was isolated.

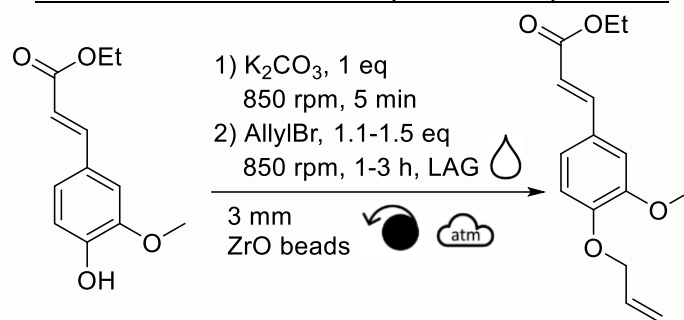
b. Comparison with reaction in solution

To evaluate the advantages brought by the aforementioned mechanochemical conditions compared to those in solution, an allylation reaction was performed in solution under classical stirring by using DMF as a solvent.¹⁶ The reaction was conducted at 50 °C with the minimal volume of DMF required to obtain a homogeneous solution under stirring, which corresponded to a η ratio of 0.84 $\mu\text{L}/\text{mg}$ in these conditions. The temperature of the reaction was set at 50 °C to be as close as possible to the milling conditions (50 °C was the temperature of the reaction media in the ball-mill right after milling was stopped in the best conditions described in the previous paragraph). Like in ball-milling conditions, a complete conversion was attained after 3h of reaction and the allylated vanillin was isolated in 86% yield (87% yield for ball-milling conditions). Yet, one can highlight that under these solution-based conditions, the amount of DMF reached more than 4 times the amount required under ball-milling ($\eta = 0.84 \mu\text{L}/\text{mg}$ in solution vs $\eta = 0.2 \mu\text{L}/\text{mg}$ for ball-milling).

II) Mechanochemical allylation of ethyl ferulate

The allylation of vanillin being successful by using ball milling, it was decided to apply these conditions to ethyl ferulate, a naturally occurring synthon of interest that has been used for the synthesis of renewable compounds such as non-toxic alternatives to bisphenol A.^{6,36} At first, 180 mg of ethyl ferulate was first reacted with 112 mg of K₂CO₃ (1.0 eq) in a 20 mL ZrO reactor containing 80 beads of the same material (5 mm diameter). As for vanillin, after 5 min milling at 850 rpm at room temperature, 77.6 μL of allyl bromide (1.1 eq) were added to the reactor and the reaction mixture was agitated at 850 rpm. After 3 h of milling, an HPLC analysis of the crude revealed that 49% of ethyl ferulate was allylated (Table 6, entry 1).

Table 5: Mechanochemical allylation of ethyl ferulate



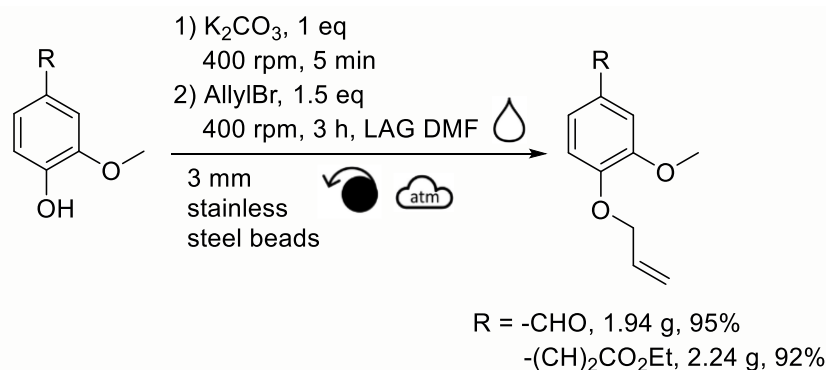
Entry ^a	LAG	Allyl bromide equivalents	Reaction time (h)	Bead diameter (mm)	Conversion ^b (%)
1	No LAG	1.1	1	5	49 ± 2
2	No LAG	1.5	3	5	50 ± 6
3	DMF $\eta = 0.2$	1.5	3	3	97 ± 1

^a Vanillin:K₂CO₃ 1:1, rotational speed: 850 rpm, beads and reactor are made of ZrO. For each size of beads, the total weight of beads was kept constant (32 g). Symbols utilized in this scheme are those proposed by Michalchuk *et al.*²⁴ Their signification is explained in the SI. ^b Estimated by calculating the HPLC surface area ratio of the peaks corresponding to the allylated ethyl ferulate over ethyl ferulate. Conversions are presented as an average of three samples taken at three different spots of the reaction mixture. The standard deviation therefore represents the homogeneity of the distribution of the reactants and products in the reaction mixture.

In the same conditions, only ~37% of vanillin was allylated (Table 1, entry 1), thus demonstrating a better reactivity of ethyl ferulate compared to vanillin in these conditions. As for vanillin in the same conditions (Table 1, entry 5), increasing the excess of allyl bromide to 1.5 equivalents and the milling time to 3 hours did not significantly improve the conversion (50%, Table 5, Entry 2). Yet when DMF was used as a liquid additive ($\eta = 0.2 \mu\text{L}/\text{mg}$), ethyl ferulate was converted almost quantitatively (97%, Table 5, entry 3). After work-up, allylated ethyl ferulate was isolated with 82% yield. Of note, allylated vanillin is a liquid in our reaction conditions. On the opposite, allylated ethyl ferulate is a solid. Gratifyingly, in these reaction conditions, conversion does not seem to be influenced by the physical states of the reactants and products. Although it is known that “hot spots” can be generated during milling, it is worth mentioning that, in our reaction conditions, no trace of the thermally-favored Claisen rearrangement product (Scheme 1, second step) was detected neither for vanillin nor for ethyl ferulate.

III) Scale-up and benchmarking

This mechanochemical allylation reaction was further studied at a higher scale. For this, a Retsch PM100 planetary ball mill equipped with a 250 mL stainless steel reactor containing ~2080 stainless steel beads (3 mm diameter) was utilized (instead of the Fritsch P7 and 20 mL ZrO reactor). Thus, 1.61 g of vanillin produced 1.94 g of allylated vanillin (95% yield, Scheme 2) after having been milled for 3 h at 400 rpm in the 250 mL reactor. Following a similar procedure, 2.05 g of ethyl ferulate furnished 2.24 g of allylated ethyl ferulate (92% yield, Scheme 2).



Scheme 2: Mechanochemical allylation of vanillin and ethyl ferulate at the gram scale (Symbols utilized in this scheme are those proposed by Michalchuk *et al.*²⁴ Their signification is explained in the SI.)

The efficiency and the environmental impact for the allylation of vanillin under mechanochemical and solution conditions were then compared (Table 6). As one cannot compare the sustainability of processes based only on their yields, the *E* factor was calculated for all selected procedures. *E* factor, which represent how many kgs of waste are produced for a kg of product, is nowadays largely accepted as a useful and simple measure to rapidly give an idea on the sustainability of a chemical reaction.^{3,37–39} Although many conditions describing the allylation of vanillin with K_2CO_3 and allyl bromide were reported in the literature, only the reaction conditions with the best yield and *E* factor are detailed in the table 6. While DMF was the best liquid additive for the allylation of vanillin in a ball-mill (furnishing allylated vanillin in 95% isolated yield), less problematic solvents such as acetone and ethanol provided better yields when used under classical stirring conditions (100% and 98%, Table 6, entries 1 and 2, respectively).^{40,41} Yet these procedures presented *E* factors above 3, indicating that they produced more than 3 times the amount of waste than the amount of allylated vanillin. A lower *E* factor of only 2.47 could be obtained by Ayer *et al.* when using DMF as a solvent, *albeit* the reaction lasted 68 hours.¹⁴ Other research groups obtained allylated vanillin in shorter reaction times by using DMF, yet by running the reaction at higher temperatures (65 and 70 °C, Table 6, entries 4 and 5, respectively), and with higher *E* factors (5.46 and 5.51, respectively, Table 6, entries 4 and 5).^{42,43} These differences led us to perform the vanillin allylation reaction with DMF as a solvent under classical stirring conditions while *i)* trying to minimize as much as possible the amount of DMF *ii)* keeping the same excesses of K_2CO_3 and allyl bromide as for the ball milling conditions. In such conditions, allylated vanillin could be obtained in 86% yield after 3 hours of reaction at 50 °C in DMF, with an *E* factor of 4.09. When performing the allylation in a ball-mill by using DMF as a liquid additive, allylated vanillin was isolated in yields comparable to the previously described procedures in solution (87% and 95% isolated yields for ball-milling conditions, Table 6, entries 7 and 8, respectively; 86-100% yield range for reactions performed in solution). Yet, the ball-milling conditions enabled to reach the lowest *E* factors of 2.33 and 2.06, for the mg-scale and the gram-scale synthesis, respectively (Table 6, entries 7 and 8). Similar trend was also obtained for the allylation of ethyl ferulate, with an *E* factor of 1.98 and 1.66, for the mg-scale and gram-scale respectively. Such results clearly indicate the advantages provided by ball-milling for the development of both efficient and waste-less allylation of lignin-derived phenolic synthons.

Table 6: Comparison of reaction conditions, yields and *E* factors for the allylation of vanillin

Entry	Author, year	Solvent	Reaction time (h)	Temperature (°C)	Yield (%)	<i>E</i> Factor ^a
1	Srikrishna et al, 2007 ⁴⁰	Acetone	5	Reflux	100	3.61
2	Hoffmann et al, 2014 ⁴¹	Ethanol	6	Reflux	98	3.34
3	Ayer et al, 1991 ¹⁴	DMF	68	RT	99	2.47
4 ^b	Chate et al, 2012 ⁴²	DMF	1	65	92	5.46
5	Kevwitch et al, 2012 ⁴³	DMF	24	70	96	5.51
6	This work, in solution	DMF	3	50	86	4.09
7 ^c	This work, ball-milling at mg-scale	DMF	3	Self-heating ^d	87	2.33
8 ^e	This work, ball-milling at g-scale	DMF	3	Self-heating	95	2.06

^a Work-up solvents were not taken into account. ^b Reaction run under ultrasonication. ^c 80 ZrO beads (32 g, d = 3 mm) in a 20 mL ZrO reactor. ^d Temperature reached a maximum of ~50 °C right after milling was stopped. ^e 2080 stainless steel beads (180 g, d = 3 mm) in a 250 mL stainless steel reactor

Conclusion

The present work demonstrates that mechanochemistry is a versatile, efficient and waste-less method for the allylation of bio-based phenols such as vanillin and ethyl ferulate. It was demonstrated in this study that mechanical parameters (*i.e.* bead choice, rotational speed, LAG) are as important as the chemical parameters (*i.e.* stoichiometry, reaction time). Both of them were examined and their effects on the conversion of vanillin to the allylated derivative were reported. For example the bead choice enabled to double the conversion. The method was also applied to the allylation of another bio-based phenol, ethyl ferulate. Their allylated corresponding compounds were isolated in high yields (vanillin: 87%, ethyl ferulate: 82%). Also, the method was scaled-up to the gram scale furnishing allylated vanillin and allylated ethyl ferulate with 95% and 92% yield, respectively. Finally, *E* factors were calculated and compared to results obtained in solution, indicating a clear superiority for the ball-milling approach over the solution-based procedure (2.06 vs 2.47).

Acknowledgements

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Experimental Section

• Chemicals

Vanillin (99%), allyl bromide (99%) and potassium carbonate (99%) were all purchased from Sigma Aldrich. Ethyl ferulate was synthesized following the already reported procedure.² Sodium hydroxide was purchased from Fischer scientific. Cyrene[®] was graciously provided by Circa group. All other solvents were obtained from VWR, Sigma Aldrich, Fischer Scientific and Alfa Aesar.

• Materials

Small scale mechanochemical reactions were performed in a Fritsch Pulverisette 7 premium line planetary ball mill with 20 mL inner-volume reactors containing 3, 5, or 10 mm diameter beads. Reactors and beads were made of zirconium oxide (noted ZrO) or stainless steel. Gram scale mechanochemical reactions were performed in a Retsch PM100 planetary ball mill with a 250 mL inner-volume reactor and 3 mm diameter beads, both made of stainless steel. Reactions were performed at room temperature, without control of the temperature by external heating or cooling. A slight increase in reactor temperature was observed, due at least in part to bead frictions during grinding.

• Chemical Analysis

UHPLC

UHPLC analyses were performed on an Agilent technologies 1220 Infinity LC using a Chromolith high resolution RP-18e 50-4.6 mm column and a linear gradient of 0 to 100% CH₃CN/0.1% TFA in H₂O/0.1% TFA over 3 min, detection at 214 nm. Flow rate: 3 mL/min.

LCMS

Mass spectra were obtained using a LCMS with ESI using a Water Alliance 2695 as LC, coupled to a Waters ZQ spectrometer with electrospray source, a simple quadrupole analyzer and a UV Waters 2489 detector. Analyses were carried out using a linear gradient of 0 to 100% CH₃CN/0.1% TFA in H₂O/0.1% TFA over 2.5 min, detection at 214 nm. Flow rate: 3 mL/min.

NMR

NMR analyses were performed at the "Plateforme d'Analyse et de Caractérisation" of the Pôle Chimie Balard, Université de Montpellier. ¹H NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer and chemical shifts are reported in ppm using DMSO-*d*₆ peak as an internal standard (2.50 ppm). Peaks are reported as s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet; coupling constant are reported in Hz. ¹³C NMR spectra were recorded on a Bruker Avance III HD 101 MHz spectrometer and are reported in ppm using DMSO-*d*₆ peak as an internal standard (39.52 ppm).

FTIR

IR spectra were recorded on an Agilent Cary 630 FTIR Spectrometer and are reported in cm⁻¹.

- **Methods and procedure**

General procedure for the mechanochemical allylation of vanillin at small scale

The total mass of reagents (vanillin, potassium carbonate and allyl bromide) was fixed at 400 mg for all small scale assays. Vanillin (1.0 eq) and potassium carbonate (1.0 eq) were added in the reactor. Beads were then added. The reactor was closed and stirred at the chosen rotational speed for 5 min to obtain a homogeneous mixture. If any, LAG solvent (80 μL , 0.2 $\mu\text{L}/\text{mg}$) was added followed by the addition of allyl bromide (1.1-1.5 eq) were then added. The reactor was closed and stirred for 1 to 3 cycles of 1 h separated by 30 min breaks. The reactor was opened and three reaction samples were collected at different locations in the reactor and solubilized in a mixture of aqueous 1M HCl and acetonitrile (50/50 v/v) for further analysis by HPLC. The reaction mixture inside the reactor was then solubilized with 5 mL of EtOAc, 5 mL of H₂O, and finally 10 mL of an aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was extracted twice with 10 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated vanillin as a pale yellow liquid.

Optimized conditions for the mechanochemical allylation at small scale

3-Methoxy-4-(2-propen-1-yloxy)benzaldehyde (allylated vanillin), CAS : 22280-95-1

Vanillin (129 mg, 0.85 mmol) and potassium carbonate (117.2 mg, 0.85 mmol, 1.0 eq) were added in the reactor. 370 ZrO beads of 3 mm diameter (32 g) were then added. The reactor was closed and stirred at 850 rpm for 5 min to obtain a homogeneous mixture. DMF (80 μL , 0.2 $\mu\text{L}/\text{mg}$) and allyl bromide (110 μL , 1.27 mmol, 1.5 eq) were then added. The reactor was closed and stirred at 850 rpm following 3 cycles of 1 h separated by intervals of 30 min. Three samples were collected at different locations in the reactor and solubilized in a mixture of aqueous 1M HCl and acetonitrile (50/50 v/v) for further analysis by HPLC where no trace of vanillin was detected. The reaction mixture inside the reactor was then solubilized with 5 mL of EtOAc, 5 mL of H₂O, and finally 10 mL of an aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was then extracted twice with 10 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated vanillin as a pale yellow liquid (143 mg, 87% yield).

¹H NMR (ppm, 600 MHz, DMSO-*d*₆) δ (ppm): 9.84 (s, 1H), 7.53 (d, *J* = 8.2, 1H), 7.40 (s, 1H), 7.17 (d, *J* = 8.3, 1H), 6.17 – 5.92 (m, 1H), 5.42 (d, *J* = 17.3, 1H), 5.29 (d, *J* = 10.5, 1H), 4.68 (d, *J* = 5.4, 2H), 3.84 (s, 3H).

¹³C NMR (ppm, 101 MHz, DMSO-*d*₆) δ (ppm): 191.3 (s), 153.0 (s), 149.3 (s), 133.0 (s), 129.8 (s), 125.9 (s), 118.2 (s), 112.4(s), 109.7 (s), 69.0 (s), 55.5 (s).

3-[3-Methoxy-4-(2-propen-1-yloxy)phenyl]-2-propenoic acid ethyl ester (allylated ethyl ferulate), CAS : 54744-76-2

Ethyl ferulate (164 mg, 0.74 mmol) and potassium carbonate (102 mg, 0.74 mmol, 1.0 eq) were added in the reactor. 370 ZrO beads of 3 mm diameter (32 g) were then added. The reactor was closed and stirred at 850 rpm for 5 min to obtain a homogeneous mixture. DMF (80 μL , 0.2 $\mu\text{L}/\text{mg}$) and allyl bromide (96.4 μL , 1.11 mmol, 1.5 eq) were then added. The reactor was closed and stirred at 850 rpm following 3 cycles of 1 h separated by intervals of 30 min. Three samples were collected at different locations in the reactor and solubilized in a mixture of aqueous 1M HCl and acetonitrile (50/50 v/v) for further analysis by HPLC where no trace of vanillin was detected. The reaction mixture inside the reactor was then solubilized with 5 mL of EtOAc, 5 mL of H₂O, and finally 10 mL of an

aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was then extracted twice with 10 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated ethyl ferulate as a pale orange powder (160 mg, 82% yield).

M.p.: 70-74 °C

¹H NMR (ppm, 600 MHz, DMSO-*d*₆) δ (ppm): 7.58 (d, *J* = 16.0 Hz, 1H), 7.37 (s, 1H), 7.21 (d, *J* = 8.4, 1H), 6.97 (d, *J* = 8.4, 1H), 6.56 (d, *J* = 15.9, 1H), 6.12 – 5.94 (m, 1H), 5.39 (d, *J* = 17.3, 1H), 5.26 (d, *J* = 10.5, 1H), 4.59 (d, *J* = 5.3, 2H), 4.17 (q, *J* = 7.1, 2H), 3.81 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (ppm, 101 MHz, DMSO-*d*₆) δ (ppm): 166.7 (s), 149.9 (s), 149.3 (s), 144.7 (s), 133.6 (s), 127.2 (s), 122.9 (s), 118.0 (s), 115.9 (s), 113.0 (s), 110.7 (s), 68.9 (s), 60.0 (s), 55.8 (s), 14.4 (s).

Reaction in a 250 mL stainless steel reactor in the PM100 planetary ball mill (scale-up assay)

3-Methoxy-4-(2-propen-1-yloxy)benzaldehyde (allylated vanillin), CAS : 22280-95-1

The total mass of reagents (vanillin, potassium carbonate and allyl bromide) was fixed at 5 g for all scale-up assays. Vanillin (1.61 g, 10.58 mmol) and potassium carbonate (1.46 g, 10.56 mmol, 1.0 eq) were added in the reactor. 2080 stainless steel beads of 3 mm diameter (180 g) were then added. The reactor was closed and stirred at 400 rpm for 5 min to obtain a homogeneous mixture. DMF (1.0 mL, 0.2 μL/mg) and allyl bromide (1.38 mL, 15.90 mmol, 1.5 eq) were then added. The whole reactor was stirred at 400 rpm following 3 cycles of 1 h separated by 1 h breaks. Three samples were collected at different locations in the reactor and solubilized in a mixture of aqueous 1M HCl and acetonitrile (50/50 v/v) for further analysis by HPLC. The reaction mixture inside the reactor was then solubilized with 50 mL of EtOAc, 50 mL of H₂O, and finally 50 mL of an aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was then extracted twice with 50 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated vanillin as a pale yellow liquid (1.94 g, 95% yield).

3-[3-Methoxy-4-(2-propen-1-yloxy)phenyl]-2-propenoic acid ethyl ester (allylated ethyl ferulate), CAS : 54744-76-2

The total mass of reagents (ethyl ferulate, potassium carbonate and allyl bromide) was fixed at 5 g for all scale-up assays. Ethyl ferulate (2.05 g, 9.23 mmol) and potassium carbonate (1.28 g, 9.26 mmol, 1.0 eq) were added in the reactor. 2080 Stainless steel beads of 3 mm diameter (180 g) were then added. The reactor was closed and stirred at 400 rpm for 5 min to obtain a homogeneous mixture. DMF (1.0 mL, 0.2 μL/mg) and allyl bromide (1.2 mL, 13.84 mmol, 1.5 eq) were then added. The whole reactor was stirred at 400 rpm following 3 cycles of 1 h separated by 1 h breaks. Three samples were collected at different locations in the reactor and solubilized in a mixture of aqueous 1M HCl and acetonitrile (50/50 v/v) for further analysis by HPLC. The reaction mixture inside the reactor was then solubilized with 50 mL of EtOAc, 50 mL of H₂O, and finally 50 mL of an aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was then extracted twice with 50 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated ethyl ferulate as a pale orange powder (2.24 g, 92% yield).

Allylation reaction in solution

Vanillin (1 g, 6.57 mmol) and potassium carbonate (0.908 g, 6.57 mmol, 1.0 eq) were added in a 10 mL round-bottom flask. A minimum quantity of DMF (2.6 mL) and allyl bromide (0.85 mL, 9.82 mmol,

1.5 eq) were added. The reaction was stirred for 3 h at 50 °C and then concentrated under vacuum. The crude was analyzed by ¹H NMR to determine the conversion. The reaction mixture inside the reactor was then solubilized with 20 mL of EtOAc, 20 mL of H₂O, and finally 20 mL of an aqueous solution of sodium hydroxide 1M was added. The crude solution was then transferred into a separatory funnel and the organic layer was recovered. The aqueous layer was then extracted twice with 20 mL of EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to afford allylated vanillin as a pale yellow liquid (1.09 g, 86% yield).

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