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Green metrics in mechanochemistry

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The development of new green methodologies and their broader adoption for promoting sustainable development in chemistry laboratories and industry play a significant role in society, due to the economic importance of chemistry and its widespread presence in everyday life. Therefore, a sustainable approach to chemistry contributes to the well-being of the worldwide population and complies with the United Nations Sustainable Development Goals (UN SDGs) and the European Green Deal. The review highlights how batch and continuous mechanochemical methods are an eco-friendly approach for organic synthesis, with a lower environmental footprint in most cases, compared to solution-based procedures. The assessment is objectively based on the use of green metrics (e.g., atom and real atom economy, *E*-factor, process mass intensity, material parameter recovery, Eco-scale, stoichiometric factor, etc.) and indicators (e.g. DOZN tool and life cycle assessment, LCA, studies) applied to organic transformations such as synthesis of the amide bond, carbamates, heterocycles, active pharmaceutical ingredients (APIs), porphyrins, porous organic polymers (POPs), metal- or acid-catalysed processes, multicomponent and condensation reactions, rearrangements, etc. The generalized absence of bulk solvents, the precise control over the stoichiometry (i.e., using agents in a stoichiometrically rather than in excess), and the more selective reactions enabling simplified work-up procedures are the distinctive factors, marking the superiority of mechanochemical processes over solution-based chemistry.

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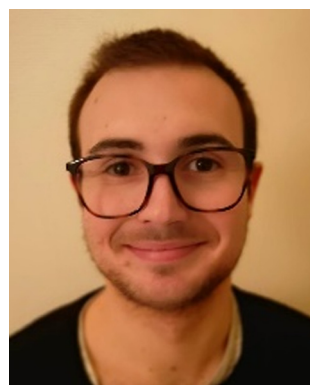
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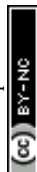
Nicolas FANTOZZI obtained his MSc in organic chemistry at Université Grenoble-Alpes. He completed his PhD in 2019 at Bordeaux University (France) on fluorescent supramolecular probes for neurotransmitters detection. Then, he moved to Université de Montpellier (France) as a postdoc position where he worked on the synthesis of active pharmaceutical ingredients by mechanochemistry. His research focuses on green and sustainable chemistry.



Jean-Noël Volle

Jean-Noël VOLLE obtained a Master of Science (DEA) at the University Lyon 1 in 1996, and he completed his PhD at the University of Lausanne in 2001 under the supervision of Prof. Manfred Schlosser. In 2002, he spent height months in the group of Martinus Gijs at Ecole Polytechnique Fédérale de Lausanne (EPFL), thus moved at National Graduate School of Chemistry of Montpellier (ENSCM) in 2003 as postdoctoral research fellow.

Thereafter, he occupied a temporary teacher-researcher (ATER) at ENSCM for an eleven-month period in 2004–2005, and in late 2005, he became “Maître de Conférences” in the same academic institution. Currently, his researches are developed in the group of Prof. David VIRIEUX, located in the Institute Charles Gerhardt of Montpellier (ICGM) in the Molecular Chemistry and materials department.



Introduction

Chemistry plays a significant role in society because of its economic importance and widespread presence in everyday life. Unfortunately, since it is everywhere, it is often overlooked. Products or processes taken for granted, such as drinking water, pasteurization, or medicines, were borne from advances in the Chemistry field – which is ultimately the science of change.

Over the years, chemistry has evolved towards increasing complexity and diversity, from molecules to materials, from appealing structures to incredibly complex industrial processes.

However, chemistry is not only science but also industry, many chemical processes have an industrial edge, and consequently, it has an extraordinary impact on economic and social life. Therefore, it is unsurprising that “chemistry” is often summoned to deal with industrial and societal issues. Several costs and availability of raw materials, energy, safety in the use of products, community protection, and the battle against pollution, *inter alia*.

In the last century, the intensification of human tasks has involved chemistry with some disastrous results such as damage to the protective ozone layer, global warming, air pollution, and the limitless exploitation of natural resources. To address them, various measures have been taken over the past 50 years to reduce the adverse effects the production of chemicals can have on the environment.

The recognition of the need to reduce the adverse effects of the chemical industry on the environment to safeguard future generations has been the driving force behind the development of green chemistry. It is not a separate branch of chemistry but an aspect that permeates every process design stage.

Green chemistry is “the science that promotes the discovery, design, and use of chemicals and processes to reduce or remove the use and production of hazardous substances,” which can ultimately be summarized in one word: sustainability. The concept of sustainability is strongly connected to circular economy (*i.e.*, an economic system based on reusing materials in subsequent productive cycles, reducing waste to a minimum). Another important aspect is the reduction of energy consumption. Have we gone far enough? Is it still possible to push chemistry toward an eco-friendlier future?

Applying the 12 principles of green chemistry – formulated by Anastas and Warner in 1998¹ – to the industrial sector may seem challenging since many parameters can be considered. For instance, comparing different processes to the same product or evaluating them during development is not straightforward unless a shared metric is used. This difficulty, has been the driving force for the rapid emergence of green metrics over the last few years.

Green metrics

Green chemistry metrics are a collection of indicators used to describe several aspects relating to the principles of green chemistry for a given chemical process.



Andrea Porcheddu

Andrea Porcheddu received a Chemistry degree with first-class honors from the University of Sassari (Italy) in 1995. He completed his PhD in 1999 under the supervision of Prof. Taddei and accomplished post-doctoral studies in 2000 at Louis Pasteur University (Strasbourg, Fr). In 2001, he moved back to Sassari University, where he was appointed Assistant Professor. In January 2015, he joined the Chemistry Department of the

University of Cagliari (Italy), where he currently has a permanent position as a Full Professor. His expertise includes preparing compounds with complex molecular architecture and finding more environmentally friendly alternatives for synthesis using advanced technologies, Borrowing Hydrogen and Transfer Hydrogenation strategies, microwaves, blue-LEDs, IR-Irradiation. His main scientific interest currently covers mechanochemistry, focusing on value-added compounds for the industry and Active Pharmaceutical Ingredients. Prof. Porcheddu is the author or co-author of more than 125 scientific publications in refereed international journals (H index, Scopus = 39).



David Virieux

David Virieux completed his PhD in 1998 at the University of Montpellier, supervised by Prof. Henri-Jean Cristau. His doctoral research centered on polyphosphoryl compounds for selectively extracting actinides. He went to the USA at Rhône-Poulenc Ag Co to contribute to the development of small molecules potentially effective as insecticides. In late 1999, he rejoined Prof. Cristau's team at the ENSCM (Montpellier) and was later promoted to a full

professorship in 2007. His research, conducted at the Institute Charles Gerhardt of Montpellier, revolves around specific facets of organophosphorus chemistry. These encompass a spectrum of applications within life sciences, including agrochemical and medicinal chemistry, and the development of new synthetic methodologies. Notably, his research places emphasis on organocatalysis, multicomponent reactions, and enantioselective synthesis. In 2014, he played a key role in founding Phost'In Therapeutics, an innovative player in the field of Glyco-Immuno-Oncology, currently advancing a drug candidate through phase 1 clinical trials.



These metrics allow measuring changes in a chemical process's performance by quantifying its overall efficiency or environmental impact. Notably, and directly related to mechanochemistry, central to this review, most efforts to minimize the environmental footprint of a chemical process have highlighted the need for using safer, less toxic, and more benign solvents or eliminating solvents. Also, reducing the number and quantities of reagents and auxiliaries is an effective way to minimize environmental impact.

However, the final evaluation heavily depends on a series of pressing questions: how do we define "greenness"? What are the appropriate indicators to measure the effectiveness of a chemical transformation while minimizing environmental impact? How to reduce waste production and/or energy consumption in a chemical process?²

These metrics generally encourage the development of new methodologies and facilitate the broader adoption of green chemistry technologies for promoting sustainable development in laboratories and industry. Table 1 reports the green chemistry metrics used to assess the greenness of mechanochemical processes.

One of the most commonly used metrics is atom economy (AE) (Table 1, entry 1), also named atom efficiency, and identified as principle no. 2 among the 12 principles of green chemistry.¹ Introduced by Barry Trost in 1991, AE is directly related to the search for synthetic efficiency, where the

maximum number of atoms present in the reactants should be incorporated into the reaction products.³ On a scale between 0 and 100, the higher the value. The better is the AE of the process.

AE is a metric that can be calculated '*a priori*' (*i.e.*, before performing experiments). Therefore, when several methods are available to access the same target product, the calculation of the AE for each synthesis will drive the appropriate choice towards selecting the process displaying the highest AE value.

Related to AE and to take into account the reaction's yield and stoichiometry, Real Atom Economy (RAE) – Table 1, entry 2 – can also be calculated:⁴ to RAE should be close to 100%.

In contrast to AE, the environmental factor (*E*-factor) – Table 1, entry 3 – is an '*a posteriori*' metric that can only be calculated once the experiment has been conducted. This parameter focuses on the waste(s) generated during a reaction,⁵ and it takes into account reagents, solvent losses throughout the synthesis, and work-up and purification steps, as well as all the additives used during the process (*e.g.*, drying agents, silica gel, *etc.*) with respect to the formed product mass (which takes into account also the yield). While water is generally excluded from this calculation, energy losses should be usually included, which might not be trivial to be measured and calculated. Also, in its basic definition, fuel use has to be included. On a scale between 0 and 100, the *E*-factor has to be as close as possible to 0 to account for an environmentally-friendly process.



Felipe García

Felipe García is originally from the coastal town of Gijón (Spain) and gained both his BSc and MSc degrees at Oviedo University. In 2001, he moved to the University of Cambridge to carry out his graduate studies as a Cambridge European Trust and Newton Trust Scholar under the supervision of Prof. D. S. Wright. He then gained a Junior Research Fellowship at Wolfson College (2005) and was appointed College Lecturer in Inorganic

Chemistry at Newnham and Trinity Colleges (2006). In March 2011, he moved to Nanyang Technological University as an Assistant Professor. In 2022, he returned to the University of Oviedo as a Margarita Salas Senior researcher (funded by FICYT). In 2024, he will transition to Monash University (Australia) to advance his research career. Felipe has published over 100 papers on Main Group Chemistry and maintains a strong interest in the synthesis of novel compounds for industrial and biological applications.



Evelina Colacino

Evelina Colacino received her double PhD (with European Label) in 2002 at the University of Montpellier II (France) and at the University of Calabria (Italy). She was Research Fellow at the Catholic University of Louvain (Belgium, 2003), Scientist at Sigma-Tau Pharmaceuticals (Italy, 2004) and Post-Doctoral Fellow at the University of Montpellier II (France, until 2007). Associate Professor (since 2013) of Organic and Green

Chemistry, she develops eco-friendly methodologies by mechanochemistry, focusing on the preparation of Active Pharmaceutical Ingredients (medicinal mechanochemistry). She promotes sustainability in Higher Education by integrating the fundamentals and the practice of green chemistry and mechanochemistry in organic chemistry courses and teaching laboratories. Member of the Advisory Board of the Green Chemistry Commitment and the International Mechanochemical Association, she chairs the European Programmes COST Action CA18112 'Mechanochemistry for Sustainable Industry (2019–2023) and Horizon Project IMPACTIVE (Innovative Mechanochemical Processes to synthesise green ACTIVE pharmaceutical ingredients, 2022–2026).



Table 1 Green chemistry metrics applied to mechanochemical synthesis

| Metric | Abbreviation | Formula | Optimal value | Ref. |
|-----------------------------|------------------|---|---------------|---------|
| Atom economy | AE | $\frac{\text{Formula weight product (kg kmol}^{-1}\text{)}}{\text{Formula weight of all reactants used in reaction (kg kmol}^{-1}\text{)}} \times 100$ | 100% | 3 |
| Real atom economy | RAE | $\frac{\text{Actual weight of desired product (kg)}}{\text{Total weight of all raw materials in process (kg)}}$ | 1 | 4 |
| Environmental factor | <i>E</i> -Factor | $\frac{\text{Mass of wastes (kg)}}{\text{Mass of the product of interest (kg)}}$ | 0 | 5 |
| Process mass intensity | PMI | $\frac{\text{Total mass used in the process (kg)}}{\text{Mass of product (kg)}}$ | 1 | 6 |
| Reaction mass efficiency | RME | $\frac{\text{Mass of product (kg)}}{\text{Total mass of reactants used in reaction (kg)}} \times 100$ | 100% | 7 |
| Material recovery parameter | MRP | $\frac{\text{Total mass of reaction and postreaction solvents + mass of catalyst recovered (kg)}}{\text{Total mass of reaction and postreaction solvents + mass of catalysts used (kg)}}$ $0 < \text{MRP} < 1$ | 1 | 8 and 9 |
| Stoichiometric factor | SF | $1 + \frac{\text{Total mass of excess reagents (kg)}}{\text{Total mass of stoichiometric reagents (kg)}}$ | 1 | 10 |
| Mass intensity | MI | $\frac{\text{Total mass of input materials excluded water (kg)}}{\text{Mass of product (kg)}}$ | 1 | 7 |
| Mass productivity | MP | $\frac{\text{Mass of product (kg)}}{\text{Total mass input materials excluded water (kg)}} \times 100$ | 100% | 11 |
| Molar efficiency | Mol. E | $\frac{\text{Moles of product}}{\text{Moles of reactants + Moles of catalysts + Moles of solvents + Moles of additives}}$ | 1 | 12 |

Another mass-based environmental process waste metric is process mass intensity (PMI), Table 1, entry 4, defined as the total mass in kg of raw materials (reagents, solvents, *etc.*) used (input of materials) to produce 1 kg of the product (output of the synthesis).⁶ The PMI is a metric used at the forefront of a process, and it can also be readily calculated from the *E*-factor (PMI = *E*-factor + 1). Therefore, the ideal value of PMI corresponds to 1. Therefore, when comparing two processes, the one with the lowest PMI will be the greenest.

The reaction mass efficiency (RME) – Table 1, entry 5 – is the percentage mass of the target product expressed in kg with respect to the mass of all reactants. Both AE and chemical yield are considered in the calculation.⁷ The higher the RME score, the more environmentally friendly the process will be.

As part of RME, the material recovery parameter (MRP), which considers solvent from reaction and extraction, indicates the possibility of reusing solvents. It should be between 0 and 1, the best value being 1.¹⁰ Stoichiometric factor (SF) allows to consider the excess reagents used throughout a process.⁷ The SF value of 1 corresponds to stoichiometric reactions (*i.e.*, carried out with no excess reagents), whereas an SF > 1 indicates stoichiometric excess used.

Related to chemical production efficiency, Constable and Curzons developed the mass intensity (MI) and mass productivity (MP) parameters.^{7,11} Mass intensity and mass productivity are related to PMI and RME, respectively, excluding water. Therefore, for these indicators, the MI should be close to 1, and MP should be close to 100% efficiency.

In the same way, molar efficiency should be close to 100% and can be calculated following this equation.¹²

In 2006, Van Aken introduced the Eco-scale,¹³ a qualitative metric evaluating the quality of an organic transformation,

taking into account yield, cost of the reaction components, safety, and conditions of reaction (temperature, duration), and it includes work-up and purification to give a score between 0 and 100 where 100 is the best score.

In addition to the 12 principles for greener chemistry and the parameters mentioned above, generic evaluation approaches such as life cycle assessment (LCA)^{14,15} or more chemically specific tools like DOZN 2.0¹⁶ can be used for a quantitative evaluation of the environmental impact of chemical processes.

The DOZN 2.0 tool is a free web-based software able to quantitatively assess the greenness of a process or a product against the 12 principles of green chemistry – which are only qualitative. Therefore, each of the 12 green chemistry principles is scored by the DOZN 2.0 tool, taking into account data input from the reaction and process conditions and extracting data for reactants and chemicals from the globally harmonized system (GHS) and safety data sheet (SDS) information. Then, the 12 principles of green chemistry are divided into three subgroups: improved resource use (group 1), increased energy efficiency (group 2) and reduced human and environmental hazards (group 3). The software delivers an ‘aggregate score’ averaging and normalizing the scores obtained for each subgroup, ranging from 0 to 100. Generally speaking, an aggregate score below 1 indicates a green process. However, the closer to zero is the aggregate score, the greener the process will be. The DOZN 2.0 tool is a harmonized approach to greenness assessment, allowing to compare the greenness of any product or process by using the values obtained for their respective aggregate scores. Both these methods (LCA and DOZN) are more complex, considering additional parameters, such as global warming and ecotoxicity, for which advanced software is also required for the complete assessment.



Mechanochemical methods

Mechanochemical processes have been acknowledged by the International Union of Pure and Applied Chemistry (IUPAC) among the “top ten emerging technologies in chemistry,”¹⁷ responding to the growing need for sustainable reaction conditions and clean processes.

The reactions are carried out by grinding reagents with ball-mill devices such as vibrating (VBM), planetary (PBM), SPEX mills, Tumbler ball-mill or single-screw device (SSD) using mechanical forces to enable chemical reactivity (Fig. 1).¹⁸

The use of mortar and pestle is a traditional and widely used tool for manual grinding and milling processes (*e.g.*, chemistry, pharmacy, culinary arts, *etc.*). Mechanochemical reactions conducted with a mortar and pestle rely on the mechanical energy generated by manual grinding. The solid reagents are placed in the mortar, and the pestle is used to apply pressure and friction, causing the particles to collide and react. This grinding process facilitates solid-state reactions without additional solvents or heating.

The mortar and pestle technique offers several advantages. First, it allows precise control over the grinding process, enabling researchers to tailor the particle size and distribution. Using a mortar and pestle can also be advantageous in small-scale reactions or when specific reaction conditions are required.

However, it's important to note that the manual nature of the process can be time-consuming and labour-intensive, making it less suitable for large-scale or high-throughput applications. In such cases, automated ball mills are often

preferred for their efficiency and ability to handle larger quantities.

Ball mills are versatile tools that have been used for wide range of milling applications. There are several types of mills that have been commonly used to perform mechanochemical reactions. Vibratory mills typically contain a jar that is shaken from side to side at high frequency causing the grinding media and reagents to impact and collide (Fig. 1a). This type of mill has been commonly used for the synthesis of organic and inorganic compounds and the mechanical alloying of materials.

The planetary ball mill action consists of one or more grinding jars that rotate around their axis while also rotating around a central axis (Fig. 1b). This dual rotation creates effective mixing and grinding of the reactants. In contrast to vibratory mills, which can only perform reactions at the multigram scale, these devices can work on scales of hundreds of grams.

The SPEX ball mill (Fig. 1c) operates similarly to the vibratory mill, with the vial and the grinding balls being shaken or agitated in a figure-of-eight motion. The mechanical action enables rapid and efficient grinding of various materials, including metals, ceramics, minerals, and polymers. This tool has been commonly used for mechanical alloying (blending elemental powders to form alloys), sample pulverization, and material synthesis.

Overall, ball mills are a versatile and powerful tool for mechanical milling and grinding, providing researchers with an efficient means to process and manipulate materials for various scientific and industrial purposes.

Twin-screw extruders are widely used in various industries, including polymer processing, food processing, pharmaceuticals, and chemical manufacturing (Fig. 1d and e). They are versatile tools that offer precise control over the mixing, compounding, and extrusion of materials. Twin-screw extruders consist of two intermeshing screws housed in a barrel. The screws rotate in the same direction but have opposite helical orientations. This design enables the screws to generate a strong forward conveying action while creating intense shear and mixing forces, which promotes intense mixing and thorough dispersion of additives (if used). In addition, the material can be forced through a die at the end of the barrel to shape and form the output materials.

Twin-screw extruders offer numerous advantages, including precise control over processing parameters, high productivity, efficient mixing and compounding, and the ability to process a wide range of materials. As a result, they are widely used in manufacturing plastic products, food processing (such as extruded snacks), pharmaceutical formulations, and various chemical processes where precise control over mixing, compounding, and extrusion is essential.

Finally, a drill press with a counter-clockwise rotating drill bit was recently used to demonstrate that excellent mechanochemistry can be achieved with a tight budget (Fig. 1f).

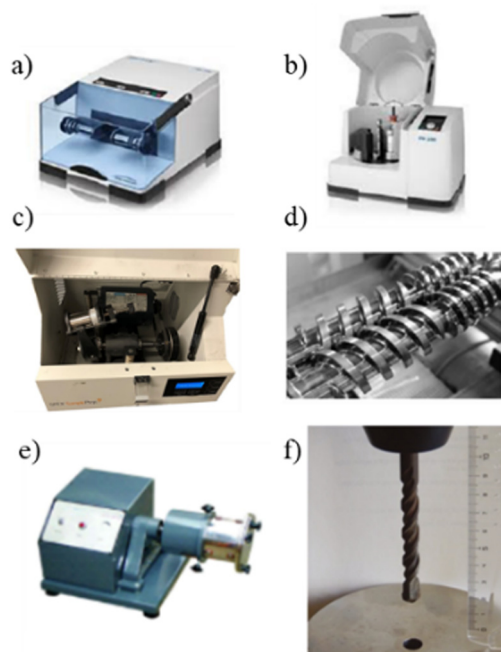


Fig. 1 Milling devices: (a) vibrational ball-mill, (b) planetary ball-mill, (c) SPEX 8000 shaker mill, (d) twin-screw Extrusion, (e) tumbler ball-mill, (f) single-screw device. Adapted with permission of the American Chemical Society from ref. 19–21.

Controlling mechanochemical reactivity

There are several variables that have to be fine-tuned during any mechanochemical process (Fig. 2). In terms of batch



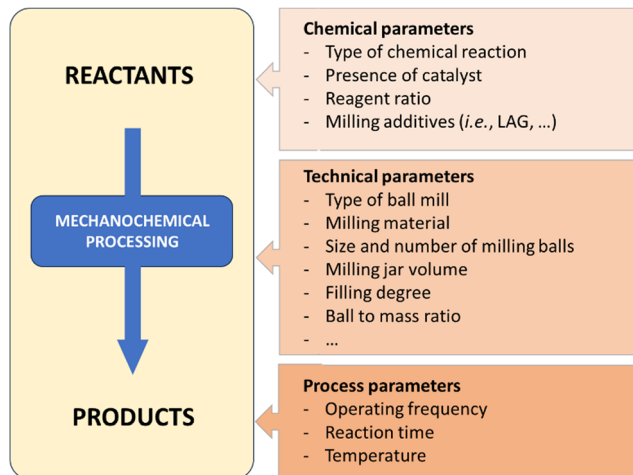


Fig. 2 Selected parameters to be taken into consideration during a ball-mill mechanochemical process.²²

processes, milling media (*i.e.*, jars and balls), can be found in a variety of materials (stainless-steel, tungsten carbide, zirconia, Teflon, *etc.*). Each material has a specific density and hardness, which is a straightforward way to control the energy input – which ultimately influences chemical reactivity. Chemical resistance also differs between materials and will affect the potential leaching of metal ions (*e.g.*, Fe, Co, *etc.*) or metal contamination resulting from prolonged milling. Additional ways to control the reaction is by changing the frequency or rotation speed of the mills, filling degree, number and size of balls, jar volume and geometry, *etc.*

Any chemical reactor requires ideal operating temperature to accommodate the nature (*i.e.*, endothermic or exothermic) of the transformation taking place. Similar to standard batch solution-based reactors, batch mechanochemical vessel have an unfavourable surface area-to-volume ratio making heat removal challenging as the size of the reactor and/or the exothermicity of the reaction increases, which restricts the application of batch or semi-batch mechanochemical reactors to either laboratory-scale or transformations that are not overly exothermic and/or particularly heat sensitive. However, this limitation has been partially circumvented by developing custom-made temperature-controlled reactors and commercial equipment with temperature control for batch and continuous processes. This addresses and/or mitigates the challenges mentioned above with traditional mechanochemical techniques.²³

Related to temperature effects, and despite most mechanochemical reactions reported in the literature relying on mechanical energy to initiate or promote chemical transformation without needing external heating at room temperature. Some mechanochemical reactions require the input of thermal energy for optimal results. Heating can provide to initiate the reaction with mechanochemical activation is not enough to surpass the activation energy barrier and proceed at a reasonable rate. In addition, applying heat can improve reaction kinetics, resulting in better yields and faster reaction rates.^{24–32}

Moreover, the combination of heating and mechanical forces can cause solid-state transformations (*e.g.*, phase transitions, structural changes, *etc.*), which can aid in achieving specific transformations or activating desired reaction pathways. Also, precise control of the reaction temperature implies better manipulation of the reaction conditions, which can result in optimised reaction rates, selectivities, and product yields.³³

Mechanochemical synthesis can also be controlled by incorporating liquid additives into mechanochemical reactions (*i.e.*, liquid assisted grinding, LAG). They act as lubricants, enhancing mixing and reaction kinetics. In this regard, it is important to note that the amount of liquids used is a very small quantity relative to the amounts used in their solution-based counterparts, hence its addition does not constitute as bulk solvent use. LAG reactions are characterised by an empiric parameter called η (*eta*) (expressed in μL per mg of solid reactants) is used to describe, and normalise, the amount of liquid additive added. The formal definition allows to distinguish quantitatively among neat grinding, LAG conditions, slurry and reactions in ‘solution’. In particular, for $\eta = 0 \mu\text{L mg}^{-1}$ the reaction occurs by neat grinding. For η values comprised between 0 and $1 \mu\text{L mg}^{-1}$, the reaction occurs under LAG, if η values are between 1 and $6 \mu\text{L mg}^{-1}$ the reaction is considered a slurry, while for η is above $6 \mu\text{L mg}^{-1}$, no mechanochemical effect can be evoked and the reaction is considered to occur in solution.³⁴

In contrast to LAG, often, to optimise mechanochemical reactions, it is necessary to ensure that all reagents form a solid mixture, since the presence of liquid reagents can negatively affect the rheology of the mixture resulting in a paste-like consistency that hinders the energy transfer during the grinding process – thus rendering the process ineffective.³⁵ In addition, extensive research has demonstrated that the mixture’s rheology can significantly impact the kinetics of the chemical reaction. Factors such as particle size, surface area, and the presence of additives (liquid or solid) affect the texture of the mixture, consequently affecting the reaction kinetics (*i.e.*, different reaction rates and pathways).³⁶

Understanding and controlling the reaction mixture’s texture is crucial for achieving the desired reaction rates and outcomes in mechanochemistry. Therefore, to improve the rheology and enhance mechanical action during impacts, it is common practice to include solid additives, such as silica and sodium sulfate, in the mixture. They are typically affordable solid green components that do not actively participate in the chemical reaction.

Advantages of mechanochemistry

In addition to the solvent-free, or virtually solvent-free, nature of mechanochemical reactions, which intrinsically reduces the process’s environmental footprint. Mechanochemistry has shown other advantages – from higher yields and selectivity to access new compounds and “impossible molecules” – that have made it increasingly popular among synthetic chemists (Fig. 3).³⁷ Moreover, the possibility of employing traditionally poorly insoluble reagents provides mechanochemical reactions an edge over conventional solution-based methods in a wide



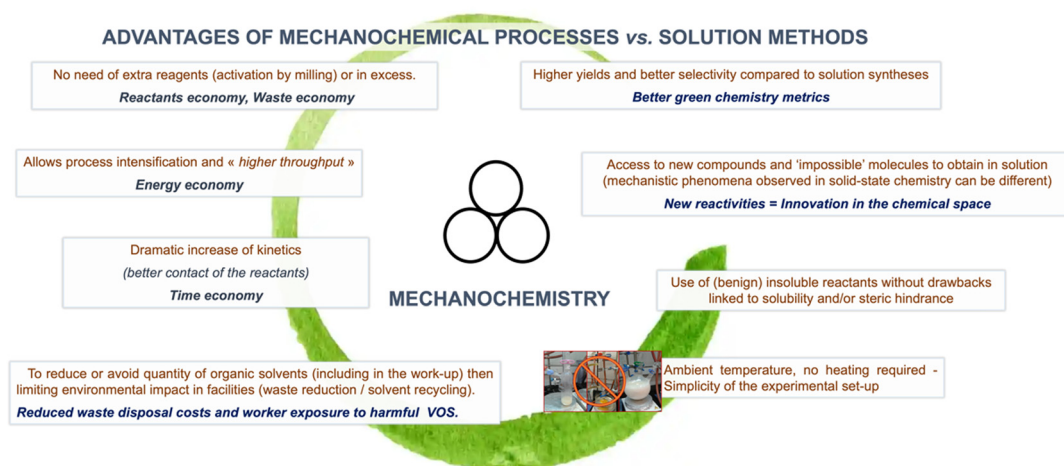


Fig. 3 Advantages of mechanochemistry reported in the literature. Hanusa's formalism to represent reactions activated by mechanochemistry was used.³⁸

range of technologically relevant fields (*i.e.*, perovskite synthesis, polyaromatics, *etc.*).

Another aspect that is particularly relevant to this review, in addition to the elimination of bulk solvents, is that in contrast to traditional solution-based chemistry, where reactions often require excess reagents to achieve full conversion. Mechanochemical reactions can often be performed with a equimolar amount of reagents. This can be attributed to the efficient mixing of reagents caused by the milling action, which enhances reagent reactivity, allowing for complete utilization of the starting materials. This helps minimise the need for excess reagents, reducing waste generation, simplifying product purification, and enhancing atom economy.

Mechanochemistry and green chemistry

While the ball-milling devices mentioned above are limited to batch syntheses, twin-screw extrusion (TSE) is used as a larger-scale, continuous-flow mechanochemical method.^{39,40} However, even if mechanochemistry complies with several green chemistry principles, the quantitative assessment of the greenness of mechanochemical reactions and processes in comparison with solution based-approaches or other similar mechanochemical syntheses is possible only by a systematic calculation of green metrics.^{41–43}

Even though it is well accepted that mechanochemistry fits the 'green toolbox', green metrics calculations are not yet systematically undertaken for both batch and in continuous processes.

This review wishes to highlight this aspect, moving away from subjective assessments of the environmental footprint of mechanochemical reactions. Therefore, the reviewed articles provide a quantitative assessment and compare the environmental footprint of mechanochemical reactions in a quantitative way, which allows direct comparison with other synthetic methods. Even though several mass-based environmental process waste metrics exist, this review mentions only those applied in mechanochemical synthesis.

We would like to highlight at this stage that despite many mechanochemical reports claiming to be environmentally better than their solution-based counterparts, they could not be included since they do not provide the experimental details required for the calculation of green metrics. Moreover, since we only focus on the reports comprising green metric calculations many relevant examples from a wide range of areas (organic synthesis,^{44–48} catalysis,^{49,50} APIs,⁵¹ organometallic complexes,^{38,52} main group compounds,⁵³ metal organic frameworks,⁵⁴ co-crystals,⁵⁵ *etc.*) fall outside of scope of this review.

Green metrics used in mechanochemical reactions

Synthesis of amide bond: access to amides, peptides, and carbamates

Amide is one of the most common functional groups (FG) encountered in nature as it plays a critical role in the structure and properties of the "molecules of life," such as peptides and proteins. This moiety is the most frequently encountered FG in bioactive molecules developed for pharmaceutical and agrochemical applications. A survey published in 2006 highlighted that throughout the synthesis of 128 drug candidates, the occurrence of *N*-acylation reactions to produce amide bonds was found to be 66% (*i.e.*, 84/124).⁵⁶ In 1999, an analysis of the comprehensive medicinal chemistry (CMC) database based on drug-like compounds underlined that the carboxamide functional group represented up to 27% of the bioactive molecules referenced.⁵⁷ Amidation (*N*-acylation) represents a critical reaction in medicinal chemistry.⁵⁸ It was consequently selected in the top green chemistry research priorities by the American Chemical Society Green Chemistry Pharmaceutical Roundtable (ACS GCIPR) in 2007 and 2018.^{59–61}

Classically, amide bond formation generally requires the activation of the carboxylic acid group by coupling reagents.⁶²



Nevertheless, numerous non-classical methods were also developed.⁶³ Most of these methods are solution-based, have low atom economy and present safety issues due to solvents and toxic reagents. This section reports the environmental benefits of amide-bond formation provided by mechanochemical processes.

In peptide chemistry, temporary protection of the α -amino function is generally required to enhance selectivity. *tert*-Butyloxycarbonyl (Boc), benzyl-oxycarbonyl (Cbz), 9-fluorenylmethyl-oxycarbonyl (Fmoc) are typical protecting groups; however, their use often requires the use of large quantities of toxic solvents (DMF, DCM, *etc.*). To solve this issue, Colacino *et al.* developed a solvent-free one-pot, two-step procedure for amino acid *N*-protection using a PBM (Scheme 1).⁶⁴ In this approach, equimolar amounts of amino acids **1** are first transformed into the corresponding metal carboxylate **2** ($M = Na, K$) by milling with potassium carbonate (1 equiv.) in the presence of sodium chloride as a milling additive to act as a grinding agent and avoid paste-like mixture. The preparation of protected amino acids with Boc and Cbz groups was conducted in the PBM employing stainless steel or tungsten carbide (only for the Fmoc group) jars (12 mL), containing 24 balls (5 mm \varnothing) of the same material as the jar, and the mixture was ground at 500 rpm for 2 h. Thereafter, grafting of the protecting groups was accomplished by applying continuous (500 rpm) or cycled

milling (300 rpm, three cycles of 1 h, 10 min intervals between each cycle), inversed rotation (reversal of regular rotation direction) of the deprotonated amino acids (1 equiv.) with the desired protecting reagent (1 equiv.) and NaCl for 2 to 3 h. NaCl was used as grinding auxiliary to keep the mixture as a floating powder, avoiding the formation of a sticky paste after the first milling step, making otherwise useless any milling effect.

Following a simplified work-up, pure *N*-protected amino acids **3-4** were isolated by precipitation in water. For Fmoc protecting group, several reaction conditions were employed for preparation of short series of amino acids **5**. When (L)-Fmoc-Phe-OH amino acid **1** was used as reagent, the same stainless-steel jars were used compared to Boc and Cbz groups, and the reactions afforded after 2 h at 650 rpm (second step) and work-up the protected amino acid **5** in 87% yield. Adapting material and reaction conditions, five other amino acids were also obtained in 25–95% yields. These Fmoc amino acids were produced using a stainless steel (12 mL or 20 mL) or a tungsten carbide (50 mL) jar, containing 24 to 80 balls, and grinding at 500 rpm for first step (2 h) and 500, 650 or 750 rpm (one case in cycled mode) for second step (2–3 h).

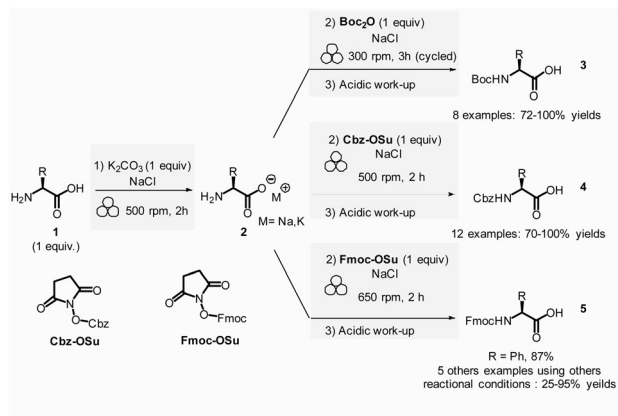
In this case, the reaction outcome depended on the milling rotation speed. In particular, the yield was doubled at higher milling speed (650 rpm) and the Fmoc amino acids were obtained with full selectivity (*i.e.*, no formation dibenzofulvene by-product was observed, even in traces, despite the presence of a base into the reaction medium). Moreover, the reaction outcome (yields and selectivity) was not influenced by the nature of the milling media used, the same results being obtained materials having different density and hardness (*e.g.*, stainless-steel *vs.* tungsten carbide) were used.

This example paved also the way towards the unprecedented introduction of green chemistry metrics applied to a mechanochemical syntheses, in order to compare their greenness *versus* the corresponding solution-based methods.

The environmental factor (*E*-factor) determined for the *N*-protected amino acids Cbz-Phe-OH, and Fmoc-Phe-OH were lower than the corresponding solution-based reactions (Scheme 1). In contrast, the *E*-factor score for Boc-Phe-OH, was better in solution for solvent-based Boc-protection due to the liquid-liquid extraction work-up required for mechanochemical synthesis (265 for mechanochemistry *vs.* 62 in solution).

Aav *et al.* described amidations using uronium-type coupling reagents (COMU and TCFH) *via* mechanochemical activation (Scheme 2).⁶⁵ Typically, the coupling reactions of carboxylic acids derivatives **6** with protected amino acids, *N*-Boc-piperazine or aniline derivatives **7** were performed in a ZrO₂-coated jar (14 mL) containing three ZrO₂ balls (7 mm \varnothing). The reaction needed a slight excess of COMU (1.1 equiv.) or TCFH reagents (1.1–1.3 equiv.), a large significant excess quantity of base (K₂HPO₄, 3 equiv.), under liquid-assisted grinding (LAG)³⁴ conditions, using a small amount of not harmful ethyl acetate ($\eta = 0.19 \mu\text{L mg}^{-1}$). This procedure gave a ranging of 70–96% yields in amides **8**.

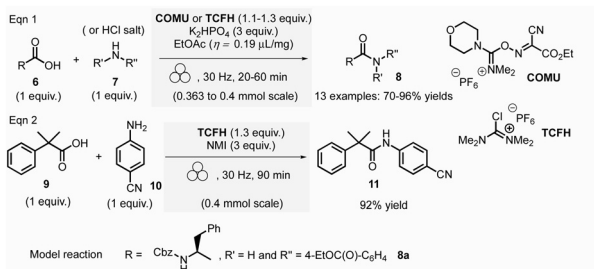
Reaction times ranged from 20–60 min at 30 Hz employing a VBM. Notably, the coupling of hindered carboxylic acid **9** with



| Green metrics | | | | |
|--|------------------|----------|-----------------|------|
| Compound | <i>E</i> -factor | PMI | | |
| Mechanochemical route | | | | |
| Boc-Phe-OH | 265 | 266 | | |
| Cbz-Phe-OH | 8 | 9 | | |
| Fmoc-Phe-OH | 6 | 7 | | |
| Solution-based route ^[24c] | | | | |
| Boc-Phe-OH | 62 | 63 | | |
| Cbz-Phe-OH | 20 | 21 | | |
| Fmoc-Phe-OH | 288 | 289 | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | size |
| PBM | SS or WC | 12 mL | 24 | 5 mm |

Scheme 1 Amino acids protection with Boc, Cbz, and Fmoc groups by mechanochemistry.





Green metrics

| Compound | RME (%) | PMI | | |
|--------------------------------------|------------------|----------|-----------------|------|
| Mechanochemical route | | | | |
| 8 (with COMU) | 46 | 196.3 | | |
| 8 (with TCFH) | 53 | 203.7 | | |
| Solution-based route | | | | |
| 8 (with COMU) | 35 | 1464.7 | | |
| 8 (with TCFH) | NA | NA | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | size |
| VBM | ZrO ₂ | 14 mL | 3 | 7 mm |

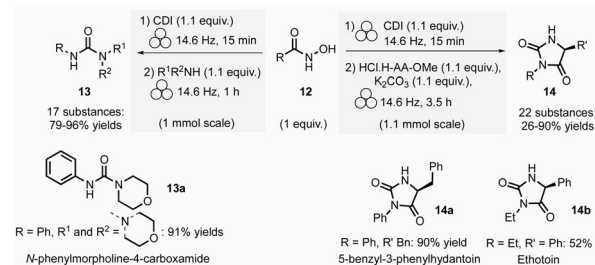
Scheme 2 Mechanical synthesis of amides using uronium-type reagents.

poor nucleophilic amine **10** in the presence of TCFH/1-methylimidazole (NMI) was also efficient; however, it required a longer milling time (90 min at 30 Hz). The TCFH/NMI system under LAG conditions (EtOAc) was successfully applied for the polyamidation of the six carboxylic acid functions of biotin[6]juril with 80% of yield and 99% of purity (detected by HPLC).

Better yields were obtained with both COMU/ K_2HPO_4 and TCFH/ K_2HPO_4 under mechanochemical activation for the model reaction (Scheme 2, eqn (1)) (86–92% vs. 70–96%).⁶⁶ The isolation of the reaction products was readily performed by filtration and water wash for the mechanochemical process, whereas column chromatography was required in conventional solution approaches. Green metrics such as reaction mass efficiency (RME) and product mass intensity (PMI) showed unambiguously that mechanochemical procedures outperformed solution-based method. By mechanochemistry, RME was 46% and 53%, respectively, for COMU and TCFH activating agents, compared to 35% for a solution-based procedure using COMU. However, RME was not calculated for the corresponding solution-based process involving TCFH. PMI (COMU/ K_2HPO_4) was also substantially lowered by over 7-fold (196.3 vs. 1464.7 in solution), underlining that mechanochemical reaction produced less waste.

The only notable drawback concerning this reaction is linked to the reproductive toxicity of tetramethylurea produced as a byproduct of TCFH-activated reaction.

Non-symmetrical ureas and hydantoin (including pharmaceutical ingredient ethotoin)⁶⁷ were mechanochemically synthesized in 2019 by Colacino, Porcheddu, *et al.* (Scheme 3).^{68,69} The one-pot/two-step sequence, employs hydroxamic acid **12** as starting material. First, activation of hydroxamic acid by



Green metrics

| Compound | E-factor | | | |
|--------------------------------------|------------------|----------|-----------------|------|
| Mechanochemical route | | | | |
| 13a | 1.21 | | | |
| 14a | 1.91 | | | |
| 14b | 4.84 | | | |
| Solution-based route | | | | |
| 13a | 103 | | | |
| 14a | 3.05 | | | |
| 14b | 193 | | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | size |
| SPEX | ZrO ₂ | 45 mL | 40 | 5 mm |

Scheme 3 Urea and hydantoin mechanochemical synthesis through Lossen rearrangement.

1,1-carbonyldiimidazole (1.1 mmol), followed by a subsequent Lossen transposition afforded *in situ* the reactive isocyanate. Reactions were performed using a SPEX shaker mill. Milling hydroxamic acid (1.0 mmol) and CDI (1.1 mmol) into a ZrO₂ jar (45 mL) containing 40 ZrO₂ balls (5 mm \varnothing) at 14.6 Hz for 15 min. In a second step, amine (1.1 mmol) was added, and the reaction mixture was ground for one more hour. In contrast to solution-based approaches, the reaction did not require the presence of a base to occur. Finally, the trituration of the resulting solid with a 15% w/w citric acid aqueous solution, followed by filtration and drying under vacuum with P₂O₅, produced the pure ureas **13**. Seventeen ureas **13** were obtained using this methodology in yields ranging from 79% to 96%. When amino esters were used instead of amines in the second step, hydantoin species were obtained in 26% to 90% yields after 3.5 h of milling.

This mechanochemical procedure avoided using toxic isocyanates, alkyl halides or dialkylsulfates as reagents and DMF or DMAc as solvents providing a safer and greener approach to these species. It is worth noticing that this method allowed to selectively prepare: (i) *N*-methylated hydantoin not accessible by conventional solvent-based procedures due to safety reasons (*e.g.*, use of flammable and harmful methylisocyanate), (ii) *N*-phenyl substituted hydantoin, which are not accessible by other mechanochemical procedures⁷⁰ and (iii) long chain *N*-alkylated hydantoin directly from hydroxamic acids obtained directly from commercially available reactants (*e.g.*, carboxylic acids),⁷¹ which bypasses the steps required to obtain non commercially available isocyanates. Consequently, the *E*-factor was better than traditional solution-based procedures.^{72–74}



For instance, for *N*-phenylmorpholine-4-carboxamide **13a**, the *E*-factor (without work-up) was 1.21 (91% yield) vs. 103 (99% yield) in solution.

The *E*-factor remains favourable towards mechanochemical procedures for 5-benzyl-3-phenylhydantoin **14a** (1.91 with 90% yield vs. 3.05 with 79% yield, in solution), while for ethotoin **14b**, the *E*-factor was 4.84 (52% yield) vs. 193 (65% yield) for mechanochemical vs. solutions-based approaches, which requires a column chromatography purification step.

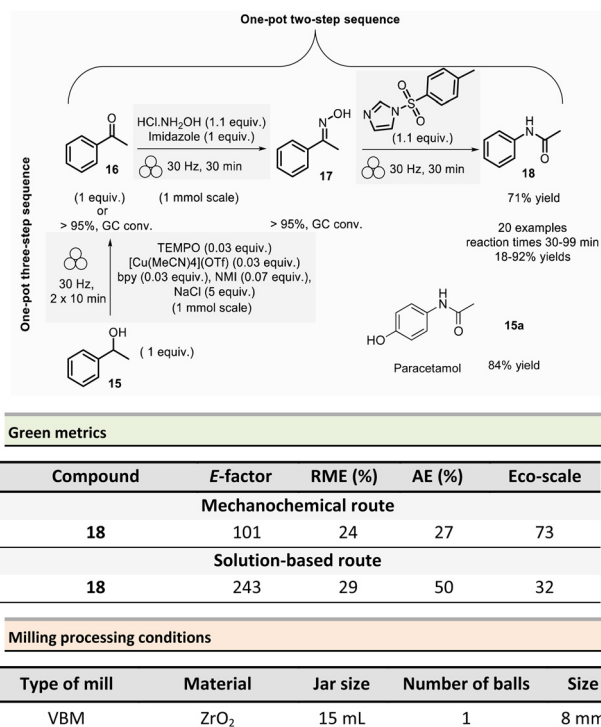
In 2021, Mocci *et al.* developed a mechanochemical procedure for the Beckmann rearrangement reaction (BKR) to access amides from *in situ* synthesized oximes.⁷⁵ The BKR generally requires strong acids, harsh conditions, and hazardous reagents. Even though milder conditions could be employed, toxic coupling reagents (*e.g.*, cyanuric chloride, BOPCl) could not be avoided. As a representative example, *N*-phenylacetamide **18** was obtained in a one-pot/two-step synthesis using a VBM. The first step was performed on 1.0 mmol scale by milling acetophenone **16** (1 equiv.), hydroxylamine hydrochloride (1.1 equiv.), and imidazole (1 equiv.) at 30 Hz for 30 min in a ZrO₂ jar (15 mL) with one ZrO₂ ball (8 mm \varnothing). To the *in situ* formed oxime intermediate **17**, *p*-toluenesulfonylimidazole (1.1 mmol) was added, and the mixture was then milled at 30 Hz for further 30 min to afford *N*-phenylacetamide **18** (Scheme 4).

To eliminate the imidazolium tosylate by-product, the reaction crude was triturated with water, 10% w/w citric acid aqueous solution, and 10% w/w potassium carbonate aqueous solution, filtered off, and dried *in vacuo* over Na₂SO₄.

Furthermore, varying the ketones and the reaction times (30–99 min), allowed a large scope of *N*-acetyl, *N*-aryl, or *N*-alkyl amides to be produced in 18–92% yields. It is worth highlighting that this methodology enables an affordable route to the active pharmaceutical ingredient (API) paracetamol **18a** in 84% yield from 4-(1-hydroxyethyl)phenol, as illustrated so far in Scheme 4 for the obtention of phenylacetamide **18**. The first step consisted in the oxidation of 1-phenylethanol **15** (1.0 mmol scale) into acetophenone using a combination of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)/air as oxidant, [Cu(MeCN)₄]OTf as the catalyst, *N*-methylimidazole and 2,2'-bipyridyl (bpy) as ligands, and sodium chloride as a milling agent used to avoid paste-like mixture. Interestingly, grinding the mixture twice for 10 min at 30 Hz, allowed the formation of acetophenone in yields over 95% determined by gas chromatography (GC). Subsequent steps remained unchanged, and phenylacetamide **18** was isolated in 71% overall yield (Scheme 4).

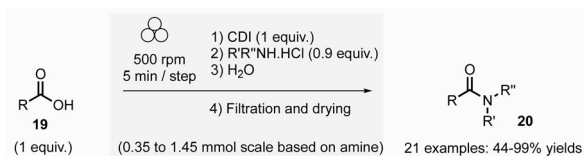
Green metrics were calculated for the mechanochemical preparation of phenylacetamide **18** according to the one-pot, two-step sequence and compared to a similar solution-based process.⁷⁶ In solution, a mixture of acetophenone (1 equiv.), NH₂OH·HCl (1.6 equiv.), and sodium acetate (2 equiv.) was refluxed for 1 h in EtOH/H₂O (4:1).⁷⁷ Then, the newly obtained acetophenone oxime (1 equiv.), was reacted with *p*-toluenesulfonyl chloride (0.02 equiv.), and ZnCl₂ (0.02 equiv.) in dry MeCN during 1 h at reflux.⁷⁶ The yields were comparable for the two procedures (91% vs. 86% in solution). However, AE and RME were better in solution, with 50% for AE and 29% for RME, compared to the mechanochemical method (27% for AE and 24% for RME). Green metrics favour solution-based procedures due to the only waste produced being acetic acid, sodium chloride, and water. Whereas the mechanochemical method produced imidazolium chloride and 4-methylbenzenesulfonate imidazolium waste. Finally, the mechanochemical procedure displayed an *E*-factor of 101 and an Eco-scale score of 73, while solution-based techniques scored 243 and 32, respectively.

In 2012, Métro *et al.* developed a mechanochemical acylation of nucleophiles (mostly amines) using *N,N*-carbonyldiimidazole (CDI) as activating agent.⁷⁸ Twenty-one amides **20** were obtained from carboxylic acid derivatives **19** in good to almost quantitative yields (44–99%) (Scheme 5). Typically, during the two-step optimized procedure, the carboxylic acid activation was accomplished with CDI under 5 min at 500 rpm in a PBM (using stainless-steel grinding media with 50 balls of 5 mm diameter). Then, amine hydrochlorides were added, and the mixture was milled for a further 5 min at 500 rpm. The by-products were imidazole hydrochloride, carbon dioxide, and a small amount of unreacted carboxylic acid starting material. Typically, the amides were readily purified by aqueous work-up under grinding conditions (5 min, 500 rpm), filtration, washing with deionized water, and drying under vacuum. Using the developed approach, teriflunomide, an active metabolite of Leflunomide approved by the FDA for treating multiple sclerosis, was also synthesized with 81% yield. In addition, this methodology was also extended to the formation of C–O, C–S, and C=C bonds.



Scheme 4 *N*-Phenylacetamide preparation by mechanochemical Beckmann rearrangement.





Green metrics

| Compound | E-factor | Eco-scale |
|------------------------------|----------|-----------|
| Mechanochemical route | | |
| 20 | 20.8 | 79 |
| Solution-based route | | |
| 20 | 41.9 | 67 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| PBM | SS | 12 mL | 50 | 5 mm |

Scheme 5 CDI-mediated amidation by mechanochemistry.

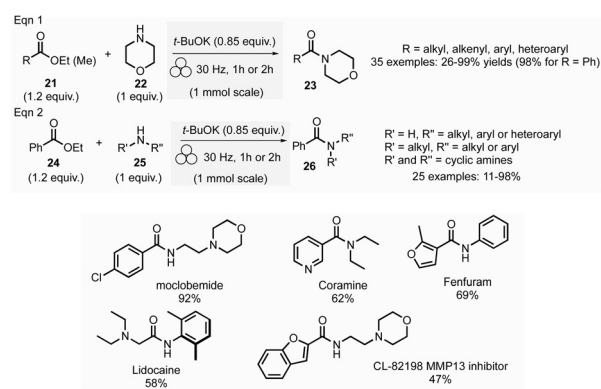
Careful characterization by ICP-MS or gravimetric analysis of the final products showed ppm traces of metal impurities (Fe, Zr, Cr, Y, Si) which originated from the degradation of the milling balls and jar during the grinding process.⁷⁹ Metal contamination was drastically diminished by optimizing reaction times and milling media used by assessing the use of zirconium oxide, agate, or PTFE milling media. The studies showed that stainless-steel was the most suitable grinding media for this reaction since it took less time, gave the best yield, and metal particle contaminants could be removed by simple filtration without the need for harmful EtOAc.

Evaluation of the environmental impact of this solvent-free preparation of *N*-benzylbenzamide with CDI was also compared to other classical solution procedures using (*N,N'*-diisopropylbenzyl-amine-2-boronic acid (IBA), *N,N'*-dicyclohexylcarbodiimide (DCC),⁸⁰ thionyl chloride (SOCl₂),⁸¹ *N,N'*-carbodiimidazole (CDI)⁸² in THF and sulfated tungstate.⁸³ Among all species tested, the CDI reagent furnished the best yield with 92% for both reactions in solution and without solvent. The *E*-factor score calculated for mechanical milling was 20.8, which is half of that calculated for CDI in THF (41.9). None of the other coupling reagents had better metrics. Finally, with an Eco-scale score of 79, the mechanical method was excellent compared to all the different reactions conditions in solution (Eco-scale between 44 and 67).

Browne *et al.* developed an original and efficient ball milling method for direct amide bond formation using methyl or ethyl esters as starting materials (from reagents **21** and **24**),⁸⁴ circumventing the need of any activating reagent, usually needed when using carboxylic acids as starting materials. The solvent-free reaction was carried out using an amine (from **22** and **25**), 1.2 equivalent of ester, and a substoichiometric amount of potassium *tert*-butoxide (0.85 mol%) as a base. Typically, 1.0 mmol scale reactions were milled at 30 Hz for 1 or 2 h (depending on substrates) using a stainless-steel milling jar (14 mL) with one stainless-steel ball (4 g) (Scheme 6). The only by-product of the reaction was the corresponding primary alcohol (*i.e.*, methanol or ethanol). Using this method, several

dozens of amides **23** and **26** were synthesized in moderate to high yield (11% to 99%). The reaction substrate scope comprises aromatic, alkyl, alkenyl, and heteroaromatic esters as electrophiles, and primary, secondary or cyclic amines as nucleophiles. Ammonium salts can also be used as starting materials. However, an excess of base (*i.e.*, 1.85 equivalent) was required. Moreover, this methodology was successfully applied to synthesizing five relevant pharmaceuticals and agrochemicals species (*i.e.*, CL-82198 MMP13 inhibitor, Lidocaine, Coramine, Fenfuram and Moclobemide) in 47 to 92% yields. Notably, this procedure was also upscaled ten-fold for the synthesis of Moclobemide, by increasing the size of the milling reactor and the number of balls, affording similar yields. Using the model reaction reported in Scheme 6, eqn (1) (ethyl benzoate and morpholine), mechanical methods afforded complete amidation, whereas only 8% of the target amide was obtained in solution. This reaction's AE was consistently higher (55%) than those performed using traditional solution methods. For instance, in the best solution conditions (phosgene/Et₃N), an AE of 47% was determined. Even if the difference in AE is not so high, the mechanochemical method has the advantage of avoiding toxic and harmful chemicals (*e.g.* phosgene). Moreover, concerning PMI, the mechanochemical amide bond formation was greener than the solution counterpart (PMI = 1.94 *vs.* a similar solution reaction reported by Yoon and coworkers, PMI = 59.28).⁸⁵

In 2022, Wadouachi *et al.* reported the one-pot/two-step mechanochemical synthesis of four potential surfactants (4*S*)-*N*-alkyl-4,5-bis-sulfoxy-pentanamides **29** from bio-based (*S*)- γ -hydroxymethyl- γ -butyrolactone **27** (2H-HBO) in a one-pot



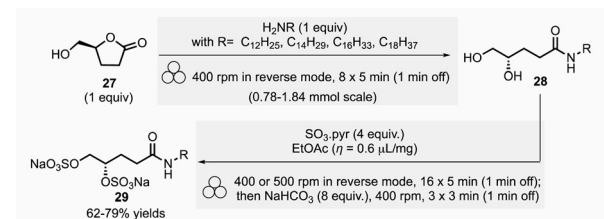
Green metrics

| Compound | AE (%) | PMI |
|------------------------------|--------|-------|
| Mechanochemical route | | |
| 23 | 55 | 1.94 |
| Solution-based route | | |
| 23 | 47 | 59.28 |

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| VBM | SS | 14 mL | 1 | NA |

Scheme 6 Direct amide bond formation from ester in mechanochemistry.





Green metrics

| Compound | AE (%) | E-factor | PMI | RME (%) |
|------------------------------|--------------------|----------------------|--------------------|--------------------|
| Mechanochemical route | | | | |
| 28 | | | | |
| 29 | 79-82 ^a | 1.6-1.7 ^a | 2.6-3 ^a | 33-38 ^a |
| Solution-based route | | | | |
| 28 | 100 | 6-7 | 7-8 | 12-14 |
| 29 | 81-83 | 18-25 | 19-26 | 4-5 |

^a over 2 steps.

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|------------------|----------|-----------------|------|
| PBM | ZrO ₂ | 20 mL | 80 | 5 mm |

Scheme 7 Bis-sulfoxy-pentanamide synthesis with one-pot/two-step procedure by ball-milling.

two-step process (Scheme 7).⁸⁶ This short sequence consisted of an aminolysis of 2H-HBO 27 followed by a disulfation reaction using a PBM. The optimized conditions consisted of grinding 2H-HBO (1 equiv.) with alkylamine (1 equiv.) in a ZrO₂ jar (20 mL), charged with eighty ZrO₂ balls (5 mm \varnothing) under an inert argon atmosphere. The rotation was at 400 rpm in reverse mode (regular reversal of rotation direction) for 47 min (8 cycles of 5 min with 1 min rest between each cycle). The disulfation was accomplished by adding SO₃-pyridine complex (4 equiv.) and a drop of EtOAc ($\eta = 0.6 \mu\text{L mg}^{-1}$) into the jar under argon. The complete conversion occurred after 95 min (16 cycles of 5 min with 1 min rest) at 400 rpm or 500 rpm in reverse mode. The mixture was then milled again for 11 min (3 cycles of 3 min with 1 min pause between cycles) in the presence of NaHCO₃ (8 equiv.). The final disulfate 29 was recovered after an aqueous work-up and purification step using reverse phase chromatography in good yields (77%, 62%, and 79% for dodecylamine, tetradecylamine, and hexadecylamine and octadecylamine, respectively).

It is worth to note that sulfation of oligoglucuronanes usually requires heating in DMF for prolonged time, with improved results in term of reaction kinetic when microwave-assisted heating is used, allowing to reduce the amounts of by-products due to the decomposition of the carbohydrates. Contrarily, the reaction conducted by mechanochemical activation does not require any external heating to occur, and the by-products are absent or only formed in traces.

To assess the environmental footprint of the mechanochemical strategy, authors also prepared the same four surfactants according to the following a two-step solution procedure: (i) (step 1) alkylamine (1.05 equiv.), 2H-HBO 27 (1 equiv.) in 2-propanol ($c \approx 0.1 \text{ mM}$) were stirred at 50 °C for 48 h, followed

by purification by recrystallization (71–83% yield of amide 28). (ii) (step 2) 28 was then reacted with SO₃-Pyr (4 equiv.) in dry pyridine ($c \approx 0.1 \text{ mM}$) at room temperature for about 48 h, then MeOH (10 equiv.) was added, and the mixture was stirred for additional 30 min at room temperature, in the presence of NaHCO₃ (8 equiv.). The crude was dissolved in water and purified on reverse column chromatography (59–73% yields).

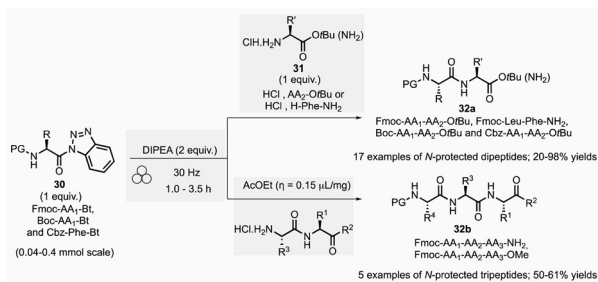
The green metrics, without work-up, calculated for the surfactants highlighted the superior green performance of the mechanochemical procedure. The AE was comparable for both methods, with 81–83% for step 2 of the solution-based process vs. 79–82% for the mechanochemical one. On the other hand, the E-factor is less favourable for conventional solution procedures, being 6–7 for step 1 and 18–25 for step 2 vs. 1.6–1.7 by mechanochemistry. Along the same trend, PMI was 7–8 for step 1 and 19–26 for step 2 vs. 2.6–2.7 for the mechanochemical sequence. Both metrics confirmed that, in addition to the experimental simplicity of the set-up, mechanochemical synthesis provides better green metrics. Finally, RME continued to show the same trend with 12–14% for step 1 and 4–5% for step 2 vs. 33–38% when using the reported ball milling strategy.

In 2017, Colacino *et al.* published a new ball-milling method for the synthesis of dipeptides and tripeptides using *N*-protected α -aminoacyl benzotriazoles 30 as building-blocks (Fmoc-AA₁-Bt, Boc-AA₁-Bt, or Cbz-Phe-Bt) and amino esters hydrochloride 31 (HCl-H₂N-AA₂-OtBu or HCl-H-Phe-NH₂) in the presence of Hünig base (*N,N*-diisopropylethylamine, DIPEA) (Scheme 8).⁸⁷ *N*-Acylbenzotriazoles 30 are air- and water-stable reagents while remaining more reactive than the corresponding *N*-acylimidazoles.

The typical mechanical procedure for synthesizing protected dipeptides was carried out in a stainless-steel jar with 2 stainless-steel balls (5 mm \varnothing) at 30 Hz using a VBM for 1 to 3.5 h. After precipitation, by adding water to the reaction mixture, and filtration, the protected dipeptides 32a (PG-AA₁-AA₂-OtBu) were readily isolated in 20 to 98% yields. In addition, LAG (ethyl acetate, $\eta = 0.15 \mu\text{L mg}^{-1}$) was beneficial for preparing five protected tripeptides 32b (Fmoc-AA₁-AA₂-AA₃-OtBu and Fmoc-AA₁-AA₂-AA₃-NH₂) in yields ranging from 50 to 61%. The LAG procedure was also used to synthesize a more complex biotinylated peptide (Biotin-Ahx-RGDfV-NH₂ linear peptide).

Comparative green metrics based on the synthesis of three different peptides demonstrated the environmental advantage of mechanochemistry versus the standard solution-based procedures.⁸⁸ For *N*-protected dipeptide Fmoc-Leu-Phe-NH₂, both reaction time and yield were improved by mechanochemistry compared to the solution-based process (1h vs. 24 h and 91% vs. 55% yield). The E-factor was once more in favour of mechanochemical activation (401 vs. 59 678) due to the recovery of the final product in solution required an additional HPLC purification step, negatively impacting the E-factor value. Likewise, the reaction mass efficiency (RME) was better for mechanochemistry (0.49) than for the reaction in solution (0.29). In addition to eco-friendly parameters, the added value of this mechanochemical activation lays in a lower production





Green metrics

| Compound | E-factor | RME (%) | | |
|--------------------------------------|----------|----------|-----------------|------|
| Mechanochemical route | | | | |
| 32 | 401 | 0.49 | | |
| Solution-based route | | | | |
| 32 | 59 678 | 0.29 | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | SS | 5 mL | 2 | 5 mm |

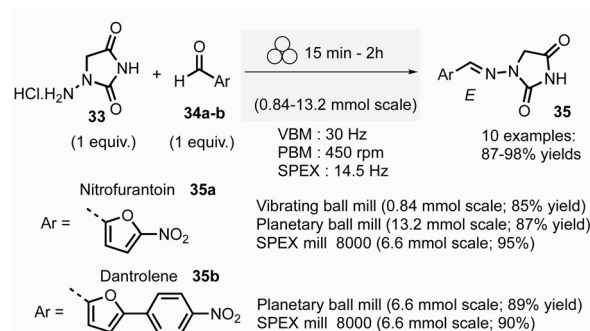
Scheme 8 Protected dipeptides formation from *N*-acylbenzotriazoles by mechanochemistry.

cost calculated to produce 1 g of dipeptide (54€ vs. 298€ in solution), with an evident economic advantage in view of a synthesis in larger scales, where costs are usually multiplied.

Mechanochemical methods were also successful in the formation of C–N bonds (*e.g.*, imine synthesis, *N*-acyl hydrazones, amins, *etc.*).

In 2018, Colacino, Porcheddu, *et al.* synthesized hydrazone-based APIs, namely nitrofurantoin **35a** and dantrolene **35b**, by ball-milling.⁸⁹ Nitrofurantoin was successfully obtained using a VBM at a 0.84 mmol scale from the equimolar reaction of 1-aminohydantoin hydrochloride **33** and 5-nitro-2-furfural **34a**. The mixture was milled at 30 Hz for 30 min in a stainless-steel jar (5 mL) with 2 balls (5 mm \varnothing). Complete conversion of starting materials was observed, and a simple work-up consisting of adding water, followed by filtration and drying, afforded pure nitrofurantoin **35a** in 85% yield (Scheme 9). Moreover, no base was needed to generate the free reactive amine during the reaction.

To assess the influence of different milling apparatuses, the same reaction was also conducted on a larger scale and it furnished 87% yield in 2 h using a PBM (Schemes 9, 13.2 mmol scale, zirconium oxide jar and balls, 600 rpm). When using a SPEX mill, 95% yield was reached in only 15 min (Scheme 9, on a 6.6 mmol scale, using zirconium oxide jar and balls). It is worth noticing that, independently on the milling apparatus used (VBM, PBM or SPEX), the use of stainless steel or zirconium oxide milling media led to the same results, while the reaction was incomplete when agate jars were used, clearly indicating, in this case, that the hardness and the density of the milling media are some of process parameters to be taken into account when optimising a mechanochemical process. In the latter, complete conversion was obtained using the reactants



Green metrics

| Compound | AE (%) | E-factor | PMI | |
|--------------------------------------|------------------|----------|-----------------|-------|
| Mechanochemical route | | | | |
| 35a | 81 | 0.29 | 1.29 | |
| 35b | 85 | 0.30 | 1.30 | |
| Solution-based route | | | | |
| 35a | 81 | 16 | 17 | |
| 35b | 85 | 239 | 240 | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| SPEX | ZrO ₂ | 50 mL | 2 | 12 mm |

Scheme 9 Hydrazones synthesis by ball-milling, applied to the mechanochemical preparation of active pharmaceutical ingredients nitrofurantoin **35a** and dantrolene **35b**.

equimolar amounts, allowing the recovery of pure nitrofurantoin **35a** directly by “scratching it out the powder” from the jar. In the case of the synthesis of dantrolene **35b** (from reagents **33** and **34b**), the reaction needed 2 h with both PBM and SPEX mills to afford 89% and 90% yields, respectively (Scheme 9). Seven hydrazones were prepared using the PBM protocol developed in excellent yields (87–96%) and recovered by precipitation in water. When 2-hydroxybenzaldehyde was used as the substrate, a VBM (1.32 mmol, 30 Hz, 2 h) was preferred (instead of the previous PBM protocol), providing the corresponding hydrazone with the best results (98% yield).

When considering the green metrics for nitrofurantoin **35a** and dantrolene **35b**, yields (both $\geq 90\%$) and AE (81% and 85% respectively, for **35a** and **35b**) were comparable for both mechanochemical and solution-based process, however, the *E*-factor was better for the mechanochemical process (for nitrofurantoin **35a**: 0.29 vs. 16 and for dantrolene **35b**: 0.30 vs. 239 by mechanochemistry vs. in solution respectively). Consequently, also, the PMI (*E*-factor + 1) resulted sensibly lower for mechanochemistry (1.29 and 1.30 for **35a** and **35b** respectively) compared to solution-based reactions (17 and 240 **35a** and **35b** respectively).^{90–92} Moreover, the mechanochemical strategy avoids using toxic solvents (DMF, ACN), excess reagents, corrosive highly concentrated solutions of strong acids, and bases for synthesis and workup. Also, there is no need for pH adjustments or heating–cooling thermal cycles – which strongly reduces the environmental impact and production cost and improves the process's safety. For example, only considering



the costs of reagents and solvents, the calculated price for 1 g of dantrolene **35b** by mechanochemistry was calculated to 54.7€, compared to the 133.9€ needed for a solution-based reaction.

To evaluate the greenness of this reaction, Colacino *et al.* pioneered the use of DOZN 2.0 tool for nitrofurantoin synthesis, to quantitatively assess a mechanochemical process against the 12 principles of green chemistry (*vide supra*).⁹³ The aggregated scores obtained using different mechanochemical devices both in batch (SPEX) and continuous (TSE) processes were compared with the solution counterparts (Fig. 4). For the mechanochemical processes, the best aggregate scores were obtained when using SPEX (0.05) and TSE (0.06) in accordance with their associated shorter reaction times, better yields, no need for work-up, and improved resources use (*e.g.*, no excess of reagents). These methods outperformed VBM and PBM, which display aggregate scores of (1.64 and 0.67, respectively) which required trituration with water to recover the final product. Another essential feature is productivity, TSE apparatus is 2.33 more productive than SPEX (*ca.* 1.5 g)⁸⁹ over a period of 15 min, delivering *ca.* 3.5 g⁹⁴ of nitrofurantoin **35a**.

When comparing mechanochemical procedures to solution-based counterparts,⁹² better scores were obtained by mechanochemistry for 8 out of the 12 principles of green chemistry. The major difference in energy efficiency is due to the need to heat the solvent during batch synthesis. In the end, regarding the space-time yields (STY), the productivity is higher using TSE (68 000 kg m⁻³ day⁻¹) compared to solvent-batch synthesis (430 kg m⁻³ day⁻¹) and also higher compared to estimated continuous flow synthesis for fine chemicals (4000 kg m⁻³ day⁻¹).⁹⁵

The Saha group developed the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **38** in the presence of Brønsted acid catalyst either using a mortar-pestle or a tumbler ball mill (Scheme 10)²⁰ In optimized conditions, for a 0.73 mmol scale, equimolar amounts of anthranilamide **36** and benzaldehyde **37** were ground in the presence of *para*-toluenesulfonic acid (10 mol%) for 3 min in a mortar. After simple trituration in water, pure product **38** was collected with a 95% yield.

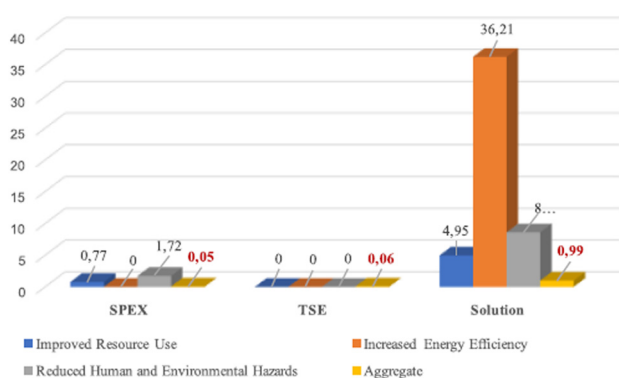
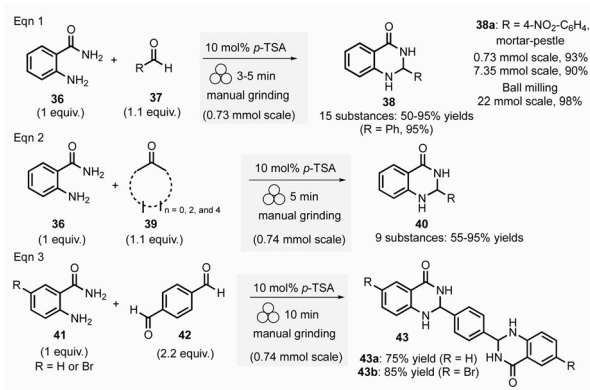


Fig. 4 Greenness comparison between SPEX, TSE, and solution synthesis in a batch of nitrofurantoin **35a** using DOZN 2.0 tool. Adapted with permission of the American Chemical Society from ref. 93.



| Green metrics | | | | |
|--------------------------------------|----------|----------|-----------------|-----------|
| Compound | AE (%) | RME (%) | E-factor | Eco-scale |
| Mechanochemical route | | | | |
| 38a | 89.04 | 80.45 | 0.243 | 81.93 |
| Solution-based route | | | | |
| 38a | NA | NA | NA | NA |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| Mortar and pestle | NA | NA | NA | NA |

Scheme 10 Dihydroquinazolin-4(1*H*)-ones and bis-quinazolinones formation by ball-milling.

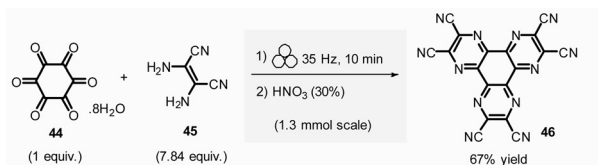
This methodology was extended to aromatic aldehydes, and by varying the reaction time from 3 to 15 min a library of fifteen 2,3-dihydroquinazolin-4(1*H*)-ones **38** with yields ranging from 50 to 95% was synthesized. Moreover, a gram-scale synthesis using anthranilamide and *p*-nitrobenzaldehyde afforded 90% yields (which is close to the 93% yield obtained for 0.1 g scale) after 10 min of grinding (Scheme 10).

The extension of this methodology to ketones at a 0.74 mmol scale permitted the formation of nine dihydroquinazolinones **40** in 55% to 95% yields. Similarly, the mechanochemical synthesis of two bis-dihydroquinazolinones from either 4-bromoanthranilamide or anthranilamide with terephthalaldehyde afforded the desired products in good yields (75% and 85%, respectively).

In order to improve efficiency and productivity, a tumbler ball milling apparatus was used for the multigram synthesis of 2-(4-nitrophenyl)-2,3-dihydroquinazolinone **38a**. The best reaction conditions were obtained using anthranilide (3.0 g, 0.013 mol) and 4-nitrobenzaldehyde (3.65 g, 0.024 mol) in a stainless-steel reactor vessel (200 mL) loaded with ninety stainless-balls (7.9 mm \varnothing), and 4 h grinding at 40 rpm. The corresponding dihydroquinazolinone **38a** was isolated in almost quantitative yields (98%).

For the model reaction (R = 4-NO₂-C₆H₄) performed on a gram scale (7.35 mmol) employing a mortar and pestle, the calculated green metrics demonstrated the environmentally friendly nature of the process (AE = 89.04%, RME = 80.45%, E-factor of 0.243 and, an excellent Eco-scale of 81.93). Nevertheless, no comparison with solution-based reaction was mentioned by the authors.





Green metrics

| Compound | AE (%) | MP | PMI | GWP |
|--------------------------------------|------------------|----------|-----------------|-------|
| Mechanochemical route | | | | |
| 46 | 78.04 | 22.04 | 4.54 | 175 |
| Solution-based route | | | | |
| 46 | 78.04 | 0.04 | 2760.69 | 783 |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | ZrO ₂ | 10 mL | 2 | 10 mm |

Scheme 11 Mechanochemical synthesis of hexaazatriphenylenehexacarbonitrile HAT(CN)₆, **46**.

Borchardt *et al.* described an efficient and eco-friendly ball-milling synthesis of HAT(CN)₆ (**46**, hexaazatriphenylenehexacarbonitrile)⁹⁶ (Scheme 11).^{97,98} The optimized two-step sequence required first to react hexaketocyclohexane octahydrate **44** (1.3 mmol, 1.0 equiv.) with an excess of diaminomaleonitrile **45** (7.84 equiv.) in the presence of water ($\eta = 0.1 \mu\text{L mg}^{-1}$, LAG conditions) using a ZrO₂ milling vial (10 mL) charged of two ZrO₂ mill balls (10 mm \varnothing).

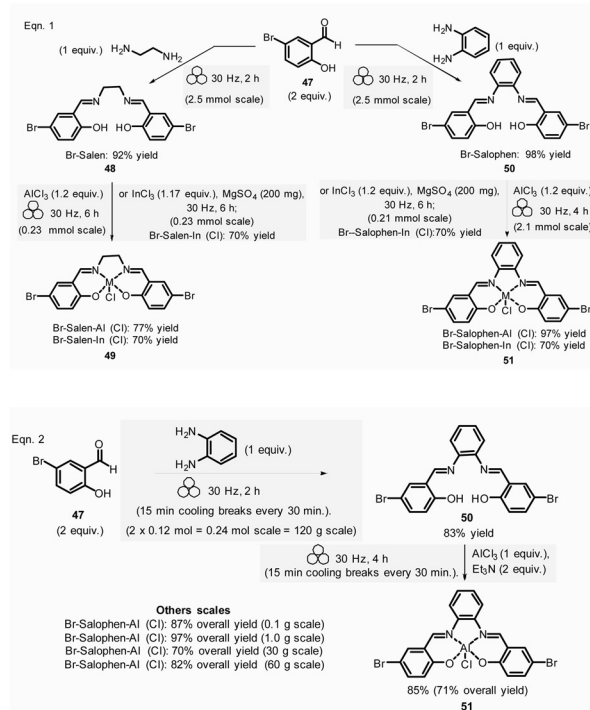
The mixture was ground at 35 Hz for 10 min, then the mixture was treated in a glass flask with nitric acid (30%) at 110 °C for 1 h. After a simple work-up, the pure HAT-CN was isolated in 67% yield compared to the 50% yield obtained by traditional solution-based methods.

Concerning green metrics, while AE was equal for both mechanochemistry and solution (78.04%), PMI and MP (mass productivity) were better for the mechanical process (PMI: 4.54 vs. 2760.69 and MP: 22.04 vs. 0.04, respectively). Moreover, the LAG-mechanochemical reaction occurred sensibly faster (10 min vs. 420 min). The authors assessed the environmental impact of the mechanochemical process by calculating its global warming potential (GWP). To the best of our knowledge, the use of this metrics is unprecedented in the field, not commonly measured by chemists, but preferentially used by process engineers. The global warming potential (GWP) measures how much energy the emissions of 1 ton of a gas will absorb over a given period, relative to the emissions of 1 ton of carbon dioxide (CO₂). This reaction displayed a more favourable GWP 175 vs. 783 CO₂ equivalents than in solution.

Mechanosynthesis of various salen **48** and salophen **49** ligands and their complexes, including metals such as Zn, Ni, Pd, Cu, Co, and Mn(Cl), has been accomplished at both laboratory- and multigram-scales using ball mills and twin screw extruders (TSE).^{99–103} Nevertheless, in 2021, Garcia *et al.* reported the mechanosynthesis of four Br-salen or Br-salophen complexes with aluminium or indium on a small scale (0.1–1 g) using a VBM.¹⁰⁴ The four complexes were readily

produced using a two-step sequence, which started by condensation of bromosalicylaldehyde **47** (2 equiv.) with either 1,2-phenylenediamine (1 equiv.) or ethylenediamine (1 equiv.). The resulting Br-salen **48** and Br-salophen **49** ligands were isolated in 92% and 98% yields, respectively (Scheme 12, eqn (1)). The complexes were prepared by subsequent treatment of Br-salen or Br-salophen with either AlCl₃ or InCl₃. The mixture was milled for 4 h at 30 Hz. After washing the crude with water and a drying step, the complexes were obtained in good to excellent yields (70–97%) (Scheme 12, eqn (1)).

The large-scale synthesis (30–120 g) of Br-salophen-Al(Cl) complex **51** in a PBM was also developed. For 0.24 mol scale (120 g), the reaction consisted in grinding for 2 h with 15 min cooling breaks every 30 min at 30 Hz, a mixture of 5-bromosalicylaldehyde **47** (2 equiv.) and 1,2-phenylenediamine (1 equiv.) in two stainless-steel jars (250 mL) containing stainless-steel balls (balls mass = 500 g overall). The purpose of the cooling breaks during the cycled milling (8 cycles of 15 min with



Green metrics

| Compound | E-factor | PMI | Energy consumption | |
|--------------------------------------|----------|----------|-------------------------|------|
| Mechanochemical route | | | | |
| 51 | 2.88 | 19.87 | 288 MJ.kg ⁻¹ | |
| Solution-based route | | | | |
| 51 | 4.96 | 40.82 | 384 MJ.kg ⁻¹ | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | SS | 250 mL | 50 | 10 |

Scheme 12 Mechanochemical preparation of Br-salen and Br-salophen ligands and their corresponding complexes.



30 minutes breaks in between two cycles) avoids any possible thermal activation of the reaction or decomposition of the reactants, due to the heat that might be produced if a continuous milling for 2 h was achieved. The Br-salophen **49** was recovered after simple water removal by drying in 83% yield. Further, complex Br-salophen-Al **51** synthesis was achieved on \approx a 0.1 mol scale by treatment of Br-salophen **49** (1 equiv.) with aluminium chloride (1 equiv.) and triethylamine (2 equiv.) charged in an oven-dried stainless-steel milling jar. The mixture was ground at 30 Hz in 4 cycles of 30 min each with a 15 min pause between them. After washing the reaction crude with water, the final product was recovered by filtration in 71% overall yield (after drying).

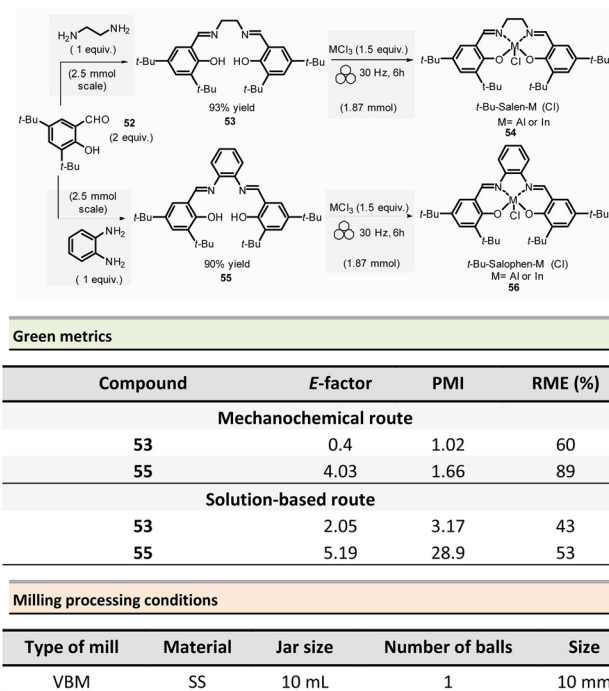
Comparison of *E*-factors calculated for Br-salophen-Al (Cl) **51** at five different scales (0.1 g, 1 g, 30 g, 60 g, and 120 g) emphasized the effectiveness of mechanochemistry over conventional solution-based method (Scheme 12, eqn (2)). For instance, on 240 mmol scale, *E*-factor was of 2.88 vs. 4.96 with solvent. Furthermore, the authors mentioned that when the reaction was done without an HCl trapping agent (*i.e.*, in the absence of triethylamine base) the *E*-factor would have been only 0.65 for mechanochemistry and 2.81 in solution.

PMI values were also favourable towards mechanochemistry, with lower PMI values than the corresponding solution-based synthesis. On a larger scale (0.24 mol), the calculated PMI value for the solventless reaction was 19.87 (1.65 without Et₃N) vs. 40.82 (23.35 without Et₃N) in the solvent procedure.

Energy consumption and costs for the five scales reported (0.1 g, 1 g, 30 g, 60 g, and 120 g) were lower than in solution for all mechanochemical procedures. To perform these calculations, as a rough measure, the energy consumption assessment was approximated to the maximum power consumption (as stated in the apparatus technical specifications) during the milling process and negligible power consumption when idle. Whereas for the solution-based methodology, the hot plate was presumed to be at maximum power while heating and negligible power when only stirring. The obtained energy consumption was translated into industrial production cost using US electricity prices from official sources.¹⁰⁵

For example, at 0.24 mol scale, the energy consumption for ball-milling using a PBM was 288 MJ kg⁻¹, whereas utilising a hotplate stirrer, the value rose to 384 MJ kg⁻¹. The calculated energy consumption was 25% lower, translating into lower production costs (average cost of 5.18 USD kg⁻¹ and 6.87 USD kg⁻¹, respectively, for milling- and solution-based processes). Based on these results, it could be anticipated that the difference could be even more favourable at a larger scale as solvent costs were not considered.

In 2022, the same group reported the synthesis of four sterically hindered fluorescent salen and salophen complexes.¹⁰⁶ The optimized preparation of 3,5-di-*tert*-butyl functionalized salen **53** and salophen **55**, ligands and their respective aluminium and indium complexes were obtained on a 2.5 mmol scale (Scheme 13). For this purpose, 3,5-di-*tert*-butylsalicylaldehyde **52** (2 equiv.) and ethylene diamine (1 equiv.) were ball-milled in a stainless milling media (one 10 mL jar loaded with one 10 mm \varnothing ball at 30 Hz for 2 h) affording the target salen ligand **53** in 93%



Scheme 13 Mechanochemical *t*-Bu-salophen complexes formation with aluminium and indium metals.

yield. For salophen ligand **55** (from 1,2-phenylene diamine), a catalytic amount of acetic acid (70 μ L) was added to enable ligand formation in a 90% yield. Their corresponding salen and salophen metal complexes were obtained in 70% to 88% yields, respectively, by reacting the corresponding ligand (1 equiv.) with AlCl₃ or InCl₃ (1.5 equiv.) and MgSO₄ (\approx 13 equiv.) at 30 Hz for 6 h. The green metrics calculated for *t*-Bu-salen **53** and *t*-Bu-salophen **55** ligands and their respective complexes showed lower *E*-factors than in solution (0.4 and 4.03 vs. 2.05 and 5.19 in solution, for salen and salophen complexes, respectively). For instance, for the *t*-Bu-salen-Al (Cl) complex, the *E*-factors were 3.02 for the mechanochemical synthesis and 4.76 for its preparation in solution.¹⁰⁶ Mechanochemistry displayed the same trend for PMI (1.02 to 1.66) versus 3.17 to 28.9 for solution-based reactions. For the *t*-Bu-salen-Al (Cl) complex, PMI was 1.13 for mechanochemistry vs. 39.7 in solution. In all cases, RMEs were more favourable mechanochemical procedures than their solution counterparts (60–89% vs. 43–53%, respectively). Then, for the *t*-Bu-salen-In (Cl) complex, the RME was 60% in mechanochemistry and 49% for traditional solvent-based procedures.

Energy efficiency costs were also calculated at different scales (from 0.1 g to 120.0 g) for the four complexes (*t*-Bu-salen-M(Cl) and *t*-Bu-salophen-M(Cl), M = Al and In). For each scale, estimated energy consumption and approximative electricity cost were systematically lower than in the solution. For the larger scale (120 g), the estimated energy consumption was 384 MJ kg⁻¹ for mechanical activation, whereas the value was higher (512 MJ kg⁻¹) in solution. The predicted energy savings was 25%, making the ball-milling production cheaper than conventional “wet” routes (10.4€ kg⁻¹ vs. 13.8€ kg⁻¹,



respectively). It is worth highlighting that the significant energy and cost difference calculated for the 0.1 g-scale, with a 16-fold production cost for conventional laboratory scales (18 681.0€ kg⁻¹ and 1,167.3€ kg⁻¹ for solution *vs.* mechanochemistry).

Multicomponent reactions and synthesis of heterocycles

This section reports the mechanochemical preparations of heterocycles and compares them with similar solution-based reactions. Multicomponent reactions (MCR) are also included in this section.^{107–109} MCR presents an intrinsically high atom economy and is often environmentally benign. A synergistic combination of solvent-free processes with multicomponent transformations would be relevant for synthesizing a wide range of organic compounds, including APIs.¹¹⁰ Some of these reactions were recently reviewed with in the contexts of pharmaceuticals,¹¹¹ and several mechanochemical MCR were already described.^{112–115} However, here we reported the ones where green metrics have been calculated.

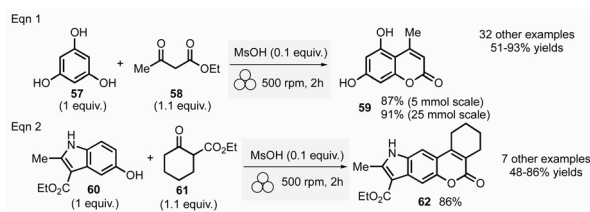
Coumarin **59** synthesis by Pechmann condensation was recently revisited by Ranu team.¹¹⁶ This original reaction, published in 1883,¹¹⁷ consisted of the condensation of a phenol derivative with a β -ketoester catalyzed by Brønsted acids (such as sulfuric acid). Despite several advantageous modifications, which included the use of milder acids, this process still requires a large quantity of acid, as well as having a limited substrate scope.

Ranu *et al.* proposed a catalytic and solvent-free milling process that avoids hazardous solvents, excess acid, and high temperatures. The optimized model reaction (Scheme 14, eqn (1)) was carried out at 5.0 mmol scale by mixing phloroglucinol **57**, ethyl acetoacetate **58** (1.1 equiv.), and methylsulfonic acid as catalyst (10 mol%) in a stainless-steel jar (10 mL) containing ten stainless-steel balls (5 mm \varnothing) in a PBM rotating at 500 rpm for 2 h. The coumarin **59** was recovered in 87% yield

after dilution of the residue in ethanol, followed by crystallization. At a 25 mmol scale, the yield rose to 91%. Employing this methodology, thirty-two coumarins were prepared in yields ranging from 50 to 93% from a wide range of phenol derivatives and β -ketoesters. Furthermore, an extension of this technique enables access to seven pyrano-annulated indoles (48–86%). For the model reaction presented in Scheme 14 (eqn (2)), only one pyranindole regioisomer **62** was formed. Eco-scale scores for the synthesized coumarins and pyranindoles varied from 71 to 90.5 and 68.5 to 83, respectively. More specifically, for the mechanochemical synthesis of 5,7-dihydroxy-4-methyl-2H-chromen-2-one **59** (Scheme 14, eqn (1)), the Eco-scale score and *E*-factor obtained were 89.5 and 0.67, respectively, whereas in solution the reported values were 87.5 and 0.76, respectively.¹¹⁸

The eco-friendly advantage (*i.e.*, better metrics) displayed by the mechanochemical approach was attributed to the higher yields obtained (87% *vs.* 81%), after a work-up consisting of a precipitation in water of the product, followed by a filtration and a crystallisation in EtOH.

In 2022, Porcheddu *et al.* described an indole and indoline synthesis by Fischer and interrupted Fischer indolization using a ball-milling strategy to avoid the harsh and harmful conditions generally required for these reactions (Scheme 15)¹¹⁹ Traditional indole synthetic procedures required the presence of strong acids or Lewis acids,¹²⁰ high temperatures, and toxic solvents. More eco-friendly methods were also developed using EtOH and/or water solvents. However, they either required large quantities of *p*-toluene sulfonic acid (6 equiv.),¹²¹ or the use of toxic ionic liquids bearing sulfonic acid groups.^{122–124}



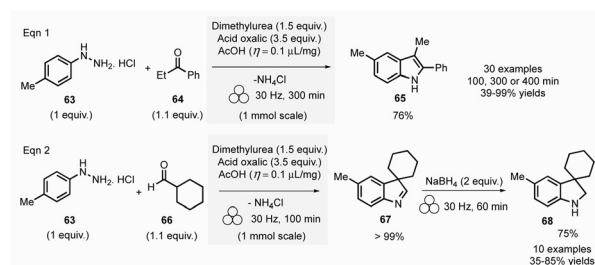
Green metrics

| Compound | <i>E</i> -factor | Eco-scale |
|------------------------------|------------------|-----------|
| Mechanochemical route | | |
| 59 | 0.67 | 89.5 |
| Solution-based route | | |
| 59 | 0.76 | 87.5 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| PBM | SS | 10 mL | 10 | 5 mm |

Scheme 14 Coumarins and pyranindoles mechanochemical synthesis via Pechmann condensation.



Green metrics

| Compound | <i>E</i> -factor | Eco-scale |
|------------------------------|------------------|-----------|
| Mechanochemical route | | |
| 65 | 42.9 | 74 |
| 68 | 214.3 | 52.5 |
| Solution-based route | | |
| 65 | 79.9 | 64 |
| 68 | 278.4 | 45 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|------------------|----------|-----------------|------|
| VBM | ZrO ₂ | 15 mL | 20 | 3 mm |

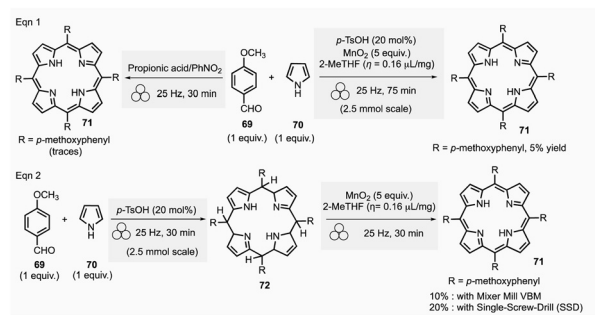
Scheme 15 Indole by Fischer mechanochemical synthesis and indolines by interrupted Fischer indolisation.



To address these issues, an environmentally sustainable and optimized approach based on mechanochemical methodologies was developed (Scheme 15). This procedure, conducted at 1.0 mmol scale, consisted in milling 4-methylphenylhydrazine hydrochloride **63** (1 equiv.), propiophenone **64** (1.1 equiv.), oxalic acid (3.5 equiv.), and dimethylurea (1.5 equiv.) under LAG conditions (acetic acid, $\eta = 0.1 \mu\text{L mg}^{-1}$). The reaction was carried out in a 15 mL ZrO₂ milling jar containing 20 milling balls ($\varnothing = 3$ mm, balls mass = 6.5 g overall) for 300 min at 30 Hz. After water addition and filtration, the pure product was recovered in 76% yield. The authors also studied the recyclability of the dimethylureas/oxalic acid mixture. This mixture was successfully reused four times with only a slight yield reduction (from 76% for 1st batch to 70% for 4th batch). By optimizing reaction time (*i.e.*, 100, 300, or 400 min), thirty indoles were obtained by either reacting various arylhydrazines hydrochloride with ketones or mixing 4-methylphenylhydrazine hydrochloride with aldehydes or ketones in yields ranging from 39% to 99%. Moreover, the developed methodology was successfully extended to indolines **68**. Interrupted Fischer indole reaction of 4-methylphenylhydrazine hydrochloride **63** with cyclohexane carboxaldehyde **66** furnished almost quantitatively indolenine **67** (Scheme 15, eqn (2)). Further, indolenine **67** was mechanically reduced by the addition of sodium tetraborohydride (30 Hz, 60 min) to produce the corresponding indoline **68**. Using this procedure, ten other indolines were synthesized in yields ranging from 35 to 85%.

The green metrics of this process were compared to solution-phase reactions. In solution, indoles **65** were obtained by reacting phenylhydrazine hydrochloride and cyclohexanone using acidic clay conditions.¹²⁵ Indoline **68** were obtained by reacting 4-phenylhydrazine hydrochloride **63** and cyclohexane carboxaldehyde **66** in the presence of acetic acid and sodium triacetoxborohydride.¹²⁶ For the synthesis of indole and indoline in solution, Eco-scale values were 64 and 45, respectively, and the *E*-factor reached 79.9 and 278.4. A comparison of Eco-scale scores obtained for the mechanochemical synthesis (74 for indole and 52.5 for indoline syntheses), indicates that ball-milling protocols are greener than solution-based procedures. Even, *E*-factor values were undoubtedly in favour of mechanical activation, with lower values of 42.9 for indole and 214.3 for indoline than in solution. In 2007, a one-step microwave protocol was developed to produce porphyrins reacting pyrrole and aldehyde in the presence of propionic acid in nitrobenzene at 120 °C for 10 min (20% yield for R = *p*-methoxyphenyl).¹²⁷ Conventional heating in solution for the synthesis of porphyrin **71** (Scheme 16, R = 4-MeOC₆H₄) resulted in low yields (*i.e.*, 20%).

In 2019 and 2020, Pineiro *et al.* revisited the synthesis of substituted *meso*-porphyrins using mechanochemistry.^{21,128} While neat mechanical activation using a VBM resulted in only traces of porphyrin **71**,¹²⁸ grinding a mixture of pyrrole **70** (1 equiv.), 4-methoxybenzaldehyde **69** (1 equiv.), catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH, 20 mol%) and MnO₂ (5 equiv.) under LAG conditions (2-MeTHF, $\eta = 0.16 \mu\text{L mg}^{-1}$) in a stainless-steel grinding jar containing two stainless-steel balls



Green metrics

| Compound | <i>E</i> -factor | Eco-scale |
|------------------------------|------------------|-----------|
| Mechanochemical route | | |
| 71 (VBM) | 22 | 14 |
| 71 (SSD) | 10.37 | 17 |
| 71 (MW) | 8 | 37 |
| Solution-based route | | |
| 71 | 58 | 15.5 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| VBM | SS | 10 mL | 2 | 7 mm |

Scheme 16 One and two-step porphyrin syntheses by mechanochemistry.

(7 mm \varnothing) afforded porphyrin in 5% yield after 75 min at 25 Hz.¹²⁸

An alternative two-step mechanical synthesis was also evaluated by the same group and revealed to be better for overall yield in porphyrin (10%) than one-pot synthesis. The first step consisted of preparing a porphyrinogen scaffold, which was subsequently oxidized into the porphyrin during the second step. The first reaction used 20 mol% of *p*-toluenesulfonic acid and the same equipment as the one-step procedure at 25 Hz for 30 min. Porphyrinogen oxidation was achieved by grinding at 25 Hz for 30 min at room temperature the mixture of porphyrinogen, MnO₂ (5 equiv.), and 2-MeTHF ($\eta = 0.16 \mu\text{L mg}^{-1}$), yielding 10% of the targeted porphyrin. However, the same reaction in solution appeared to be more efficient, furnishing the porphyrin **71** with a 19% yield.¹²⁸ In any case, four other porphyrins (R = aryls) were mechanochemically synthesized by a two-step strategy in low yields ranging from 7% to 27%.¹²⁸

The same group reported in 2020, a new automated mechanostirrer device adapted for mechanochemistry. This new tool comprises a stainless-steel cylindrical reactor (4.33 mL) equipped with a stainless-steel mobile single-screw drill (SSD device) rotating at 250 rpm. The SSD device's rotational movement grinds the reactants placed in the stainless-steel cylindrical reactor (Fig. 1). The authors claimed that this new device combines the mortar's simplicity and an automated apparatus's reproducibility. This new equipment was thus used to form porphyrin **71** (R = 4-MeOC₆H₄), and it proved to be practically effective, giving the same yield than solution-based methodologies, *i.e.*, 20% of yield (Scheme 16, eqn (2)).²¹



Notably, the modest yield obtained is comparable to those observed for the best solution-based methodologies.

For the two-step procedures (Scheme 16, eqn (2)), the Eco-scale values were comparable ($R = 4\text{-MeOC}_6\text{H}_4$, 2-MeTHF, MnO_2 , 10% yield) with values of 14 and 17 for the reaction carried out using the VBM and the SSD setup, respectively, while the solution counterpart (*i.e.*, 2-MeTHF/ MnO_2) was similar with a value of 15.5. However, *E*-factor values were better for mechanical milling, with values of 22 and 10.37 for VBM and SSD. In contrast, solution-based methods displayed an *E*-factor of 58. On the other hand, the microwave one-step procedure with a small amount of water (200 °C, 10 min; 14% yield) had the lowest footprint of all the reported syntheses with *E*-factor and Eco-scale calculated values of 8 and 37, respectively.

In 2021, Pineiro *et al.* prepared a series of metalloporphyrins from their corresponding metal-free porphyrins by sono- or mechanochemical activations.¹²⁹ Generally speaking, conventional approaches to metalloporphyrins metalloporphyrins involve the complexation of a metal salt by porphyrin in solution. The major drawbacks of this methodology derive from the use of hazardous solvents (*e.g.*, DMF, $\text{CHCl}_3/\text{MeOH}$) and the need for a significant excess of metal salts required.

A safer procedure was proposed by Pineiro *et al.* by grinding the porphyrin ($R = 3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$, 50 mg) with 5 or 10 equivalents of the corresponding salt (*i.e.*, Zn(II) , Cu(II) , Co(II) , Mn(III) , Pd(II) , Pt(II)) in the presence of NaOH (0.5 or 10 equiv.) in a stainless-steel jar (10 mL) containing two stainless-steel balls (7 mm \varnothing) at 25 Hz for 30–300 min (Scheme 17). Furthermore, a liquid–liquid extraction with ethyl acetate/water, followed by drying and solvent removal, furnished the

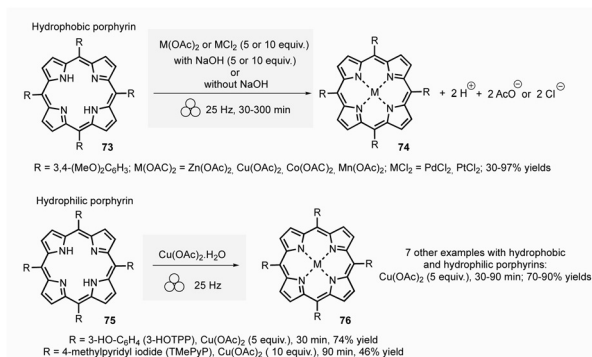
corresponding metalloporphyrins in yields ranging from 30% for $\text{Mn(OAc)}_2 \cdot 4\text{H}_2\text{O}$ to 97% for $\text{Zn(OAc)}_2 \cdot 2\text{H}_2\text{O}$. Using a similar mechanochemical route, a selection of hydrophobic porphyrins 73 [*i.e.*, $R = \text{C}_6\text{H}_5$, 3,5- $\text{Cl}_2\text{-C}_6\text{H}_3$, 3-HO-4-MeO- C_6H_3 , 3,4,5-(MeO)₃- C_6H_2] and hydrophilic porphyrins 75 [*i.e.*, $R =$, 3,4-(MeO)₂- C_6H_3 , 3,5-(MeO)₂- C_6H_3 , 3-HO- C_6H_4 (3-HOTPP), 3-NO₂- C_6H_4 , and methylpyridinium (TMePyP)] afforded the corresponding copper-complexes 74 and 76 in yields ranging from 70 to 90%.

On the other hand, sonochemistry was preferentially used for water-soluble porphyrins counterparts [*i.e.*, $R = 3\text{-HO-C}_6\text{H}_4$, (3-HOTPP), 4-HO₂C- C_6H_4 , 4-HSO₃- C_6H_4 and methylpyridyl iodide (TMePyP)]. When these reactions were carried out under ultrasound conditions with 1 equivalent of metal salt [Zn(II) , Cu(II) and Mn(II)] dissolved in an alkaline solution (NaOH, 2 M), porphyrin complexes were obtained in 32 to 85% yields. Specifically, in the case of Cu(II) salt, 2 equivalents were needed to afford a quantitative yield.

Concerning green metrics, the stoichiometric amount of copper acetate used during the sonochemical route helps explain the better atom economy displayed compared to mechanochemistry with porphyrins 3-HOTPP and TmePyP – which required a significant excess. However, *E*-factor values obtained for sonochemistry (27.3) and mechanochemistry (2.1), as well as Eco-scale scores calculated for sonochemistry (67) and mechanochemistry (72), unequivocally reflect the greenness of the mechanical methodologies.

The SSD device's rotational movement grinds the reactants placed in the stainless-steel cylindrical reactor (Fig. 1). This new device combines the mortar's simplicity and an automated apparatus's reproducibility.²¹ The apparatus was successfully employed for di- and tri-component reactions to prepare several chalcones 78 (71% to 99% yields) (Scheme 18, eqn (1)), 3,4-dihydropyrimidinones (55–98%) (Scheme 18, eqn (2)), 4,6-diaryldihydropyrimidinones and 4,6-diaryldihydropyrimidinethiones (Scheme 18, eqn (3), 47–96% yields) and 5-(4-iodophenyl)-1,3-diphenyl-1*H*-pyrazoline (Scheme 18, eqn (4), 42% yield). Almost all reactions performed with this custom-made SSD device (except for pyrazoline formation) afforded equal or superior yields than other mechanochemical- or solution-based methods.^{128,130–139} For diphenyl chalcone 78, the *E*-factor score was significantly better using the SSD device (0.17) than any green procedures (solvent-free procedure ground with mortar and pestle) previously reported (*E*-factor: 0.39 to 0.51).^{130–132} In contrast, the Eco-scale (74.5) was slightly worse than the solvent-free protocol (grinding with mortar and pestle) developed by Shan *et al.* (Eco-scale score of 78).¹³¹

The SSD device was also used for the Biginelli synthesis of 3,4-dihydropyrimidine-2-(1*H*)-thione 79 by reacting methyl acetate, benzaldehyde and urea. The *E*-factor and Eco-scale scores were equal to 0.22 and 76, respectively. However, an already existing protocol by M'Hamed *et al.* using solvent-free and ball mill strategy was better in terms of *E*-factor (0.16) and Eco-scale (81).¹³³ *E*-Factor and Eco-scale for the SSD preparation of 4,6-diphenyldihydropyrimidinone 80 were 0.78 and 63, respectively, which are environmentally favourable when compared to performing the in acetonitrile

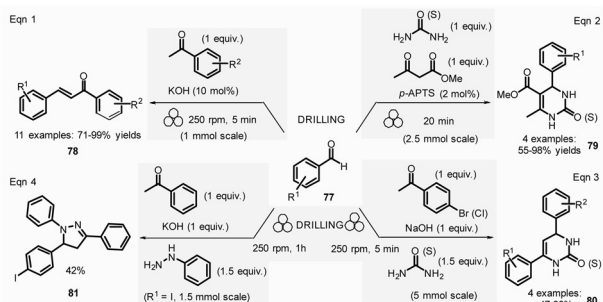


Green metrics

| Compound | <i>E</i> -factor | Eco-scale | | |
|--------------------------------------|------------------|-----------|-----------------|------|
| Mechanochemical route | | | | |
| 76 | 2.1 | 72 | | |
| Solution-based route | | | | |
| 76 (by sonochemistry) | 27.3 | 67 | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | SS | 10 mL | 2 | 7 mm |

Scheme 17 Metalloporphyrin synthesis by mechanochemistry.





Green metrics

| Compound | E-factor | Eco-scale |
|-------------------------------|----------|-----------|
| Mechanochemical route | | |
| 78 (SSD) | 0.17 | 74.5 |
| 78 (mortar and pestle) | 0.39 | 78 |
| 79 (SSD) | 0.22 | 76 |
| 79 (PBM) | 0.16 | 81 |
| 80 (SSD) | 0.78 | 63 |
| 81 (SSD) | 1.70 | 18 |
| 81 (PBM) | 2.72 | 40.5 |
| Solution-based route | | |
| 78 | NA | NA |
| 79 | NA | NA |
| 80 | NA | NA |
| 81 | NA | NA |

Milling processing conditions

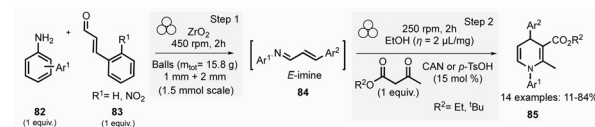
| Type of mill | Material | Jar size | Number of balls | Size |
|----------------------|----------|----------|-----------------|------|
| PBM (for 79) | SS | 45 mL | 22 | 10 |
| PBM (for 81) | SS | 35 mL | 35 | 5 |

Scheme 18 Mechanochemical synthesis of chalcones, dihydropyrimidones (or thiones), and a 1H-pyrazoline.

under basic or acidic conditions.^{135–137} The SSD procedure still remained relevant when compared to solvent-free microwave reaction under acidic conditions for **80**.¹³⁶ For 5-(4-iodophenyl)-1,3-diphenyl-1H-pyrazoline **81**, the E-factor (1.70) was slightly more favourable for the SSD device than the high-speed ball milling counterpart (2.72),¹³⁸ but the Eco-scale was more favourable for ball milling (40.5) compared to 18 by SSD device).

In 2022, Blazquez-Barbadillo *et al.* synthesized unsymmetrical 1,4-diaryl-1,4-dihydropyridines **85** by a one-pot, two-step mechanochemical reaction (Scheme 19).¹¹⁵ The reaction is ball-milled in a PBM for 2 h for the first step with 1 equivalent of aldehyde **83** and 1 equivalent of aromatic amine **82** to produce intermediate E-imine **84**. Subsequently, an equimolar amount of β-ketoester, catalyst, and ethanol are added, and the reaction vessel and ball-milled for additional 2 hours. The final unsymmetrical 1,4-diaryl-1,4-dihydropyridines **85** were purified by silica gel column chromatography, also used in the solution-based process. The greenness of the reaction was compared to the solution based-procedure using DOZN 2.0 tool.¹⁶

An aggregate score of 1 was obtained for both methods. However, the individual scores for the subgroups of principles showed better resource use (group 1) and a better reduced



Green metrics

| Compound | DOZN scores | |
|------------------------------|-------------|---------|
| | Group 1 | Group 2 |
| Mechanochemical route | | |
| 85 | 5.50 | 11.76 |
| Solution-based route | | |
| 85 | 9.14 | 32.5 |

Milling processing conditions

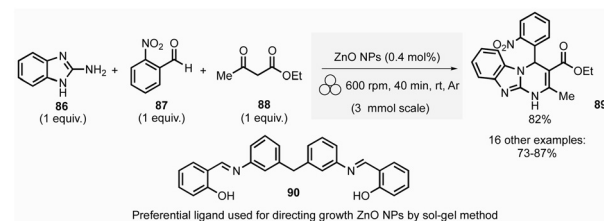
| Type of mill | Material | Jar size | Number of balls ^a | Size |
|--------------|------------------|----------|------------------------------|------------|
| PBM | ZrO ₂ | 12 mL | 15.8 g | 1 and 2 mm |

^a Due to the small size of the balls, the total weight of balls is indicated instead.

Scheme 19 1,4-Dihydropyridine synthesis by ball-milling.

human and environmental hazards (group 3) (5.50 vs. 9.14 and 11.76 vs. 32.5, respectively) for the ball-milling method compared to solution-based procedures.

Jang *et al.* described an MCR mechanical synthesis of 2-aminobenzimidazoles and pyrimidines derivatives using ZnO nanoparticles (ZnO NPs) as the catalyst.¹⁴⁰ The most effective ZnO NPs catalyst was prepared *via* a sol-gel method employing a specific directing agent (Scheme 20). Under optimal reaction conditions at room temperature and under an inert argon atmosphere, the condensation reaction of equimolar amounts of 2-aminobenzimidazole **86** (3.0 mmol), 2-nitrobenzaldehyde **87** (3.0 mmol), and ethyl acetoacetate **88** (3.0 mmol), catalysed by ZnO NPs (0.4 mol%), occurs in a tungsten carbide jar containing 20 milling balls (5 mm Ø) at 600 rpm for 40 min. The corresponding benzoimidazopyrimidine



Green metrics

| Compound | E-factor | Eco-scale |
|------------------------------|----------|-----------|
| Mechanochemical route | | |
| 89 | 0.28 | 67 |
| Solution-based route | | |
| 89 | 0.24 | 66 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| PBM | WC | 80 mL | 20 | 5 mm |

Scheme 20 Model reaction for benzoimidazopyrimidine synthesis by mechanochemistry.



89 was isolated in 82% yield by recrystallization from a water/acetone mixture. Interestingly, the catalyst was recycled up to 5 times without any efficiency loss. This method produces a higher yield, in a shorter reaction time, with a more straightforward purification step than other protocols reported in the literature. When condensations were led with different alkyl-, aryl- or heteroarylaldehydes from 2-aminobenzimidazole and ethyl acetoacetate, pyrimidines were isolated in range of 73–87% yield (16 examples). When 2-aminobenzothiazole were employed as starting material, 5 other pyrimidines were produced in 72–82% yields, and finally, when urea or thiourea were used, 4 other compounds were obtained in 77–80% yields. It is noticed that a large-scale reaction (60 mmol) was also performed between 2-aminobenzimidazole, benzaldehyde and ethyl acetoacetate, and an equivalent yield to the smaller scales was observed.

For the reaction presented in Scheme 20, an Eco-scale score of 67 and an *E*-factor of 0.28 were obtained. These values showed to be better^{141–144} or comparable (66 and 0.24)¹⁴⁵ to other methodologies reported with or without solvents. In addition, Jang *et al.* method¹⁴⁰ is better than Liu's method¹⁴⁵ in solution due to both reduced reaction time (40 min *vs.* to 3 h) and temperature (room temperature *vs.* 100 °C, respectively).

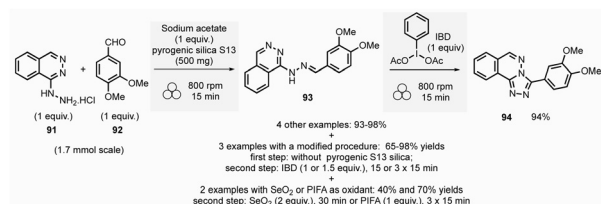
Baltas *et al.* developed a mechanochemical route to annulated 1,2,4-triazoles **94** using a one-pot, two-step strategy (Scheme 21).¹⁴⁶ For this purpose, equimolar amounts of 1-hydrazinophthalazine hydrochloride **91** and 3,4-dimethoxybenzaldehyde **92** absorbed on silica were ground with sodium acetate producing the corresponding hydrazine **93**.

This reaction was conducted on a 1.7 mmol scale with zirconium oxide jars (20 mL) containing five ZrO₂ balls (10 mm \varnothing) and milled at 800 rpm for 15 min in a PBM. Moreover, adding iodobenzene diacetate (IBD, 1 equiv.) as an oxidizing agent afforded the intramolecular cyclization product

after milling at 800 rpm for 15 min. The annulated triazole **94** was obtained in 94% yield. A small library of triazoles was synthesized employing the same strategy on four nonphenolic aromatic aldehydes (yields 93–98%), or using a modified procedure for three heteroaryl carboxaldehydes (conditions for the 1st step: without pyrogenic silica, 800 rpm, 3 \times 15 min, 2nd step: IBD = 1 or 1.5 equiv., 800 rpm, 3 \times 15 min; yields 65–98%). Selenium oxide or PIFA were also used as an oxidant in the reaction with *p*-hydroxy-benzaldehyde or vanillin, leading to the corresponding annulated 1,2,4-triazoles **94** in 40% or 70% yield (conditions first step: pyrogenic silica, 800 rpm, 15 min, and second step: SeO₂ = 2 equiv., 800 rpm, 30 min). Based on these results, the use of an oxidant based on hypervalent iodine salts (*e.g.*, IBD) not only delivered a better yield of 1,2,4-triazoles **94**, but displayed a lower toxicity profile compared to the use of SeO₂.

Green metrics for each mechanochemical step were calculated and compared for the mechanochemical synthesis (Scheme 21, conditions used in the 1st step: without pyrogenic silica and 2 \times 15 min, and in the 2nd-step 3 \times 15 min) and solution methods (conditions in the 1st step: EtOH, AcONa, reflux, 1 h and in the 2nd-step: IBD, CH₂Cl₂, 4 h). The *E*-factor calculated for the mechanochemical synthesis was 4 for the 1st-step and 12 for the 2nd-step, whereas for the solution-based protocol were higher (14 and 84, respectively).

Sharma *et al.* developed a 3-component reaction leading to fused pyrano-spirooxindoles *via* manual mortar and pestle grinding.¹⁴⁷ Equimolar amounts of isatin **95** and malononitrile were first ground for 10 min, followed by the addition of dimedone and then a further 15 min grinding (Scheme 22). Using malonitrile or ethyl cyanoacetate with several isatin derivatives or acetanaphthalenequinone, and different cyclic 1,3-diketones, a series of sixteen amino-2-oxospiro[indoline-3,4'-pyran]-3'-carbonitriles were produced in excellent yields (87–96%). After filtration and washing with water, pure pyrano-spirooxindole **96** was obtained in 94% yield. From the model reaction shown in Scheme 22 (5.0 mmol scale), an excellent *E*-factor (0.054), as well as good atom economy (95%), reaction mass efficiency (95%), and carbon economy (94.91%), were calculated. However, no comparison with other methodologies was provided by the authors.



Green metrics

| Compound | <i>E</i> -factor |
|------------------------------|------------------|
| Mechanochemical route | |
| 93 | 4 |
| 94 | 12 |
| Solution-based route | |
| 93 | 14 |
| 94 | 84 |

Milling processing conditions

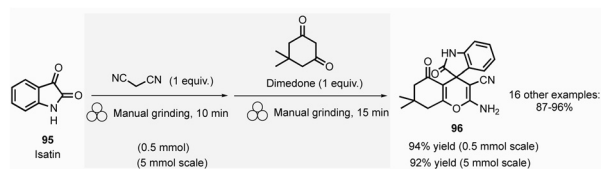
| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|------------------|----------|-----------------|-------|
| PBM | ZrO ₂ | 20 mL | 5 | 10 mm |

Scheme 21 One-pot two-step sequence for annulated 1,2,4-triazole by mechanochemistry.

Catalytic processes mediated by transition metals or acids

Bolm *et al.* described a new solvent-free method for *N*-sulfonylations of sulfoximines and sulfonimidamides by disulfides mediated by silver oxide.¹⁴⁸ The typical reaction (Scheme 23, eqn (1)) consisted in grinding equimolar amounts of *S*-methyl *S*-phenyl sulfoximine **97** (1 equiv.) with diphenylsulfide **98** (1 equiv.), in the presence of silver oxide (0.5 equiv.) and silica gel (60 mg), in a stainless-steel milling jar (10 mL) loaded with one stainless-steel ball (10 mm \varnothing) for 90 min at 30 Hz under atmospheric conditions. The resulting phenylthioimino sulfanone **99** was isolated in high yields (92%). On a larger scale



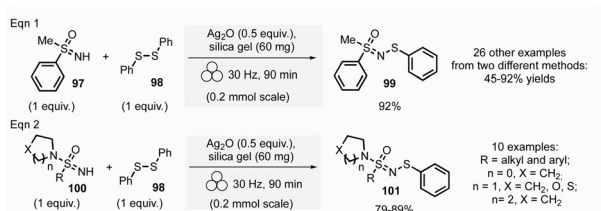


Green metrics

| Compound | E-factor | AE (%) | RME (%) | CE (%) |
|--------------------------------------|----------|----------|-----------------|--------|
| Mechanochemical route | | | | |
| 96 | 0.054 | 95 | 95 | 94.91 |
| Solution-based route | | | | |
| 96 | NA | NA | NA | NA |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| Mortar and pestle | NA | NA | NA | NA |

Scheme 22 Model reaction for 2-amino-2-oxospiro[indoline-3,4'-pyran]-3'-carbonitrile synthesis by manual grinding.

(5.0 mmol), and modifying the reaction conditions (30 Hz for 10 min followed by heating for 30 min in an oven at 80 °C), the corresponding sulfenyl product **99** was obtained in 85% yield after purification by column chromatography. The authors extended this methodology (0.2 mmol scale, 30 Hz for 90 min) to a wide range sulfoximines and sulphides substrates. Twenty-seven *N*-sulfenylation products were obtained in yields ranging from 45 to 92%. Sulfonimidamides **100** were also tested with success on diphenylsulfide **98**, leading to a library of ten compounds **101** in yields ranging from 79% to 89% yields (Scheme 23, eqn (2)). The efficiency of the *N*-sulfenylation of *S*-methyl *S*-phenyl sulfoximine with diphenylsulfide was compared to the reaction in solution (dichloroethane, 80 °C, 7 h, air atmosphere, 90% yield). An *E*-factor of 2.3 was obtained by



Green metrics

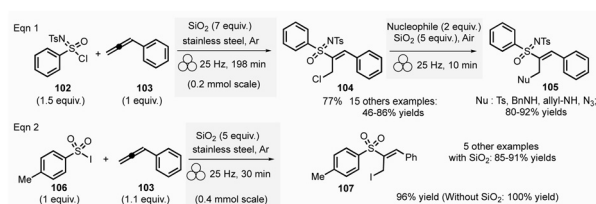
| Compound | E-factor | | | |
|--------------------------------------|----------|----------|-----------------|-------|
| Mechanochemical route | | | | |
| 99 | 2.3 | | | |
| Solution-based route | | | | |
| 99 | 27.6 | | | |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | SS | 10 mL | 1 | 10 mm |

Scheme 23 *N*-Sulfenylations of sulfoximines and sulfonimidamides by mechanochemistry.

mechanical milling (30 Hz, 90 min), unambiguously highlighting the superiority of ball-milling over the solution-based strategy (*E*-factor 27.6). A further advantage could be attributed to mechanochemistry is its efficiency for *N*-sulfenylation of *S*-methyl *S*-phenyl sulfoximine with dialkyl disulfides – not achieved in solutions, as previously mentioned.

In 2022, Bolm *et al.* developed a regioselective chlorosulfoximidation of allenes by ball milling.¹² Surprisingly, the reaction appeared to be catalyzed by traces of metal coming from the stainless-steel jar. The traces of metal generate a sulfoximidoyl radical, which subsequently adds to allene. The typical reaction procedure consisted in grinding sulfoximidoyl chloride **102** (1.5 equiv.), phenylallene **103** (1 equiv.), and silica (7 equiv.) in a stainless-steel milling jar (10 mL) containing 10 stainless-steel balls (5 mm \varnothing) at 25 Hz for 198 min under argon (Scheme 24, eqn (1)). The chlorosulfonylalkene **104** was obtained after column chromatography in 77% yield. Fifteen compounds were synthesized by mixing *N*-tosyl arylsulfoximidoyl chlorides, with mono- or disubstituted allenes. Notably, all the reactions performed were fully regioselective, leading to a single isomer in 46 to 82% yields. The obtained chlorosulfonylalkenes **104** were subsequently reacted with a series of heteroatom-based nucleophiles (sodium toluenesulfinate, benzylamine allylamine, and sodium azide). Reactions were performed on a 0.1 mmol scale with a stainless-steel milling jar (5 mL) containing one stainless-steel ball (7 mm \varnothing) at 25 Hz for 10 min under an air atmosphere. The corresponding substituted products **105** were obtained in excellent yields (80–92%).

Notably, *p*-toluenesulfonyl iodide **106** was also able to react with phenylallene **103** (Scheme 24, eqn (2)). The reaction was carried out in a stainless-steel milling jar (10 mL) containing ten stainless-steel balls (5 mm \varnothing) at 25 Hz for 30 min under argon. The iodovinylsulfonyl derivative obtained **107** was



Green metrics

| Compound | E-factor | MI | RME (%) | ME (%) |
|--------------------------------------|----------|----------|-----------------|--------|
| Mechanochemical route | | | | |
| 107 | 0.85 | 1.85 | 93.4 | 13.4 |
| Solution-based route | | | | |
| 107 | 17.08 | 18.08 | 61.1 | 1.3 |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| VBM | SS | 10 mL | 10 | 5 mm |

Scheme 24 Chlorosulfoximidation of phenylallene followed by subsequent nucleophilic substitutions, and iodosulfonations of arylallenes by mechanochemistry.



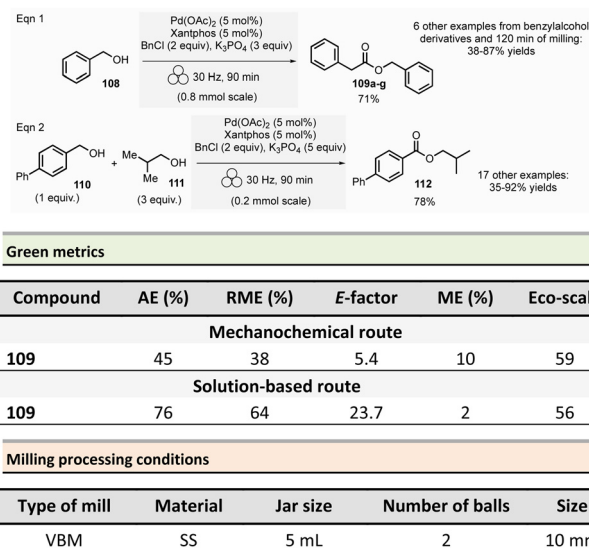
isolated in 96% yield or even quantitatively in the absence of silica. Five other alkenes were also obtained from aryl allenes in the presence of silica (85–91%).

Comparison of green metrics (Scheme 24, eqn (2)) was favourable to mechanochemistry with respect to solution methods (*E*-factor: 0.85 vs. 17.08, mass intensity: 1.85 vs. 18.08, RME: 93.4% vs. 61.1%, molar efficiency: 13.4% vs. 1.3%).¹⁴⁹ These parameters were even better when milling in the absence of silica (100% yield). In such conditions, an *E*-factor of 0.03, a mass intensity of 1.03, a RME of 97.2% and a molar efficiency of 47.6% were obtained. An extra underlining advantage was the absence of purification.

The same team also published a palladium-catalyzed oxidative procedure for the esterification of alcohols by ball-milling.¹⁵⁰ The previous green protocols for this reaction generally used heterogeneous catalysis or microwave irradiation,^{151–153} which required high temperature, high pressure, organic solvents, and excess alcohol.

Bolm *et al.* also developed a new mechanochemical method for the self-esterification of alcohols using Pd(OAc)₂ (5 mol%) and xantphos (5 mol%) as the catalytic system, in the presence of benzyl chloride (2 equiv.) and K₃PO₄ (3 equiv.) as a base. The best yields were observed when the reaction was carried out in a 0.8 mmol scale milling of compound **108** for two hours at 30 Hz using a stainless-steel milling jar (5 mL) loaded with two milling balls (10 mm \varnothing). In this manner, from benzyl alcohol (**108**) seven esters **109** were obtained in yields ranging from 38% (4-NO₂C₆H₄CH₂OH) to 87% (4-MeO-3-FC₆H₃CH₂OH) after a column chromatography). The method is versatile because it is possible to obtain mixed esters starting from two different alcohols. In the best reaction conditions, at 0.2 mmol scale, one stainless-steel ball was used to react [1,1'-biphenyl]-4-yl methanol derivative **110** (1 equiv.), 2-methyl-propan-1-ol **111** (3 equiv.) and K₃PO₄ (5 equiv.) using the same amounts of catalyst, ligand, and oxidant. After purification on column chromatography, these conditions gave the desired ester **112** (78% yield). In addition, chromatographic purification was required to eliminate two side-products – [1,1'-biphenyl]-4-yl-methyl-[1,1'-biphenyl]-4-carboxylate (4%) and isobutyl isobutyrate (20%), still present in the reaction mixture. Applying this procedure, seventeen mixed esters were obtained starting from various benzyl alcohols and primary or secondary alkyl alcohols (35–92% yields).

The metrics for the mechanochemical self-esterification were compared with those for solution-based protocols: with values of AE (45%) and RME (38%) for the ball-milling method (Scheme 25, eqn (1)). In solution, the AE was 76%, and the RME was 64%. For this specific method, the green metrics are better for the solution-based process, due to the greener nature of the oxidant used (O₂), replaced by two equivalents of benzyl chloride in the ball-milling reaction.¹⁵⁴ Nevertheless, the *E*-factor and the molar efficiency (5.4 and 10%, respectively) are better than in solution (23.7 and 2%, respectively) due to the absence of solvent during the ball-milling process. The Eco-scales for both mechanochemistry and in solution were comparable (59 vs. 56). For the cross-esterification (Scheme 25, eqn (2)),



Scheme 25 Palladium-catalyzed oxidative self-esterification and cross-esterification by mechanochemistry.

the AE was better in solution than in ball-milling (79% vs. 50%).¹⁵⁵ Nevertheless, RME (24% vs. 30%), *E*-factor (30.7 vs. 7.9), molar efficiency (1 vs. 7), and Eco-scale (31 vs. 60) are favourable to the mechanochemical routes.

Guo *et al.* reported the mechanochemical cross-coupling reaction of 2-mercatobenzothiazoles and bromoacetophenone derivatives. The catalytic response is mediated by a transition metal-*N*-Heterocyclic carbene (metal-NHC) complex ([NiLBr]PF₆) **118** (Scheme 26, eqn (1)).¹⁵⁶ For instance, the [NiLBr]PF₆ complex was readily obtained using a four-step mechanochemical synthesis. The benzimidazole **113** and 2-chloromethylpyridine **114** were first ground in the presence of NaOH and water ($\eta = 0.01 \mu\text{L mg}^{-1}$) to produce *N*-pyridylmethylbenzimidazole **115** (95% yield). This compound was then treated with dibromomethane under milling conditions to afford benzimidazolium salt **116** ([H₂L]Br₂, 38% yield).

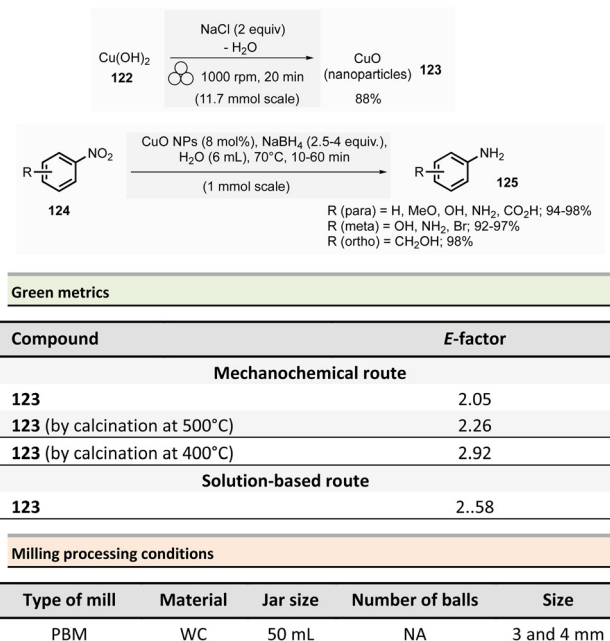
Then, [H₂L]Br₂ was reacted by manual grinding (agate mortar and pestle) with Ni(OAc)₂ under LAG conditions ($\eta = 0.71 \mu\text{L mg}^{-1}$) [MeCN/H₂O (1:1) or MeCN/MeOH (1:1)] to afford [NiL]Br₂·2H₂O and [NiL]Br₂·MeOH **117** almost quantitatively. Lastly, to the obtained 1:1 mixture of complexes, an anion exchange reaction was performed by manual mixing with ammonium hexafluorophosphate affording the catalyst [NiLBr]PF₆ **118** in 97% after recrystallization.

Catalyst **118** (1.8 mol%) was then used for the reaction of 2-bromoacetophenone **120** (1 equiv.) with 2-mercaptobenzothiazole **119** (1 equiv.) under manual grinding (agate mortar) in order to avoid potential catalytic activity of balls which are used under ball milling process. The use of 30 μL of methanol in LAG conditions ($\eta = 0.08 \mu\text{L mg}^{-1}$) enabled 93% yield (61% with 1.2 mol% of catalyst) of the desired product **121** after purification by silica gel chromatography (Scheme 26, eqn (2)). By comparison, only 25% yield was obtained in solution at room temperature with 1.2 mol% of catalyst loading. Eight other benzothiazolylthioketones **121a-i** were synthesized in low



to good yields (16–88%). Although for the reaction presented in Scheme 26 (eqn (2)), the *E*-factor was 0.520, and the Eco-scale score equals 76.5, no comparison was made with the solution-based protocol.

In 2021, Barcellos *et al.* published a simple and efficient one-step mechanochemical preparation of copper oxide(II) nanoparticles (CuO NPs), which were later employed to catalyze the reduction of nitroarenes.¹⁵⁷ Several other mechanochemical routes to CuO NPs were previously reported using diverse copper sources (*e.g.*, Cu(OAc)₂·2H₂O,^{158,159} CuSO₄·5H₂O,¹⁶⁰ CuCl₂·2H₂O,¹⁶⁰ and Cu(OH)₂¹⁶¹). After calcination at 400 °C and 500 °C, the NPs obtained from Cu(OAc)₂·2H₂O presented an average size of 75 nm and 86 nm, respectively. Smaller CuO NPs (7 nm to 34 nm) were obtained by grinding CuSO₄·5H₂O and CuCl₂·2H₂O at slow rotating (290–300 rpm) for 1–3 h in the presence of sodium hydroxide/sodium chloride. A similar particle size was observed by grinding sodium chloride with Cu(OH)₂. Finally, Barcellos *et al.* managed the synthesis of ultra-small and quasi-spherical CuO NPs (7.84 ± 2.08 nm) in gram-scale by a straightforward and fast eco-friendly one-pot protocol (Scheme 27, eqn (1)). The reaction was carried out by milling Cu(OH)₂ (122, 1 equiv.) and sodium chloride (2 equiv.) acting as a grinding agent and avoiding paste-like mixture, for 20 min at high-speed (1000 rpm) using high-energy tungsten carbide mill jars containing tungsten carbide balls (3 and 4 mm Ø, 1:1 w/w). The quasi-spherical nanoparticles of copper oxide 123 were recovered after repeated water treatment and drying steps with 88% yield.

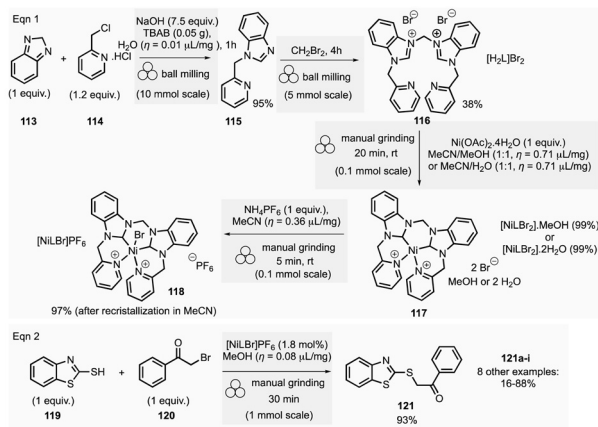


Scheme 27 Mechanochemical preparation of CuO nanoparticles and nitroarene reductions mediated by CuONPs in water.

Green metrics assessment for the NPs synthesized from different copper salts was also performed. Comparing the atom economy (AE), Cu(OH)₂ turned out to be the best metal precursor as per the Barcellos' procedure, with an AE of 81.54%, followed by CuCl₂ (59.17%). Considering a yield of 88%, the real atom economy (RAE) was 71.8%. Moreover, for the same reaction, the *E*-factor was equal to 2.05 when water was not considered. The "complete" *E*-factor reached 38.63 when water is taken into consideration.

If NaCl could be recycled during the process, the *E*-factor would have been only 0.39. Among all the methods described in the literature, mechanical preparations of CuONPs from Cu(OAc)₂/urea,¹⁵⁹ and Cu(OAc)₂/ammonium oxalate¹⁵⁸ followed by calcination at 500 °C and 400 °C resulted greener with an *E*-factors of 2.26 and 2.92 vs. 38.63, respectively. Nevertheless, such *E*-factor calculations were performed with an estimated yield of 99%. The mass of oxygen during the calcination step was also not considered, which can skew the comparison between these different protocols. It can be noticed that the solution-based procedure (Cu(NO₃)₂·3H₂O¹⁶²) displayed comparable *E*-factor values (2.58 and 28.04 for *E*-factor and complete *E*-factor, respectively). Finally, the catalytic efficiency of the nanoparticles prepared by Barcellos *et al.* was determined by reduction of nitroarenes 124, using 8 mol% of catalyst and 2.5 to 4 equivalents of NaBH₄ in water at 70 °C for 10–60 min. For all reactions, aniline derivatives 125 were produced in excellent yields (92–98%). Moreover, using nitrobenzene as substrate, CuONPs catalyst could be reused five times without significant loss of efficacy.

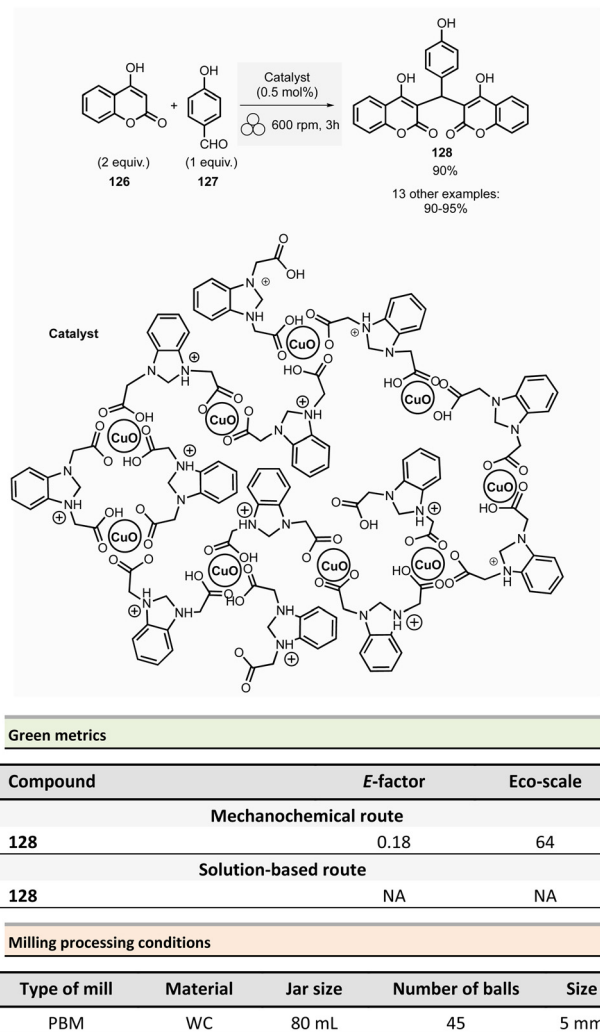
In an original article, Singh *et al.* described the synthesis of fourteen bis-coumarins in 90 to 95% yields by mechanical ball-milling. The reaction consisted of a double condensation



| Green metrics | | |
|-------------------------------|------------------|-----------|
| Compound | <i>E</i> -factor | Eco-scale |
| Mechanochemical route | | |
| 121 | 0.520 | 76.5 |
| Solution-based route | | |
| 121 | NA | NA |
| Milling processing conditions | | |
| Type of mill | Material | Jar size |
| Mortar and pestle | agate | NA |

Scheme 26 Metal-NHC catalyzed alkylation of 2-mercaptobenzothiazole (by manual grinding or ball-milling).

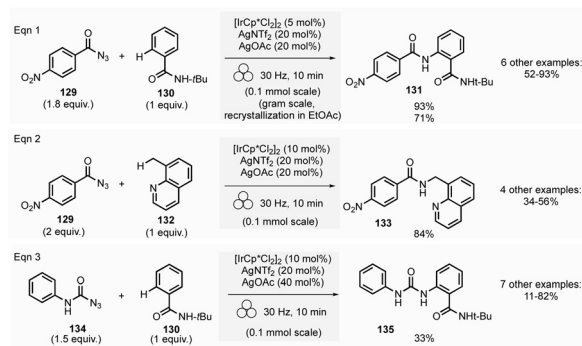




Scheme 28 Model reaction of bis-coumarin synthesis by mechanochemistry.

of 4-hydroxycoumarin **126** with various aryl or heteroaryl aldehydes **127** with a zwitterionic liquid coated CuO as catalyst (Scheme 28).¹⁶³

As a representative example, 4-hydroxycoumarin **126** (2 equiv.), 4-hydroxybenzaldehyde **127** (1 equiv.), and the catalyst (0.5 mol%) were milled at 600 rpm for 3 h in a grinding jar containing 45 tungsten carbide balls (5 mm \varnothing). A simple water and methanol washing afforded the bis coumarin **128** in 90% yield (95% from benzaldehyde). Most of the methods describing the condensation reaction of 4-hydroxycoumarin **126** with 4-hydroxybenzaldehyde in solution gave lower yields (66–93%),^{164,165} except for work by Su *et al.* where a higher yield (97%) was obtained by performing the reaction under reflux in ethanol.¹⁶⁶ However, this reaction required a longer reaction time (24 h) when compared to the mechanochemical route (3 h). In addition, the catalyst employed during the mechano-catalytic reaction was reused 10 times without any loss of efficiency. When the mechanochemical reaction was carried out at a 10 mmol scale, the Eco-scale score was equal to 64 and the E-factor to 0.18.



| Green metrics | |
|------------------------------|---------|
| Compound | RAE (%) |
| Mechanochemical route | |
| 131 | 47 |
| 133 | 38 |
| Solution-based route | |
| 131 | 24 |
| 133 | 8 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|-------|
| VBM | Teflon | 10 mL | 1 | 10 mm |

Scheme 29 C–H amidation of acyl and carbamoyl azides mediated by Ir(III) catalyst by mechanochemistry.

Gon Kim *et al.* developed the direct aryl C–H amidation of acyl and carbamoyl azides mediated by an iridium(III) catalyst (Scheme 29).¹⁶⁷ Acyl azides are thermally unstable and prone to Curtius rearrangement into isocyanates at 50 °C. To avoid the formation of isocyanate, the C–H activation was attempted at room temperature.^{168,169} In their preliminary work, Gon Kim *et al.* investigated the stability of 4-nitrobenzoyl azide under solvent-free milling (1 h, 30 Hz) using different milling apparatuses and conditions. The energy transferred to the reaction system had to be controlled to limit the formation of isocyanate. Their studies highlighted that a Teflon jar (2.2 g cm⁻³) with stainless-steel balls was the best-performing milling media. In comparison, ZrO₂ (5.7 g cm⁻³), stainless-steel (7.9 g cm⁻³), or tungsten carbide (15.6 g cm⁻³) jars and balls produced 7 to 21% of the undesired Curtius rearrangement. Further, C–H amidation optimization was carried out at 0.1 mmol scale by reaction of *p*-nitrobenzoyl azide **129** (1.8 equiv.) and *t*-butylbenzamide **130** (1 equiv.) (Scheme 29, eqn (1)). The best conditions found for this reaction consisted in grinding both substrates with the catalyst (*i.e.*, [Cp*IrCl₂]₂, 5 mol%), and a combination of silver salts (AgNTf₂, 20 mol%, and AgOAc 20 mol%). The mixture was milled in a Teflon jar (10 mL) with one stainless-steel ball (10 mm \varnothing) for 10 min at 30 Hz producing the desired bis amide **131** in 93% yield. A gram-scale synthesis afforded desired product **131** after 20 min of grinding, followed by recrystallization in ethyl acetate in 71% yield (Scheme 29, eqn (1)). A combination of various benzoyl azides **134** and benzamides **130** or 8-methylquinoline **132** in the presence of 5 to 10 mol% of iridium catalyst was



studied either by ball-milling or in solution (1,2-dichloroethane). Eleven other amides were formed. Yields were better by mechanical stirring or very close to those obtained in 1,2-dichloroethane (Scheme 29, eqn (1) and (2)).

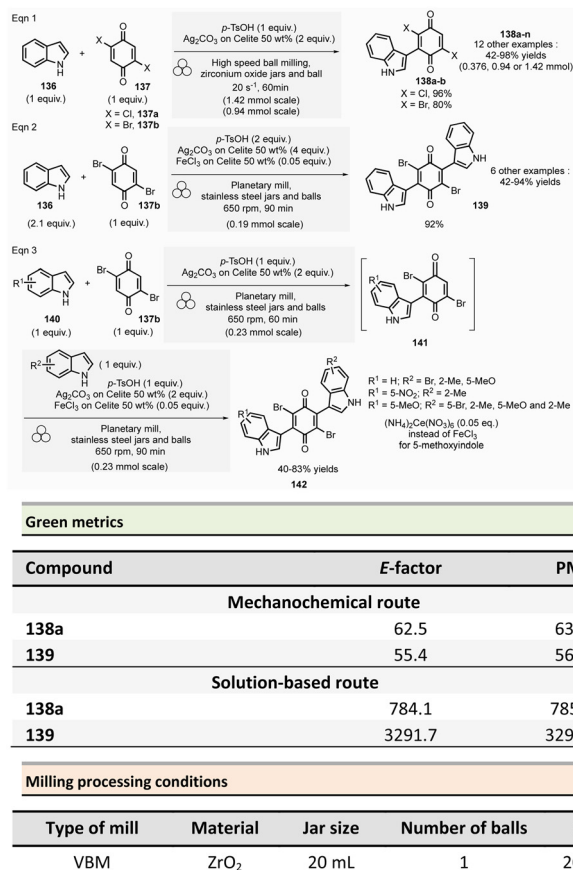
Authors also extended this C–H amidation to carbamoyl azides by both mechanical grinding and solution phase reactions. Eight ureas were obtained in 11 to 82% yields. Notably, in all cases, yields were in favour of mechanochemistry. The authors calculated the RAE for the first two reactions (Scheme 29, eqn (1) and (2)). For *N*-(*tert*-butyl)-2-(4-nitrobenzamido)benzamide **131**, the RAE was better for the ball-mill method (47%) compared to the solution-based process (24%). For 4-nitro-*N*-(quinolin-8-ylmethyl)benzamide **133** synthesis, RAE was almost 5-fold better in mechanochemistry than in solution (*i.e.*, 38% *vs.* 8%, respectively).

Bis-indolylquinones are substances having multiple pharmacological activities. Menéndez *et al.* proposed an original synthesis of mono-indolylquinones or bis-symmetrical and unsymmetrical indolylquinones by mechanochemistry.¹⁷⁰ Mono-indolylquinones **138** were prepared, by grinding with a high speed ball-milling (HSBM), indole **136** (1 equiv.), 2,5-chloro- or 2,5-dibromoquinone **137** (1 equiv.), Fetizon reagent (Ag₂CO₃ on Celite, 2 equiv.) used as an oxidant in the presence of *p*-TsOH (1 equiv.) acting as Brønsted acid for 1 h at 20 Hz in a zirconium oxide jar (20 mL) containing one zirconium ball (20 mm Ø) (Scheme 30, eqn (1)). After purification by precipitation, the final products **139** (X = Cl or Br) were recovered in 96% and 80% yields, respectively (Scheme 30, eqn (1)). An extension of this reaction afforded 12 other indolylquinones **138** isolated in 42% to 98% yields.

Interestingly, this methodology allowed the preparation of symmetrical bis-indolylquinones **139** using a PBM (instead of HSBM due to unsatisfying results) rotating at 650 rpm for 90 min with changes in rotation direction every 2 min (reverse rotation). In a stainless-steel jar (12 mL) filled with thirty balls (5 mm Ø), indole **136** (2 equiv.) was ground with *p*-TsOH (2 equiv.), Fetizon reagent (4 equiv.) and FeCl₃ (5 mol%) on Celite (or CAN 5 mol% for 5-methoxyindole) (Scheme 30, eqn (2)).

The corresponding bis-indolylquinone **139** was synthesized in 92% yield. Six other products were prepared in 42% (from 5-bromo-1*H*-indole) to 94% yield (for 5-methoxy-2-methyl-1*H*-indole). Consecutively unsymmetrical bis-indolylquinones **142** were prepared using a one-pot, two-step synthetic route. The first step occurred in the conditions described above (650 rpm for 1 h) with indoles **136** (1 equiv.), Fetizon reagent (2 equiv.) and *p*-TsOH (1 equiv.). After completion of the reaction, the second step was launched by the addition of the second indole **136** (1 equiv.), *p*-TsOH (1 equiv.), Fetizon reagent (2 equiv.) and FeCl₃ (5 mol%) on Celite. The mixture was ground for 90 min. After a work-up, unsymmetrical bis-indolylquinones **142** were isolated in 40% to 83% yields.

All the mechanical reactions took place in shorter times than in solution (26–62 h). Furthermore, green metrics for mono-indolylquinone **138a** (X = Cl, Scheme 30, eqn (1)), the *E*-factor, and PMI showed to be better (62.5 and 63.5,



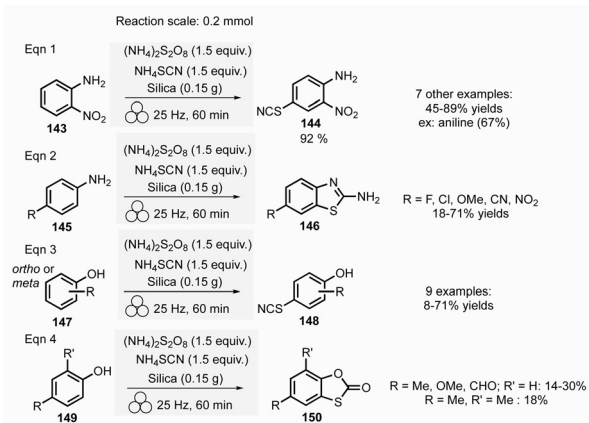
Scheme 30 Mechanochemical preparation of indolylquinones.

respectively) compared to solution-based reaction (784.1 and 785.1).¹⁷¹ In the same way, for the synthesis of bis-indolylquinone **139** (Scheme 30, eqn (2)), the difference between mechanochemistry (*E*-factor; 55.4, and PMI: 56.4) and the reaction in solution (*E*-factor: 3291.7, and PMI: 3292.7) was also in favourable to mechanical milling.¹⁷²

In 2020, Malvestiti *et al.* developed a mechanical protocol for the thiocyanation of aryl compounds *via* C–H functionalization.¹⁷³ Ball-mill reactions were all performed on a 0.2 mmol scale, without solvent, in short reaction times. The best conditions found for thiocyanation of *ortho*- and *meta*-substituted anilines were to grind together anilines (1 equiv.), ammonium thiocyanate (1.5 equiv.), and ammonium persulfate (1.5 equiv.) in the presence of silica (150 mg) in a stainless-steel jar (5 mL) with two balls (7 mm Ø) at 25 Hz for 1 h (Scheme 31, eqn (1)). When the reaction was performed in a Teflon jar a lower yield of 72% was obtained for **144**.

Starting from 2-nitroaniline **143**, the final product **144** was recovered in 92% yield. Next, the reaction was extended to seven anilines leading to the corresponding thiocyanate derivatives in 45% to 92% yields. The mechanochemical thiocyanation was fully regioselective, and only the *para*-amino thiocyanates **144** were observed. In the presence of a reactive neighbouring group, a further reaction occurred. Then 3-aminophenol afforded 6-aminobenzoxathiol-2-one in low yield (15%).





Green metrics

| Compound | AE | 1/SF | MRP | RME (%) | E-factor |
|------------------------------|------|------|------|---------|----------|
| Mechanochemical route | | | | | |
| 144 | 0.38 | 0.72 | 0.42 | 0.077 | 12.0 |
| Solution-based route | | | | | |
| 144 | 0.34 | 0.59 | 0.23 | 0.042 | 22 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|------|
| VBM | SS | 5 mL | 2 | 7 mm |

Scheme 31 Thiocyanation of aniline and phenol derivatives by mechanochemistry.

For *para*-substituted anilines **145**, the thiocyanation cannot occur in *para*-position (Scheme 31, eqn (2)).

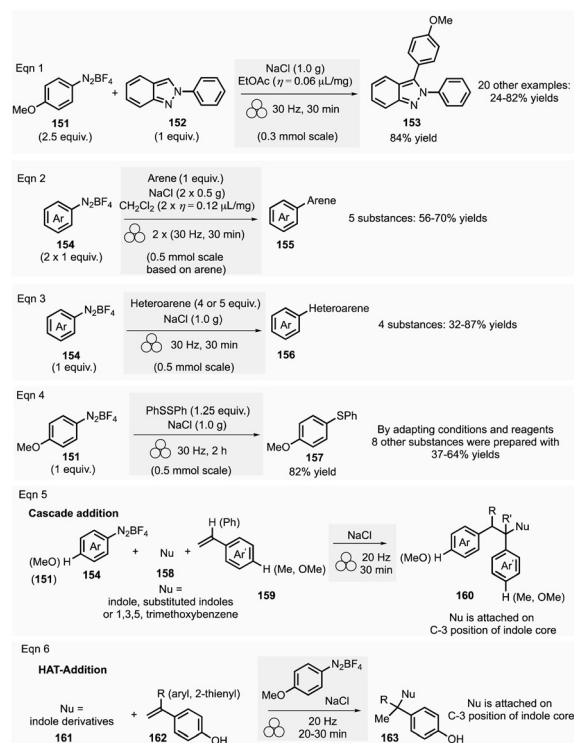
Consequently, the 2-aminobenzothiazoles **146** were isolated in 18–71% yields. The methodology was also applied to phenol derivatives (Scheme 31, eqn (3)).

Ortho- and *meta*-substituted phenols **147** led preferentially to *para*-thiocyanation products **148** in 8% to 94% yields (R = H, *para*-thiocyanation afforded 96% yield). The nature of the second group strongly influences the overall yields. As expected, electron-withdrawing groups have a detrimental effect, whereas the presence of an electron-donating one appeared favourable. By contrast with *para*-substituted anilines, *para*-substituted phenols gave benzooxathiol-2-ones **150** only in low yields (14–30%) (Scheme 31, eqn (4)). The mechanochemical thiocyanation was also extended to others arenes such as *N,N*-dimethylaniline, anisole, 1,2,3- and 1,3,5-trimethoxybenzene, thioanisole, 1-naphthol, and indole. The resulting thiocyanates were obtained in low to excellent yields (33–89%).

The green metrics were calculated for aniline as substrate, only considering the reaction without purification steps. AE values for ball-mill and solution reactions were comparable (0.38 vs. 0.34), while the yield was better for the solvent process (67% vs. 90%).¹⁷⁴ For the other parameters, ball-milling was significantly more favourable. The inverse of the stoichiometric factor (1/SF) was equal to 0.72 in mechanical milling, whereas it was only 0.59 for the conventional reaction. The MRP and RME values were 0.42 and 0.077 versus 0.23 and 0.042 in solution.

E-Factor exhibited the same tendency (12.0 vs. 22). These metrics stated the importance of avoiding both solvent use and reagents excess.

Yu *et al.* described the mechanochemical aryl radical formation by homolytic cleavage of aryldiazoniums.¹⁷⁵ The C–H (hetero)arylation of 1*H*- and 2*H*-indazoles, *N*-methyl-3-methylindole, benzothiazole, 2-methylthiophene, phenyl derivatives was developed. Typically, the reaction was performed on 0.3 mmol scale (Scheme 32, eqn (1)): 4-methoxyphenyldiazonium tetrafluoroborate **151** (2.5 equiv.), 2-phenyl-2*H*-indazole **152** (1.0 equiv.), NaCl (1.0 g) acting as a grinding agent and avoiding paste-like mixture, and one drop of EtOAc ($\eta = 0.06 \mu\text{L mg}^{-1}$) or CH₂Cl₂ (for 4-nitroaryldiazonium) were ground at 30 Hz for 30 min in a stainless-steel jar (15 mL) containing one stainless-steel ball (14 mm \varnothing). Ethyl acetate as LAG additive was necessary for the reaction.



Green metrics

| Compound | AE (%) | RME (%) | E-factor | Eco-scale |
|------------------------------|--------|---------|----------|-----------|
| Mechanochemical route | | | | |
| 153 | 58.7 | 22.1 | 3.5 | 75 |
| 157 | 39.1 | 32 | 2.1 | 71 |
| Solution-based route | | | | |
| 153 | 57.6 | 4.3 | 22.1 | 46 |
| 157 | 4.9 | 3.7 | 25.8 | 51 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|----------|----------|-----------------|-------|
| VBM | SS | 15 mL | 1 | 14 mm |

Scheme 32 C–H (hetero)arylations, C–H sulfonylations, cascade- and HAT-additions using aryldiazonium tetrafluoroborates by ball-milling.



The mixture was removed from the jar and purified by column chromatography to afford indazole **153** an 84% yield. Similarly, twenty others *1H* and *2H* indazoles were obtained in yields ranging from 24% to 87% (Scheme 32, eqn (1)). When 1,3,5-trimethoxybenzene, 1,3,5-trimethylbenzene, 1,4-dimethylbenzene, *N*-methyl-3-methylindole, benzothiazole, and 2-methylthiophene were used as substrates, modified conditions were applied. With arenes, two equivalents of aryldiazonium salt were added stepwise (1 equivalent each time) and ball-milled in the presence of NaCl (0.5 g each time) and CH₂Cl₂ as LAG additive ($\eta = 0.12 \mu\text{L mg}^{-1}$) added in two equivalent portions for each cycle (30 minutes twice, Scheme 32, eqn (2)). In the case of heteroarenes (eqn (3)), it was necessary to have 4 or 5 equiv. and no LAG additive for the homocoupling of heteroarenes. Besides, a simplified purification (liquid-liquid extraction) was adopted for arene coupling instead of the required column chromatography for heteroarenes. Final products were recovered in 56 to 70% yields for arenes (5 substances, Scheme 32, eqn (2)) and 32–87% yields for heteroarenes (4 substances, Scheme 32, eqn (3)).

Similarly, aryl- and heteroarylthioethers or arylpinacol boronate esters were obtained by transformation of heteroaryl- or aryldiazonium tetrafluoroborates, with dialkyl- or diarylsulfide or bis(pinacolato)diboron substrates in the presence of NaCl (Scheme 32, eqn (4)).

For instance, on a 0.5 mmol scale, milling methoxyphenyl-diazonium tetrafluoroborate (1 equiv.) with diphenyldisulfide (1.25 equiv.) and NaCl (1.0 g) at 30 Hz for 2 h, afforded, after column chromatography, the corresponding diarylthioether in 82% yield (Scheme 32, eqn (3)). Eight other thioethers were obtained in yields ranging from 37% to 64% and two aryl pinacolboronate esters in 52% yield when Ar = 4-ClC₆H₄- and 62% yield with Ar = 4-MeOC₆H₄-. As a representative example (4-methoxyphenyl)(phenyl)sulfane was scaled-up to an 8.0 mmol-scale milling for 3 h affording 62% yield. For such reactions, sodium chloride acted as an activator. Most halogen salts (NaCl, KCl, NaBr) were effective, while NaBF₄ and neutral alumina did not give the target products. The homolytic fragmentation was attributed to the relative instability of *in situ* formed aryl diazonium chlorides. The authors also demonstrated that the excess NaCl could be recycled and reused at least five times without significant yield loss (78% yield after the fifth time).

Yu *et al.*¹⁷⁵ also reported that 1,3,5-trimethoxybenzene or indole derivatives could undergo a C–H cascade addition starting from aryldiazoniums, and styrene derivatives in the presence of NaCl (Scheme 32, eqn (5)). Direct hydrogen atom transfer (HAT) addition of aryl radical was also efficient on position 3 of indoles starting from 4-hydroxystyrene derivatives (Scheme 32, eqn (6)). Finally, the aryl radical reaction promoted by NaCl was also extended to prepare five APIs (including dantrolene).

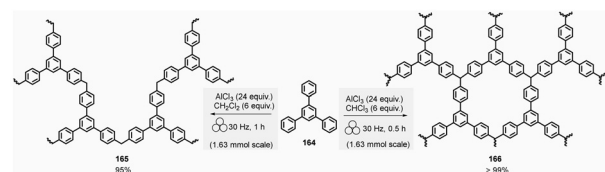
Green metrics were calculated for 2,3-diphenyl-2*H*-indazole synthesized by mechanochemistry and in solution (Scheme 32, eqn (1)).¹⁷⁶ An AE of 58.7% was found instead of 57.6% in solution, an *E*-factor of 3.5 vs. 22.1, a RME of 22.1% vs. 4.3% and a good Eco-scale score of 75 vs. 46 in solution. A similar

trend was observed for (4-methoxyphenyl)(phenyl)-sulfane **157** (Scheme 32, eqn (4)). Indeed, a better AE of 39.1% was calculated in the solventless process compared to 4.9% for the reaction done in solution.^{177,178} The *E*-factor value obtained was excellent, with 2.1 vs. 25.8 in solution. Even RME was better, with 32% compared to that one in solution, which was 3.7%. Finally, Eco-scale score was 71 in mechanochemistry and only 51 for solution-based reactions.

Generally speaking, especially for metal-catalysed reactions, the removal of the catalyst at the end of the process is a need. In this regard, any post-synthetic treatment, by liquid-liquid extraction or worst, when a purification by column chromatography is required, will negatively affect the green metrics and the entire environmental footprint of the mechanochemical process. This aspect has to be carefully evaluated with the purpose to design/conceive mechanochemical syntheses leading to a straightforward recovery of the final product, keeping at the minimum the number of operations required during the work-up procedures.

Miscellaneous

Borchardt's group published a synthesis of porous organic polymers (POPs) using ball-milling techniques. These POPs were synthesized by applying a Friedel-Crafts alkylation between 1,3,5-triphenylbenzene **164** (TPB) and an excess of a cross-linking reagent (CH₂Cl₂ or CHCl₃) in the presence of AlCl₃ (Scheme 33).¹⁷⁹ Similarly to the solution-based method, the use of harmful CH₂Cl₂ or CHCl₃ can not be avoided here, being linking agents. The advantage of conducting the synthesis by ball-milling limits the amount used, contrarily to the corresponding solution-based method, where they also act as solvents, and thus used in very large excess. The typical reaction consisted in grinding under an inert atmosphere, TPB **164** (1 equiv., 1.63 mmol) with CH₂Cl₂ or CHCl₃ (6 equiv.) and AlCl₃ (24 equiv.) for 1 h (CHCl₃) or 0.5 h (CH₂Cl₂) at 30 Hz in a ZrO₂ jar (50 mL) with twenty-two ZrO₂ balls (10 mm \varnothing), following by



Green metrics

| Compound | AE (%) | MI | MP | <i>E</i> -factor |
|------------------------------|--------|-------|------|------------------|
| Mechanochemical route | | | | |
| 165 | 47.12 | 10.56 | 9.47 | 8.42 |
| Solution-based route | | | | |
| 165 | 47.12 | 31.42 | 3.18 | 30.34 |

Milling processing conditions

| Type of mill | Material | Jar size | Number of balls | Size |
|--------------|------------------|----------|-----------------|-------|
| VBM | ZrO ₂ | 50 mL | 22 | 10 mm |

Scheme 33 Porous organic polymers (POPs) preparation by mechanochemistry.



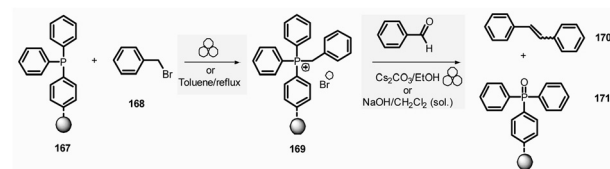
washing the resulting solid with water and acetone to remove the AlCl_3 excess and the residual starting material. A flexible and a rigid polymer were obtained in 95% (CH_2Cl_2) and quantitative yields (CHCl_3), respectively.

The solution-based reaction required a longer time (48 h) and a cleaning of the polymer using a Soxhlet extractor for 24 h.¹⁸⁰ Both procedures highlight that mechanical milling is advantageous by reducing the reaction time and the amount of cross-linking agent necessary. Regarding their properties, both polymers adsorb CO (4.37 mmol CO_2 per g for CH_2Cl_2 -based polymer and 4.74 mmol CO_2 per g for CHCl_3 -derivative).

These values were very close to those observed for the polymers synthesized in solution (4.35 mmol and 4.71 mmol CO_2 per g for CH_2Cl_2 - and CHCl_3 -based polymers, respectively). Additionally, selectivity between N_2/CO_2 was calculated using ideal adsorption solution theory (IAST) method displaying 73.98 (90/10) for CH_2Cl_2 and 93.81 (90/10) for CHCl_3 .¹⁸¹ Authors demonstrated that the specific surface areas (SSA_{BET}) of CH_2Cl_2 -based POPs depended on the number of equivalents of cross-linking agents used. A value of $1220 \text{ m}^2 \text{ g}^{-1}$ was observed for six equivalents and $1670 \text{ m}^2 \text{ g}^{-1}$ with 15 equivalents. This latter value was very close to SSA_{BET} observed in solution with CH_2Cl_2 ($1685 \text{ m}^2 \text{ g}^{-1}$). By contrast, SSA_{BET} of CHCl_3 -POPs remained not affected ($1280 \text{ m}^2 \text{ g}^{-1}$ for six equivalents and $1270 \text{ m}^2 \text{ g}^{-1}$ with 15 equivalents).

Regarding the green metrics, without considering the work-up, AE values revealed the same in solution and for mechanical reactions (47.12% for CH_2Cl_2 and 37.01% for CHCl_3). For CH_2Cl_2 , MI was equal to 10.56 vs. 31.42 (ball milling vs. solution), MP 9.47 vs. 3.18 and E -factor 8.42 vs. 30.34. These results highlighted that mechanochemical milling was more environmentally friendly than the solution methods. Accounting for the work-up, E -factor for mechanochemistry reached 295.68, which is higher than in solution (278.27). This detriment could be compensated if the water used for the work-up in mechanochemistry could be reused. In this ideal case, E -factor would become lower for the mechanochemical process (134.87) than the procedure carried out in solution. The other green metrics (without work-up) for the CHCl_3 cross-linked polymer followed the same trend. However, if work-up is included, a slight advantage was given to mechanochemistry with an E -factor of 261.89 vs. 297.94 for the solution process.

In 2014, James Mack compared Eco-scale values between mechanochemistry and the corresponding reaction in solution to answer how much greener mechanochemical reactions are. For this purpose, a supported Wittig reaction was developed, and the merits of each approach were determined (Scheme 34).¹⁸² In solution, benzyl triphenylphosphonium bromide **169** was prepared by mixing benzylbromide **168** (1 equiv.) with triphenylphosphine **167** (1.5 equiv.) in refluxing toluene for 3 h. The phosphonium salt was then isolated by filtration and then dried. Then, the phosphonium salt, benzaldehyde (1 equiv.), and NaOH (excess) were diluted in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1:1), and the mixture was refluxed for 30 min. The stilbene was then recovered pure after a work-up and column chromatography in 55% yield with a 56:44 E/Z ratio. In contrast, in mechanochemistry, the preparation of



| Green metrics | | | | |
|-------------------------------|----------|-----------|-----------------|------|
| Compound | | Eco-scale | | |
| Mechanochemical route | | | | |
| 170 | | | | 77 |
| Solution-based route | | | | |
| 170 | | | | 35 |
| Milling processing conditions | | | | |
| Type of mill | Material | Jar size | Number of balls | Size |
| SPEX | SS | NA | 1 | 5 mm |

Scheme 34 Wittig reaction by mechanochemistry.

stilbene was performed according to a one-pot, two-step sequence. The phosphonium salt was first prepared by combining benzyl bromide with a polymer-supported triphenylphosphine (1.64 mmol of PhCH_2Br per gram of polymer) in a stainless-steel jar with a stainless-steel milling ball (5 mm \varnothing). The mechanical milling was then carried out on a SPEX shaker mill for 2 h. Subsequently, cesium carbonate (2.63 mmol per gram of resin), ethanol (2 mL per gram of resin), and benzaldehyde (1.54 mmol per gram of polymer) were added in the jar, and the mixture was milled for 2 h. After addition of ethyl acetate, filtration, and removal of solvent, the pure stilbene **170** was obtained in 73% yield with a 54:46 E/Z ratio.

The mechanochemical procedure displayed an Eco-scale of 77, which is consistent with a green reaction. By contrast, the Eco-scale for solution-based strategy was much lower (35). For the authors, the better Eco-scale score exhibited by mechanochemistry was directly linked to strong penalties of the solution-based process, *i.e.* a lower yield, use of less safe solvents (cyclohexane used for the chromatography) and reactants (NaOH). In addition, the work-up, specifically the purification by column chromatography, has a detrimental impact on the metrics. Another advantage in favour of mechanochemistry not considered by Eco-scale is the reaction set-up time. Mechanochemical reactions are often faster to set-up than solution counterparts. This Wittig reaction required 5 hours and 11 min for the overall procedure by mechanochemistry compared to the 7 hours and 37 min needed in solution.

Life cycle assessment in mechanochemistry

In 2022, Spatari *et al.* reported the first example of life cycle environmental impact for the production of the API nitrofurantoin **35a** by TSE (*i.e.*, continuous flow mechanochemistry) and compared the obtained metrics with the solvent-batch synthesis.¹⁸³ In the mechanochemical process, no solvent was used, along with no excess of reagents, leading to fewer resources consumed and less waste/s produced. Many APIs





Scheme 35 Model reaction for life cycle assessment of continuous flow mechanochemical synthesis of nitrofurantoin **35a**.

are synthesized by batch processes in solution, leading to high energy consumption and consequently a high release of CO₂ (from 10 to more than 1000 kg of CO₂ equiv. per kg of API).¹⁸⁴

Life cycle assessment (LCA) in the chemical field can evaluate the sustainability of a reaction considering resource consumption, environmental impact, and effects on human health. Prior to the LCA for the nitrofurantoin synthesis, a life cycle inventory (LCI) was conducted for both the TSE process and solvent-batch synthesis (Scheme 35).

The LCI included the 2-semicarbazidoacetic acid **172** and the aminohydantoin hydrochloride **33** in the inventory. 5-Nitrofurfural was not considered since it is absent from the ecoinvent database,¹⁸⁵ and the same ratio is used in both methods. Life cycle impact assessment (LCIA), like global warming, terrestrial and ecotoxicity (freshwater), ionizing radiation, human non-carcinogenic toxicity, and fossil resource scarcity, were also taken into account. The rate of synthesis by TSE is 0.23 g min⁻¹, and the production of 1 kg of nitrofurantoin required 6.61 kW h. The unique by-product is hydrochloric acid which is trapped by a scrubber. For the production of 1 kg of nitrofurantoin, lower PMI (1.2 vs. 25), lower wastewater (<0.01 vs. 19), and lower cost (4.5\$ vs. 37.6\$) are obtained by the TSE process compared to the solvent-batch synthesis.^{186–188} The LCIA metrics followed the same trends, which are ten times smaller by TSE process than solvent-batch synthesis. We can notice a more significant energy consumption (mainly electricity) by TSE compared to the batch protocol in solution, which does not affect the life cycle score. The use of eight equivalents of 1-aminohydantoin hydrochloride in solution significantly impacts LCA. It is also noticed that toxic ammonia and hydrazine used to produce 2-semicarbazidoacetic acid **172** negatively impacts terrestrial and freshwater ecotoxicity.

Based on an annual need in the US of 4323 ± 301 kg of nitrofurantoin per year, a reduction from 2624 (solvent-batch synthesis) to 330 tons of CO₂ (by TSE process) has been estimated. In addition, avoiding solvent use allows for reduces terrestrial ecotoxicity from 120 140 tons of toxic emissions to 14 850 tons. Ultimately, these reductions in environmental footprint also appear in terms of operating costs, from \$162 000 for solvent-batch synthesis to \$19 000 by TSE.

Industrial implementation

Since most industrial applications of mechanochemistry are protected by patents, detailed process information and their green metrics are difficult to obtain. However, the number of patents on comprising mechanochemical methodologies is rapidly increasing¹⁸⁹ illustrating an acceleration in industrial adoption (Fig. 5).^{190,191}

Top 1000 results by filling date

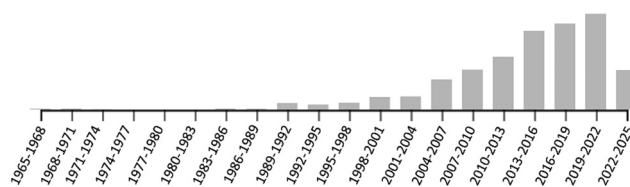


Fig. 5 Number of patents involving mechanochemistry over time. Google patent search accessed on 19th July 2023.

Conclusions and outreach

In conclusion, there is no perfect and universal parameter to assess a chemical process's overall sustainability. Combining several complementary parameters is necessary to fully embrace the complexity of this subject. In this respect and concerning mechanochemical procedures, widespread green indicators suggested it has an edge over mainstream solution-based methodologies by exhibiting a lower environmental footprint in most cases. According to the green metrics discussed throughout this review, this difference can be primarily attributed to three distinctive factors: (i) the generalized absence of bulk solvents, (ii) precise control over the stoichiometry (*i.e.*, using agents in a stoichiometrically rather than in excess), and (iii) more selective reactions enabling simplified work-up procedures.

In addition, emerging large-scale methods and tools, such as TSE, despite their sporadic use in organic synthesis, have the potential to be disruptive technology within the chemical industry.^{39,51,190,191} The trust of industrial chemists and chemical engineers needs to be gained to achieve the required technology readiness level for their implantation. This can only be enabled by (i) steadily growing a broader panel of mechanochemical organic and inorganic reactions, (ii) expanding the current pool of knowledge and know-how within industrially relevant fields, (iii) promoting the combination of existing well-established methodologies such as metal-catalysis, photocatalysis, *etc.* with ball-milling to reach even greener reactions, and (iv) increasing the awareness and training in mechanochemistry for the future generations of researchers and chemical professionals. This is not a chimaera, and it is already happening, as witnessed by the ongoing research and training activities developed within the European Programme COST Action CA18112 'Mechanochemistry for Sustainable Industry'^{192–194} All this, in turn, will create the synergy required for greater use of mechanochemistry by industries that would benefit the environment.¹⁹²

We hope the key examples highlighted in this review serve as a pitstop for academic and industrial chemists to fully consider mechanochemical technologies in their reaction and/or process design (or redesign).

We believe implementing environmentally promising technologies – such as mechanochemistry, *inter alia* – would lead to a more sustainable future and, ultimately, the survival of our specie.



Conflicts of interest

There are no conflicts to declare.

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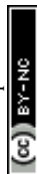
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