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 and widespread presence in everyday life. Therefore, a sustainable approach to chemistry contributes to the well-being of worldwide population and comply with the United Nations Sustainable Development Goals (UN SDGs) and the European Green Deal. The review highlights how mechanochemical methods in batch and in continuous 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 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.

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 In 1998[1] - 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.

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

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number and quantities of reagents and auxiliaries is an effective way to minimise 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 N°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 to 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%.

Table 1. Green chemistry metrics applied to mechanochemical synthesis**.**

Metric	Abbreviation	Formula	Optimal value	Reference
Atom Economy	AE	$\frac{\text{Formula weight product (kg/kmol)}}{\text{Formula weight of all reactants used in reaction (kg/kmol)}} \times 100$ FW: Formula weight in g.mol^{-1}	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	E-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	$\frac{\text{Total mass of reaction and postreaction solvents} + \text{mass of catalyst recovered (kg)}}{\text{Total mass of reaction and postreaction solvents} + \text{mass of catalysts used (kg)}}$ $0 < \text{MRP} < 1$	1	8,9
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	$\frac{\text{Moles of product}}{\text{Moles of reactants} + \text{Moles of catalysts} + \text{Moles of solvents} + \text{Moles of additives}}$	1	12

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 close to 0 to account for an environmentally-friendly process.

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 respecto the mass of all reactants. Both AE and chemical yield are considered in the calculation.[7] The higher the RME score, the better 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. 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 **Ecoscale**.[13] Ecoscale is 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 2.0**[16] 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 imput 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. These both 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[18] (**Figure 1**).

While the devices mentioned above are limited to batch syntheses, twin-screw extrusion (TSE) is used as a larger-scale, continuous-flow mechanochemical method.[22,23] 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.,[24,25,26]

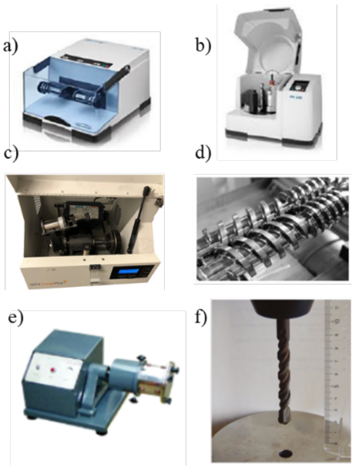


Figure 1: Milling devices: (a) Vibrational ball-mill (Retsch), (b) Planetary ball-mill (Retsch), (c) SPEX 8000 shaker mill, (d) Twin-Screw Extrusion, (e) Tumbler Ball-mill, (f) Single-Screw Device. Adapted with permission of the American Chemical Society from 19,20,21.

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. The reviewed articles provide assessment in a quantitative way, 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.

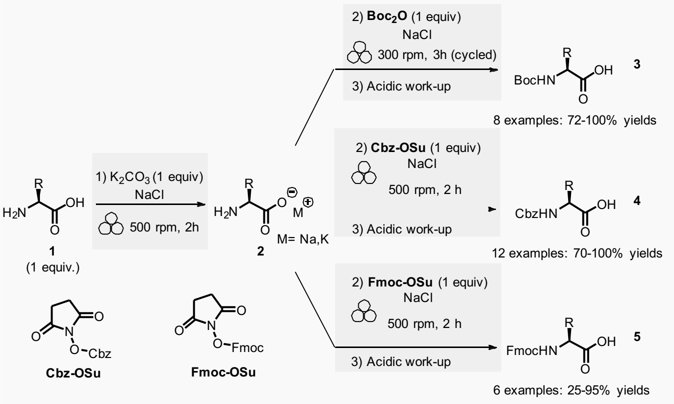
Green metrics used in Mechanochemical reactions

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). [27] 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.[28] Amidation (N-acylation) represents a critical reaction in medicinal chemistry.[29] 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.[30,31,32]

Classically, amide bond formation generally requires the activation of the carboxylic acid group by coupling reagents. [33] Nevertheless, numerous non-classical methods were also developed. [34] 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.

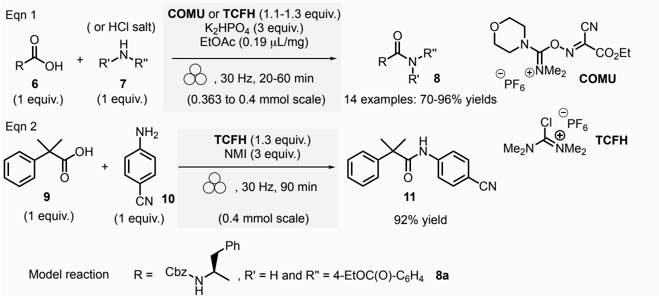
In peptide chemistry, temporary protection of the α-amino function is generally required to enhance selectivity. *Tert*-butyloxycarbonyl (Boc), benzyl-oxycarbonyl (Cbz), 9-fluorenylmethyloxycarbonyl (Fmoc) are typical protecting groups; however, their use often requires the use of large quantities of 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**).[35] In this approach, amino acids 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. This reaction was conducted in the PBM employing stainless steel or tungsten carbide (only for the Fmoc group) jars, containing 24 balls (5 mm Ø) of the same material as the jar, and the mixture was ground at 500 rpm for 2h. Thereafter, grafting of the protecting groups was accomplished by 300-500 rpm continuous or cycled milling (three cycles of 1 h, 10 min intervals between each cycle), inversed rotation (regular reversal of rotation direction) of the deprotonated amino acids (1 equiv.) with the desired protecting reagent (1 equiv.) and NaCl for 2 to 3h. Following a simplified work-up, pure *N*-protected amino acids were isolated by precipitation in water.



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

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

The environmental factor (E-factor) determined for three *N*-protected amino acids (*i.e.*, Boc-Phe-OH, Cbz-Phe-OH, and Fmoc-Phe-OH) were lower than the corresponding solution-based reactions (E-factor of 8 and 6 *vs* 20 and 288 for mechanochemistry and solution, respectively). In contrast, the E-factor score 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).

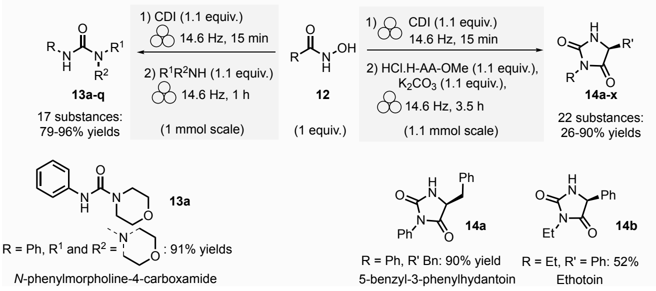


Scheme 2: Mechanical synthesis of amides using uronium-type reagents.

Aav *et al.* described amidations using uronium-type coupling reagents (COMU and TCFH) *via* mechanochemical activation (**Scheme 2**).[36] Typically, the coupling reaction was performed in a ZrO_2-coated jar (14 mL) containing three ZrO_2 balls (7 mm Ø). 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 (K_2HPO_4, 3 equiv.), under liquid-assisted grinding (LAG)[37] conditions, using a small amount of not harmful ethyl acetate (η = 0.19 µL/mg). Reaction times ranged from 20-60 min at 30 Hz employing a VBM. Notably, the coupling of hindered carboxylic acid **9** with 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]uril 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) (96-92% *vs* 70%).[38] 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 methode. 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.

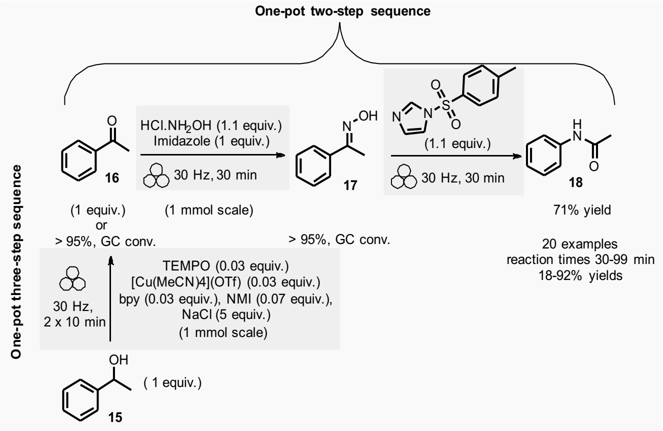


Scheme 3: Urea and hydantoin mechanochemical synthesis through Lossen rearrangement.

Non-symmetrical ureas and hydantoins (including pharmaceutical ingredient Ethotoin)[39] were mechanochemically synthesized in 2019 by Colacino, Porcheddu, *et al.* and coll (**Scheme 3**).[40,41] The one-pot/two-step sequence, emplous hydroxamic acid as starting material. First, activation of hydroxamic acid by 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 ZrO_2 jar (45 mL) containing 40 ZrO_2 balls (5 mm ø) 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 P_2O_5, produced the pure ureas **13**. Seventeen ureas 13a-q were obtained using this methodology in yields ranging from 79% to 96%. When amino esters – instead of amines in the second step – were used, hydantoins 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 hydantoins not accessible by conventional solvent-based procedures due to safety reasons (*e.g.*, use of flammable and harmful methylisocyanate), ii) *N*-phenyl substituted hydantoins, which are not accessible by other mechanochemical procedures [42] and iii) long chain *N*-alkylated hydantoins directly from hydroxamic acids obtained directly from commercially available reactants (e.g., carboxylic acids),[43] which bypasses the steps required to obtain non commercially available isocyanates. Consequently, the E-factor was better than traditional solution-based procedures.[44,45,46] 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.

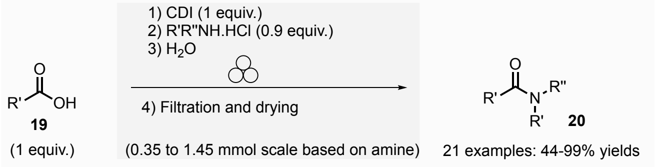
The E-factor remains favourable towards mechanochemical procedures for 5-benzyl-3-phenylhydantoin **14a** (1.91 with 90% yield *vs* 3.05 with 79% yield, in solution), while for Ethotoin **14b**, the E-factor was 4.84 (52% yield) *vs* 193 (65% yield) for mechanochemical *vs* solutions-based approaches,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



Scheme 4: N-phenylacetamide preparation by mechanochemical Beckmann rearrangement.

In 2021, Mocci et *al.* developed a mechanochemical procedure for the Beckmann Rearrangement Reaction (BKR) to access amides from *in situ* synthesized oximes. [47] 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 (1 equiv.), hydroxylamine hydrochloride (1.1 equiv.), and imidazole (1 equiv.) at 30 Hz for 30 min in a ZrO_2 jar (15 mL) with one ZrO_2 ball (8. mm ø). To the *in situ* formed oxime intermediate, *p*-toluenesulfonylimidazole (1.1 mmol) was added, and the mixture was then milled at 30 Hz for further 30 min (**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 Na_2SO_4. Furthermore, varying the ketones and the reaction times (30-99 min), allow 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 **18** (phenylacetamide) from safe 1-phenylethanol. The first step consists in of the oxidation (1.0 mmol scale) of 1-phenylethanol 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. 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.[48] In solution, a mixture of acetophenone (1 equiv.), $NH_2OH \cdot HCl$ (1.6 equiv.), and sodium acetate (2 equiv.) was refluxed for 1h in $EtOH/H_2O$ (4:1).[49] Then, the newly obtained acetophenone oxime (1 equiv.), was reacted with *p*-toluenesulfonyl chloride (0.02 equiv.), and $ZnCl_2$ (0.02 equiv) in dry MeCN during 1h at reflux.[48] The yields were comparable for the two procedures (91% vs 86% in solution). However, AE and RME were better in solution, with 49.7% for AE and 29.53% for RME, compared to the mechanochemical method (27% for AE and 23.84% for RME). Green metrics favour solution-based procedures due the only waste produce being acetic acid, sodium chloride, and water. Whereas the mechanochemical procedure produced imidazolium chloride and 4-methylbenzenesulfonate imidazolium waste. Finally, the mechanochemical procedure displayed an E-factor of 101 and an ecoscale score of 73, while solution-based procedures scored 243 and 32, respectively.



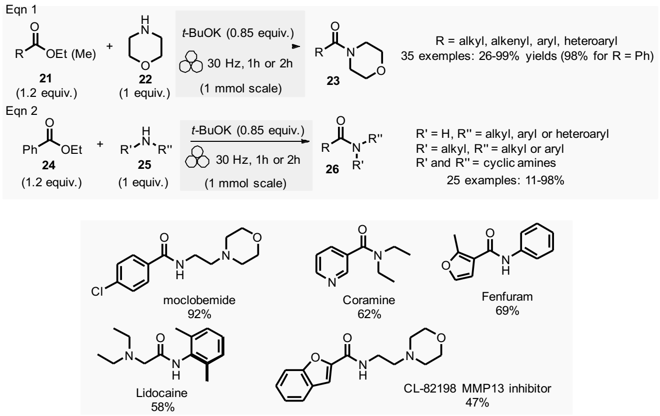
Scheme 5: Amidification synthesis with CDI in mechanochemistry

In 2015, Métro et al. developed a mechanochemical acylation of nucleophiles (mostly amines) using N,N-carbonyldiimidazole (CDI) as activating agent.[50] Twenty-one amides were obtained in good to almost quantitative yields (44-99%) (**Scheme 5**). Typically, during the two-step optimized producedure, the carboxylic acid activation was accomplished with CDI under 5 min at 500 rpm in a PBM (using stainless-steel grinding media). 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.

Careful characterization by ICP-MS or gravimetric analysis of the final products showed traces of metal impurities (Fe, Zr, Cr, Y, Si which originated from the degradation of the milling balls and jar during the grinding process. 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 contaminants can be removed by simple filtration without the need for harmful EtOAc.

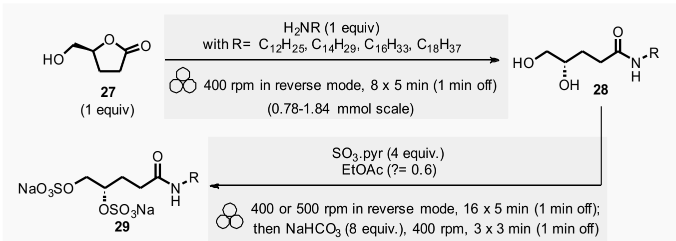
Evaluation of the environmental impact of this solvent-free preparation of N-benzylbenzamide with CDI was also compared to other classical solution procedures using (N,N-diisopropylbenzyl-amine-2-boronic acid (IBA),[51] N,N'-dicyclohexylcarbodiimide (DCC),[52] thionyl chloride (SOCl2),[53] N,N'-carbodiimidazole (CDI)[54] in THF and sulfated tungstate.[55] 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 Ecoscale score of 79, the mechanical method was excellent compared to all the different reactions conditions in solution (Ecoscale between 44 and 67).

Browne *et al.* developed an original and efficient ball milling method for amide bond formation using methyl or ethyl esters as starting materials.[56] Notably, the developed process did not require any activating reagent. The solvent-free reaction was carried out using an amine, 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 were synthesized in moderate to high yield (11% to 98%). 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 agropharmaceuticals 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.



Scheme 6: Direct amide bond formation from ester in mechanochemistry

This reaction's AE was consistently higher (55%) than those performed using traditional solution methods. For instance, in the best solution conditions (phosgene/Et_3N), 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).[57]



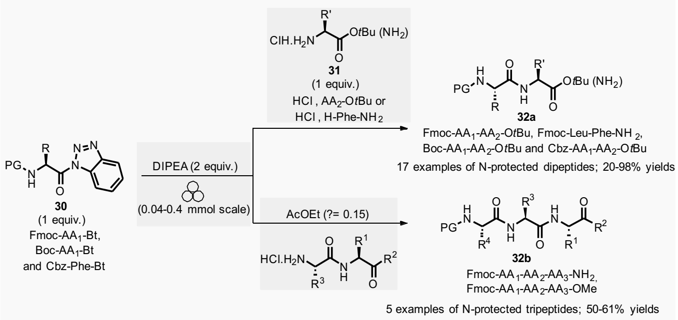
Scheme 7: Bis-sulfooxypentanamide synthesis with one-pot/two-step procedure by ball-milling.

In 2022, Wadouachi *et al.* reported the one-pot/two-step mechanochemical synthesis of four potential surfactants (4S)-N-alkyl-4,5-bis-sulfooxypentanamides 29 from bio-based (S)-γ-hydroxymethyl-γ-butyrolactone 27 (2H-HBO) in a one-pot two - step process (Scheme 7). [58] This short sequence consisted in of an aminolysis of 2H-HBO 27 followed by a disulfation reaction using a PBM. The optimized conditions consisted on grinding 2H-HBO (1 equiv.) with alkylamine (1 equiv.) in a ZrO2 jar (20 mL), charged with eighty ZrO2 balls (5 mm ø) 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 (η = 0.6 µL/mg) 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).

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 ≈ 0.1 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 ≈ 0.1 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-AA_1-Bt, Boc-AA_1-Bt, or Cbz-Phe-Bt) and amino esters hydrochloride ($HCl·H_2N$-AA_2-O*t*Bu or HCl·H-Phe-NH_2) in the presence of Hünig base (*N,N*-diisopropylethylamine, DIPEA) (**Scheme 8**).[59] *N*-acylbenzotriazoles **30** are air- and water-stable reagents while remaining more reactive than the corresponding *N*-acylimidazoles.



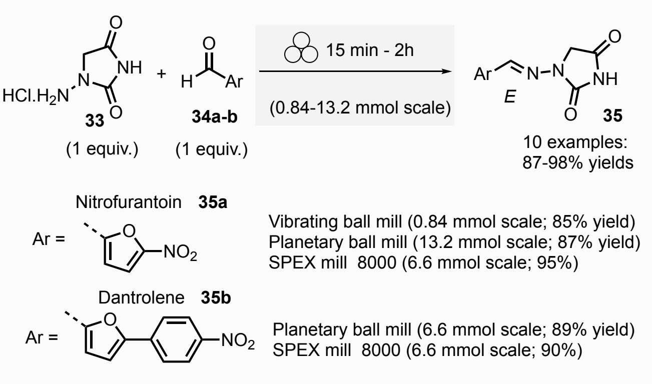
Scheme 8: Protected dipeptides formation from N-acylbenzotriazoles in mechanochemistry

The typical mechanical procedure for synthesizing protected dipeptides was carried out in a stainless-steel jar with 2 stainless-steel balls (5 mm) 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-AA$_1$-AA$_2$-O*t*Bu) were readily isolated in 20 to 98% yields. In addition, LAG (ethyl acetate, η = 0.15) was beneficial for preparing five protected tripeptides **32b** (Fmoc-AA$_1$-AA$_2$-AA$_3$-O*t*Bu and Fmoc-AA$_1$-AA$_2$-AA$_3$-NH$_2$) in yields ranging from 50 to 61%. The LAG procedure was also used to synthesize a more complex biotinylated peptide (Biotin-Ahx-RGDfV-NH$_2$ 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.[60] For *N*-protected dipeptide Fmoc-Leu-Phe-NH$_2$, both reaction time and yield were improved by mechanochemistry compared to the solution-based process (1h *vs* 24h and 91% *vs* 55% yield). The E-factor was once more in favour of mechanochemical activation (401 *vs* 59678)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, mechanochemical activation displayed lower production cost to produce 1 g of dipeptide (54€ *vs* 298€ in solution).

In 2018, Colacino, Porcheddu, *et al.* synthesized hydrazone-based APIs, namely Nitrofurantoin **35a** and Dantrolene **35b**, by ball-milling.[61] 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 ø). 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 furnished 87% yield in 2 h using a PBM (**Scheme 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).



Scheme 9: Hydrazones synthesis by ball-milling, applied to the mechanochemical preparation of Active Pharmaceutical Ingredients.

In the latter, complete conversion was obtained using the reactants stoichiometric 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**, 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 ≥ 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).[62,63,64] Moreover, the mechanochemical strategy avoids using toxic solvents (DMF, ACN), excess of 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, the calculated price for 1g of Dantrolene **35b** by mechanochemistry was 54.7€, which is lower than 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*).[65] The aggregated scores obtained using different mechanochemical devices both in batch (SPEX) and continuous (TSE) processes were compared with the solution counterparts (**Figure 2**).

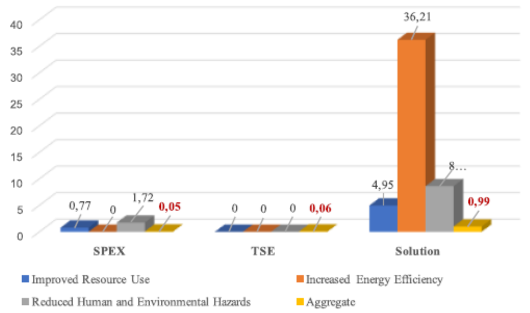
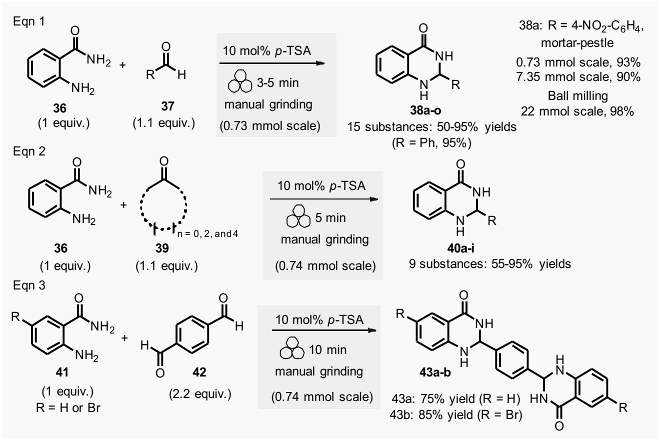


Figure 2: Greenness comparison between SPEX, TSE, and solution synthesis in a batch of Nitrofurantoin **35a** using DOZN 2.0 tool. Adapted with permission of the American Chemical Society from ref 65.

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)[61] over a period of 15 min, delivering *ca.* 3.5 g[66] of nitrofurantoin **35a.**

When comparing mechanochemical procedures to solution-based counterparts,[64] 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 (4,000 kg.m^{-3}.day^{-1}).[67]



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

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.

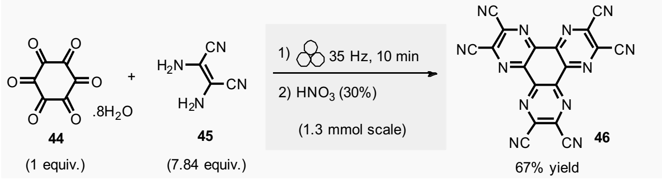
This methodology was extended to aromatic aldehydes, and by varying the reaction time from 3 to 15 min a library of fifteen 2,3-dihydroquinazolin-4(1*H*)-ones **38a-o** with with yields ranging from 50 to 95% was synthesized. Moreover, a gram-scale synthesis using anthranilamide and *p*-nitrobenzaldehyde 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 **40a-i** in 55% to 95% yields. Similarly, the mechanosynthesis of two bis-dihydroquinazolinones from either 4-bromoanthranilamide or anthranilamide with terephthaldehyde afforded the desired products in good yields (75% and 85%, respectively).

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

For the model reaction (R = 4-NO_2-C_6H_4) 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 Ecoscale of 81.93). Nevertheless, no comparison with solution-based reaction was mentioned by the authors.

Borchardt *et al.* described an efficient and eco-friendly ball-milling synthesis of hexaazatriphenylenehexacarbonitrile **46** (HAT-CN)[68] (**Scheme 11**).[69,70] 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 (η = 0.1 µL/mg, LAG conditions) using a ZrO_2 milling vial (10 mL) charged of two ZrO_2 mill balls (10 mm Ø).

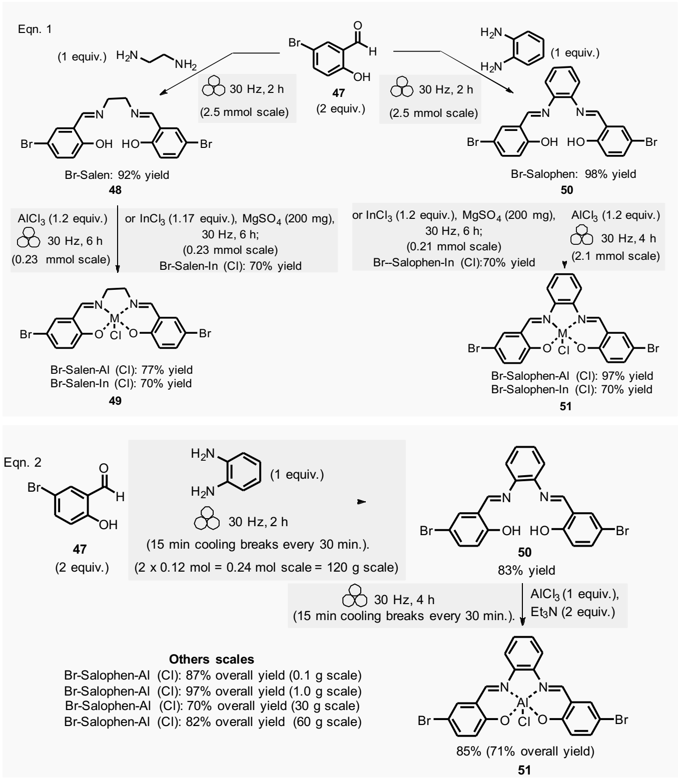


Scheme 11: Mechanochemical synthesis of hexaazatriphenylenehexacarbonitrile (HAT-CN) **46.**

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 1h. 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) and displayed a more favourable global warming potential (GWP) 175 *vs* 783 CO_2 equivalents than in solution. The 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 (CO_2).

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).[71,72,73,74,75] 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 (0.1-1g) using a VBM.[76] 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 $AlCl_3$ or $InCl_3$. 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).



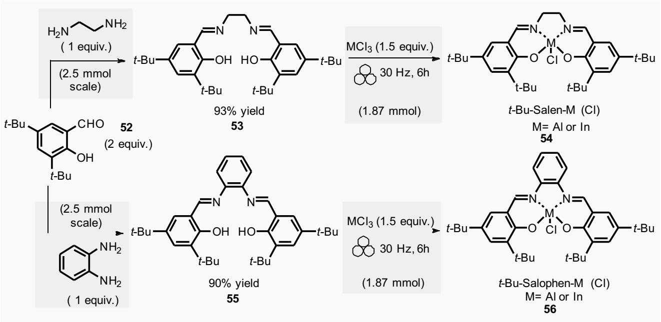
Scheme 12: Mechanochemical preparation of Br-Salen and Br-Salophen ligands and their corresponding complexes.

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 Br-salophen **49** was recovered after simple water removal by drying in 83% yield. Further, complex Br-Salophen-Al **51** synthesis was achieved on ≈ 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 mechanosynthesis 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 whenr the reaction was done without an HCl trapping agent (i.e., in the absence of triethylamine base) the E-factor would have been be only 0.65 for mechanosynthesis and 2.81 in solution.

PMI values were also favourable towards mechanosynthesis, 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 Et_3N) *vs* 40.82 (23.35 without Et_3N) in the solvent procedure.

Energy consumption and costs for the five scales reported 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.[77] 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



Scheme 13: Mechanochemical *t*-Bu-salophen complexes formation with Aluminium and Indium metals

In 2022, the same group reported the synthesis of four sterically hindered fluorescent Salen and Salophen complexes.[78] 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. 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 ø ball at 30 Hz for 2 h) affording the target Salen ligand **53** in 93% yield. For Salophen ligand **55** (from 1,2-phenylene diamine), a catalytic amount of acetic acid (70 µL) 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 $AlCl_3$ or $InCl_3$ (1.5 equiv.) and $MgSO_4$ (≈ 13 equiv.) at 30 Hz for 6 h.

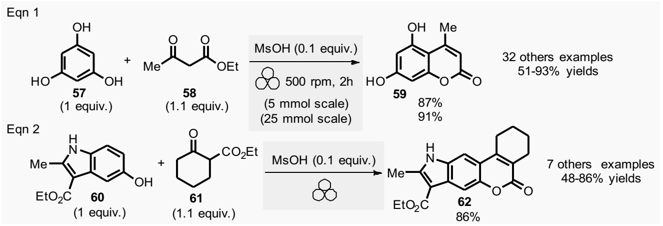
The green metrics calculated for *t*-Bu-Salen **53** and *t*-Bu-Salophen **55** ligands and their respective complexes showed lower E-factors than in solution (0.4 and 4.03 *vs* 2.05 and 5.19 in solution, for salen and salophen complexes, respectively). For instance, for the *t*-Bu-Salen-Al (Cl) complex, the E-factors were 3.02 for the mechanochemical synthesis and 4.76 for its preparation in solution.[78] Mechanochemistry displayed the same trend for PMI (1.02 to 1.66) versu*s* 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 mechanosynthesis 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 0.1g-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

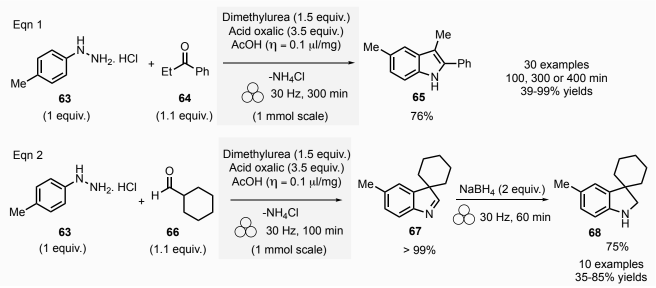
This section reports the mechanochemical preparations of heterocycles and compares them with similar solution-based reactions. Multicomponent reactions (MCR) are also included in this section.[79,80,81] MCR presents an intrinsically high atom economy and is often environmentally benign. A synergistic combination of solvent-free processes with multicomponent transformations would be relevant for synthesizing a wide range of organic compounds, including APIs.[82] Some of these reactions were recently reviewed with in the contexts of Pharmaceuticals,[83] and several mechanochemical MCR were already described.[84,85,86,87] However, here we reported the ones where green metrics have been calculated.

Coumarine **59** synthesis by Pechmann condensation was recently revisited by Ranu team.[88] This original reaction, published in 1883,[89] consisted on 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.



Scheme 14: Coumarines and pyranoindole mechanochemical synthesis via Pechmann condensation.

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 (Ø 5 mm) 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 coumarines 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 pyranoannulated indoles (48-86%). For the model reaction presented in **Scheme 14** (**Eqn 2**), only one pyranoindole regioisomer **62** was formed. Ecoscale scores for the synthesized coumarins and pyranoindoles varied from 71 to 90.5 and 68.5 to 83, respectively. More specifically, for the mechanosynthesis of 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **59** (**Scheme 14**, Eqn 1), the Ecoscale 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.[90]



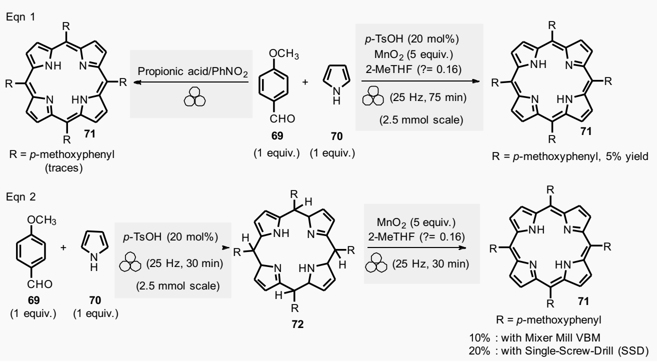
Scheme 15: Indole by Fischer mechanochemical synthesis and indoline by interrupted Fisher indolisation.

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 Fisher indolisation using a ball-milling strategy to avoid the harsh and harmful conditions generally required for these reactions (**Scheme 15**)[91] Traditional indole synthetic procedures required the presence of strong acids or Lewis acids,[92] 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.),[93] or the use of toxic ionic liquids bearing sulfonic acid groups.[94,95,96]

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, $\eta = 0.1$ µL/mg). The reaction was carried out in a 15 mL ZrO_2 milling jar containing 20 milling balls (Ø = 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 Fisher 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 synthetized 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 was obtained by reacting phenylhydrazine hydrochloride and cyclohexanone using acidic clay conditions.[97] Indoline **68** were obtained by reacting 4-phenylhydrazine hydrochloride **63** and cyclohexane carboxaldehyde **66** in the presence of acetic acid and sodium triacetoxyborohydride.[98] For the synthesis of indole and indoline in solution, Ecoscale values were 64 and 45, respectively, and the E-factor reached 79.9 and 278.4. A comparison of Ecoscale scores obtained for the mechanochemical synthesis (74 for indole and 52.5 for indoline syntheses), idicate 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).[99] Conventional heating in solution for the synthesis of porphyrin **71** (**Scheme 16**, R = 4-$MeOC_6H_4$) resulted in low yields (*i.e.*, 20%). In 2019 and 2020, Pineiro *et al.* revisited the synthesis of substituted *meso*-porphyrins using mechanochemistry.[100,21] While neat mechanical activation using a VBM resulted in only traces of porphyrin **71**,[100] grinding a mixture of pyrrole **70** (1 equiv.), 4-methoxybenzaldehyde **69** (1 equiv.), catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH, 20 mol%) and MnO_2 (5 equiv.) under LAG conditions (2-MeTHF, $\eta = 0.16$) in a stainless-steel grinding jar containing two stainless-steel balls (Ø 7 mm) afforded porphyrin in 5% yield after 75 min at 25 Hz.[100]



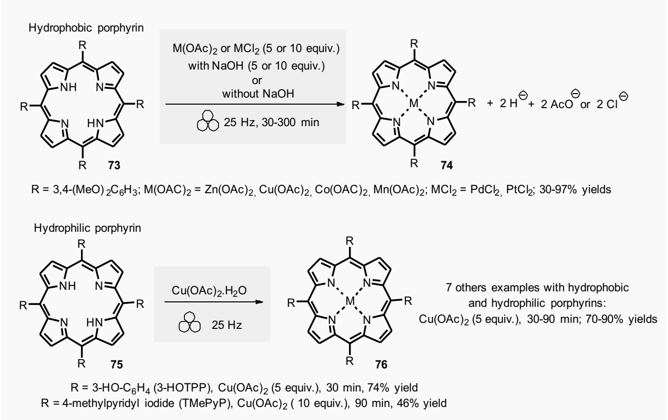
Scheme 16: One and two-step porphyrin syntheses by mechanochemistry.

An alternative two-step mechanical synthesis was also evaluated by the same group. 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, MnO_2 (5 equiv.), and 2-MeTHF ($\eta = 0.16$), 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.[100] In any case, four others porphyrins (R = aryls) were mechanochemically synthesized in low yields ranging from 7% to 27%.[100]

In 2020, Pineiro reported a new two-step process employing a rotating single-screw drill (SSD) enclosed in a fixed stainless-steel cylindrical chamber to produce porphyrin **71** in 20% yield (R = 4-$MeOC_6H_4$) (**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 Ecoscale values were comparable (R = 4-$MeOC_6H_4$, 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 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 Ecoscale 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.[101] Generally speaking, conventional approaches to metalloporphirins 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, $CHCl_3$/MeOH) and the need for a significant excess of metal salts required.



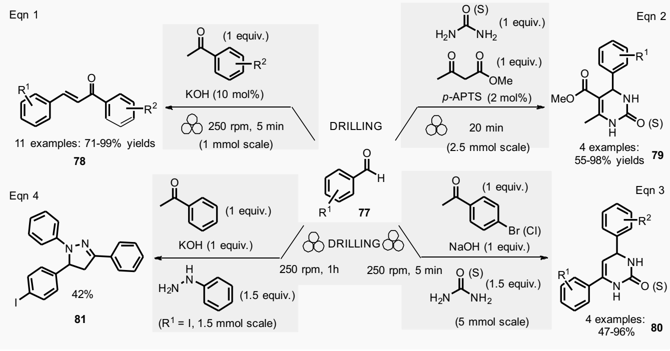
Scheme 17: Metalloporphyrin synthesis by mechanochemistry.

A safer procedure was proposed by Pineiro et *al.* by grinding the porphyrin (R = 3,4-$(MeO)_2C_6H_3$, 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 (Ø 7 mm) 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 $Mn(OAc)_2·4H_2O$ to 97% for $Zn(OAc)_2·2H_2O$. Using a similar mechanochemical route, a selection of hydrophobic porphyrins **73** [*i.e.*, R = C_6H_5, 3,5-Cl_2-C_6H_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-NO_2-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-HO-C_6H_4, (3-HOTPP), 4-HO_2C-C_6H_4, 4-HSO_3-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, 2M), 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 Ecoscale scores calculated for sonochemistry (67) and mechanochemistry (72), unequivocally reflect the greenness of the mechanical methodologies.

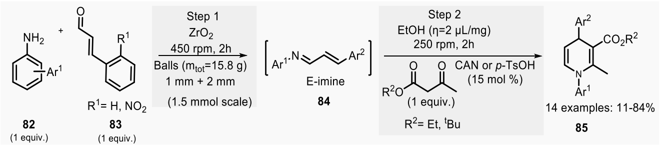
In 2020, the Pineiro group developed a new automated mechanic-stirrer device adapted for mechanosynthesis. The new tool comprises a stainless-steel cylindrical reactor (4.33 mL) equipped with a stainless-steel mobile single-screw drill (SSD device) rotating at 250 rpm.



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

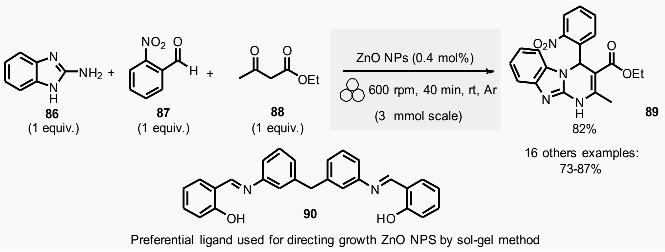
The SSD device's rotational movement grinds the reactants placed in the stainless-steel cylindrical reactor (**Figure 1**). This new device combines the mortar's simplicity and an automated apparatus's reproducibility.[21] This equipment was successfully employed for di- and tri-component reactions to 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 the custom custom-made SSD device (except for pyrazoline formation) afforded equal or superior yields than other mechanochemical- or solution-based methods.[102,103,104,105,106,107,108,109,110,100,111] 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).[102,103,104] In contrast, the Ecoscale (74.5) was slightly worse than the solvent-free protocol (grinding with mortar and pestle) developed by Shan *et al.* (Ecoscale score of 78).[103]

An SSD device was also used for the Biginelli synthesis of 3,4-dihydropyrimidine-2-(1*H*)-thione **79** by reacting methyl acetoacetate, benzaldehyde and urea. The E-factor and Ecoscale scores were equal to 0.22 and 76, respectively. However, an already 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 Ecoscale (81).[105] E-Factor and Ecoscale 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 under basic or acidic conditions.[107,108,109] The SSD procedure still remained relevant when compared to solvent-free microwave reaction under acidic conditions for **80**.[108] For 5-(4-Iodophenyl)-1,3-diphenyl-1*H*-pyrazoline **81**, the E-factor (1.70) was slightly more favourable for the SSD device than the high-speed ball milling counterpart (2.72),[110] but the Ecoscale was more favourable for ball milling (40.5) compared to 18 by SSD device).



Scheme 19: 1,4-dihydropyridine synthesis by ball-milling.

In 2022, Blazquez-Barbadillo *et al.* synthesized unsymmetrical 1,4-diaryl-1,4- dihydropyridines **85** by a one-pot, two -step merchanochemical reaction (**Scheme 19**). [87] The reaction is ball-milled in a PBM for 2 h for the first step with 1 equivalent of aldehyde and 1 equivalent of aromatic amine. Subsequently, 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 tools. 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 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.

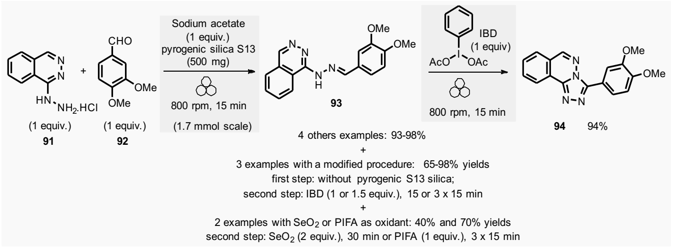


Scheme 20: Model reaction for benzoimidazopyrimidine synthesis by mechanochemistry.

Jang *et al.* described an MCR mechanical synthesis of 2-aminobenzimidazoles and pyrimidines derivatives using ZnO nanoparticles (ZnO NPs) as the catalyst.[112] 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 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 **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 others pyrimidines were produced in 72-82% yields, and finally when urea or thiourea were used, 4 others compounds were obtained in 77-80% yields. It is to notice that a large-scale reaction (60 mmol) was also performed between 2-aminobenzimidazole, benzaldehyde and ethyl acetoacetate, and an equivalent yield was observed as smaller scale.

For the reaction presented in **Scheme 20**, an Ecoscale score of 67 and an E-factor of 0.28 were obtained. These values showed to be better[113,114,115,116] or comparable (66 and 0.24) [117] to other methodologies reported with or without solvents. In addition, Jang *et al.* method[112] is better compared to Liu's method[117] in solution due to both reduced reaction time (40 min *vs* to 3h) and temperature (room temperature *vs* 100°C, respectively).

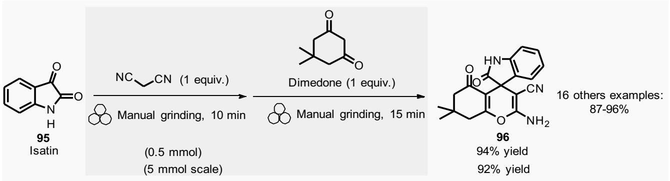
Baltas *et al.* developed a mechanochemical route to annulated 1,2,4-triazoles **94** using a one-pot, two-step strategy (**Scheme 21**).[118] For this purpose, 1-hydrazinophthalazine hydrochloride **91** and 3,4-dimethoxybenzaldehyde **92** absorbed on silica were ground with sodium acetate producing the corresponding hydrazine **93**.



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

This reaction was conducted on a 1.7 mmol scale with zirconium oxide jars (20 mL) containing five ZrO_2 balls (10 mm ø) 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 × 15 min, 2nd step: IBD = 1 or 1.5 equiv., 800 rpm, 3 × 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: SeO_2 = 2 equiv., 800 rpm, 30 min).

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 × 15 min, and in the 2nd-step 3 × 15 min) and solution methods (conditions in the 1st step: EtOH, AcONa, reflux, 1h and in the 2nd-step: IBD, CH_2Cl_2, 4h). 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).

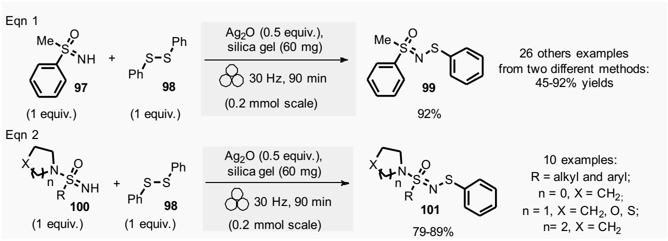


Scheme 22: Model reaction for 2-amino-2-oxospiro[indoline-3,4′-pyran]-3′-carbonitrile synthesis by manual grinding.

Sharma *et al.* developed a 3-component reaction leading to fused pyrano-spirooxindoles *via* manual mortar and pestle grinding.[119] 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

Catalytic processes mediated by transition metals or acids.

Bolm *et al.* described a new solvent-free method for *N*-sulfenylations of sulfoximines and sulfonimidamides by disulfides mediated by silver oxide.[120] The typical reaction (**Scheme 23**, Eqn 1) consisted in grinding *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 ø) for 90 min at 30 Hz under atmospheric conditions. The resulting phenylthioimino sulfanone **99** was isolated in high yields (92%). On a larger scale (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 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 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.



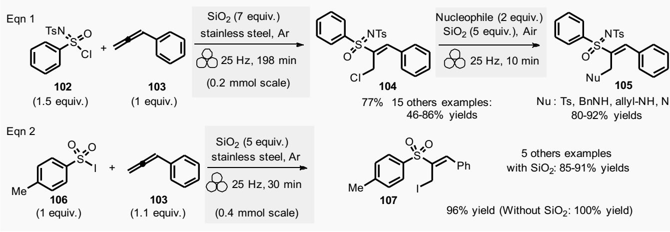
Scheme 23: *N*-sulfenylations of sulfoximines and sulfonimidamides in mechanochemistry.

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 generates 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 ø) 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 ø) at 25 Hz for 10 min under an air atmosphere. The corresponding substituted products 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 ø) at 25 Hz for 30 min under argon. The iodovinylsulfonyl derivative obtained **107** was isolated in 96% yield or even quantitatively in the absence of silica. Five other alkenes were also obtained from arylallenes in the presence of silica (85-91%).

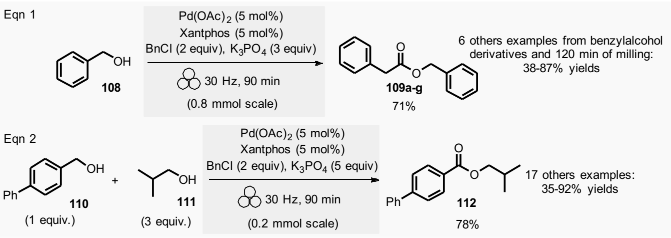
Comparison of green metrics (**Scheme 24**, Eqn 2) was favourable to mechanochemistry with respect to solution methods (E-factor: 0.85 vs 17.08, mass intensity: 1.85 vs 18.08, RME: 93.4% vs 61.1%, molar efficiency: 13.4% vs 1.3%).[121] These parameters were even better when milling in the absence of 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. [122] The previous green protocols for this reaction generally used heterogeneous catalysis or microwave irradiation,[123,124,125] which required high temperature, high pressure, organic solvents, and excess alcohol.



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

Bolm *et al.* developed a new methodology 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 K_3PO_4 (3 equiv.) as base. The best yields were observed when the reaction was carried out in a 0.8 mmol scale milling for two hours at 30 Hz using a stainless-steel milling jar (5 mL) loaded with two milling balls (10 mm ø). In this manner, seven esters **109a-g** were obtained in yields ranging from 38% ($4\text{-}NO_2C_6H_4CH_2OH$) to 87% ($4\text{-MeO-}3\text{-}FC_6H_3CH_2OH$) 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 K_3PO_4 (5 equiv) using the same amounts of catalyst, ligand, and oxidant. After purification on column chromatography, these conditions gave the desired compound (78% yield). In addition, chromatographic purification was required to eliminate two side-products – [1,1'-biphenyl]-4-ylmethyl [1,1'-biphenyl]-4-carboxylate (4%) and isobutyl isobutyrate (20%), still present in the reaction mixture.

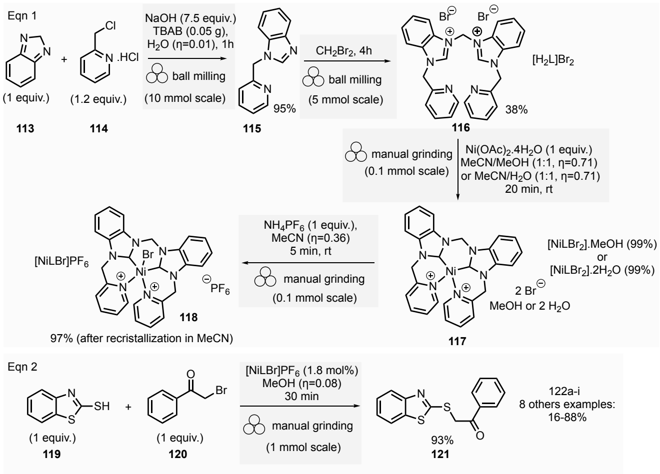


Scheme 25: Palladium-catalyzed oxidative self-esterification and cross-esterification in mechanochemistry.

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 (O_2), replaced by two equivalents of benzyl chloride in the ball-milling reaction.[126] 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 Ecoscales for both mechanochemistry and in solution were comparable (59 *vs* 56). For the cross-esterification (**Scheme 25**, Eqn 2), the AE was better in solution than ball-milling (79% *vs* 50%).[127] Nevertheless, RME (24% *vs* 30%), E-factor (30.7 *vs* 7.9), molar efficiency (1 *vs* 7), and Ecoscale (31 *vs* 60) are favourable to the mechanochemical routes.

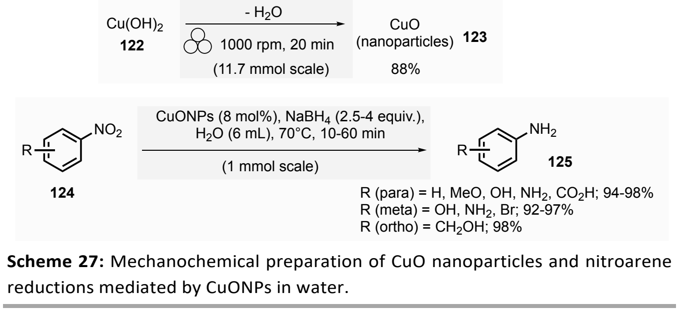
Guo *et al.* reported the mechanochemical cross-coupling reaction of 2-mercatobenzothiazoles and bromoacetophenone derivatives. The catalytic response is mediated by a transition metal-*N*-Heterocyclic Carbene (metal-NHC) complex ([NiLBr]PF_6) **118** (**Scheme 26**, Eqn 1).[128] For instance, the [NiLBr]PF_6 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 (η = 0.01) to produce *N*-pyridylmethylbenzimidazole **115** (95% yield). This compound was then treated with dibromomethane under milling conditions to afford benzimidazolium salt **116** ($[H_2L]Br_2$, 38% yield).



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

Then, $[H_2L]Br_2$ was reacted by manual grinding (mortar and pestle) with $Ni(OAc)_2$ under LAG conditions (η = 0.71) [MeCN/H_2O (1:1) or MeCN/MeOH (1:1)] to afford $[NiL]Br_2{\cdot}2H_2O$ and $[NiL]Br_2{\cdot}MeOH$ **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 $[NiLBr]PF_6$ **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.). The use of 30 µL of methanol in LAG conditions (η = 0.08) 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 Ecoscale score equals 76.5, no comparison was made with the solution-based protocol.



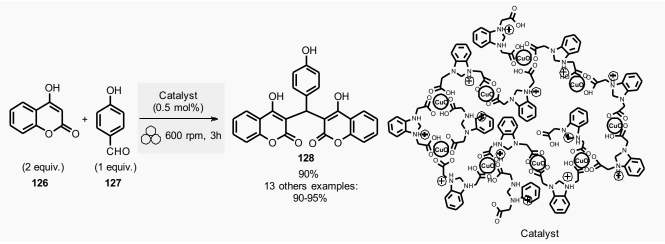
Scheme 27: Mechanochemical preparation of CuO nanoparticles and nitroarene reductions mediated by CuONPs in water.

In 2021, Barcellos *et al.* published a simple and efficient one-step mechanochemical preparation of copper oxide (II) nanoparticles (CuONPs), which were later employed to catalyze the reduction of nitroarenes.[129] Several other mechanochemical routes to CuONPs were previously reported using diverse copper sources (*e.g.*, $Cu(OAc)_2{\cdot}2H_2O$,[130,131] $CuSO_4{\cdot}5H_2O$,[132] $CuCl_2{\cdot}2H_2O$,[132] and $Cu(OH)_2$[133]). After calcination at 400 °C and 500 °C, the NPs obtained from $Cu(OAc)_2{\cdot}2H_2O$ presented an average size of 75 nm and 86 nm, respectively. Smaller CuONPs (7 nm to 34 nm) were obtained by grinding $CuSO_4{\cdot}5H_2O$ and $CuCl_2{\cdot}2H_2O$ 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 CuONPs (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 $Cu(OH)_2$ (1 equiv) and sodium chloride (2 equiv.) 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 were recovered after repeated water treatment and drying steps with 88% yield.

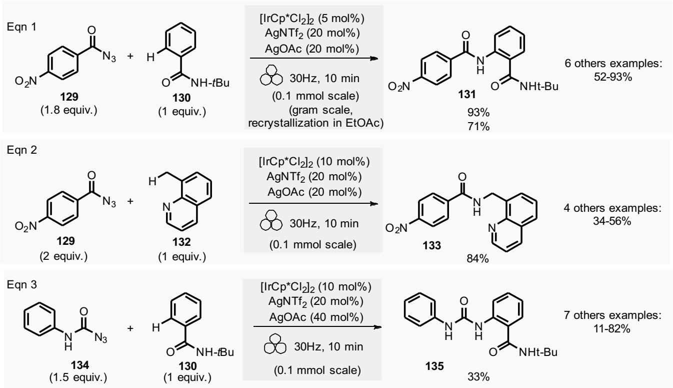
Green metrics assessment for the NPs synthesized from different copper salts was also performed. Comparing the atom economy (AE), $Cu(OH)_2$ turned out to be the best metal precursor as per the Barcellos' procedure, with an AE of 81.54%, followed by $CuCl_2$ (59.17%). Considering a yield of 88%, the 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,[131] and $Cu(OAc)_2$/ ammonium oxalate[130] followed by calcination at 500 °C and 400 °C are 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 ($Cu(NO_3)_2{\cdot}3H_2O$ [134]) 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 a series of nitroarene reductions using 8 mol% of catalyst and 2.5 to 4 equivalents of $NaBH_4$ in water at 70 °C for 10-60 min. For all reactions, aniline derivatives 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 of 4-hydroxycoumarin **126** with various aryl or heteroaryl aldehydes with a zwitterionic liquid coated CuO as catalyst (**Scheme 28**).[135]



Scheme 28: Model reaction of bis-coumarine synthesis by mechanochemistry.



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

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 3h in a grinding jar containing 45 tungsten carbide balls (5 mm ø). 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%),[136,137] except for work by Su *et al.* where a higher yield (97%) was obtained by performing the reaction under reflux in ethanol.[138] However, this reaction required a longer reaction time (24h) when compared to the mechanochemical route (3h). In addition, the catalyst employed during the mechanocatalytic reaction was reused 10 times without any loss of efficiency. When the mechanochemical reaction was carried out at a 10 mmol scale, the Ecoscale score was equal to 64 and the E-factor to 0.18.

Gon Kim *et al.* developed the direct aryl C-H amidation of acyl and carbamoyl azides mediated by an iridium (III) catalyst (**Scheme 29**).[139] 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.[140,141] 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 jar (2.2 g/cm^3) with stainless-steel balls was the best-performing milling media. In comparison, ZrO_2 (5.7g/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.*, $[Cp^*IrCl_2]_2$, 5 mol%), and a combination of silver salts ($AgNTf_2$, 20 mol %, and AgOAc 20 mol%). The mixture was milled in a Teflon jar (10 mL) with one stainless-steel ball (10 mm ø) 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-dichlorethane). Eleven different 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).

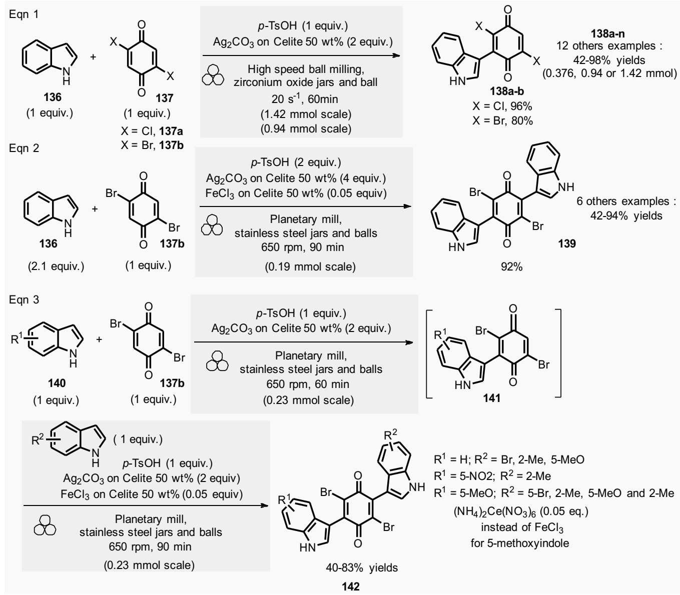
Authors also extended this C-H amidation to carbamoyl azides by both mechanical grinding and solution phase reactions. Eight ureas were obtained in 11 to 82% yields. Notably, in all cases, yields were in favour of mechanochemistry.

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.[142] Mono-indolylquinones **138** were prepared, by grinding indole **136** (1 equiv.), 2,5-chloro- or 2,5-dibromoquinone **137** (1 equiv.), Fetizon reagent (Ag_2CO_3 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 **138a-n** isolated in 42% to 98% yields.

Interestingly, this methodology allowed the preparation of symmetrical bis-indolylquinones **139** using a PBM 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 $FeCl_3$ (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 1h) 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 addition of the second indole **136** (1 equiv.), *p*-TsOH (1 equiv.), Fetizon reagent (2 equiv.) and $FeCl_3$ (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.



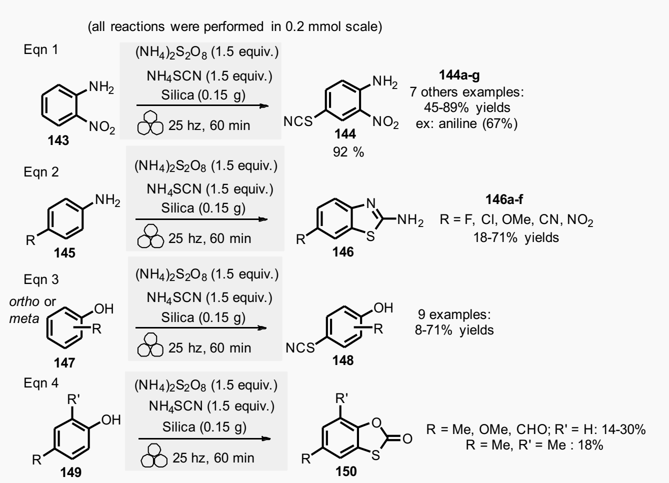
Scheme 30: Mechanochemical preparation of indolylquinones.

All the mechanical reactions took place in shorter times than in solution (26-62h). 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, respectively) compared to solution-based reaction (784.1 and 785.1).[143] 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.[144]

In 2020, Malvestiti *et al.* developed a mechanical protocol for the thiocyanation of aryl compounds *via* C-H functionalization.[145] 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).

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 **144a-g** were observed. In the presence of a reactive neighbouring group, a further reaction occurred. Then 3-aminophenol afforded 6-aminobenzooxathiol-2-one in low yield (15%). For *para*-substituted anilines, the thiocyanation cannot occur in *para*-position (**Scheme 31**, Eqn 2).

Consequently, the 2-aminobenzothiazoles **147a-f** were isolated in 18-71% yields. The methodology was also applied to phenol derivatives (**Scheme 31**, Eqn 3).

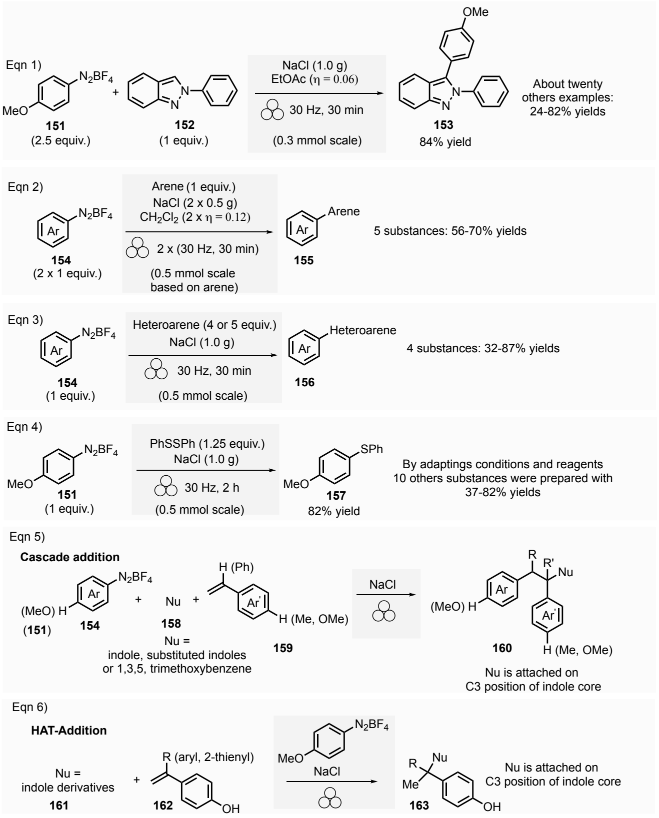


Scheme 31: Thiocyanation of aniline and phenol derivatives in mechanochemistry.

Ortho- and *meta*-substituted phenols led preferentially to *para*-thiocyanation products **148** in 8% to 94% yields. 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%).[146] 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.[147] The C-H (hetero)arylation of 1*H*- and 2*H*-indazoles, *N*-methyl-3-methylindole, benzothiazole, 2-methylthiophene, phenyl derivatives was developped. 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) and one drop of EtOAc (η = 0.06) or CH_2Cl_2 (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 ø). Ethyl acetate as LAG additive was necessary for the reaction.



Scheme 32: C-H (hetero)arylations, C-H sylfenylations, 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 other 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 CH_2Cl_2 as LAG additive (η = 0.12) 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 boronates 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 methoxyphenyldiazonium 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). Ten other ethers were obtained in yields ranging from 37% to 82%. 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 $NaBF_4$ 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).

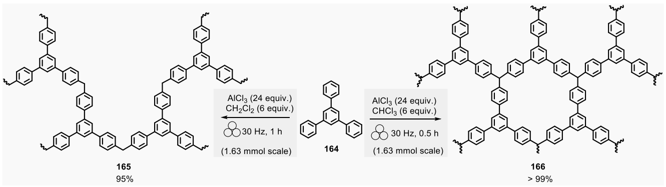
Yu *et al.*[147] also reported that 1,3,5-trimethoxybenzene or indole derivatives could undergo a C-H cascade addition starting from aryldiazoniums, and styrene derivatives in the presence of NaCl (**Scheme 32**, Eqn 5). Direct Hydrogen Atom Transfer (HAT) addition of aryl radical was also efficient 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 32a**).[148] 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 ecoscale score of 75 *vs* 46 in solution. A similar trend was observed for (4-methoxyphenyl)(phenyl)-sulfane **157** (**Scheme 32d**). Indeed, a better AE of 39.1% was calculated in the solventless process compared to 4.9% for the reaction done in solution.[149,150] 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, ecoscale score was 71% in mechanochemistry and only 51% for solution-based reactions.

Miscellaneous

Borchardt's team 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 a cross-linking reagent (CH_2Cl_2 or $CHCl_3$) in the presence of $AlCl_3$ (**Scheme** 33).[151] The typical reaction consisted in grinding under an inert atmosphere, TPB **164** (1 equiv., 1.63 mmol) with CH_2Cl_2 or $CHCl_3$ (6 equiv.) and $AlCl_3$ (24 equiv.) for 1h ($CHCl_2$) or 0.5 h ($CHCl_3$) at 30 Hz in a ZrO_2 jar (50 mL) with twenty two ZrO_2 balls (10 mm ø), following by 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.

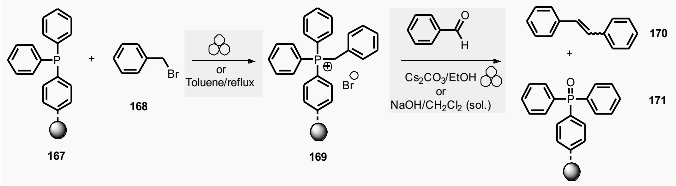
The solution-based reaction required a longer time (48 h) and a cleaning of the polymer using a Soxhlet extractor for 24 h.[152] Both procedures highlight that mechanical milling is advantageous by reducing the reaction time and the amount of cross-linking agent necessary. Regarding their properties, both polymers adsorb CO (4.37 mmol CO_2/g for CH_2Cl_2-based polymer and 4.74 mmol CO_2/g for $CHCl_3$- derivative.



Scheme 33: Porous organic polymers (POPs) preparation in mechanochemistry.

These values were very close to those observed for the polymers synthesized in solution (4.35 mmol and 4.71 mmol CO_2/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 $CHCl_3$.[153] 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 m^2/g was observed for six equivalents and 1670 m^2/g with 15 equivalents. This latter value was very close to SSA_{BET} observed in solution with CH_2Cl_2 (1685 m^2/g). By contrast, SSA_{BET} of $CHCl_3$-POPs remained not affected (1280 m^2/g for six equivalents and 1270 m^2/g 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.



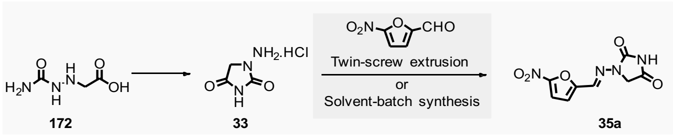
Scheme 34: Witting reaction by mechanochemistry.

In 2014, James Mack compared Ecoscale 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**).[154] 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 CH_2Cl_2/H_2O (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 stilbene was performed according to a one-pot, two-step sequence. The phosphonium salt was first prepared to combining benzyl bromide with a polymer-supported triphenylphosphine (1.64 mmol of PhCH2Br per gram of polymer) in a stainless-steel jar with a stainless-steel milling ball (ø 5 mm). The mechanical milling was then carried out on a SPEX shaker mill for 2 h. Subsequently, caesium 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 Ecoscale of 77, which is consistent with a green reaction. By contrast, the Ecoscale for solution-based strategy was much lower (35). For the authors, the better Ecoscale 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 Ecoscale 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 by TSE (*i.e.*, continuous flow mechanochemistry) and compared the obtained metrics with the solvent-batch synthesis.[155] 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 are synthesized by batch processes in solution, leading to high energy consumption and consequently a high release of CO_2 (from 10 to more than 1000 kg of CO_2 equiv per kg of API).[156]
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: Model reaction for life cycle assessment of continuous flow mechanochemical synthesis of nitrofurantoin **35a**

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,[157] 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 kWh. 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.[158,159,160] 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 CO_2 (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.

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 fullembrace this subject's complexity. 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.[161,22,162,163] 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 chimera, 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'[164,165,166] All this, in turn, will create the synergy required for greater use of mechanochemistry by industries that would benefit the environment.[164]

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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