Mechanochemistry 2.0: Advancing mechanochemical synthesis by combining different energy sources

Valentina Martinez‡, Tomislav Stolar‡, Bahar Karadeniz*†, Ivana Brekalo,*† Krunoslav Užarević*†

[1]Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

†Email: bahar.karadeniz@irb.hr, krunoslav.uzarevic@irb.hr, ibrekalo@irb.hr
‡These authors contributed equally
*These authors jointly supervised this work

[H1] **Abstract**

Mechanochemical processing of bulk solids has developed in the last three decades into a powerful and popular tool for the green synthesis and transformation of various classes of materials. Due to its efficiency and unique reactivity, mechanochemistry is becoming an integral part of synthetic laboratories and industrial procedures. However, despite its increasing popularity and usefulness, mechanochemistry is primarily based on simple techniques like grinding by hand -where the outcome often depends on the consistency and strength of the experimentalist - or milling in comminution devices, where a certain level of control is achieved through defining the frequency of milling and the weight of the milling media. Recently, however, mechanochemical reactivity started being complemented and altered by other energy sources commonly used in solution-based chemistry. Milling under controlled temperature, or photo-, sono-, and electro impulses in newly developed experimental setups has led to reactions not achievable by conventional mechanochemical processing. This Perspective describes the new reactivity discovered through these combinations of energy inputs, as well as the advances in equipment tailored to synthetic mechanochemistry that enabled them. We propose that these techniques – here termed thermo-mechanochemistry, sono-mechanochemistry, electro-mechanochemistry, and photo-mechanochemistry – represent a significant advance in modern mechanochemistry and herald a new level of solid-state reactivity: Mechanochemistry 2.0.

[H1] Introduction

Mechanochemistry, i.e., chemical reactivity caused by the application of mechanical force, has developed in the last three decades into a popular, green, and powerful tool for the synthesis and transformation of bulk solids.[1–5] This technique, where the solid reactants transform into products by grinding, milling, or shearing without the need for excessive amounts of organic solvents, is now applied for the preparation of a wide range of solid materials: soft supramolecular solids,[6,7] organic compounds,[8,9] discrete and non-porous coordination compounds,[10] extended metal-organic-[11] and covalent organic frameworks,[12] amorphous materials,[13–15], inorganic materials,[16] and many others. While known from antiquity[17], the technique was widely reintroduced to laboratories in the late 1980s primarily due to its sustainability benefits in waste generation and the time and energy required to prepare new materials. It rapidly developed into one of the critical synthetic tools in line with the principles of Green Chemistry[18], and has recently been highlighted as a technique that could help achieve the United Nations Sustainable Development Goals (UN SDGs) and the European Green Deal.[19] What distinguished mechanochemistry from other synthetic techniques, and made it into a popular and vibrant research field, is its extraordinary reactivity. Mechanochemical transformations offer an unprecedented level of selectivity[20] and control over the stoichiometric composition of the product,[21,22] and a whole branch focused on direct catalysis with the milling equipment is developing rapidly.[23] Even simple mechanochemical processing can lead to stabilization of supramolecular,[24] organic,[25] or coordination compounds[26] not accessible by other synthetic methods, which can in some cases be used as unique precursors towards more complex and unconventional materials.[27] Mechanochemical processing is used to activate and react gaseous reactants, leading to catalytic oxidation or reduction of gases, functionalization of 2D materials, and also to the synthesis of a variety of organic compounds.[28,29] Therefore, it is no wonder that many research laboratories and industrial facilities are rapidly adopting mechanochemistry. It has recently been termed "Chemistry 2.0"[30] and, in 2019, listed as "a technique that may change the world" by the IUPAC.[31]

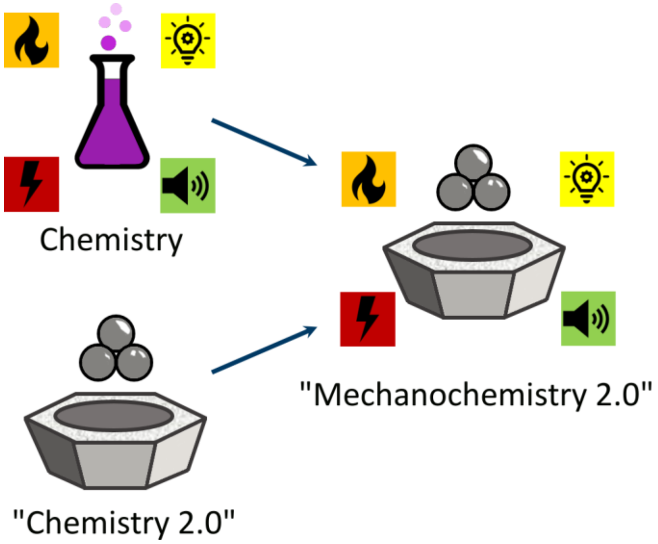

Fig. 1 | **Schematic representation of the premise of this Perspective.** Combining different energy inputs standard in traditional chemistry with mechanochemical ("Chemistry 2.0"[30]) instrumentation gives rise to a paradigm-shifting new approach to mechanochemistry, "Mechanochemistry 2.0".

Despite its tremendous popularity and many new reports, there are still drawbacks related to preparative mechanochemistry. Its mechanisms are not understood enough, scale-up is still in its infancy and barely studied, and, most importantly, the basic variables available to experimentalists are rather limited. Unlike traditional solution chemistry, where controlling the temperature, exposing the reaction setup to light, or running an electrical current through an experimental setup are all standardized and well explored, these variables have long been unavailable to the mechanochemist. Mechanochemical processing still primarily relies on basic techniques like milling and grinding by hand, or in comminuting devices. While a certain level of control over the outcome of the synthesis is available, it is predominantly achieved through simply defining the frequency of milling, the weight of the milling media, or by liquid or ionic additives.[32–34]

However, considerable recent interest in mechanochemistry, as well as the direct insight into milling reaction mechanisms provided through advanced monitoring techniques, initiated a change in experimental methods and instrumentation, but more importantly, a shift in the mindset of mechanochemists. Mechanochemical procedures are getting more complex and controlled. They are also often complemented with direct reaction monitoring or calculations, which help rationalize the observed transformations, develop a model of mechanochemical reactivity, and optimize the reaction conditions. Following this, several successful transfers from laboratory to pilot scales or continuous mechanochemical processing have already been accomplished.[35,36]

The need for combining mechanochemical reactivity with other energy sources, primarily heat, has been recently emphasized as a central issue for preparative mechanochemistry.[37] In 2013 Bowmaker stated: "*This highlights two points: (i) the fact that standard mechanochemical synthesis methods lack a means of temperature control and (ii) that there might be classes of chemical reaction, e.g. those that require heating to overcome an activation energy barrier, that are not suitable for standard mechanochemical synthesis*."[38] Since then, significant progress in complementing mechanochemistry with other energy sources has been made, involving milling under controlled temperatures or photo-, sono-, and electro-impulses in newly developed experimental setups (FIG. 1). Despite still being somewhat rare, these reports show huge potential for advancing the field, where the synergy in the combination of mechanochemistry with other energy sources may indeed unlock a new level of solid-state reactivity.

In this Perspective, we will focus on new advances in the mechanochemistry of bulk solids accomplished through complementing mechanical action with other energy sources. First, we will briefly overview the current state-of-the-art standard mechanochemical reaction setups and techniques. We will continue by presenting the existing reports on combining mechanical energy with other sources of energy input, which we here name sono-mechanochemistry, thermo-mechanochemistry, photo-mechanochemistry, and electro-mechanochemistry, and discuss the benefits found in the direction the field is currently taking.

[H1] **Standard mechanochemical instrumentation and synthetic techniques**

Several excellent reviews cover the phenomenon of conventional synthetic mechanochemistry[1–5], differences in the energetics of standard mechanochemical reactors, and mechanistic aspects of mechanochemical processing.[39,40] Describing all of these aspects in detail exceeds the scope of this Perspective, and we will provide here only a concise overview of the fundamentals of mechanochemistry and instrumentation to facilitate following the Perspective's content.

The official IUPAC definition of a mechanochemical reaction is "*a chemical reaction that is induced by the direct absorption of mechanical energy*".[41] On a fundamental level, any chemical reaction requires the molecules or atoms of the reagents to come into close contact while at the same time having enough energy to react. Mechanochemistry satisfies both prerequisites by introducing mechanical energy, as a mixture of (hydrostatic) pressure and shear, to reagents.[40] The shear component removes layers of atoms/molecules from the material surface, comminutes the particles, and mixes the milled material, enabling more accessible contact between the atoms and molecules of reagents. The pressure component, on the other hand, introduces internal plastic stress into the particles of the reagents. This stress must be released by various relaxation methods, including heat, amorphization, aggregation state change, or plastic deformation, all of which include the motion of the atoms/molecules of the reagents and give them kinetic energy, potentially large enough to produce a chemical reaction.

Since antiquity[17], this mechanical energy needed for the reaction of a bulk material was introduced through simple hand grinding using the ubiquitous mortar and pestle (FIG. 2a), so mechanochemistry could be easily performed by any experimentalist. However, due to safety concerns and reproducibility issues stemming from working in an open system where the introduced mechanical energy largely depends on the physical vigor of the experimentalist, mechanochemists adopted commercial comminution devices – mills - starting with the first mechanical mill built by Ostwald in the mid-1920s.[42] All mills have a similar method of operation where the milling media in motion exerts a mechanical force on the interior walls of the milling vessel and the reagents inside. Commonly used mills in synthetic laboratories are ball mills, such as mixer mills (FIG. 1b) and planetary mills (FIG. 1c), differentiated by the type of motion of the milling vessel. The most popular materials for milling vessels and media (milling balls) are hard materials such as stainless steel, tungsten carbide, titanium carbide, agate, zirconia, and alumina, but also some plastics such as polytetrafluoroethylene (PTFE), and poly(methyl methacrylate) (PMMA). Materials such as copper, nickel, platinum, brass, or bronze can be used for the vessel or milling media and even serve as heterogeneous catalysts,[23,43] as was successfully demonstrated for cycloaddition-, click-, Suzuki-, and Sonogashira reactions.[44–47] The main controllable technological parameters in the mechanochemical process are the frequency of oscillation, hardness of the milling material, and the quantity and weight of milling media.

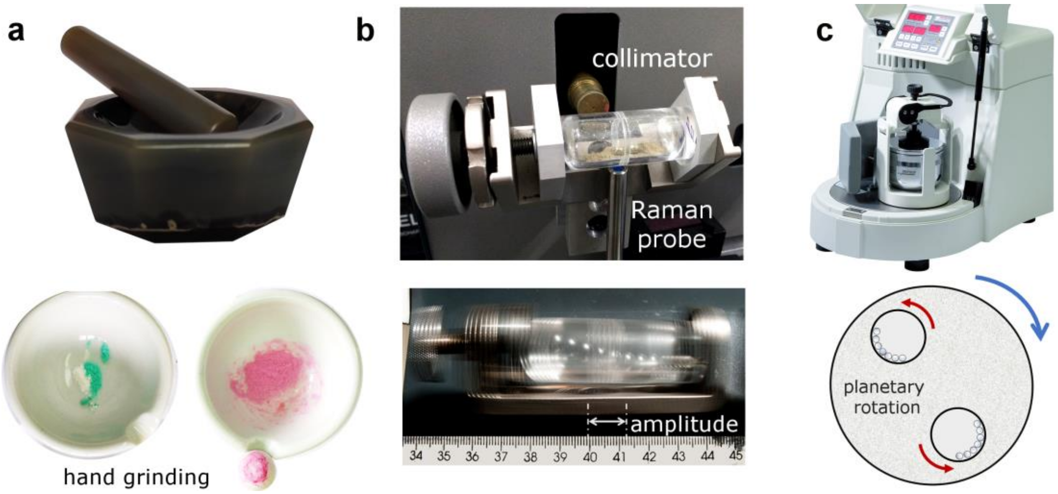

Fig. 2 | **Example of three standard modes of mechanical energy input. a** | Top: Standard laboratory agate mortar and pestle for manual grinding. Bottom: before/after images of the reaction between nickel acetate and dimethylglyoxime producing red nickel bis(dimethylglyoximate) complex by manual grinding. **b** | Top: mechanical mixer mill adapted for tandem *in situ* synchrotron powder X-ray diffraction and Raman spectroscopy monitoring. The synchrotron X-ray beam collimator and Raman probe point at the lower part of a clear plastic jar made from PMMA (poly(methyl methacrylate)). Bottom: composite of several sequential short-exposition images of the movement of a 4 g stainless-stainless ball in a PMMA jar mounted on a mixer mill operated at 25 Hz. **c** | Top: an image of a planetary mill with one jar. Bottom: bird-view schematic of a 2-stage planetary milling stage, indicating the different rotational directions of the milling stage and jars.

The field of preparative mechanochemistry experienced significant growth in the early 2000s, with the introduction of additives to mechanochemical procedures. These additives may be liquids (liquid-assisted grinding, LAG)[33,34], ionic solids (ion-assisted grinding, IAG, and ion-and liquid-assisted grinding),[48] non-ionic additives such as polymers (polymer-assisted grinding, POLAG)[49], or small molecule non-ionic solids[50]. While many reports claim these additives to be added in a "catalytic" amount, their exact role is complex and specific for a particular system. It is well known that even a minimal amount of additives can stabilize certain solid forms, enhance particle diffusion and partial dissolution of the reactants, and may activate the reaction through coordination or changes in proticity or basicity of the system,[51–53] but cases where the additive slows down or prevents chemical reaction were also reported.[51,54]

The mechanisms and kinetics of mechanochemical reactions have been intensively studied since the invention of real-time and *in situ* techniques for monitoring mechanochemical reactions by powder X-ray diffraction[55,56], X-ray absorption spectroscopy (XAS)[57] and Raman spectroscopy.[58,59] These advanced methods enabled direct insight into mechanochemical conversions without interrupting the milling process. They revealed how seemingly simple milling processes often take complex reaction pathways involving short-lived intermediate phases or amorphous matrices. Complementing the experimental techniques, various computational studies such as DFT calculations[60] and molecular-dynamics simulations[61–64] were performed to further elucidate the solid-state reactions at the molecular level. The unconventional reactivity and efficiency of mechanochemistry render it a viable alternative to solution procedures with many additional benefits, and the mechanochemical reactor may soon be seen as a ubiquitous part of almost every synthetic laboratory. It is therefore crucial that new advances in mechanochemical instrumentation and procedures are explored, including the combination of mechanical energy with other energy sources.

[H1] **Thermo-mechanochemistry**

Mechanochemical processing and thermal energy are inherently related and hard to separate. Mechanical energy transferred to the system during milling is in part absorbed by the material and milling media, while the rest gets released as heat.[65,66] In fact, while it is known today that many mechanochemical reactions proceed through non-thermochemical mechanisms,[67] it was often postulated that mechanochemical reactivity results from this secondary thermochemical effect. Hot-spot theory[68,69] and the magma-plasma model[70], two popular theories of mechanochemical reactivity, are predominantly focused on the thermochemical effects of milling. Both theories postulate that mechanical action in the form of lateral friction or direct impacts dramatically increases local temperatures at the friction or impact sites (up to thousands of degrees Celsius) for a very brief period. However, a large amount of recent experimental and theoretical work shows that thermochemical phenomena are unlikely to be the primary force behind mechanochemical reactivity,[40,71] and evidence of a difference between mechano- and thermochemical reactivity goes back more than a century. For example, Carey Lea observed that silver halides reduce and decompose by mechanochemistry, but heating causes them to melt without any reduction observed.[72] This and his following work[73,74] became a foundation for defining mechanochemistry as a separate sub-discipline of chemistry, alongside thermochemistry, electrochemistry, and photochemistry.[17] Many other systems studied later supported the same conclusion.[4,75]

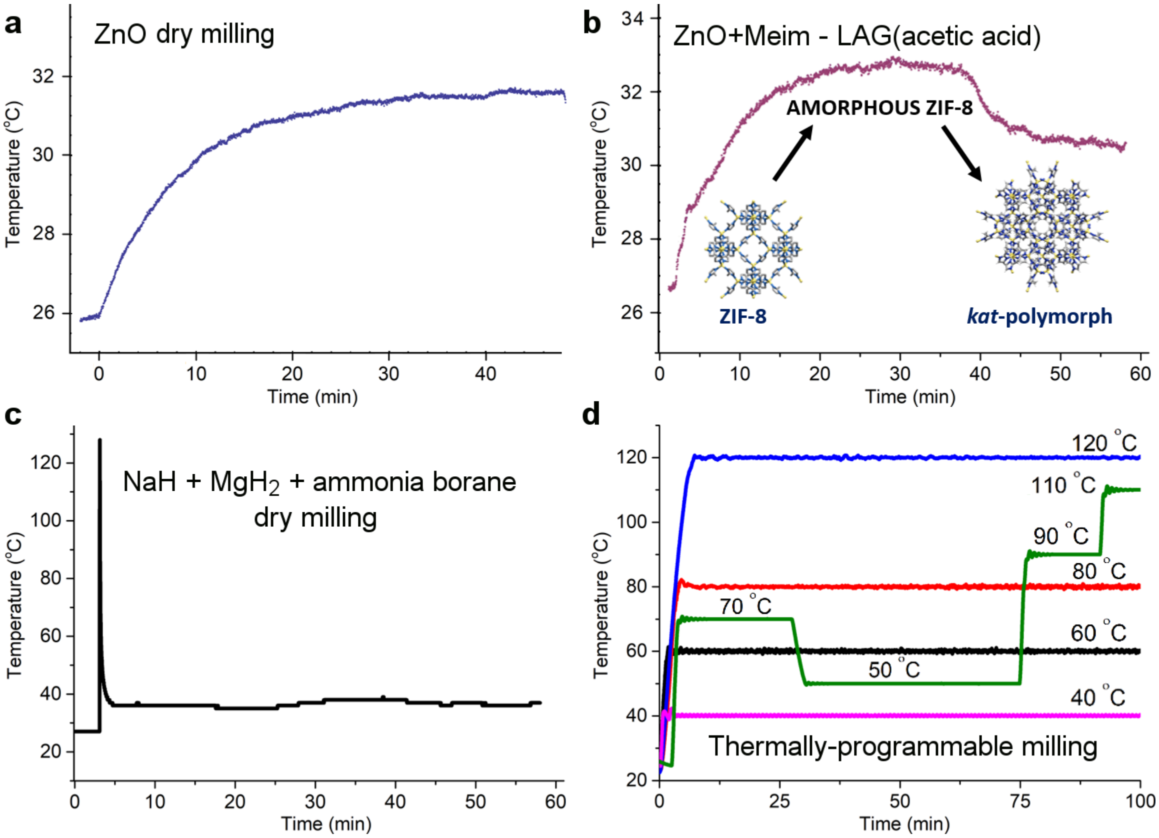

Fig. 3 | **Different thermochemical effects in mechanochemistry.** **a** | Dry milling of zinc oxide. The temperature rises monotonously until reaching an equilibrium between the invested and dissipated energy. **b** | Liquid-assisted milling of zinc oxide and 2-methylimidazole (Meim). A thermal profile where each thermal event corresponds to a change in the phase composition. The amorphization of formed ZIF-8 leads to a stable temperature plateau at ca. 32 °C, and the recrystallization of amorphous ZIF-8 to the kat-Zn(Meim)$_2$ phase results in a drop in temperature due to the different plastic properties of the kat-polymorph. **c** | Thermal profile of the milling of sodium- and magnesium hydrides mixture with ammonium borane. A dramatic jump in temperature of the reaction mixture (to 128 °C) upon the start of the milling when NaH reacts with ammonia borane in a strongly exothermic reaction. The reaction mixture cools down rapidly, reaching a stable plateau at ca. 36 °C. **d** | Milling reactor with a proportional−integral−derivative temperature controller enables dynamic changes in the temperature of the milled material. Panels **a** and **b** adapted from REF[66], CC BY 3.0, Royal Society of Chemistry. Panel **c** adapted with permission from REF[76], American Chemical Society. Panel **d** adapted with permission from REF[77], American Chemical Society.

While thermochemical effects in mechanochemistry may not be the primary source of mechanochemical reactivity, the bulk temperature of the milled reaction mixture does typically rise, and can therefore influence the course and outcome of the reaction. The rise is primarily due to collisions and friction during milling. It occurs until equilibrium is achieved when the thermal energy dissipated by radiation and convection equals that produced through mechanical action

(FIG. 3a). Reaction mixture temperature may also fluctuate during milling when the plastic properties of the material change (FIG. 3b), or due to the endergonic or exergonic nature of specific reactions, albeit in a shorter period (FIG. 3c).[5,76] Mechanically-induced self-propagating reactions represent an extreme of the latter.[78] These temperature fluctuations may affect the progress of a mechanochemical reaction, but importantly, they are outside the experimentalists' control and cannot be reliably used to govern reactivity.

Intentional control of reaction temperature during milling began with cryomilling in the early 20th century, when milling vessels were cooled by immersion in cryogens to disrupt living cell tissue[79-81]. It was later shown that lowering the temperature of flexible materials under the glass-transition temperature (Tg) results in brittle materials that can be pulverized by mechanical action. Milling at temperatures below Tg is also often used as an alternative for preparing amorphous solids, where the cryogen prevents thermally induced recrystallization.[15] Cryomilling has thus remained popular in biology and pharmaceutical industry.

However, intentional control of reaction temperature in the service of *synthetic* mechanochemistry was first reported in 1998 by Kaupp, who utilized a milling vessel wrapped in tubing containing a cooling liquid, which was connected to a chiller. The setup was initially used for the facile and quantitative mechanochemical synthesis of sensitive iminium salts.[82] Here, cooling prevented the formation of the eutectic phase, thus enabling the direct formation of crystalline products and preventing passivation of the reactant surfaces by amorphous matrices. Simultaneously, the mechanical action facilitated the reaction by exposing new reactive surfaces and mixing the material. The same apparatus was used later for solvent-free protection of amines, carboxylic acids, or enols by phenylboronic acid.[83]

With a similar setup, the Mack group used sub-ambient-temperature ball milling to increase diastereoselectivity during the reduction of a cyclohexanone derivative (FIG. 4a).[84] When milling at -10 °C, the diastereomeric excess (*de*) significantly increased compared to ambient temperature milling. Interestingly, *de* fell with increasing milling frequency. The authors established that temperature differences of as low as 5 °C affect both yields and enantioselectivity of several other reactions, including asymmetric aldol condensation catalyzed by (*S*)-proline, enantioselective A^3 coupling (aldehyde-alkyne-amine reaction), and Diels Alder reactions.[11] Generally, the selectivity of mechanochemical reactions drops with increasing temperature, hardness of milling media, or the milling frequency, while at the same time, the reactivity rises.[85] Very recently, the real-time *in operando* monitoring of milling under elevated temperature revealed that even a moderate increase of the bulk temperature of a reaction mixture comprised of high melting point solids might dramatically influence not only the kinetics but also the mechanisms of reaction.[71]

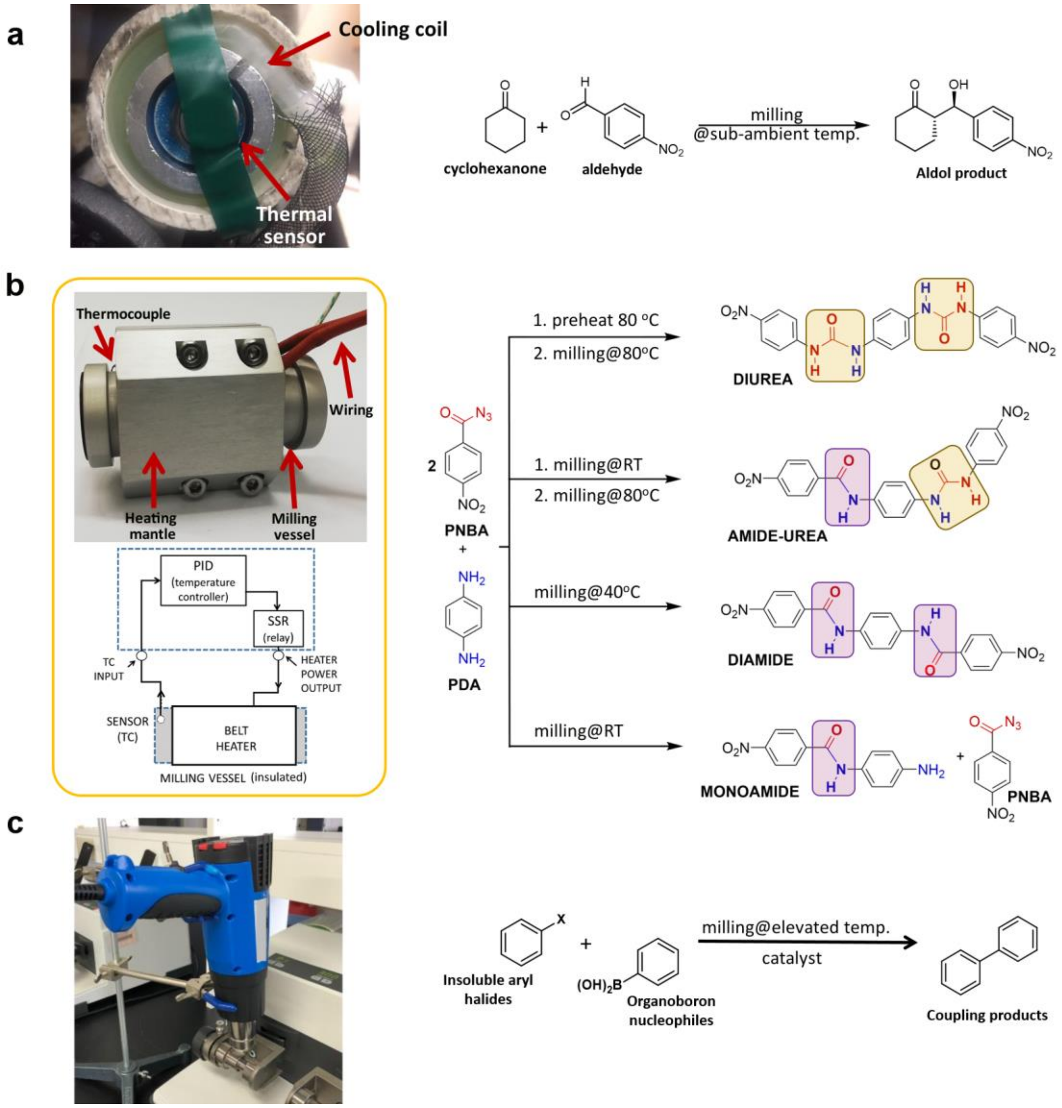

Fig. 4 | **Three different types of experimental setups for controlling the temperature of a milled reaction mixture. a** | cryomilling setup by Mack and Andersen, used for asymmetric aldol synthesis. **b** | Milling jar with a heater system connected to the proportional–integral–derivative temperature controller device. The preparation of four different derivatives containing amido and urea groups (monoamide, amide-amide, urea-amide, and urea-urea) from the same reaction mixture by temperature control during milling. **c** | Thermo-mechanochemistry *via* a simple heat gun heating setup and its application to Suzuki-Miyaura coupling. Panel **a** adapted with permission from REF[84], Wiley-VCH. Panel **b** adapted with permission from REF[77], American Chemical Society. Panel **c** adapted with permission from REF[86], American Chemical Society.

Similarly, the Schüth group showed that sub-ambient-temperature ball milling can improve the selectivity and reactivity of the heterogeneous catalytic oxidation of CO.[29] Ball milling of a Cu/Cr_2O_3 catalyst mixture in the presence of O_2, CO, and an excess of H_2 under cryogenic conditions (stream of cooled nitrogen at -40 °C) enabled preferential CO oxidation with excellent selectivity and reactivity compared to milling at higher temperatures. Similar conversion, but with much poorer selectivity, was only achieved when using pre-milled catalysts at temperatures higher than 100 °C. This result was explained by the apparent negative activation energy for mechanochemical CO oxidation and the critical role of *in situ* generated active sites and defects on Cu/Cr_2O_3 catalyst surfaces during ball milling.

Aside from mechanochemistry at sub-ambient temperatures, there are many benefits to milling at elevated temperatures. The Ito group recently reported the mechanochemical palladium-catalyzed Suzuki-Miyaura cross-coupling of insoluble aryl halides at different temperatures, heating the milling vessel with a simple heating gun (Fig. 4c).[86] While the reaction does not proceed at room temperature, milling at elevated temperatures led to complete conversion, in some cases accessing products not available by solution-based synthesis. The same group later developed the robust and unprecedented synthesis of magnesium-based carbon nucleophiles, i.e., Grignard reagents, from poorly soluble aryl bromides and in air[16], by milling at elevated temperatures.[87] The prepared Grignard reagents can be immediately coupled to organic aldehydes without prior workup, giving nucleophilic addition products, some of which are unobtainable by conventional solution-based synthesis. Calcium-based heavy Grignard reagents were very recently prepared by the same group in an analogous fashion, and once more heating the milling vessel to 60˙C proved crucial for reaction success.[88] The same setup was also applied for the palladium-catalyzed C-N cross-coupling of aryl halides and carbazoles, where ball milling at elevated temperatures helped dissociate carbazoles from off-cycled palladium and enabled rapid and efficient cross-coupling without regards for the substrate (in)solubility.[89]

Despite the obvious benefits of temperature-controlled ball milling, instrumentation capable of precise temperature control (especially at temperatures above 100 °C) was unavailable until recently. In 2019 our group presented a new setup with modified vessels containing a heater element managed through a proportional−integral−derivative (PID) temperature controller device (FIG. 4b).[77] Here, the temperature during milling can be precisely controlled at temperatures up to 250 °C. The PID controller allows for adaptive and programmable thermal regimes during milling (FIG. 3d), which enabled the preparation of four different derivatives containing amido and urea groups (monoamide, amide-amide, urea-amide, and urea-urea) from the same reaction mixture, solely by varying temperatures during milling. The same setup allowed for the prebiotically plausible solvent-free synthesis of oligopeptides. Ball milling of glycine or alanine with TiO_2 at elevated temperatures dramatically enhanced oligomerization, but also altered the selectivity of the reaction towards cyclic oligomers.[90]

Importantly, temperature control of mechanochemical reactions is also possible on larger scales, primarily through what is becoming a popular methodology for solid-state flow synthesis, reactive twin-screw extrusion (TSE).[91] TSE instrumentation is commonly used for extruding raw materials for polymer production. However, there are nowadays many examples of using TSE for the continuous large-scale mechanochemical synthesis of a wide range of chemicals, from supramolecular systems[36] and organics,[92] to extended coordination materials.[93,94] Temperature control is provided as a standard feature of the TSE instrument, with heaters embedded in chambers surrounding the screws. While not commonly applied for TSE production, control over the temperature of the reaction mixture during extruding could be critical for the successful transfer of mechanochemistry to an industrial scale. In their pioneering work on TSE synthesis of metal-organic frameworks, the James group demonstrated how raising the temperature of the extruder barrels can open a pathway towards materials otherwise inaccessible by mechanochemical procedures.[93] The authors even managed to prepare the Al(fumarate)(OH) MOF - a widely sought material with high application potential due to its stability in water and high affinity towards methane, which was never prepared through conventional mechanochemical procedures - by extrusion at 150 °C. High-temperature TSE is not only beneficial in the scale-up of MOF syntheses, but it can also greatly aid organic mechanochemistry. For example, the Knoevenagel condensation of barbituric acid and vanillin was unsuccessful with room temperature TSE, but raising the temperature to 160 °C resulted in quantitative conversion into Knoevenagel product, with no byproducts observed. The authors concluded, "*Overall, there is a need to be able to control the temperature of mechanochemical processes as well as improve their scalability if mechanochemistry is to become widely applicable as a chemical manufacturing technique*".[92]

[H1] **Sono-mechanochemistry**

Sound at different frequencies and power scales has long been used in the chemical laboratory to enhance solubility, reduce particle size, or catalyze and enable chemical transformations. Although the classification of sonochemistry as a part of mechanochemistry remains a matter of debate,[95] sonochemical treatment is known to give similar results to typical mechanochemical synthesis.[96]

Considering the similarities between “classic” mechanochemistry and sonochemistry, it is unsurprising that researchers have sought to combine sound agitation with grinding.

Ultrasound generally uses sound waves of high frequencies (20-200 kHz) propagating through a liquid medium to create acoustic cavitation: the appearance, growth, and collapse of small vapor-filled bubbles (FIG. 5a). When these microbubbles collapse, they result in high-pressure and high-temperature hot spots within the liquid medium (5000 K, 1000 atm), promoting a chemical reaction.[97]

Ultrasound-induced cavitation can alter reaction mechanisms (e.g. formation of radical species that trigger secondary reactions), improve reaction rates, cause nucleation and crystal growth even at low supersaturations, transfer reagents across phases in multiphase reactions, and much more.[98] Ultrasound irradiation is introduced into the reaction system using ultrasonic transducers (e.g. an ultrasonic bath or probe), which operate at a fixed frequency. The reaction outcome often depends on the frequency, acoustic power, and temperature of the liquid medium.[99]

Early examples of devices that combine ultrasonic irradiation and ball milling have been reported by Mordyuk[100] and Chen[101] research groups (FIG. 5b and c).

The Mordyuk group developed a system (FIG. 5b) in which an ultrasound generator transmits vibrations to milling balls *via* a vibrator, somewhat similar to Suslick’s setup for solution syntheses (which has no impellers).[102] By milling metal powders in an ultrasound-assisted ball mill,[103] pseudo-alloys can be produced in a much shorter time than in conventional mechanochemical synthesis[100], and impurities present within metal nanopowders can be introduced into metal particles during ultrasonic treatment, enhancing their microstructure.[104,105] This type of milling can also initiate phase transformations[106] or activate powders for further processing,[107,108] thus reducing the time of mechanical activation needed for obtaining target products.[109,110]

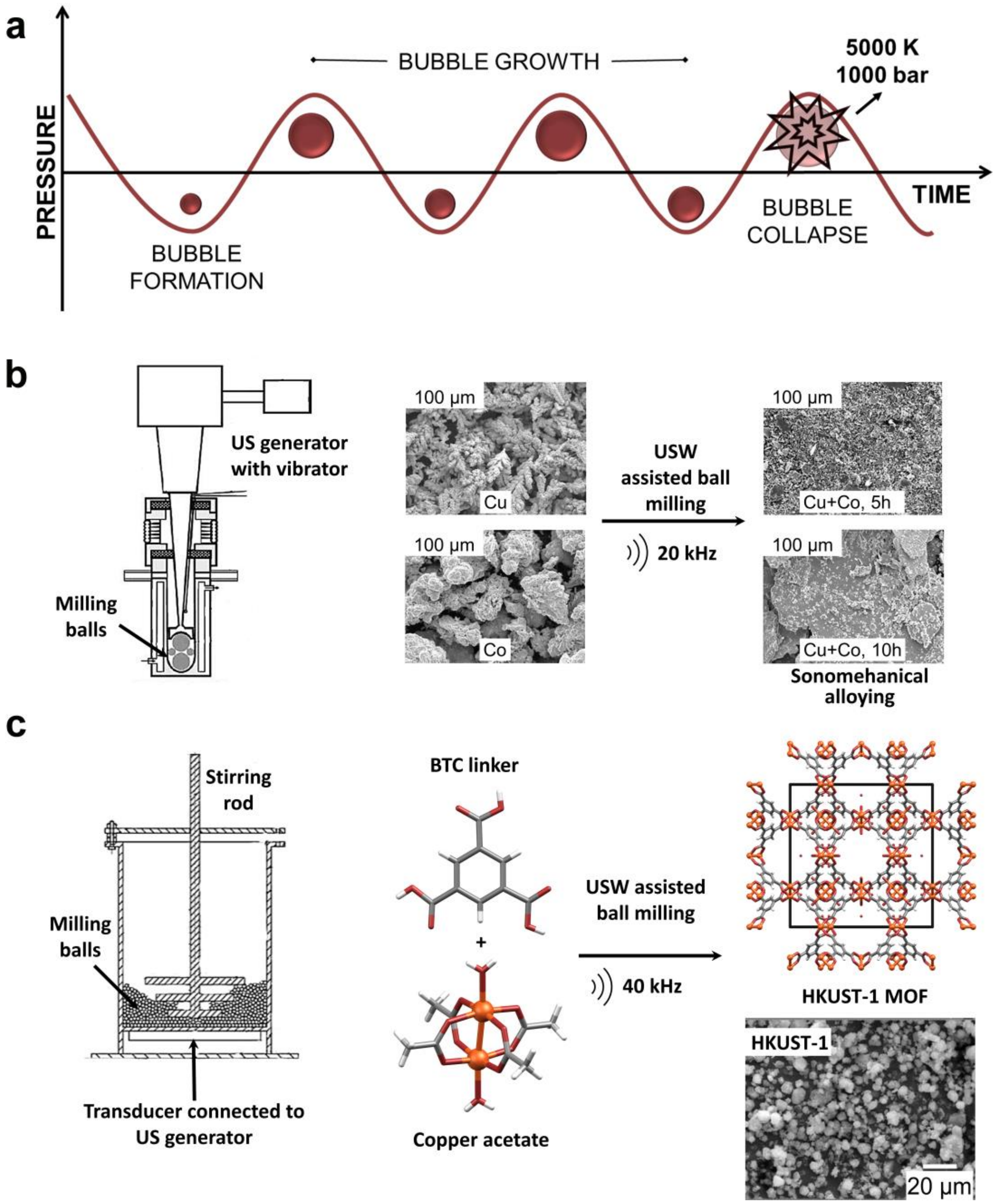

Fig. 5 | **Acoustic cavitation and different sono-mechanochemical setups.** **a** | Bubble growth process during ultrasound irradiation resulting in bubble collapse. **b** | Schematic representation of a device for ultrasonic wave-assisted ball milling used for sonomechanical alloying; and **c** | schematic representation of a device for ultrasonic wave-assisted ball milling used for HKUST-1 synthesis. Panel **b** adapted with permission from REF[100], Elsevier, and REF[110] CC BY-ND, G. V. Kurdyumov Institute for Metal Physics of the National Academy of Sciences of Ukraine. Panel **c** adapted with permissions from REF[111], Elsevier, and REF[112], Wiley-VCH.

The Chen group designed a device for solid-liquid ball milling assisted by ultrasonic waves, consisting of a raker stirrer, steel balls, and an ultrasound generator (FIG. 5c).[101] In a range of inorganic systems, this new mill performed better than conventional ball milling or ultrasonic synthesis alone and enabled reactions in water at temperatures under 100 °C. For example, the synthesis of metal nanoparticles under sono-mechanochemistry was much more efficient regardless of metal source (metal chips, metal salts), presumably due to *in situ* production of OH radicals and H_2O_2.[101,113] Sono-mechanochemistry also enabled the conversion of metal oxides to the corresponding magnetic ferrite nanoparticles. In contrast, simple milling provided a solid solution of metal oxides. The syntheses can be optimized by changing the ball milling parameters (e.g., a ball to powder ratio, amount of liquid) and metal source.[111] This method has been used to quickly and efficiently produce MOFs (FIG. 5c) with good adsorption properties.[112] The results were comparable to mechanochemical grinding methods,[114] with a strong potential for scale-up.

Although arguably not presenting a combination of grinding with another energy source, another interesting sonochemical method is Resonant Acoustic Mixing, RAM, a relatively new impeller-free technology that has sparked significant interest in preparative materials chemistry.[115] In RAM, the entire experimental setup vibrates vertically at low frequencies (~60 Hz) and mixes the sample by inducing micro-scale turbulence resulting from the propagation of acoustic waves through the mixing medium. The entire system vibrates in resonance creating micro-scale vortices allowing for efficient energy transport and mixing.[116,117] Mixing time, frequency and acceleration can all be adjusted. High accelerations (95 *g)* are excellent for easy and controllable synthesis of stable materials, while low accelerations (30 *g)* allow synthesis of more sensitive materials.[118]

In terms of mechanochemical synthesis, it was recently shown that liquid-assisted RAM (LA-RAM) can rival liquid-assisted grinding (LAG) in synthesis of supramolecular solids.[119] Screening for pharmaceutical co-crystals of carbamazepine using LA-RAM resulted in a higher success rate than LAG methods,[120] and while only laboratory-scale amounts products have been isolated, there are indications that scale-up is also possible.[121] The absence of grinding media (balls, rods etc.) is particularly useful in producing energetic materials[122], increasing the safety of the synthetic process while preserving high yields.[123,124] A strong potential for scale-up, even to industrial scales, makes RAM even more appealing.

[H1] **Photo-mechanochemistry**

Light is one of the most important driving forces of chemical reactions, both in nature and in the laboratory. Photosynthesis, the ozone photolysis cycle, photovoltaics, and radical polymerizations are just some examples of light-dependent phenomena.[125] In synthetic chemistry, light can drive reactions unavailable by thermal activation by creating radical or excited state species that are much more reactive than ground-state ones.[126] A combination of mechanical and light energy activation has, therefore, all the prerequisites to provide exciting new synthetic options.

Photo-mechanochemistry has so far been applied mainly in [2+2] cycloaddition reactions[127–129] and the activation of organocatalytic reactions.[130] As early as 1987, Toda *et al.* showed that mechanochemistry can induce the cocrystallization of several diols by using a test tube shaker. When one of those complexes containing chalcone was irradiated during milling, a stereoselective [2+2] cycloaddition was achieved, with the diol dissociating from the product during milling and acting as a catalyst.[131] More than twenty years later Sokolov *et al.* followed this work and achieved efficient and rapid [2+2] photodimerization of trans-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) using functionalized resorcinol as a catalyst. The procedure involved cycles of mortar and pestle grinding followed by UV irradiation. This very mild grinding significantly improved turnover, and the authors concluded, "*[we] expect an automated mechanochemical processes (i.e. ball mill combined with UV light) could lead to significantly decreased reaction times and reductions in catalyst amounts.*"[132] Indeed, they later irradiated an open vortex shaker with UV light during milling, fulfilling their prediction and achieving shortened cycloaddition times (FIG. 6a). *In situ* irradiation with UV light in classic mixer or planetary mills is, however, still challenging due to the opaqueness of common milling vessel materials to UV irradiation.[133]

Irradiation by visible light sources is much simpler to combine with standard milling setups since many known hard materials are transparent in this range. König et al. developed a combined system of rod mill and blue light irradiation (FIG. 6b) in the presence of a photocatalyst to oxidize alcohols to the corresponding carbonyl compounds. By rotating the glass rod, a thin film is created between the tube and glass rod, which proved to be a critical step for efficient irradiation.[134] Štrukil *et al.* reported a new system combining ball milling in a DURAN glass vessel in a photoreactor comprised of blue LEDs for mechanochemically-assisted solid-state photocatalytic reactions. The DURAN glass vessel enabled simultaneous harsh milling and irradiation, as well as working on air-sensitive materials.[135] At the same time, Hernández used ball milling in a PMMA vessel wrapped in green or blue LEDs to study the role of the eosin Y photocatalyst on the photo-borylation of aryldiazonium salts (FIG. 6c).[130] Neat milling under green LEDs required the organic photocatalyst, while liquid-assisted milling under blue LEDs was successful even under catalyst-free conditions. This indicated the existence of a direct photolysis pathway facilitated by the formation of a liquid-substrate charge-transfer complex.[130] Hernández also observed the critical effect of increased temperature in dry milling reaction for the formation of molten reaction mixtures. This important notion indicated that the combination of more than two energy sources, photo-, thermo-, and mechanochemistry in this case, might lead to even faster and more efficient reactions.

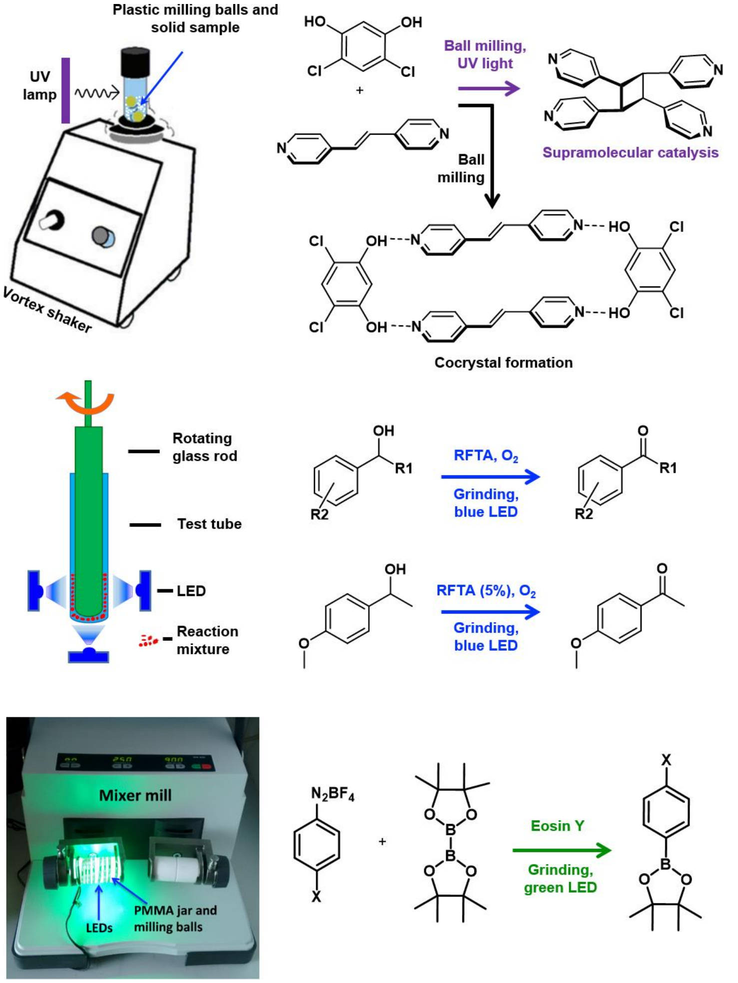

Fig. 6 | **Experimental setups and example reactions for three different types of photo-mechanochemical reactors. a** | Vortex milling under UV light, applied to supramolecularly catalysed [2+2] cycloaddition; **b** | glass rod grinding under blue light, applied to oxidation of secondary alcohols, and **c** | mixer milling under green light, applied to the photo-borylation of aryldiazonium salts. Panel **a** adapted from REF[133], Royal Society of Chemistry. Panel **b** adapted from REF[134], Beilstein Institute for the Advancement of Chemical Sciences, CC BY 3.0. Panel **c** adapted from REF[130], Beilstein Institute for the Advancement of Chemical Sciences CC BY 3.0.

[H1] **Electro-mechanochemistry**

Electrochemistry is a branch of chemistry studying the relationship between electric potential and chemical reactivity, either by applying electrical current to initiate a chemical reaction or by using chemical reduction and oxidation processes to produce electricity. Electrochemistry has been used in many applications, including fuel cells, batteries, and chemical synthesis. The use of an electrical current to tune oxidation states of chemical reaction components has been widely used in chemical synthesis, extraction, and materials production on industrial scales. [136,137] However, since using an electrical current often requires the presence of an electrolyte (commonly in liquid form), merging the use of an electrical current with mechanochemistry is still very uncommon.

The setup for electrical-discharge-assisted mechanical milling (EDAMM) was first presented in 2002 (FIG. 7a), combining high voltage, low current discharge impulses in a controlled atmosphere with two different types of modified mills: a vibratory ball mill and a magneto-mill.[138] The latter controls the movement of milling balls with an external magnetic field, enabling easier decoupling of electrical and mechanical force-induced effects. In both mills, an AC high-voltage transformer generated 30 kV, 50 Hz impulses inside the mill, resulting in either arc/spark discharge (higher gas pressure in milling jar), or a glow-type discharge (lower pressure). Even short EDAMM of a single reagent (conductive or non-conductive) resulted in strong fracturing of milled particles, while traditional milling showed much milder effects. The authors assigned this effect to the rapid Joule heating occurring during spark generation, and the behavior of the conductive substrate pointed to the existence of complex mechanisms of fracturing.

The application of EDAMM to mixtures of materials opened synthetic pathways toward new products not accessible by traditional mechanochemistry. Traditional milling of elemental Fe and B did not result in FeB product even after 500 hours. Switching to spark-type EDAMM for only 30 minutes transformed the Fe and B mixture into a phase-pure FeB product.[138] Further synthetic avenues open up when employing glow-type EDAMM. Traditionally, nitriding of metal powders with N_2 gas only happens with reactive metals (Ti, Zr, V) under prolonged milling. For other metals (such as Si and Fe), ammonia gas is used, resulting in side products and embrittlement of the milling vessel. Indeed, when using spark-type EDAMM on titanium or silicone powder in nitrogen gas, there is no visible reaction aside from particle size diminishing into the nanoscale region. However, using glow-type EDAMM for only 30 minutes resulted in the nitriding product being formed as nanocrystals, significantly shortening the reaction time in the case of Ti, and avoiding the use of ammonia in the case of Si. Subsequent spark-type EDAMM resulted in recrystallization, providing highly crystalline powders of TiN or Si_3N_4 without byproducts or any obvious milling vessel damage.[138] The authors later employed the same setup in other systems, such as the synthesis of metal carbides and nitrides (WC, ZrC, TiC), synthesis of functional oxides ($LiFePO_4$), extraction of metals (Pb, Se) from oxides and sulfides, formation of carbon nanofragments (nanotubes and nanorods), and more.[139]

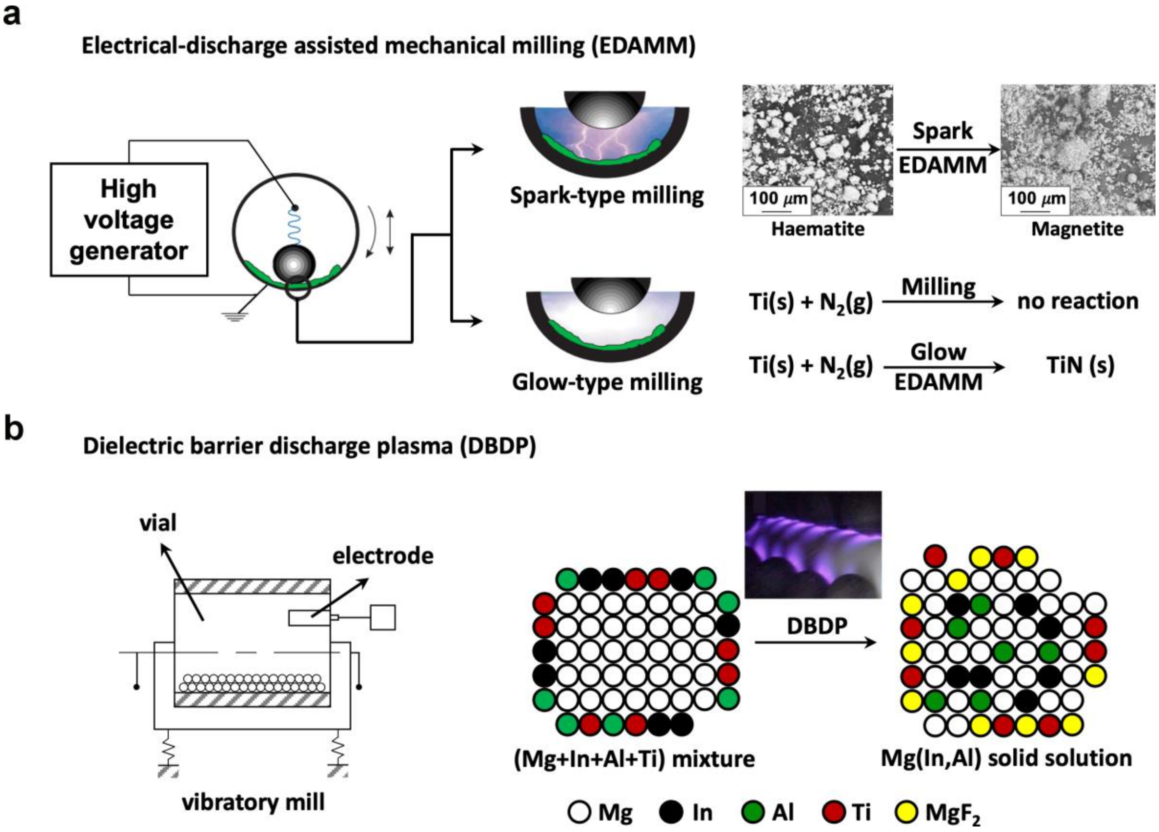

Fig. 7 | **Electro-mechanochemical setups. a** | Schematic of electrical-discharge-assisted mechanical milling instrumentation with spark- and glow-type milling. Application of spark-type milling on the reduction of haematite to magnetite. Application of glow-type milling on the nitridation of titanium. **b** | Schematic of the dielectric barrier discharge plasma (DBDP) mill. Application of DBDP to the synthesis of Mg(In,Al) solid solutions, with an inset image of the plasma created. The schematic shows a solid solution was prepared from a simple mixture of atoms represented by circles: white - magnesium, black - indium, green - aluminum, red - titanium, yellow - magnesium fluoride. Panel **a** adapted with permission from REF[138], Nature Springer. Panel **b** adapted with permissions from REF[140], Elsevier, and REF[141], Elsevier.

Another implementation of electro-mechanochemistry is a device that combines a tuneable high-energy field of dielectric barrier discharge plasma (DBDP) and a simple vibrational mill.[140] DBDP is known as a very effective non-thermal plasma source for materials' surface processing, providing high-energy electrons suitable for the formation of radicals and excited atomic states.[142] Zhu *et al.* used a modified vibratory mill (FIG. 7b), where DBDP is achieved by applying a 22 kV electric field between the milling jar – used as the ground electrode – and a high voltage electrode with a dielectric barrier mounted inside the milling jar.[140] The authors initially studied the effect of DBDP on the mechanochemical processing of metal powders (Al, Fe, or W), resulting in lump-like agglomerates of metal particles with unusually high specific surface areas (2-15 times higher than samples obtained by conventional milling). When milling a mixture of elemental tungsten and carbon, DBDP milling allowed carburization of the mixture into WC at temperatures almost 300 °C lower than with conventional milling and resulted in the synthesis of pure WC. Classical milling not only required higher carburization temperatures but also resulted in significant amounts of W_2C byproduct. The unique lump-like morphology of these powders and their resulting high surface area, together with the radical forming and atomization properties of DBDP are the likely cause of the lowering of carburization temperature in WC formation. This methodology was later also successfully applied for the preparation of Mg-based hydrogen storage materials (FIG. 7b).[141]

Electric discharge in milling can also be formed without an external electric source by adding piezoelectric material into the reaction mixture. Nearly simultaneously, the Ito and Bolm groups recently showed that the piezoelectric crystals of $BaTiO_3$ can induce electro-mechanochemical transformations when added to the reaction mixture during milling. The Bolm group showed that the addition of tetragonal $BaTiO_3$ to a reaction mixture containing Cu(II) precatalyst leads to its *in situ* reduction to Cu(I), resulting in a highly efficient copper-catalyzed atom transfer radical cyclization reaction.[143] At the same time, the Ito group showed how even the poorly piezoelectric cubic-$BaTiO_3$ could be used as an efficient and reusable catalyst for *in situ* mechanochemical redox activation and reduction of aryl diazonium salts through a single-electron transfer reaction.[144] In both reports, the yield of the product was directly dependent on the energetics of the milling process and the number of collisions in the milling vessel. A similar effect was also shown for other simple piezoelectric materials, such as ZnO. The ability of mechanochemical processing to activate even poorly piezoelectric materials, such as cubic-$BaTiO_3$, to perform efficiently may have a substantial impact on the development of piezoelectric materials as heterogeneous catalysts.

[H1] **Summary and future outlook**

In the last three decades, mechanochemistry has developed into a powerful tool for solid-state synthesis and transformation of various materials. Due to its unique reactivity, sustainability benefits, and efficiency, it is slowly becoming an unavoidable technique in the modern synthetic laboratory. Recent advances in additive-enhanced mechanochemistry and new *in situ* monitoring techniques have greatly enhanced the mechanochemist's toolbox. However, the available instrumentation, most of which is adapted from the comminution community rather than being designed with the synthetic chemist in mind, still limits further progress. In particular, recent findings indicate that a new level of mechanochemical reactivity can be unlocked by combining mechanical action with additional energy sources: heat, light, sound, or electrical impulses.

Unlike solution synthesis, where photochemistry, electrochemistry, sonochemistry, and solvothermal synthesis are standardized procedures, analogous photo-mechanochemistry, electro-mechanochemistry, sono-mechanochemistry, and thermo-mechanochemistry are scarcely reported. When they are performed, they rely primarily on simple in-house adjusted milling reactors, but even then, they have been shown to lead to extraordinary new results. Novel reactions, improved reaction rates, yields, selectivity, and products unavailable by conventional mechanochemistry or other synthetic methods, have all been reported.

As the general mechanisms of even classical mechanochemical processes are still debated, it is hard to offer an exact model of the synergy between the mechanochemical action and the additional energy source(s), particularly considering the relatively small number of current reports. It is generally accepted that mechanical action provides two crucial prerequisites for any chemical reaction: bringing reactant molecules/atoms into contact (shear component, causing molecular motion) and giving them energy to react (pressure component, causing defects and plastic deformations). When another energy source is applied to the reaction mixture simultaneously, it can lend additional and complementary energy to the molecules/atoms of reactants, ferrying them across the reaction activation barrier, even if the mechanical energy introduced through pressure is not enough on its own. Similarly, no matter how high the energy added to the reactants is, if there is an insufficient molecular motion to bring the molecules/atoms into contact, the reaction cannot occur. As a result, the exposure of the reaction mixture to simultaneous mechanical action and another energy source is superior to the step-wise exposure of the pre-milled mixture to that same energy source.

It is also evident that the other energy source can take a complex role in the processing. Besides raising the internal energy of the system to overcome the activation barrier for reaction and increasing the molecular diffusion, it can also affect the macroscopic physical parameters of the milled mixture, leading to faster breaking of the crystal particles, an increase in the bulk temperature of the mixture, and changes in the rheology of the milled sample and the physical state of its components. Decoupling the macroscopic and microscopic contributions of adding other energy sources to a mechanochemical reaction is not a simple task, but, if possible, it could provide valuable insight into the mechanisms of these new reactions.

A significant challenge for the field lies in designing new reactors and their application to specific reactions. Thermo-mechanochemistry is the most studied so far, and dedicated laboratory mills with thermal control capabilities are already commercially available, but for other energy input combinations, the current state of the art relies on in-house adaptations. The main obstacle to the development of combined reactors is the fast movement of the milling reactor and the destructive action of milling media during the processing. In techniques requiring direct contact of the additional energy source (or monitoring devices) with the reactor or the milled reaction mixture, materials resistant to mechanical wear and stable wiring will be an essential prerequisite for success. In non-direct method like photo-mechanochemistry, the opaqueness of commonly used milling vessels is the main obstacle, but one that is readily addressed by using modern polymers or hardened glass materials for vessel and impeller production.

We believe that close collaboration between experimental chemists and mechanical and electrical engineers can overcome these obstacles, and that the design possibilities are endless. For example, it is not hard to envision a mechanochemical electrolytic reactor, where the reaction mixture would be placed and milled inside a vessel built of two electrodes bridged by an inert electrolyte. In such a setup, judicious choice of the electrode material and electric current parameters may lead to, for example, reduction and stabilization of rare low-valence cations required for the catalytic process inside the cathode part, with simultaneous *in situ* production of a reactive chemical species oxidized in the anode part. Sono-mechanochemistry of solid materials is already in full swing, both with combined milling and sonochemical reactors and with the advent of RAM. It would be interesting to see if combining RAM with reactors bearing grinding media or additional energy sources would enable reactions with high activation barriers.

Similarly, combinations of more than two energy input types could be made possible. A milling vessel that could be simultaneously heated and exposed to light irradiation may lead to one-pot syntheses where thermo-mechanochemically made adducts could be activated by photo-mechanochemistry or vice versa. On the other hand, a photo-mechanochemically induced reaction could also be cooled during milling in such a setup to avoid thermally-induced side products and increase selectivity. These and many other advancements could be achieved if mechanochemists, engineers, and equipment manufacturers join forces to create dedicated synthetic mechanochemical instrumentation.

The past few decades have been marked by two critical findings in the mechanochemistry of bulk solids: milling aided by different additives, which enhanced the scope and effectiveness of mechanochemical reactions, and *in situ* monitoring methods, which provided crucial insight into the kinetics and mechanisms of mechanochemistry. Both induced tremendous advances in mechanochemical reactivity and assisted in shaping mechanochemistry into the important synthetic method it is today. The available reports for combining other energy sources with mechanochemistry have just scratched the surface of the newly available reaction space, but it is evident already that the potential is enormous. We therefore believe that recent advances in instrumentation and energy input methods herald a new revolution in the mechanochemistry of bulk solids: “Mechanochemistry 2.0”.

[H1] **References**

1. James, S. L. *et al.* Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **41**, 413–447 (2012).
2. Do, J.-L. & Friščić, T. Mechanochemistry: A Force of Synthesis. *ACS Central Science* **3**, 13–19 (2017).
3. Friščić, T., Mottillo, C. & Titi, H. M. Mechanochemistry for Synthesis. *Angewandte Chemie International Edition* **59**, 1018–1029 (2020).
4. Michalchuk, A. A. L., Boldyreva, E. v, Belenguer, A. M., Emmerling, F. & Boldyrev, V. v. Tribochemistry, Mechanical Alloying, Mechanochemistry: What is in a Name? *Frontiers in Chemistry* vol. 9 Preprint at (2021).
5. Boldyrev, V. v & Tkáčová, K. Mechanochemistry of Solids: Past, Present, and Prospects. *Journal of Materials Synthesis and Processing* **8**, 121–132 (2000).
6. Braga, D., Maini, L. & Grepioni, F. Mechanochemical preparation of co-crystals. *Chemical Society Reviews* **42**, 7638 (2013).
7. Solares-Briones, M. *et al.* Mechanochemistry: A Green Approach in the Preparation of Pharmaceutical Cocrystals. *Pharmaceutics* **13**, 790-839 (2021).
8. Wang, G.-W. Mechanochemical organic synthesis. *Chemical Society Reviews* **42**, 7668–7700.
9. Andersen, J. & Mack, J. Mechanochemistry and organic synthesis: from mystical to practical. *Green Chemistry* **20**, 1435–1443 (2018).
10. Friscic, T. Ball-milling mechanochemical synthesis of coordination bonds: discrete units, polymers and porous materials. *RSC Green Chem. Ser.* **31**, 151–189 (2015).
11. Stolar, T. & Užarević, K. Mechanochemistry: an efficient and versatile toolbox for synthesis, transformation, and functionalization of porous metal–organic frameworks. *CrystEngComm* **22**, 4511–4525 (2020).
12. Peh, S. B., Wang, Y. & Zhao, D. Scalable and Sustainable Synthesis of Advanced Porous Materials. *ACS Sustainable Chemistry & Engineering* **7**, 3647–3670 (2019).

13. Bennett, T. D. *et al.* Facile Mechanosynthesis of Amorphous Zeolitic Imidazolate Frameworks. *J Am Chem Soc* **133**, 14546–14549 (2011).

14. Stolar, T. *et al.* Scalable Mechanochemical Amorphization of Bimetallic Cu–Zn MOF-74 Catalyst for Selective CO_2 Reduction Reaction to Methanol. *ACS Applied Materials & Interfaces* **13**, 3070–3077 (2021).

15. Willart, J. F. & Descamps, M. Solid State Amorphization of Pharmaceuticals. *Molecular Pharmaceutics* **5**, 905–920 (2008).

16. Boldyreva, E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? *Chemical Society Reviews* **42**, 7719 (2013).

17. Takacs, L. The historical development of mechanochemistry. *Chemical Society Reviews* **42**, 7649–7659 (2013).

18. Ardila-Fierro, K. J. & Hernández, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **14**, 2145–2162 (2021).

19. Colacino, E., Delogu, F. & Hanusa, T. Advances in Mechanochemistry. *ACS Sustainable Chemistry & Engineering* **9**, 10662–10663 (2021).

20. Howard, J., Cao, Q. & Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chemical Science* **9**, 3080-3094 (2018).

21. Braga, D. *et al.* Solvent effect in a "solvent free" reaction. *CrystEngComm* **9**, 879–881 (2007).

22. Martinez, V. *et al.* Tunable Fulleretic Sodalite MOFs: Highly Efficient and Controllable Entrapment of C_{60} Fullerene via Mechanochemistry. *Chemistry of Materials* **32**, 10628–10640 (2020).

23. Pickhardt, W., Grätz, S. & Borchardt, L. Direct Mechanocatalysis: Using Milling Balls as Catalysts. *Chemistry – A European Journal* **26**, 12903–12911 (2020).

24. Lukin, S. *et al.* Mechanochemical carbon–carbon bond formation that proceeds via a cocrystal intermediate. *Chemical Communications* **54**, 13216–13219 (2018).

25. Štrukil, V., Gracin, D., Magdysyuk, O. V, Dinnebier, R. E. & Friščić, T. Trapping Reactive Intermediates by Mechanochemistry: Elusive Aryl N-Thiocarbamoylbenzotriazoles as Bench-Stable Reagents. *Angewandte Chemie International Edition* **54**, 8440–8443 (2015).

26. Katsenis, A. D. *et al.* In situ X-ray diffraction monitoring of a mechanochemical reaction reveals a unique topology metal-organic framework. *Nature Communications* **6**, 6662 (2015).

27. Ayoub, G. *et al.* Rational Synthesis of Mixed-Metal Microporous Metal–Organic Frameworks with Controlled Composition Using Mechanochemistry. *Chemistry of Materials* **31**, 5494–5501 (2019).

28. Bolm, C. & Hernández, J. G. Mechanochemistry of Gaseous Reactants. *Angewandte Chemie International Edition* **58**, 3285–3299 (2019).

29. Eckert, R., Felderhoff, M. & Schüth, F. Preferential Carbon Monoxide Oxidation over Copper-Based Catalysts under In Situ Ball Milling. *Angewandte Chemie International Edition* **56**, 2445–2448 (2017).

30. Do, J.-L. & Friščić, T. Chemistry 2.0: Developing a New, Solvent-Free System of Chemical Synthesis Based on Mechanochemistry. *Synlett* **28**, 2066–2092 (2017).

31. Gomollón-Bel, F. Ten Chemical Innovations That Will Change Our World: IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable. *Chemistry International* **41**, 12–17 (2019).

32. Friščić, T., Trask, A. V, Jones, W. & Motherwell, W. D. S. Screening for Inclusion Compounds and Systematic Construction of Three-Component Solids by Liquid-Assisted Grinding. *Angewandte Chemie International Edition* **45**, 7546–7550 (2006).

33. Shan, N., Toda, F. & Jones, W. Mechanochemistry and co-crystal formation: Effect of solvent on reaction kinetics. *Chemical Communications* **2**, 2372–2373 (2002).

34. Friščić, T., Childs, S. L., Rizvi, S. A. A. & Jones, W. The role of solvent in mechanochemical and sonochemical cocrystal formation: a solubility-based approach for predicting cocrystallisation outcome. *CrystEngComm* **11**, 418–426 (2008).

35. Cao, Q., Howard, J. L., Crawford, D. E., James, S. L. & Browne, D. L. Translating solid state organic synthesis from a mixer mill to a continuous twin screw extruder. *Green Chemistry* **20**, 4443–4447 (2018).

36. Stolar, T. *et al.* Control of Pharmaceutical Cocrystal Polymorphism on Various Scales by Mechanochemistry: Transfer from the Laboratory Batch to the Large-Scale Extrusion Processing. *ACS Sustainable Chemistry & Engineering* **7**, 7102–7110 (2019).

37. Hernández, J. G. C–H Bond Functionalization by Mechanochemistry. *Chemistry – A European Journal* **23**, 17157–17165 (2017).

38. Bowmaker, G. A. Solvent-assisted mechanochemistry. *Chemical Communications* **49**, 334–348 (2013).

39. Lapshin, O. V, Boldyreva, E. V & Boldyrev, V. V. Role of Mixing and Milling in Mechanochemical Synthesis (Review). *Russian Journal of Inorganic Chemistry* **66**, 433–453 (2021).

40. Delogu, F. & Takacs, L. Information on the mechanism of mechanochemical reaction from detailed studies of the reaction kinetics. *Journal of Materials Science* **53**, 13331–13342 (2018).

41. Horie, K. *et al.* Definitions of terms relating to reactions of polymers and to functional polymeric materials (IUPAC Recommendations 2003). *Pure and Applied Chemistry* **76**, 889–906 (2004).

42. Baláž, P. (Peter). *Mechanochemistry in nanoscience and minerals engineering*. (Springer, 2008).

43. Haley, R. A., Mack, J. & Guan, H. 2-in-1: catalyst and reaction medium. *Inorg. Chem. Front.* **4**, 52–55 (2017).

44. Haley, R. A., Zellner, A. R., Krause, J. A., Guan, H. & Mack, J. Nickel Catalysis in a High Speed Ball Mill: A Recyclable Mechanochemical Method for Producing Substituted Cyclooctatetraene Compounds. *ACS Sustainable Chemistry & Engineering* **4**, 2464–2469 (2016).

45. Tireli, M. *et al.* Solvent-free copper-catalyzed click chemistry for the synthesis of N-heterocyclic hybrids based on quinoline and 1,2,3-triazole. *Beilstein J. Org. Chem.* **13**, 2352–2363 (2017).

46. Vogt, C. G. *et al.* Direct Mechanocatalysis: Palladium as Milling Media and Catalyst in the Mechanochemical Suzuki Polymerization. *Angewandte Chemie International Edition* **58**, 18942–18947 (2019).

47. Fulmer, D. A., Shearouse, W. C., Medonza, S. T. & Mack, J. Solvent-free Sonogashira coupling reaction via high speed ball milling. *Green Chemistry* **11**, 1821 (2009).

48. Friščić, T. *et al.* Ion- and Liquid-Assisted Grinding: Improved Mechanochemical Synthesis of Metal–Organic Frameworks Reveals Salt Inclusion and Anion Templating. *Angewandte Chemie International Edition* **49**, 712–715 (2009).

49. Hasa, D., Schneider Rauber, G., Voinovich, D. & Jones, W. Cocrystal Formation through Mechanochemistry: from Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding. *Angewandte Chemie International Edition* **54**, 7371–7375 (2015).

50. Brekalo, I. *et al.* Use of a “shoe-Last” Solid-State Template in the Mechanochemical Synthesis of High-Porosity RHO-Zinc Imidazolate. *J Am Chem Soc* **140**, 10104–10108 (2018).

51. Arhangelskis, M. *et al.* Mechanochemical reactivity inhibited, prohibited and reversed by liquid additives: examples from crystal-form screens. *Chemical Science* **12**, 3264–3269 (2021).

52. Belenguer, A. M., Lampronti, G. I., Wales, D. J. & Sanders, J. K. M. Direct Observation of Intermediates in a Thermodynamically Controlled Solid-State Dynamic Covalent Reaction. *J Am Chem Soc* **136**, 16156–16166 (2014).

53. Tireli, M. *et al.* Mechanochemical reactions studied by in situ Raman spectroscopy: base catalysis in liquid-assisted grinding. *Chemical Communications* **51**, 8058–8061 (2015).

54. Brekalo, I. *et al.* Scale-Up of Agrochemical Urea-Gypsum Cocrystal Synthesis Using Thermally Controlled Mechanochemistry. *ACS Sustainable Chemistry & Engineering* **10**, 6743–6754, (2022).

55. Užarević, K., Halasz, I. & Friščić, T. Real-Time and In Situ Monitoring of Mechanochemical Reactions: A New Playground for All Chemists. *The Journal of Physical Chemistry Letters* **6**, 4129–4140 (2015).

56. Friščić, T. *et al.* Real-time and in situ monitoring of mechanochemical milling reactions. *Nature Chemistry* **5**, 66–73 (2013).

57. de Oliveira, P. F. M. *et al.* Tandem X-ray absorption spectroscopy and scattering forin situtime-resolved monitoring of gold nanoparticle mechanosynthesis. *Chemical Communications* **56**, 10329–10332 (2020).

58. Gracin, D., Strukil, V., Friscic, T., Halasz, I. & Uzarevic, K. Laboratory Real-Time and In Situ Monitoring of Mechanochemical Milling Reactions by Raman Spectroscopy. *Angew. Chem., Int. Ed.* **53**, 6193–6197 (2014).

59. Lukin, S., Užarević, K. & Halasz, I. Raman spectroscopy for real-time and in situ monitoring of mechanochemical milling reactions. *Nature Protocols* **16**, 3492–3521 (2021).

60. Pladevall, B. S., de Aguirre, A. & Maseras, F. Understanding Ball Milling Mechanochemical Processes with DFT Calculations and Microkinetic Modeling. *ChemSusChem* **14**, 2763–2768 (2021).

61. Delogu, F. Molecular dynamics of collisions between rough surfaces. *Physical Review B - Condensed Matter and Materials Physics* **82**, (2010).

62. Chen, Z., Vazirisereshk, M. R., Khajeh, A., Martini, A. & Kim, S. H. Effect of Atomic Corrugation on Adhesion and Friction: A Model Study with Graphene Step Edges. *Journal of Physical Chemistry Letters* **10**, 6455–6461 (2019).

63. Ferguson, M. *et al.* Insights into mechanochemical reactions at the molecular level: Simulated indentations of aspirin and meloxicam crystals. *Chemical Science* **10**, 2924–2929 (2019).

64. Ewers, B. W. & Batteas, J. D. Utilizing Atomistic Simulations to Map Pressure Distributions and Contact Areas in Molecular Adlayers within Nanoscale Surface-Asperity Junctions: A Demonstration with Octadecylsilane-Functionalized Silica Interfaces. *Langmuir* **30**, 11897–11905 (2014).

65. Butyagin, P. Y. The nature of the mechanical degradation of polymethylmethacrylate. *Polymer Science U.s.s.r.* **9**, 149–158 (1967).

66. Užarević, K. *et al.* Enthalpy vs. friction: heat flow modelling of unexpected temperature profiles in mechanochemistry of metal–organic frameworks. *Chemical Science* **9**, 2525–2532 (2018).

67. Friščič, T. & Jones, W. Recent advances in understanding the mechanism of cocrystal formation via grinding. *Crystal Growth and Design* **9**, 1621–1637 (2009).

68. F. P. Bowden, M. A. Stone & G. K. Tudor. Hot spots on rubbing surfaces and the detonation of explosives by friction. *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **188**, 329–349 (1947).

69. Fox, P. G. Mechanically initiated chemical reactions in solids. *Journal of Materials Science* **10**, 340–360 (1975).

70. P. A. Thiessen, K. Meyer & G. Heinicke. *Grundlagen der Tribochemie*. (1967).

71. Užarević, K. *et al.* Exploring the Effect of Temperature on a Mechanochemical Reaction by in Situ Synchrotron Powder X-ray Diffraction. *Crystal Growth & Design* **16**, 2342–2347.

72. Lea, M. C. Disruption of the silver haloid molecule by mechanical force. *American Journal of Science* **s3-43**, 527–531 (1892).

73. Lea, M. C. On endothermic reactions effected by mechanical force. *American Journal of Science* **s3-46**, 241 LP – 244 (1893).

74. Lea, M. C. Transformations of mechanical into chemical energy; Part III, Action of shearing stress continued. *American Journal of Science* **s3-47**, 377–382 (1894).

75. V. Boldyrev, V., G. Avakumow, E., I. Strugowa, L., Harenz, H. & Heinicke, G. Zur Tribochemischen Zersetzung von Alkali-Bromaten und -Nitraten. *ZAAC - Journal of Inorganic and General Chemistry* **393**, 152–158 (1972).

76. Milanović, I. *et al.* Mechanochemical Synthesis and Thermal Dehydrogenation of Novel Calcium-Containing Bimetallic Amidoboranes. *ACS Sustainable Chemistry & Engineering* **9**, 2089–2099 (2021)..

77. Cindro, N., Tireli, M., Karadeniz, B., Mrla, T. & Užarević, K. Investigations of Thermally Controlled Mechanochemical Milling Reactions. *ACS Sustainable Chemistry & Engineering* **7**, 16301–16309 (2019).

78. Takacs, L. Self-sustaining reactions as a tool to study mechanochemical activation. *Faraday Discuss.* **170**, 251–265 (2014).

79. Macfadyen, A. On the Influence of the Prolonged Action of the Temperature of Liquid Air on Micro- Organisms, and on the Effect of Mechanical Trituration at the Temperature of Liquid Air on Photogenic Bacteria Author (s): Allan Macfadyen Source : Proceedings of the R. *Proceedings of the Royal Society of London* **71**, 76–77 (1902).

80. Cells, O. & Barnard, M. On a method of disintegrating bacterial and other organic cells. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character* **84**, 57–66 (1911).

81. Mudd, S., Shaw, C. H., Czarnetzky, E. J. & Flosdorf, E. W. A Low Temperature Ball-mill for the Liberation of Labile Cellular Products. *The Journal of Immunology* **32**, 483 LP – 489 (1937).

82. Kaupp, G., Boy, J. & Schmeyers, J. Iminiumsalze in quantitativen Gas/Festköper- und Festkörper/Festkörper-Reaktionen. *Journal für Praktische Chemie/Chemiker-Zeitung* **340**, 346–355 (1998).

83. Kaupp, G., Reza Naimi-Jamal, M. & Schmeyers, J. Solvent-free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield. *Tetrahedron* **59**, 3753–3760 (2003).

84. Andersen, J. & Mack, J. Insights into Mechanochemical Reactions at Targetable and Stable, Sub-ambient Temperatures. *Angewandte Chemie International Edition* **57**, 13062–13065 (2018).

85. Andersen, J. M. & Mack, J. Decoupling the Arrhenius equation via mechanochemistry. *Chemical Science* **8**, 5447–5453 (2017).

86. Seo, T., Toyoshima, N., Kubota, K. & Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State Cross-Coupling of Insoluble Aryl Halides. *J Am Chem Soc* **143**, 6165–6175 (2021).

87. Takahashi, R. *et al.* Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nature Communications* **12**, 6691 (2021).

88. Gao, P., Jiang, J., Maeda, S., Kubota, K. & Ito, H. Mechanochemically Generated Calcium-Based Heavy Grignard Reagents and Their Application to Carbon–Carbon Bond-Forming Reactions. *Angewandte Chemie International Edition* (2022) doi:10.1002/anie.202207118.

89. Kubota, K., Endo, T., Uesugi, M., Hayashi, Y. & Ito, H. Solid-State C–N Cross-Coupling Reactions with Carbazoles as Nitrogen Nucleophiles Using Mechanochemistry. *ChemSusChem* **15**, e202102132 (2022).

90. Stolar, T. *et al.* Mechanochemical Prebiotic Peptide Bond Formation**. *Angewandte Chemie International Edition* **60**, 12727–12731 (2021).

91. Crawford, D. E. & Casaban, J. Recent Developments in Mechanochemical Materials Synthesis by Extrusion. *Advanced Materials* **28**, 5747–5754 (2016).

92. Crawford, D. E., Miskimmin, C. K. G., Albadarin, A. B., Walker, G. & James, S. L. Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free. *Green Chemistry* **19**, 1507–1518 (2017).

93. Crawford, D. *et al.* Synthesis by extrusion: continuous, large-scale preparation of MOFs using little or no solvent. *Chemical Science* **6**, 1645–1649 (2015).

94. Karadeniz, B. *et al.* Benign by Design: Green and Scalable Synthesis of Zirconium UiO-Metal–Organic Frameworks by Water-Assisted Mechanochemistry. *ACS Sustainable Chemistry & Engineering* **6**, 15841–15849.

95. Cintas, P., Cravotto, G., Barge, A. & Martina, K. Interplay Between Mechanochemistry and Sonochemistry. in *Polymer Mechanochemistry* (ed. Boulatov, R.) 239–284 (Springer, 2014). doi:10.1007/128_2014_623.

96. Giannakoudakis, D. A., Chatel, G. & Colmenares, J. C. *Mechanochemical Forces as a Synthetic Tool for Zero- and One-Dimensional Titanium Oxide-Based Nano-*

photocatalysts. *Topics in Current Chemistry* vol. 378 (Springer International Publishing, 2020).

97. Cravotto, G., Gaudino, E. C. & Cintas, P. On the mechanochemical activation by ultrasound. *Chemical Society Reviews* **42**, 7521–7534 (2013).

98. Chatel, G. & Varma, R. S. Ultrasound and microwave irradiation: contributions of alternative physicochemical activation methods to Green Chemistry. *Green Chemistry* **21**, 6043–6050 (2019).

99. Santos, Hugo Miguel; Lodeiro, Carlos; Capelo-Martinez, J.-L. *Ultrasound in Chemistry: Analytical Applications*. *Ultrasound in Chemistry: Analytical Applications* (WILEY-VCH, 2009).

100. Mordyuk, B. N. & Prokopenko, G. I. Mechanical alloying of powder materials by ultrasonic milling. *Ultrasonics* **42**, 43–46 (2004).

101. Chen, D. & Xiao, T. One-step synthesis of Zn to single-phase nanocrystalline ZnO by solid-liquid reaction ball milling assisted by ultrasonic wave. *Journal of the American Ceramic Society* **93**, 2675–2678 (2010).

102. Suslick, K. S. Applications of Ultrasound to Materials Chemistry. *MRS Bulletin* **20**, 29–34 (1995).

103. A. Kozlov, B. Mordyuk, G. P. Device for production of powder materials. (2002).

104. Perekos, A. O.; Mordyuk, B. N.; Rud, O. D.; Prokopenko, G. I.; Yefimova, T.V.; Ivashchuk, L. I.; Lakhnik, A. M.; Piskun, N.O.; Romanenko, S. M. Structural state and magnetic properties of the nanocrystalline Ni fabricated in a ultrasonic ball mill. *Metallofizika i Noveishie Tekhnologii* **29**, 211–223 (2007).

105. Perekos, A. E.; Mordyuk, B. N.; Kolesnik, B. H.; Prokopenko, G. I.; Efimova, V.; Zalutsky, V. P.; Ruzhitskaya, T. V.; Rud, N. D. Study of the Process of Gas Emission from Ni Nanocrystalline Powders Fabricated by Ball Grinding in Ultrasonic Mill. *Metallofizika i Noveishie Tekhnologii* **33**, 93–103 (2011).

106. Nadutov, V. M. *et al.* Influence of ultrasonic processing in a ball mill on phase-structural characteristics of superfine powder blends of copper with iron and cobalt. *Metallofizika i Noveishie Tekhnologii* **40**, 501–514 (2018).

107. Nadutov, V. M., Mordyuk, B. N., Volosevich, P. Y., Svistunov, E. A. & Perizhnyak, A. V. Effect of graphite on the degree of grinding and the structure of α-Fe powder in an ultrasonic mill. *Physics of Metals and Metallography* **104**, 415–424 (2007).

108. Nadutov, V. M. *et al.* Investigation of process of layering of the solid solutions formed by ultrasonic milling of coarse-grained powder blends of copper with cobalt and copper with iron, and its influence on their structure–phase state and magnetic properties. *Metallofizika i Noveishie Tekhnologii* **40**, 1185–1199 (2018).

109. Nadutov, V. M. *et al.* Thermal stability of solid solutions formed by ultrasonic milling of Cu-Co and Cu-Fe powder mixtures. *Ukrainian Journal of Physics* **62**, 685–691 (2017).

110. Nadutov, V. M. *et al.* Structure and magnetic properties of the Cu-Co and Cu-Fe nanopowders obtained in ultrasonic ball mill. *Metallofizika i Noveishie Tekhnologii* **39**, 525–539 (2017).

111. Yuan, Z., Chen, Z. H., Chen, D. & Kang, Z. T. Analyses of factors affecting nickel ferrite nanoparticles synthesis in ultrasound-assisted aqueous solution ball milling. *Ultrasonics Sonochemistry* **22**, 188–197 (2015).

112. Luo, Y., Chen, D., Wei, F. & Liang, Z. Synthesis of Cu-BTC Metal-Organic Framework by Ultrasonic Wave-Assisted Ball Milling with Enhanced Congo Red Removal Property. *ChemistrySelect* **3**, 11435–11440 (2018).

113. Chen, D., Liu, H. Y. & Xia, S. R. One-step decomposition of basic carbonates into single-phase crystalline metallic oxides nanoparticle by ultrasonic wave-assisted ball milling technology. *Ceramics International* **38**, 821–825 (2012).

114. Stolar, T. *et al.* In Situ Monitoring of the Mechanosynthesis of the Archetypal Metal–Organic Framework HKUST-1: Effect of Liquid Additives on the Milling Reactivity. *Inorganic Chemistry* **56**, 6599–6608 (2017).

115. Tanaka, R. *et al.* Verification of the mixing processes of the active pharmaceutical ingredient, excipient and lubricant in a pharmaceutical formulation using a resonant acoustic mixing technology. *RSC Advances* **6**, 87049–87057 (2016).

116. Low-Frequency Sonic Mixing Technology.

117. Rumeau, N.; Threlfall, D.; Wilmet, A. ResonantAcoustic® Mixing – Processing and Formulation Challenges for Cost Effective Manufacturing. in *Insensitive Munitions & Energetic Materials Technology Symposium (IMEMTS)* 1–10 (2015).

118. Titi, H. M., Do, J. L., Howarth, A. J., Nagapudi, K. & Friščić, T. Simple, scalable mechanosynthesis of metal-organic frameworks using liquid-assisted resonant acoustic mixing (LA-RAM). *Chemical Science* **11**, 7578–7584 (2020).

119. Michalchuk, A. A. L. *et al.* Ball-free mechanochemistry:: In situ real-time monitoring of pharmaceutical co-crystal formation by resonant acoustic mixing. *Chemical Communications* **54**, 4033–4036 (2018).

120. Nagapudi, K., Umanzor, E. Y. & Masui, C. High-throughput screening and scale-up of cocrystals using resonant acoustic mixing. *International Journal of Pharmaceutics* **521**, 337–345 (2017).

121. Am Ende, D. J., Anderson, S. R. & Salan, J. S. Development and scale-up of cocrystals using resonant acoustic mixing. *Organic Process Research and Development* **18**, 331–341 (2014).

122. Andrews, M. R., Collet, C., Wolff, A. & Hollands, C. Resonant Acoustic® Mixing: Processing and Safety. *Propellants, Explosives, Pyrotechnics* **45**, 77–86 (2020).

123. Anderson, S. R., Am Ende, D. J., Salan, J. S. & Samuels, P. Preparation of an energetic-energetic cocrystal using resonant acoustic mixing. *Propellants, Explosives, Pyrotechnics* **39**, 637–640 (2014).

124. Zhang, J. & Shreeve, J. M. Time for pairing: Cocrystals as advanced energetic materials. *CrystEngComm* **18**, 6124–6133 (2016).

125. Green, N. J., Xu, J. & Sutherland, J. D. Illuminating Life's Origins: UV Photochemistry in Abiotic Synthesis of Biomolecules. *J Am Chem Soc* **143**, 7219–7236 (2021).

126. Hoffmann, N. Photochemical Reactions as Key Steps in Organic Synthesis. *Chemical Reviews* **108**, 1052–1103 (2008).

127. Atkinson, M. B. J. *et al.* General application of mechanochemistry to templated solid-state reactivity: rapid and solvent-free access to crystalline supermolecules. *Chemical Communications* 5713 (2008) doi:10.1039/b812728j.

128. Ma, D.-Y. & Wärnmark, K. Mechanoassisted Supramolecular Catalysis in Solid State Synthesis. *ChemCatChem* **2**, 1059–1060 (2010).

129. Yelgaonkar, S. P., Swenson, D. C. & MacGillivray, L. R. Supramolecular chemistry under mechanochemical conditions: a small molecule template generated and integrated into a molecular-to-supramolecular and back-to-molecular cascade reaction. *Chemical Science* **11**, 3569–3573 (2020).

130. Hernández, J. G. Mechanochemical borylation of aryldiazonium salts; merging light and ball milling. *Beilstein Journal of Organic Chemistry* **13**, 1463–1469 (2017).

131. Toda, F., Tanaka, K. & Sekikawa, A. Host–guest complex formation by a solid–solid reaction. *J. Chem. Soc., Chem. Commun.* 279–280 (1987) doi:10.1039/C39870000279.

132. Sokolov, A. N., Bučar, D.-K., Baltrusaitis, J., Gu, S. X. & MacGillivray, L. R. Supramolecular Catalysis in the Organic Solid State through Dry Grinding. *Angewandte Chemie International Edition* **49**, 4273–4277 (2010).

133. Stojaković, J., Farris, B. S. & MacGillivray, L. R. Vortex grinding for mechanochemistry: application for automated supramolecular catalysis and preparation of a metal–organic framework. *Chemical Communications* **48**, 7958 (2012).

134. Obst, M. & König, B. Solvent-free, visible-light photocatalytic alcohol oxidations applying an organic photocatalyst. *Beilstein Journal of Organic Chemistry* **12**, 2358–2363 (2016).

135. Štrukil, V. & Sajko, I. Mechanochemically-assisted solid-state photocatalysis (MASSPC). *Chemical Communications* **53**, 9101–9104 (2017).

136. Schotten, C. *et al.* Making electrochemistry easily accessible to the synthetic chemist. *Green Chemistry* **22**, 3358–3375 (2020).

137. Zhu, C., Ang, N. W. J., Meyer, T. H., Qiu, Y. & Ackermann, L. Organic Electrochemistry: Molecular Syntheses with Potential. *ACS Central Science* **7**, 415–431 (2021).

138. Calka, A. & Wexler, D. Mechanical milling assisted by electrical discharge. *Nature* **419**, 147–151 (2002).

139. Calka, A. & Wexler, D. Processing of materials by electric discharge assisted mechanical milling. *Materials Science Forum* **674**, 29–39 (2011).

140. Zhu, M., Dai, L. Y., Gu, N. S., Cao, B. & Ouyang, L. Z. Synergism of mechanical milling and dielectric barrier discharge plasma on the fabrication of nano-powders of pure metals and tungsten carbide. *Journal of Alloys and Compounds* **478**, 624–629 (2009).

141. Ouyang, L., Cao, Z., Wang, H., Hu, R. & Zhu, M. Application of dielectric barrier discharge plasma-assisted milling in energy storage materials – A review. *Journal of Alloys and Compounds* **691**, 422–435 (2017).

142. Borcia, G., Anderson, C. A. & Brown, N. M. D. Dielectric barrier discharge for surface treatment: Application to selected polymers in film and fibre form. *Plasma Sources Science and Technology* **12**, 335–344 (2003).

143. Schumacher, C., Hernández, J. G. & Bolm, C. Electro-Mechanochemical Atom Transfer Radical Cyclizations using Piezoelectric BaTiO 3. *Angewandte Chemie International Edition* **59**, 16357–16360 (2020).

144. Kubota, K., Pang, Y., Miura, A. & Ito, H. Redox reactions of small organic molecules using ball milling and piezoelectric materials. *Science (1979)* **366**, 1500–1504 (2019).

[H1] **Acknowledgements**

This work has been supported in part by the "Research Cooperability" Program of the Croatian Science Foundation funded by the European Union from the European Social Fund under the Operational Programme Efficient Human Resources 2014-2020, through grant PZS-2019-02-4129. The authors acknowledge the Croatian Science Foundation (grant no. IP-2020-02-4702) for financial support. We would like to thank Ivan Kulcsár for help with slow-motion photography.

[H1] **Author contributions**

All authors made substantial contributions to discussion of content, writing, and editing of the manuscript.

[H1] **Competing interests**

Krunoslav Užarević is a shareholder in "InSolido Technologies", which produces milling reactors.

[H1] **Publisher’s note**

[H1] ToC blurb

Mechanochemistry is the science of inducing a chemical reaction through the application of mechanical force. This perspective focuses on combining traditional mechanochemistry with different energy inputs: thermo-mechanochemistry, sono-mechanochemistry, electro-mechanochemistry, and photo-mechanochemistry.