

Ball milling for mechanochemical reactions

Isaiah R. Speight¹, Karen J. Ardila-Fierro², José G. Hernández², Franziska Emmerling³, Adam A. L. Michalchuk⁴, Felipe García⁵, Evelina Colacino⁶ & James Mack⁷✉

Abstract

Mechanochemistry is an emerging field with the potential to pave the way for sustainable chemistry. Although the use of mechanical force to initiate chemical reactions has been recognized for millennia, it has often taken a backseat to thermal and photonic methods. Over the past 30 years, mechanochemistry has seen a resurgence of interest, attracting researchers across the globe. Despite its proven ability to address numerous challenges within the chemical community, mechanochemistry remains on the periphery. This Primer serves as a valuable guide for conducting mechanochemical reactions by ball milling, offering an overview of the processes, methods, tools and terminology necessary to embark on research in this field. It also highlights persistent hurdles such as equipment standardization, understanding the impact of new discoveries and the lack of predictability of reaction outcomes. The Primer's focus is on how mechanochemical ball milling is used in various chemical transformations, distinguishing it from other forms of mechanochemistry discussed in the literature. With a promising future, this Primer serves as a gateway for those aspiring to contribute to the field's advancement.

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¹Department of Chemistry, William & Mary, Williamsburg, VA, USA. ²Grupo Ciencia de los Materiales, Instituto de Química, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia, Medellín, Antioquia, Colombia.

³Department of Materials Chemistry, BAM Federal Institute for Materials Research and Testing, Berlin, Germany.

⁴School of Chemistry, University of Birmingham, Birmingham, UK. ⁵School of Chemistry, Monash University,

Clayton, Victoria, Australia. ⁶ICGM, Univ Montpellier, CNRS, ENSCM, Montpellier, France. ⁷Department of

Chemistry, University of Cincinnati, Cincinnati, OH, USA. ✉e-mail: mackje@ucmail.uc.edu

Introduction

A **mechanochemical reaction** (mechanochemistry), is defined by the International Union of Pure and Applied Chemistry (IUPAC) as a “chemical reaction that is induced by the direct absorption of mechanical energy”. This can be approached in a number of forms, such as ball milling, sonochemistry, tribochemistry, single-molecule force spectroscopy and other more specialized varieties, many of which have been reviewed over the past 10 years^{1–19}. Mechanochemical reactions can be conducted using various experimental techniques to mechanically activate the corresponding chemical system¹. Over the years, mechanochemical equipment has evolved drastically to encompass different methods of activation, scales and throughputs. The universal mechanochemical apparatus, which is readily available in most chemical laboratories, is the mortar and pestle²⁰. However, a more systematic and uniform approach to conduct mechanochemical reactions is needed due to the variations in the mechanical energy induced by mortar and pestle, an energy that is dependent upon the individual performing the grinding and grinding duration. In this Primer, we primarily focus on ball-milling techniques, with particular attention paid to mixer and planetary ball mills, which have served as the preferred instruments in the majority of mechanochemical research studies.

Aside from the simple removal of solvents, mechanochemical reactions produced by ball milling can give access to products that solution-phase chemistry may prohibit due to the limited solubility of starting reagents or the instability of products in solution¹⁷. Slow product formation due to solvent inhibition in solution can be accelerated in mechanochemical conditions. Furthermore, for many mechanochemical reactions, the yield and product purity can be enhanced with respect to the same reaction conducted in solution. These exciting results have led IUPAC to identify this methodology as one of the top ten chemical innovations that will change the world²¹.

In this Primer, we focus on how to conduct a mechanochemical reaction under ball-milling conditions and elucidate the similarities and

differences of a reaction conducted under mechanochemical conditions as compared with solution. We show how in situ analytical tools are used to track mechanochemical reactions and how these reactions can be applied to real-world industrial problems. We also describe some of the challenges in the field and areas of opportunities to move the field further. Owing to the various review articles that exist on this topic, this Primer covers mechanochemistry conceptually, without the details of specific reactions, which can be found in the literature. It is an exciting time to be in the field of mechanochemistry, and this Primer is designed to lower the barrier of entry.

Experimentation

Mechanochemical and solvothermal experimental set-ups can target similar reactions but are carried out in different ways. As solvothermal reaction systems have evolved over time from the simple round-bottomed flask to continuous stirred tank reactor, mechanochemistry has made iterative changes to the equipment utilized for synthesis. This section describes common types of ball mills used to carry out mechanochemical reactions and the variations among them. Important terminology, symbols and experimental parameters are discussed in this section. We describe product isolation techniques and comment on the safety considerations required when carrying out ball-milling mechanochemical experiments.

Ball-mill types

Commercial lab-scale mixer and planetary ball mills are available from various suppliers, providing the ability to conduct reactions from milligrams to hundreds of grams. These versatile machines can be used in single or multiple stations where milling jars are mounted. In the most common mixer mills, also called shaker or vibratory mills, the milling jar oscillates horizontally²² (Fig. 1a), but some mixer mills impart vertical²³ (Fig. 1b) or angular harmonic motions²⁴ to the milling jar (Fig. 1c). Such movements promote the collision of one or multiple

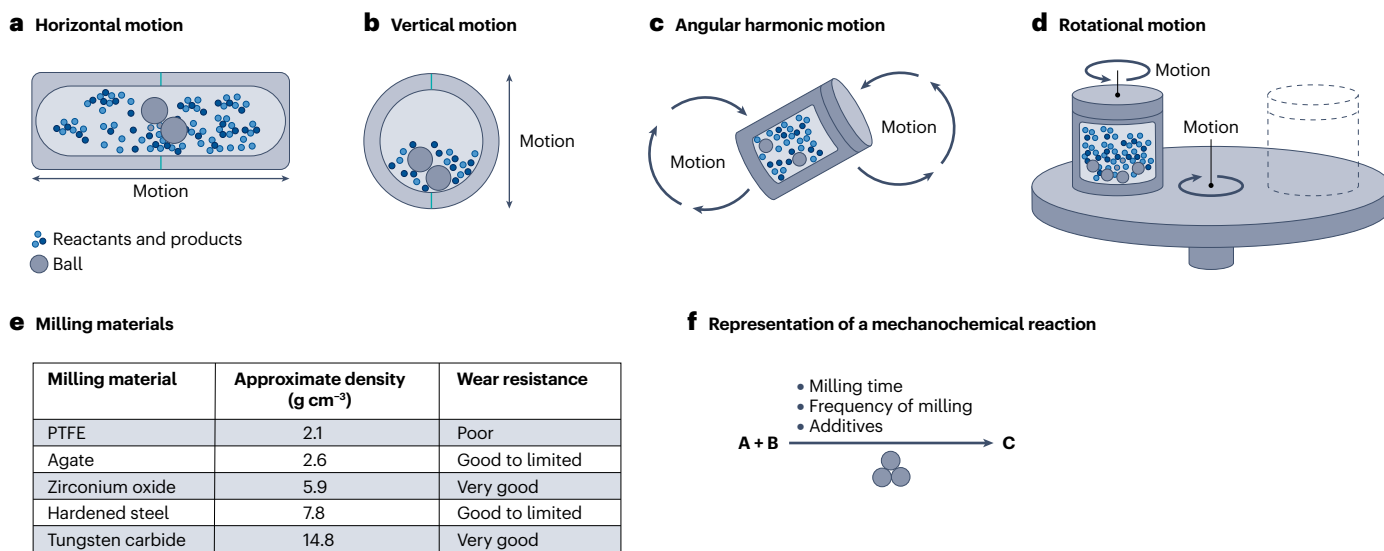


Fig. 1 | Experimental considerations for mechanochemical reactions by ball milling. **a–d**, Different types of movement experienced by the milling jars and their content. **e**, Properties of the most common milling materials used to make the milling jars and milling balls. **f**, Schematic representation of a mechanochemical reaction showing important experimental parameters

and characteristics. The three contacting balls under the reaction arrow are commonly used to represent the reaction initiated by the mechanochemical energy provided by ball milling. PTFE, polytetrafluoroethylene. Adapted from ref. 187, CC BY 4.0.

milling bodies, typically milling balls, against each other and against the inner wall of the milling jar, thus causing impact and frictional forces to be transduced to the sample. In **planetary ball mills**, one or multiple vertically placed milling jars are connected to a support disk that rotates around a common central axis while the milling jars are spun in the opposite direction around their own axes²⁵ (Fig. 1d). This trajectory is analogous to the motion of a planet that revolves around its axis and circulates around a star; it is from this motion that the name planetary mill originates. This motion produces a rotational speed that causes the milling balls to hit the wall inside the jar at high speeds, creating many high-force collisions. Therefore, friction, impact, tension and shear become the main mechanisms that enable mechanochemical transformations to take place.

Milling parameters

When optimizing a mechanochemical reaction, there are several parameters to control the yield and the selectivity of the transformation. The examples below show that there is not an ideal set of milling conditions for all mechanochemical reactions and that optimization is always required. However, understanding how parameters (such as milling time, milling frequency, milling media and temperature) in milling experiments affect the outcome of reactions will facilitate the development of new mechanochemical transformations and ensure reproducibility²⁶.

Milling time. Most mechanochemical reactions by ball milling are carried out under, or close to, solvent-free conditions. Such conditions promote highly concentrated reactions and prevent excess waste^{2,27}. As a consequence, mechanochemical reactions often exhibit an enhancement in the rate and yield as compared with the same reactions conducted in solution²⁸. Experimentally, milling times (also referred to as reaction times) in mixer mills can be set from seconds or minutes to uninterrupted milling times that can last for several hours (for example, up to 20 h)^{29–31}. Additionally, in many cases, milling cycles can be programmed to have periods of mechanical treatment followed by intermittent pauses, in a similar fashion to removing a flask from a stir plate. Here, the direction of the milling sample can also be alternated. Based on solvothermal reactions, it is often observed that longer reaction times are associated with higher conversion rates. However, as it is common for any synthetic protocol, reaching the full conversion of the reactants does not necessarily guarantee a perfect high-yielding reaction. In ball-milling experiments, long reaction times can lead to chemical, mechanical or thermal decomposition of the reactants and/or products, thus negatively impacting the yield³². In practice, milling times can be screened over a range of minutes to hours to determine whether the mechanochemical reaction occurs and to observe any relationship between the duration of the mechanical treatment and the yield or selectivity of the reaction³³. It is important to consider that long milling times cause higher energy consumption. Depending on the material of construction of the reaction vessel, long milling times could also lead to contamination of the product due to abrasion of the milling media³⁴, making isolation cumbersome.

Milling frequency. The kinetic energy transduced to the sample by the milling media during each collision depends on the milling media's speed. Experimentally, the linear or rotational speed at which the milling jar and its content is shaken or rotated can be controlled by choosing an appropriate milling frequency, which also influences

the number of collisions during a milling process. Therefore, the milling frequency is a key parameter in developing protocols for mechanochemical reactions, especially for those that are energetically challenging and do not merely depend on the proper mixing of the reactants^{35,36}. Currently, there are no predictable parameters to determine the appropriate milling frequency for specific mechanochemical reactions. Optimization often requires an iterative process to identify the appropriate frequency. The use of in situ monitoring can reduce the need for 'trial and error' experimentation, and it is discussed in detail later in this Primer.

In commercial mixer mills, the milling frequency is usually given in Hertz (Hz) and can be set from 3 Hz to 50 Hz, with most reactions carried out at 20 Hz, 25 Hz or 30 Hz. In planetary ball mills, the milling frequency is often expressed in revolutions per minute (rpm), with most commercial instruments being operational from 100 rpm to 1,100 rpm, although numerous mechanochemical reactions are reported to occur at frequencies between 400 rpm and 800 rpm. To better understand the correlation between frequency of milling, energy input and kinetics of mechanochemical reactions, various studies have demonstrated that high milling frequencies increase the reaction rate, likely due to a high energy dose being transferred to the sample^{37,38}. This helps in understanding the fundamental relationship between kinetics and energy input, enables the planning and optimization of mechanochemical reactions, and provides the basis for reproducibility across different milling devices. However, the best result of a mechanochemical reaction is not always achieved at the highest milling speed. In some cases, high milling frequencies can be detrimental to the selectivity of the transformation^{39,40}, or they can promote contamination of the product due to wearing of the milling jar and balls.

Milling media. Besides the time and frequency of milling, the milling media (that is, the milling jar and milling balls) can also influence the yield and selectivity of a mechanochemical reaction. This is because the density, hardness and elastic properties of the milling material impact the energy input to the reactants^{37,38,41}, and the composition of the milling media affects the reactivity of the sample during the milling process^{42–45}. The most often used milling materials include steel (stainless and hardened), zirconium dioxide and tungsten carbide (Fig. 1e). In addition, reactions using milling jars and balls made of alumina, silicon nitride, corundum, agate and copper are also known^{3,16,46}. To prevent unnecessary abrasion due to a mismatch between the hardness values of the milling media, it is advisable to use milling jars and balls made of the same material. Nevertheless, it is possible to find examples of reactions in which milling jars made of steel, quartz, sapphire or polymers were conducted with milling balls of various materials^{47–49}. In these cases, the use of balls coated with softer materials enables substantial energy transfer to the sample while reducing the mechanical damage of the milling jar. Additionally, the corrosiveness of the reactants or products should also be considered to prevent chemical damage of the milling media⁵⁰. The selection of an appropriate milling jar – for example, one made of a transparent material (such as poly(methyl methacrylate) (PMMA), quartz or sapphire) – allows for in situ monitoring using Raman and fluorescence benchtop spectrometers or synchrotron X-ray diffraction techniques, which are discussed in more detail later^{51–53}. Additional aspects related to the milling media, such as the size and geometry of the jars, the number and size of the balls, and the jar filling degree, influence the outcome of a mechanochemical reaction. For example, in some studies, it has been demonstrated that the activation of the reactants requires individual

collisions of at least a certain strength, thus a small number of large balls performed better than a large number of smaller balls, despite the total mass of balls being kept similar⁵⁴. However, in other systems, the efficiency of the reaction remained unaltered when varying the number or diameter of the milling balls, as long as the total mass of the milling media was kept constant^{55,56}. Therefore, the best number and size of the balls often depends on the specific mechanochemical reaction, and finding the ideal combination requires optimization of the conditions. Regarding the jar filling degree, some ball mill manufacturers recommend filling the milling jar with approximately one-third of sample and one-third of milling balls, thus keeping a proportional space for the free movement of the balls. This ratio is a good approximation for an effective grinding performance in comminution, but it is not necessarily correct when optimizing a mechanochemical reaction²³. For example, a typical milling experiment set-up includes a few hundred milligrams of sample milled in 10–15 ml milling jars with a single ball of 10 mm in diameter.

Additives and temperature. The addition of liquid or solid additives is a common practice during the optimization of mechanochemical reactions by ball milling. For example, the presence of minute (that is, microlitre) amounts of liquid during the milling process, known as liquid-assisted grinding⁵⁷, can be used to enhance the reaction rate or to alter the selectivity of a reaction compared with neat grinding experiments or reactions in solution^{58–60}. By contrast, solid additives are normally used in larger quantities than the reagents to improve the dispersion of the solid reactants, to vary the rheology of the milling mixture, and to gain processability of liquid or low-melting-point reaction mixtures⁶¹. Most commonly used milling auxiliaries such as SiO₂, Al₂O₃, NaCl or sand are chosen due to their supposed chemical inertness, but their presence during a milling process can occasionally affect the outcome of a mechanochemical reaction^{62–64}. Less explored is the impact that atmospheric gases or artificial gaseous atmospheres inside the milling jar can have on the course of a reaction⁴. Some reports have evidenced that the oxygen in the air can act as an oxidant in ball-milling experiments⁶⁵ and that gases such as CO (ref. 66), CO₂ (ref. 67), CH₄ (ref. 68) and N₂ (ref. 69) can effectively incorporate into mechanochemical reactions. Notably, the relatively small quantities of atmospheric water or oxygen trapped inside the milling jar during set up on the bench do not seem to be detrimental for most mechanochemical reactions, thus avoiding the need for a glove box. However, depending on the sensitivity of the reactants and products, control experiments are recommended to assess the influence of moisture or air on the outcome of the mechanochemical transformation^{70,71}.

Another important parameter in mechanochemical reactions by ball milling is the temperature. Normally, ball-milling experiments are carried out without external heating and in the absence of thermal control (without the possibility to sense or set the macroscopic temperature in the milling jar). Depending on the type of milling media, frequency of milling and time, the temperature of the milling jar can rise from just a few degrees to several dozen degrees because of the frictional heat⁷². However, recent studies have implemented alternatives to measure^{49,73} and to heat^{35,47,74–78} or cool³⁹ the milling jar, thus controlling the reaction rates and selectivity of some mechanochemical reactions. In addition to thermally assisted mechanochemical reactions, some ball-milling transformations have also benefited from simultaneous photochemical^{79,80} or electrical discharge activation⁸¹. A detailed discussion on how mechanochemistry can be combined with other energy sources can be found elsewhere in the literature^{77,82}.

Although most mechanochemical reactions are currently performed with a ball mill, various other mechanochemical devices are growing in popularity. A low-cost method to achieve this goal is often seen through the modified use of common laboratory equipment, such as a tube disperser or rotary evaporator⁸³. Resonant acoustic mixing has also proved to be a valuable method for performing various mechanochemical reactions; principles and potential applications can be found in recent reports^{84–88}. Twin screw extruders (TSEs) have been used as one of the alternatives to continuously process reagents rather than performing single-batch reactions, allowing for constant product generation and improving the sustainability of reactions^{89–93}. Options for instrumentation that afford the ability to switch between batch and continuous have been implemented in the form of ball milling^{92,93}. Many of the instruments previously discussed are being used to compensate for the lack of tools designed specifically for mechanochemistry; however, there is a concerted effort towards the development of these custom mechanochemical reactors⁹⁴.

Product isolation and safety considerations

Ball-milling experiments do not require any specific safety considerations beyond standard lab procedures as they do not require the use of toxic and volatile solvents^{2,27}. Moreover, methodological advantages such as the possibility to utilize safer chemicals or to circumvent the use of glove-box and Schlenk-line techniques make ball-milling protocols less laborious than traditional synthetic alternatives⁹⁵. However, as mechanochemical reactions require intensive mechanical processing of the reactants in closed milling jars, a few additional safety measures are advisable. For example, ball milling of energetic materials or contact-unstable mixtures must be avoided or carried out in small scale following all safety precautions to prevent accidents. This is the situation in which other high-impact methods such as resonant acoustic mixing can be a useful alternative to ball-milling methods^{96–98}. Hence, when working with known or potentially energetic materials or contact-unstable mixtures, differential scanning calorimetry analysis of the reagents prior to the milling experiment provides an initial measurement of the overall energetics of the starting materials⁹⁹. Additionally, experiments involving gaseous reactants or reactions that could overpressure the milling jar must be handled with care. For this, pressure sensors have proven beneficial to monitor mechanochemical reactions *in situ* and improve safety¹⁰⁰. Addressing these methodological and safety considerations are expected to facilitate the scaling-up of mechanochemical reactions. In this context, alternative mechanochemical techniques, such as reactive extrusion, have been explored to carry out safe, continuous and solventless mechanochemical reactions⁹⁰. Finally, once the most suitable ball mill has been selected, the best milling parameters have been identified and a safe and successful experiment has been conducted, the experimentalist is faced with the need to isolate the desired product (Fig. 1f). Isolation of products made by mechanochemistry does not differ from isolation after any other preparative approach. However, to minimize waste production, purification by precipitation, filtration, recrystallization or sublimation has been proven effective after ball-milling reactions^{2,17,27}. If solvent-intensive purification strategies are unavoidable to guarantee the purity of the product, then the use of safer solvents and the development of recyclability plans for waste improve the sustainability of the entire mechanochemical process.

Results

Mechanochemical transformations can involve rapidly evolving intermediates or can progress (sometimes by different routes) after the

mechanical treatment stops. This makes studying the mechanisms and kinetics of mechanochemical transformations a unique challenge. To this end, researchers have been pushed to further understand what is happening inside the milling vessel rather than only quantify the reaction after milling. Although many analytical techniques are, in principle, available to characterize mechanochemical transformations, not all techniques are suitable for all reactions. When planning a mechanochemical reaction and selecting an analysis protocol, one must first decide whether to monitor the reaction *ex situ* – usually with the focus to study the final reaction product – or *in situ* – typically to follow kinetics or reaction mechanisms⁵². For *ex situ* analysis of the product, there are essentially no limitations on the available analytical tools. In molecular synthesis, conventional solution-based characterization methods such as nuclear magnetic resonance (NMR) spectroscopy³⁵, mass spectrometry and high-performance liquid chromatography (HPLC)¹⁰¹ are commonly used. By contrast, when investigating solid-state phenomena, such as co-crystallization or polymorphism, common analysis methods include powder X-ray diffraction (PXRD), Raman spectroscopy, X-ray absorption spectroscopy, Mössbauer spectroscopy, photoelectron spectroscopy and solid-state NMR spectroscopy. It is important to note that with *ex situ* techniques, there is always the risk that the reaction continues even after the mechanochemical reactor has been stopped and samples for analysis have been prepared¹⁰² (Fig. 2). Correspondingly, one should be careful when stating that the product analysed *ex situ* represents the material inside the milling jar during the mechanochemical reaction. Detailed reviews that describe the intricacies and applications of *in situ* monitoring of mechanochemical reactions are available^{103–105}.

Time-resolved *in situ* monitoring methods

Mechanistic and kinetic studies are, in principle, possible to conduct using *ex situ* analyses¹⁰⁶. However, there is growing evidence that manipulating the sample for *ex situ* analysis can often overlook important intermediate phases⁴⁹ and in some cases even alter the course of the reaction^{107,108}. The development of time-resolved *in situ* methods overcomes many challenges associated with studying mechanochemical mechanisms and kinetics⁵² by allowing experimentalists to

follow chemical and structural changes without the need to perturb the material in any way⁵². Unfortunately, the experimental requirements for time-resolved *in situ* (TRIS) methods are often restrictive and limit the analytical methods that are available. To date, examples of TRIS monitoring have been made using X-ray diffraction^{23,109,110}, neutron diffraction¹¹¹, X-ray absorption spectroscopy^{112,113}, solid-state NMR¹¹⁴, Raman spectroscopy^{51,115,116}, thermometry^{49,74}, manometry¹¹⁷ and acoustic emissions^{48,118}. TRIS analytical methods using X-rays and neutrons require access to specialized research facilities, limiting their accessibility. By contrast, most other methods can be performed in laboratories with only small modifications to the mechanochemical reactor^{49,51,74,114,117}. In addition to their accessibility, different TRIS methods provide notably different information about a mechanochemical transformation. Indirect methods such as manometry, thermometry and acoustic emission provide only a general view for the overall reaction profile. By contrast, solid-state structural methods like X-ray diffraction provide information on the nature of the solid crystalline phases, whereas molecular structural methods like Raman and fluorescence spectroscopy provide information on changes in molecular structure. For this reason, there is growing awareness of the benefits of combining multiple TRIS methods simultaneously^{49,52,53,112,119}, though such combinations remain rare. Methods for TRIS analysis are still in their infancy²³, and much is still to be learned about how best to conduct and interpret these analyses¹²⁰. Data quality and resolution of TRIS methods are often lower than in *ex situ* experiments, making quantitative analysis difficult. Temporal resolution needs to be further improved to capture fast reaction kinetics and short-lived intermediates; therefore, not all analytical methods are suitable for mechanochemical monitoring. The simultaneous combination of several complementary techniques remains difficult but is essential for a comprehensive understanding of reactions. Frameworks for analysing complex, multi-phase TRIS data are still evolving, as distinguishing reaction mechanisms from physical mixing effects is difficult. Customized reactors that are compatible with different analytical probes while maintaining realistic milling conditions need further optimization^{22,23,109,121}. Overcoming these limitations will be critical to advancing TRIS analysis as a robust tool for mechanochemical research.

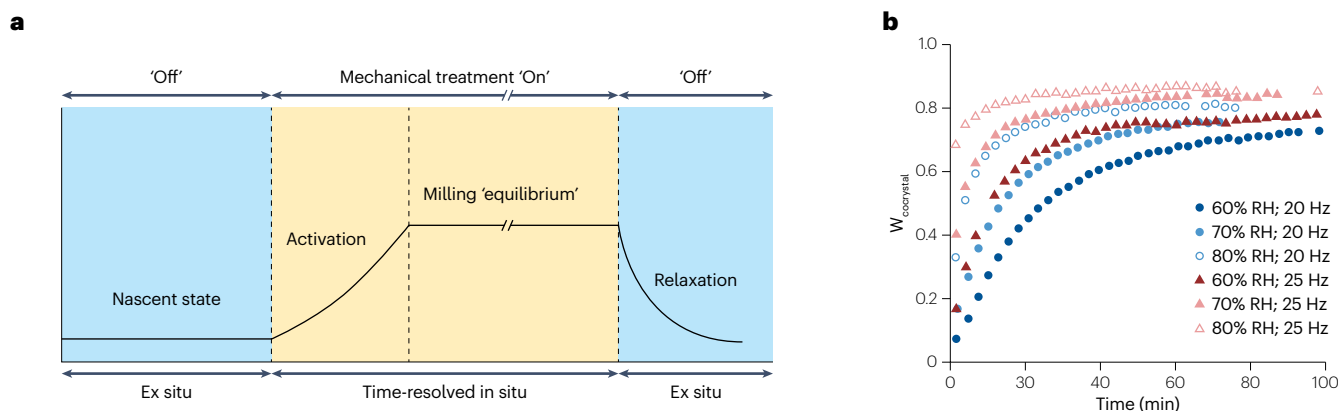


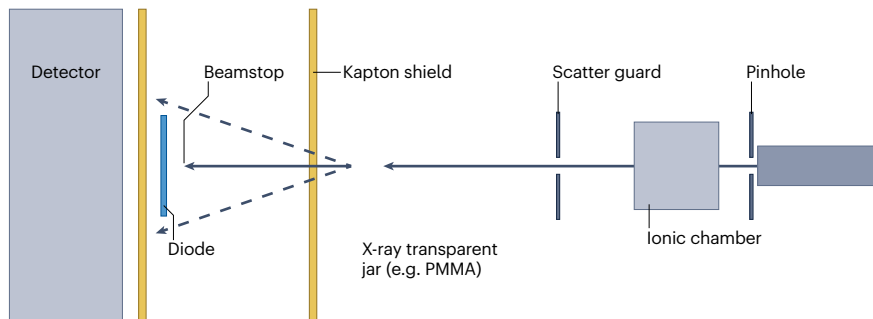
Fig. 2 | Profile of a typical mechanochemical reaction. a, Mechanical treatment drives the solid away from equilibrium, into an energetically ‘activated’ state. Once mechanical treatment is stopped, this excess energy is allowed to relax, although the relaxed state may be still ‘activated’ with respect to the nascent state. **b**, Conversion fraction ($W_{\text{cocrystal}}$) of isoniazid–benzoic acid cocrystals as a function of time in premilled mixtures (20 and 25 Hz for 5 min) stored at 40 °C

and different relative humidity (RH) values (60%, 70% and 80% RH). Cocrystal formation was monitored by quantitative analysis of sequential powder X-ray diffraction patterns, demonstrating the effect of humidity on the rate of cocrystallization. Part **a** adapted from ref. 52, CC BY 4.0. Part **b** adapted with permission from ref. 232, American Chemical Society.

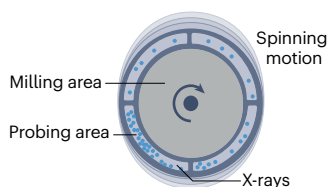
Aa Synchrotron set-ups



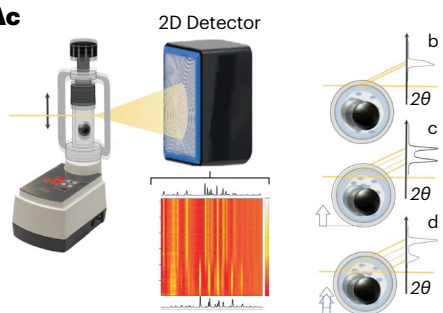
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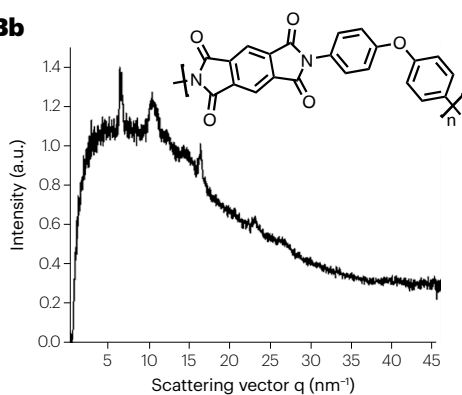
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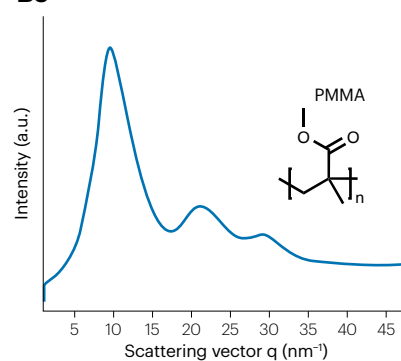
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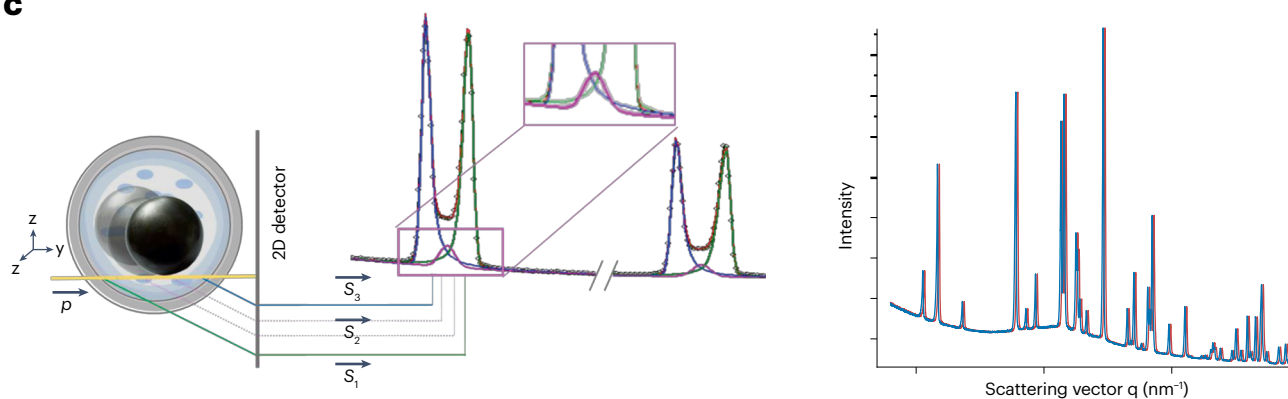
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D

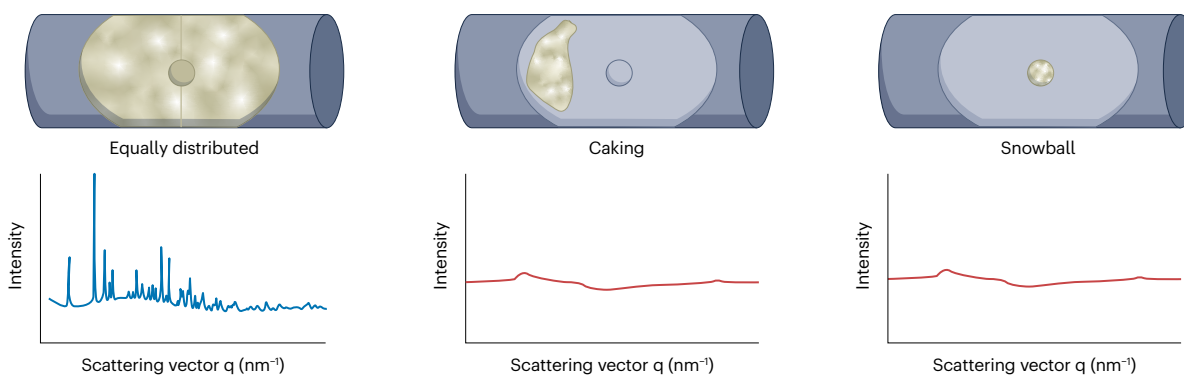


Fig. 3 | Time-resolved in situ powder X-ray diffraction to monitor ball-milling transformations. **A**, Different experimental set-ups being used for time-resolved in situ powder X-ray diffraction (TRIS PXRD): original set-up in which the X-ray beam passes through horizontally oscillating milling containers, originally designed at ID11 at the European Synchrotron Radiation Facility^{109,233}, with similar installations available at P02.1 PETRA III (refs. 53,234) and μ -spot BESSY-II (refs. 23,115) (part **Aa**); the set-up developed at the X04SA Materials Science beamline at the Swiss Light Source, Paul Scherrer Institute, where powder moves from the main milling chamber into a thin probing area with polyimide (Kapton) walls and is recycled back into the milling chamber after analysis (part **Ab**); and optimized set-up for conventional ball milling in which the X-ray beam is carefully aligned to minimize the scattering path and maximize the quality of the diffraction signal (part **Ac**). **b**, **c** and **d** are X-ray diffraction data collected for an Si standard at different positions in the milling jar. **B**, Typical set-up for TRIS PXRD at a synchrotron beamline showing the components of the beamline set-up (part **Ba**),

the X-ray scattering associated with Kapton shields (part **Bb**) and the X-ray scattering associated with a typical poly(methyl methacrylate) (PMMA) milling jar (part **Bc**). **C**, The peak profile that results from a typical TRIS PXRD experiment, depending on the location of measurement through the milling jar, alongside a typical PXRD profile. **D**, Different effects observed in milling vessels as a consequence of different rheologies and implications for the detected XRD pattern. 2θ , the scattering geometry that relates the incident and diffracted X-rays, to fulfil the Bragg condition; a.u., arbitrary units; p , primary beam; q , scattering vector; S_1 , scattering vector produced by sample located at the jar wall closer to the source; S_2 , scattering vector produced by the sample distributed randomly within the jar; S_3 , scattering vector produced by the sample located at jar wall closer to the detector. Part **Aa** reprinted from ref. 109, Springer Nature Limited. Part **Ab** adapted with permission from ref. 121, American Chemical Society. Parts **Ac**, **B** and **C** adapted from ref. 23, Springer Nature Limited.

Ongoing method development and critical evaluation of data interpretation approaches will help to establish best practices for the conduct and application of TRIS investigations.

TRIS PXRD. There have been various TRIS PXRD set-ups proposed in the literature, all with minor differences in the experimental considerations (Fig. 3A). Despite some technical differences, all TRIS PXRD set-ups have the same basic arrangement and rely on synchrotron X-ray sources (Fig. 3Ba). The monochromatic X-ray beam is first passed through a set of optical elements to cut it to the correct size (pinholes) and to measure its intensity for data normalization (ionic chamber). The beam subsequently passes through an X-ray-transparent jar (usually plastics, like PMMA) and interacts with the sample inside. The scattered beam passes through the back side of the jar, before moving through X-ray-transparent safety shields, often made of polyimide (Kapton). Although not strictly necessary, these shields are placed to protect the X-ray detector, should experimental failure occur. Finally, the primary beam is stopped by a lead block (the beam stop) while the scattered X-rays (for example, Bragg scattering) strike the detector to produce the signal. This complicated path of the X-ray beam through the experiment leads to a few distortions of the data. First, the final data comprise contributions from the interaction of the X-rays with the PMMA jar (Fig. 3Bc) and the Kapton shields (Fig. 3Bb). As both components are not (or very poorly) crystalline, they provide broad ‘humps’ to the data, giving rise to a significant background in the XRD pattern. Second, because the sample is located inside a 3D jar, and hence at different distances from the detector, the Bragg scattering becomes artificially broadened or even split (Fig. 3C). This effect causes real difficulties for data processing, but it can be minimized by carefully aligning the X-ray beam to the tangent of the milling jar to reduce its path length through the sample while any remaining artificial splitting can be corrected analytically (see Lampronti et al.²³ and its associated electronic supplementary information). Treating TRIS PXRD data using these strategies leads to very reliable and detailed data sets, sufficient for extracting with high confidence both phase composition and microstructural detail, even from only milligrams of powder²³.

An additional complication of TRIS PXRD arises from the calibration of the sample-to-detector distance, which determines how accurately we can convert the scattered intensity from the detector into a useful PXRD profile. Using a well-defined powder standard like Si, CeO₂ or LaB₆, one could realistically calibrate to the centre of the milling jar or to jar-tangent position at which the measurement is being

done, either by measuring the standard powder directly in the milling jar or by attaching an external standard to these positions on the mill. Geometrically, these points should in principle both provide the same sample-to-detector distance. However, we note that if the standard is measured directly in the milling jar, at the position where the TRIS PXRD data will be measured, one obtains also a direct measure of the instrument profile contribution to the data (see details elsewhere^{23,122}). Although in principle the movement of the ball mill during an experiment can slightly affect the alignment, any such changes seem to be below the intrinsic resolution of the method. Attempts have been made to overcome this concern by including alignment standards in the ball mill during the experiment, but care must be taken with this approach. Any material (additive) added to the sample jar can influence and alter a mechanochemical reaction and its outcome. For example, transformation between three polymorphs of the compound 2-nitrophenyl-4-chlorophenyl-disulfide only occurs in the presence of a 1.5 M impurity⁶³, and the presence of seeds of nicotinamide can produce a metastable polymorph of benzamide in pure form⁶⁴.

TRIS Raman spectroscopy. For Raman spectroscopy experiments, the mills are typically set up in darkened rooms or boxes to avoid the influence of other light sources. The Raman set-ups presented in the literature typically comprise a transparent milling jar (typically, PMMA) and a Raman probe that can be adjusted to the inner wall of the milling jar. The data treatment consists of a subtraction of the jar contribution to the Raman spectra, a base line correction and normalization of the data. Scripts are available for analysis and visualization of TRIS Raman data⁵¹.

The course of a reaction can be qualitatively followed by plotting the intensities of selected Raman bands versus time. For a detailed quantitative analysis of the reaction mixture at a given point in time, a calibration is needed. Alternatively, least-squares procedures can be performed, given that the Raman spectra of the components taking part in the reaction are measured and averaged under the same conditions, leading to a representative spectrum. These least-squares procedures specifically refer to spectral deconvolution techniques in which the Raman spectra are fitted to determine the relative contributions of different components or polymorphs in the sample. Least squares procedures thus require that one knows the system under study and its components. Alternatively, it may also be possible to extract distinct signatures of different polymorphic forms through statistical analyses, such as principal component analysis¹²³. It can be difficult to access the formation of intermediates or polymorphs from the Raman data

Table 1 | Data analysis for common TRIS methods

Method	Information content	Prior knowledge	Software
XRD	Qualitative ⁴⁶	Comparison with databases CCDC, ICDD PDF, ICSD	TOPAS, Fullprof ^a , GSAS ^a
	Quantitative ²³	Crystal structure(s), e.g. by Rietveld	
Raman Spectroscopy	Qualitative ^{115,229}	Molecular fingerprint	Custom open source ⁵¹
	Quantitative ¹²³	Reference spectra, e.g. by PCA or LS refinement	
ssNMR	Quantitative ¹¹⁴	Phase composition, crystal structure	Nmrglue ^a (ref. 230)
XAS	Semi-quantitative ¹¹²	Reference spectra	Athena ^a , Larch ^a (ref. 231)

CCDC, Cambridge Crystallographic Data Centre; GSAS, General Structure and Analysis System; ICDD PDF, International Centre for Diffraction Data Powder Diffraction File; ICSD, Inorganic Crystal Structure Database; LS, least squares; PCA, principal component analysis; ssNMR, solid-state nuclear magnetic resonance; TOPAS, Total Pattern Analysis Solution; TRIS, time-resolved in situ; XAS, X-ray absorption spectroscopy; XRD, X-ray diffraction. ^aOpen source.

if the species lack distinct Raman bands. In those cases, tandem TRIS experiments¹¹⁵ combining the benefits of XRD and Raman spectroscopy are helpful. The application of Raman spectroscopy can be limited for highly fluorescent samples, resulting in partial or complete shadowing of the Raman bands of the sample. Reducing the power of the incident laser beam can circumvent this issue in some cases.

TRIS data analysis

Analysis of data from ex situ techniques follows conventional strategies following standard protocols, and it is not discussed here. Instead, we focus our discussion on the unique challenges associated with TRIS data analysis, with a brief overview of available data evaluation strategies and requirements (Table 1). When performing any TRIS monitoring experiment, the obtained results are inherently convoluted between signals that come from the reactor and from the sample. In addition, the non-ideal sample environments and restrictions on the data collection time (that is, to achieve time resolution) in TRIS typically leads to data of poorer quality than established ex situ techniques. Specialized data processing is therefore often needed to achieve data that are ready for analysis.

The analysis and interpretation of TRIS data is itself a complicated task. In most cases, the probe used for TRIS analysis is stationary and the milling jar (and reacting powder) moves through the probe. Hence, only a small fraction of the powder, at one position in the reactor, is sampled, with the assumption that the reaction is homogeneous across the sample volume. Such assumptions become particularly problematic when the powder rheology leads to ‘clumping’ or ‘snowballing’^{120,124} (Fig. 3D). Moreover, TRIS methods generally require specialized milling jars that are transparent to the probing radiation. Unfortunately, it is becoming apparent that changing the jar material can also have a marked influence on the outcome of the reaction, changing kinetics¹²⁵, product⁴¹ and product stability¹²⁶.

Details on the analysis of data collected from Raman spectroscopy⁵¹ and PXRD²³ are given in dedicated reviews, whereas standard protocols for data acquisition/analysis from other in situ methods are not yet available but will appear as the techniques develop further.

Mechanochemistry compared with solution

There are various reactions that are different under mechanochemical conditions compared with solution. However, many of these differences can be explained by the direct changes in the kinetics or thermodynamics of the reactions under mechanochemical conditions, which are different to what is observed in solution^{35,124}. The development of

new techniques to study mechanochemical transformations suggests a need to establish a framework in which the outputs are interpreted. It is common practice to seek connections between phenomena in mechanochemical conditions against existing parameters in solution. For example, how can pH under mechanochemical conditions exist where there are no free-floating ions in a solution to measure? Although comparison with solution certainly provides a solid foundation for trying to interpret mechanochemical reactions, these direct comparisons can often lead to experimental bias, which can diminish many of the exciting and unique features of mechanochemical reactions. Instead, it is imperative to recognize that mechanochemistry is ushering in a new paradigm of the chemical sciences deserving its own foundational principles. It is important not to think that, just because the product distribution is different between a mechanochemical reaction and a solvothermal reaction, the chemistry itself is different. With that said, there are many similarities that are observed between mechanochemical ball-milled reactions and those conducted in solution.

Like many solid-state reactions, reactions conducted under ball-milling conditions are faster than the same transformations performed in solution. This is presumably due to limited need for statistical diffusion. Various reactions conducted mechanochemically are associated with higher yields and fewer by-products than solution chemistry. This reflects the lack of the conventional ‘equilibrium’ that occurs in solution and hence the ability to shift apparent equilibria or obtain out-of-equilibrium products¹²⁷. The kinetic features are also significantly different to those observed in solution. In solution, one typically sees a slow, albeit steady reaction rate (for example, zeroth, first or second order), with the rate proportional to reagent concentration. However, reactions conducted mechanochemically are often accompanied by unconventional kinetics. Many mechanochemical transformations comprise an induction period (that is, a kinetic regime preceding the reaction during which ball milling causes no chemical transformation), which can extend from seconds to hours^{128,129}, depending on the milling conditions and the system at hand. It is not yet known what causes this induction period, although growing evidence suggests it may be due to the need to activate material prior to the onset of the reaction^{128,130}. Other unconventional kinetic features can be due to auto-catalytic processes – or ‘feedback’ effects – in which an otherwise slow mechanochemical reaction self-accelerates due to the release of water^{59,124,131}.

Computational methods for prediction

Interpreting the results of mechanochemical kinetics is precluded by a lack in understanding of the mechanisms and features that affect

these reactions. In hopes to overcome this hurdle, there have been marked efforts towards developing theoretical and computational tools to model and rationalize mechanochemical reactions both at the macroscopic and microscopic scale. Macroscopic analytical kinetic models^{132–135} have been developed to help better understand the effects that dominate reaction profiles in terms of features such as mixing, collision frequency and the probability of reaction. However, such models are not predictive in nature. Growing numbers of works have used density functional theory (DFT) simulations to predict the relative stability of product phases in an attempt to rationalize the outcome of mechanochemical reactions¹³⁶. These methods rely on thermodynamic concepts though, which are not always applicable for determining product formation^{137,138}. Instead, others have included in their energy landscape calculations the effects of particle size and surface energy, which seem to be needed to capture more accurately the outcome¹³⁹. Although such methods have been helpful for rationalizing and predicting the final product phases, they do not allow us to describe the amount of energy required to initiate a mechanochemical reaction or the elementary stages that lead to a mechanochemical reaction. Recent efforts based on vibrationally driven excitation have proved to be promising in this regard to predict single-component mechanochemical reactions^{140,141}, whereas simulations of shear processes at surfaces seem promising for the simulation of the elementary stages in multi-component reactions¹⁴².

Applications

With applications to various sub-fields and industries, mechanochemistry has become a robust and impactful technique. Mechanochemical conditions can be used for a variety of chemical transformations, ranging from fundamental bond formations to complex materials and catalytic methods, with the most common applications discussed below.

Synthesis of molecular inorganic materials

The demand for sustainable chemical processes is driving the development of greener methods^{2,27}, with mechanochemistry emerging as a key solvent-free approach that complements traditional solution-based synthesis for both molecular solids and advanced materials. Although solvents are still essential for extraction and purification, the advantages of reducing their use are becoming increasingly recognized, even by sceptics within the synthetic chemistry community¹⁴³. With solvent reduction in mind, mechanochemistry has been successfully utilized for the synthesis of a wide range of main-group compounds^{144,145}, as well as metal and organometallic complexes^{146–150}, and in catalysis^{43,151}, along with other technologically relevant inorganic materials such as metal–organic frameworks (MOFs)^{152,153}, perovskites¹⁵⁴ and battery materials¹⁵⁵. One particularly exciting aspect of mechanochemistry is its ability to facilitate multicomponent, multistep reactions, as well as enabling the synthesis of compounds that are easily accessible in solution³.

Among multicomponent, multistep reactions for metal complex synthesis, notable examples include a three-component synthesis of salen complexes¹⁵⁶, a one-step, five-component route to rhenium(I) complexes from a metal carbonyl via orthogonal oxidative addition and ligand exchange¹⁵⁷ (Fig. 4a), and the direct synthesis of indium(III) complexes from ligand precursors and indium trichloride¹⁵⁸. Remarkably, such reactions can also use gaseous reactants, as shown by the synthesis of copper(II) N-heterocyclic carbene complexes directly from copper metal, an imidazolium salt and oxygen gas⁶⁵. Other multicomponent mechanochemical reactions involving molecular inorganic materials¹⁵⁹ include the direct one-step synthesis of air-stable and moisture-stable cyclophosphazanes frameworks¹⁶⁰ as well as their use in the assembly of high-order cocrystalline materials¹⁶¹. The appeal of mechanochemistry lies in its ability to achieve products

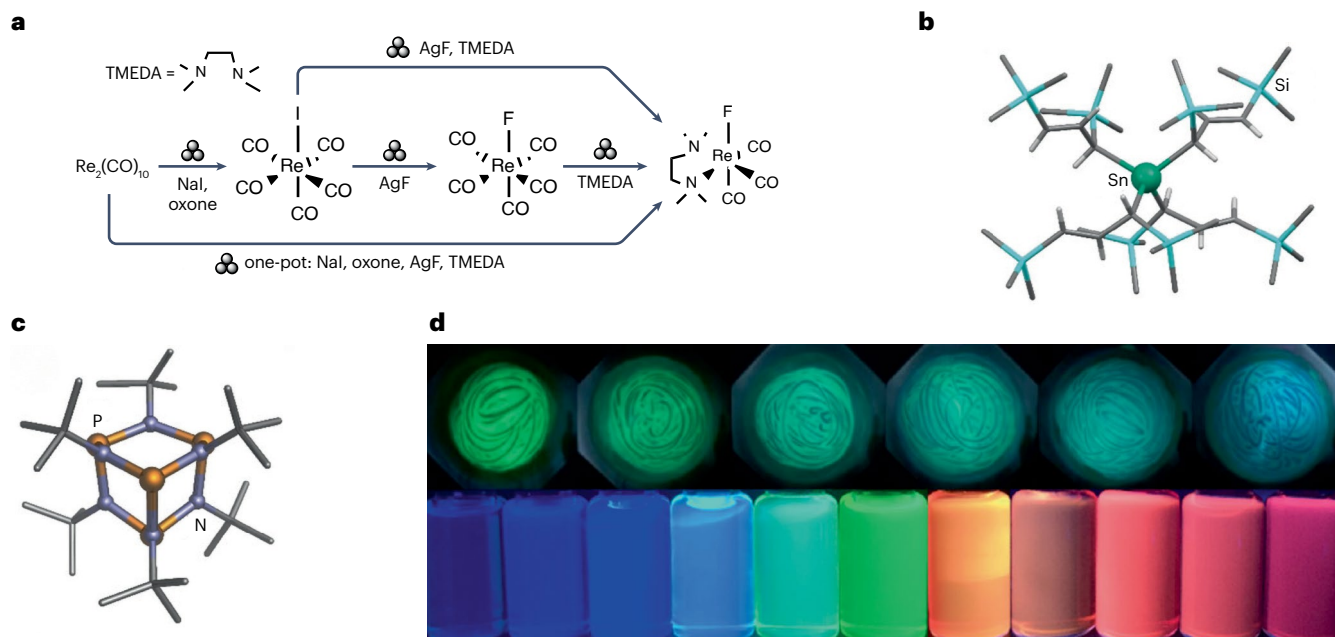


Fig. 4 | Inorganic compounds synthesized with mechanochemistry. **a**, A one-step, five-component route or a three-step sequential route for the mechanochemical synthesis of a target Re(I) complex from a simple carbonyl¹⁵⁷. **b**, Adamantoid *tert*-butylphosphazane $P_4(N^tBu)_6$ (ref. 160). **c**, Trimethylsilylated

tetraallyltin(IV)¹⁶². **d**, Representative luminescence photographs of $MAPbX_3$ ($MA = CH_3NH_3^+$, $X = Cl, Br, I$) perovskite solutions under a 365 nm ultraviolet lamp irradiation. TMEDA, tetramethylethylenediamine. Part **d** reprinted with permission from ref. 173, American Chemical Society.

or reactions that are difficult or impractical in solution¹⁷. Hanusa and colleagues demonstrated this with the synthesis of a tris(allyl) aluminium complex using a bulky bis(trimethylsilyl)allyl ligand⁸³. Solution-based methods for such complexes are notoriously challenging, often resulting in solvates or adducts. However, ball milling yielded the elusive aluminium tris-(bis(trimethylsilyl)allyl) complex as an off-white powder⁸³. Similarly, ball milling was used to synthesize trimethylsilylated tetraallyltin(IV), a stable solid that rapidly decomposes in solution¹⁶² (Fig. 4b). Theoretical calculations suggest that its stability is maintained by dispersion forces, which are likely disrupted by solvents, leading to its instability in solution. Yan and colleagues recently reported the mechanochemical synthesis of previously unreported “rectangular” Pd₂L₂ dimers. By milling the Pd precursor (TMEDA)Pd(X₂) (TMEDA = tetramethylethylenediamine; X = NO₃[−], BF₄[−], trifluoromethanesulfonate (OTf[−])) with bipyridine as a linker, they obtained the known Pd₄L₄ and Pd₃L₃ cycles, along with the novel Pd₂L₂ species¹⁶³. Using a similar self-assembly approach, they also successfully synthesized and isolated several unstable Pd cages and their intermediates¹⁶⁴.

Additional examples, in the area of molecular solids, include the synthesis of the adamantoid P₄N₆-phosphazane substituted with *tert*-butyl groups, previously deemed inaccessible using traditional methods even under prolonged heating at high temperatures¹⁶⁵ (Fig. 4c). However, it was readily obtained in quantitative yields under ball-milling conditions for 90 min. Theoretical studies confirmed that the reaction is thermodynamically favourable, highlighting the transformative potential of mechanochemistry in modern synthetic chemistry¹⁶⁶.

MOFs are microporous and tuneable functional materials that are used in gas storage, catalytic separation and so on¹⁶⁷. Since their first mechanochemical report in 2006 (ref. 168), these compounds have been effectively synthesized via neat, liquid-assisted grinding and ionic liquid-assisted grinding routes¹⁶⁹. For instance, the mechano-synthesis of the popular MOF ZIF-8 in the presence of water revealed a transient new framework polymorph with a novel katsenite topology¹⁷⁰. Although this kat-phase is metastable and rearranges upon exposure to solvent or mild heating, its discovery underscores the potential of mechanochemistry and in situ reaction monitoring for exploring and understanding the MOF phase landscape^{52,105,171}.

Mechanochemistry has also proven to be an effective method for producing perovskite materials, offering several advantages over traditional solution-based techniques¹⁷². Notably, mechanochemistry has enabled the synthesis of perovskite materials with compositions that have not been achievable in solution, such as certain formamidinium (FA)-based mixed halide perovskites. For example, the one-pot mechanochemical synthesis of FAPbX₃ (X = Cl, Br, I) has been demonstrated, resulting in materials with halogen-rich surfaces that exhibit visible full-spectral emissions and high photoluminescence quantum yields of up to 92%¹⁷³ (Fig. 4d). The direct access to metastable perovskite phases bypasses the need for a post-synthetic annealing step¹⁷⁴. Not only does this method enhance the efficiency of the synthesis and the purity of the obtained perovskites, but it also expands the range of achievable compositions. This makes mechanochemistry an invaluable technique for the development of advanced optoelectronic materials.

Overall, mechanochemistry paves the way for a sustainable future in inorganic material synthesis, unlocking innovative pathways to create advanced materials and molecular solids with unparalleled precision and environmental consciousness.

Polymer mechanochemistry

The sustainability of polymer chemistry has been improved through the implementation of mechanochemical protocols. This is especially critical given that, despite the undeniable benefits of commercial plastics, the accumulation of plastic waste has become a major environmental challenge. As early as the 1930s, studies demonstrated the potential of mechanochemical treatment to break polymeric chains¹⁷⁵. However, recent studies have revealed that combining mechanochemistry with polymer science offers benefits beyond simple polymer chain scission, decomposition or the remediation of toxic polymers¹⁷⁶. For example, sustainable, solventless monomer-to-polymer mechano-syntheses under ball-milling conditions have now been extensively documented¹⁸, even for the polymerization of monomers with varying solubility profiles¹⁷⁷. Moreover, mechanochemical depolymerization of well-defined polymers back to monomers has also been explored^{178–180}, which holds promise for advancing polymer circularity¹⁸¹. Equally important are studies focusing on mechanochemical upcycling of post-consumer plastics, such as polystyrene waste, to modify their structure and impart new properties, adding value for commercial applications¹⁸². Likewise, the mechanochemical functionalization of biopolymers, such as cellulose, has been shown to reduce waste production compared with traditional solution-based methods, while allowing access to materials with tailored properties^{183,184}. Finally, in addition to ball milling, ultrasonic cavitation has emerged as a promising tool to drive mechanochemical polymerization, for example, by activating piezoelectric materials to trigger polymerization reactions^{185–187}. Ultrasonication can also apply mechanical force to mechanophores embedded along the polymer backbone, promoting constructive chemical transformations with potential applications in catalysis, medicine and sensing, among others^{1,11,188}.

Upscaling mechanochemistry

There are over 350,000 manufactured chemicals in production¹⁸⁹, with a wide range of molecular weights, complexity levels and applications. This makes the ability to upscale mechanochemical reactions of growing importance due to the sustainability challenges faced by modern society^{2,92,93,190}. Mechanochemistry has been shown to exhibit a lower environmental footprint (including higher energy efficiency, optimized resource utilization, reduced human and environmental hazards, and so on) than the comparable commercial processes^{191,192}. Its solventless nature, together with the drive to develop environmentally responsible production methods, places mechanochemistry as a front-runner to enable greener chemical technologies¹⁹².

Although various methods have been developed to scale mechanochemical reactions, the most promising methods have involved the use of a TSE¹⁹³. Screw extruders have been around for more than 100 years and started gaining widespread use in the food industry in the 1930s¹⁹⁴. More recently, they have been adopted by the pharmaceutical industry to generate a range of solid dosage forms^{195–197}. Therefore, TSEs are a strong complement to the benchtop methods of ball milling and to other forms of mechanochemical activation. Because commercial chemical manufacturers already own and utilize this piece of equipment, the ability to translate what is observed on a benchtop ball mill to TSE conditions is key to scaling mechanochemical reactions.

Mechanochemical scale-up in academic research. Similar to what is observed in the scaling of solution-based reactions, mechanochemical conditions cannot simply be transferred from the benchtop to process reactors. Considering that the mechanochemical action of a ball mill

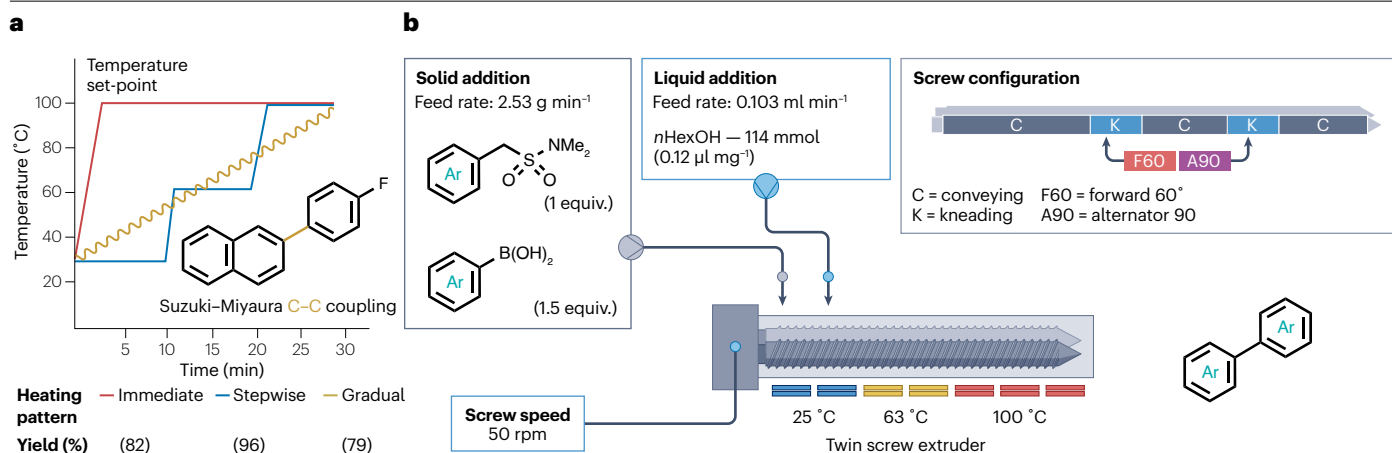


Fig. 5 | Twin screw extrusion implemented in a Suzuki–Miyaura cross coupling. **a**, Heating profile for the Suzuki–Miyaura cross coupling performed in ref. 199. **b**, Schematic protocol design for the upscaled mechanochemical

nickel-catalysed Suzuki–Miyaura coupling via twin screw extrusion. *n*HexOH, 1-hexanol; rpm, revolutions per minute. Adapted with permission from ref. 199, Wiley.

differs from the impact imparted by a TSE, additional parameters need to be considered. Milling time, milling frequency, milling media and other parameters mentioned in the previous sections need to be translated to residence time, screw configuration, feed rate and the other parameters associated with the extruder. The field is at the beginning stages of understanding the correlation between reactions conducted in a ball mill and those conducted in a TSE. Although there are various parameters that need to be considered, the two most important ones seem to be screw configuration and temperature^{198,199}. The utility of extrusion has shown promise in many areas, ranging from the synthesis of organometallics such as salen complexes²⁰⁰ and MOFs²⁰¹, to its use in organic chemistry in reductions²⁰², formation of imines²⁰³, and peptide couplings²⁰⁴. Additionally, catalytic processes have been explored for scale-up from milligram scale to multi-gram scale by twin screw extrusion, as highlighted by the Suzuki–Miyaura cross-coupling reaction shown in Fig. 5 (ref. 90).

Potential impact on sustainable chemistry

There is a significantly high potential for the incorporation of mechanochemistry in the production of chemical manufacturing to address sustainability goals. When compared with solution, the twin screw extrusion approach demonstrated reduction in process mass intensity, waste generation and operating costs, as observed in a comprehensive cradle-to-gate analysis of the mechanochemical process²⁰⁵. The process-mass-intensity reduction achieved was approximately one order of magnitude. Furthermore, the quantity of wastewater generated before treatment was notably lower (<0.01 versus 19 for solution-based processes) and the mechanochemical approach was eight times cheaper than the solvent-batch production^{206,207} (Fig. 6b,c).

Moreover, data on annual demand for active pharmaceutical ingredients in the USA between 2008 and 2018 show that using twin screw extrusion has the potential to address climate change, while reducing environmental degradation and operating costs compared with conventional solution-based methods (Fig. 6c). Active pharmaceutical ingredient data illustrate not only the environmental benefits but also the economic advantages of the implementation of mechanochemical technologies at large scales^{205,207}.

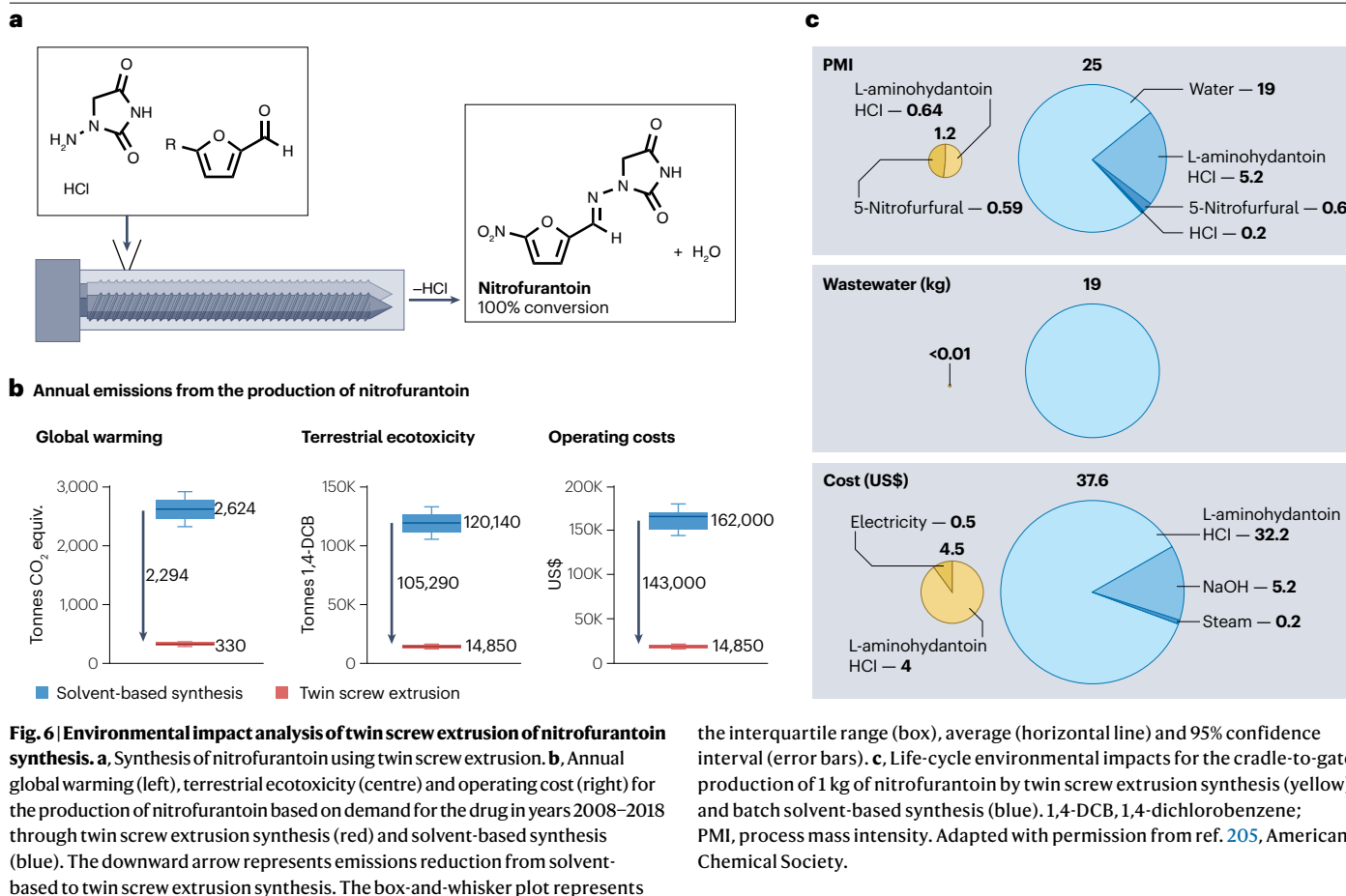
These findings have encouraged the pharmaceutical industry to begin considering mechanochemistry for upscaling early route processes. The implementation of mechanochemistry in the process stage and in manufacturing practice could reduce solvent waste tremendously while also simplifying reaction set-up and further improving the sustainability of large-scale manufacturing process. This has been showcased by work conducted at AbbVie, where researchers were able to develop a Sonogashira coupling that can be performed by twin screw extrusion²⁰⁸. This study also showcases the ability to translate their method across different extruders, a potential challenge that could cause limitations of the adoption of mechanochemistry in industrial production.

Reproducibility and data deposition

Identifying standards (for example, milling conditions, definitions, terminologies and reaction analysis) and developing them globally is crucial to capitalize the research efforts in the field of mechanochemistry and to elevate mechanochemistry as a key technology for sustainable industrial synthesis^{2,21,209,210}. Achieving such a goal requires collaborative efforts of the field in order to explore new ideas, fill gaps and avoid risking fragmentation of standard setting processes along different lines, which would generate additional detrimental barriers.

The European Programme COST Action CA18112 “Mechanochemistry for Sustainable Industry”^{211,212} has recently re-invigorated efforts to establish standards for diversifying the mechanochemistry community. Examples developed within the COST Action CA18112 include the technological bases of mechanochemical methods, the definition of a common terminology, the sharing of good practices and protocols, methods (including measurements) and tools stimulating their application, and the preparation of practical guidelines for proper data management, also avoiding effort duplication.

These standardization initiatives complement independent contributions previously¹⁴⁸ accomplished and more recently reported²¹³, aiming to propose graphical symbols to represent reactions initiated by mechanochemical energy (for example, grinding, milling, crushing or extrusion), but these symbols are not harmonized nor generally accepted. To advance this initiative, IUPAC established a task group on “Terminology and Symbolism for Mechanochemistry” to tackle this issue²¹⁴.



The use of green metrics²¹⁵ is also a practical way to standardize measurable and objective indicators. Green metrics assess how green a mechanochemical process is compared with solvent-based processes, other new and existing alternative technologies, or other similar mechanochemical processes. In 2013, Colacino et al. first used green metrics to assess the mechanochemical preparation of N-protected amino acids²¹⁶. Since 2017, the use of green metrics in mechanochemistry is witnessing an exponential increase¹⁹². Nevertheless, green metrics are not always comparable across the different scientific publications, resulting in a non-harmonized series of indicators. This leads to a narrow view on the innovation potential of mechanochemical processes and how the field can contribute to green chemistry^{2,27} and sustainability²⁰⁵.

Using the freely available software DOZN 2.0 (ref. 217) can help to standardize mechanochemistry^{191,218} via its quantitative assessment following the 12 Principles of Green Chemistry (that are indeed qualitative), in order to ensure comparability with what is already on the market. Indeed, the DOZN 2.0 tool makes use of readily available data extracted from the Globally Harmonized System of Classification and Labelling of Chemicals, providing information on the physical, health and environmental hazards of individual chemicals.

The route to standardization of mechanochemistry is already paved, and the scientific community working in the field has the responsibility to make it grow in a joint manner to utilize its full potential for business and innovation.

Limitations and optimizations

Mechanochemical reactions have the potential to be applied to various reactions, but there are still challenges to overcome. Inherently, some types of reactions need or benefit from the presence of a solvent, even though many others can do without it. For example, some reactions happen in a stepwise fashion or need low concentrations to control the desired reaction pathways. At present, there is no easy way to add or remove material from the milling process while the reactions are taking place. These processes can be very important to change or influence the equilibrium and affect the product distribution. Additionally, reactions that release a lot of heat are hard to conduct safely under mechanochemical conditions. The solvent usually helps by acting as a heat sink for these reactions, but when the said reactions are conducted under mechanochemical conditions, the heat is typically transferred directly to the reagents, which leads to charring^{190,219}. Other reactions, such as solvolysis reactions or reactions that are initiated by the presence of a solvent, are not suitable for mechanochemical conditions.

Another current challenge observed in mechanochemical reactions is the difficulty of adapting the equipment. Most of the milling equipment used for mechanochemical reactions was not originally designed for this purpose. This means that scientists have to create and modify milling jars and equipment to perform these reactions. This also requires access to a machine shop or material fabrication ability for research in this field. Moreover, many of the analytical tools that are

used to detect the products or intermediates of the mechanochemical reactions need to use a solution after the reaction. This often restricts the ability to understand the mechanism of these reactions under pure mechanochemical conditions.

For some reactions, the milling jar and milling media can cause unwanted side products or contamination of the desired products²²⁰. At times this challenge can be addressed with the use of a Teflon or non-metallic milling jar and/or milling media. However, as described in earlier sections, the milling jar and media are an important parameter to consider when conducting mechanochemical reactions. Therefore, less optimal conditions could be used to avoid the potential of metal contamination in the product.

Outlook

Mechanochemists are frequently questioned about the relatively slow adoption of this methodology compared with its potential impact. Despite the considerable potential that mechanochemistry offers with respect to increased reaction rates, new product distributions and a clearer path towards sustainable chemical processes as compared with traditional solvothermal conditions, widespread adoption has been sluggish. These potential advantages have been extensively outlined in this Primer. Therefore, the primary obstacle in the field lies not in the chemistry itself, but rather in the chemists' willingness to embrace it.

The encouraging aspect is that mechanochemistry essentially relies on the same principles of traditional solution-based chemistry. The fundamental concepts of kinetics and thermodynamics that apply to reactions in solution are equally relevant to mechanochemical reactions. Familiar concepts such as temperature, nucleophiles, electrophiles and activation barriers remain relevant in mechanochemical conditions. The difference between mechanochemical and solution-based reactions lies in the methodology of conducting the reaction, not in the core chemical principles themselves. For instance, it's widely acknowledged that reaction rates, conversions and product distributions are influenced by the type and quantity of the solvent used²²¹. Mechanochemistry operates from the same principles, albeit without a bulk solvent, providing a new avenue to observe changes in experimental results. As the field advances, we are progressively elucidating how these fundamental concepts manifest in mechanochemical settings. The ability to comprehend and forecast mechanochemical reactions in the coming decade will decrease the fear of change and lower the barriers of entry into the field.

Over the next decade, it is imperative to deepen our fundamental understanding of mechanochemical reactions and discern when mechanochemical conditions are preferable to established methods. The prediction of chemical reactivity under mechanochemical conditions is growing, with many governing principles yet to be discovered. If this methodology is to reach its full potential, predictability across the field must increase substantially. Moreover, mechanochemistry will require assistance from fields beyond chemistry, particularly materials science and mechanical engineering.

Unlike solution-based reactions, in which the solvent creates a uniform environment, allowing minor changes in reagent polarity or mixing to be overlooked, mechanochemical reactions do not have this luxury. As a mechanochemical reaction progresses, the mixing ability and rheology change, leading to variations in reaction rates and reactivity overall. Traditionally, chemists classify reactions based on chemical reactivity, often disregarding the physical state of materials. However, under mechanochemical conditions, the physical state of the reagents is as crucial as their chemical reactivity. Although these

concepts are often ignored in traditional solution-based reactions, they are fundamental in mechanochemistry^{17,47,222} and materials science²²³. Establishing synergy between these two fields would significantly benefit both.

Another critical aspect for the progression of mechanochemistry is the creation of standardized milling equipment. Mechanochemists currently rely on market-available tools, but there is a scarcity of companies dedicated to designing and manufacturing equipment for mechanochemical applications. Currently, mechanochemists must modify commercial equipment, which results in inconsistent practices. Standardization or normalization of these essential tools is a critical step forwards, necessitating innovation and uniformity in the field²²⁴. This calls for a partnership between the mechanochemical community and mechanical engineers, who can design advanced equipment for mechanochemical research. Similar to how glass blowing and stirring plate evolution transformed solution-based chemistry^{225,226}, collaboration with mechanical engineering is crucial for the progress of mechanochemistry, and such cooperative efforts are already in motion.

Summary

This Primer aims to lower the entry barrier for those interested in exploring the field of mechanochemistry. Although this Primer serves as a starting point, it is impossible for it to encompass every facet of this rapidly expanding field. The advent of green chemistry reignited interest in the field of mechanochemistry, a method that dates back to the fourth century BCE and earlier. Its solvent-free nature presented a potential solution to significantly reduce waste in the chemical industry, particularly in the pharmaceutical sector, in which solvents account for 80–90% of the mass used to create active pharmaceutical ingredients²²⁷. Mechanochemistry has since proved to be a valuable tool in the development of sustainable chemistry^{2,27,192}, and it is gaining recognition in various sectors as a promising method.

Glossary

Ball milling

The use of a milling medium (typically a spherically shaped entity) to promote a mechanochemical reaction.

Liquid-assisted grinding

The use of solvent in a milling reaction to aid in particle movement, transition state stabilization and intermediate formation.

Milling bodies

Elements used to mix and grind the sample inside the milling jar; they are commonly spherical, such as milling balls, but other shapes exist.

Milling frequency

The number of full oscillations of the milling jar in a mixer mill or the number of full rotations of the milling jar in a planetary ball mill per unit time.

Milling jars

Containers made of metal, ceramic, plastic or other material in which the mechanochemical reaction takes place. They are sometimes referred to as milling reactors, containers, vials, vessels, chambers and so on.

Time-resolved in situ methods

Experimental techniques used to directly observe and measure a chemical reaction in real time, within its actual reaction environment, by capturing data at specific time points throughout the reaction process.

Twin screw extruders

(TSEs). A system that uses two co-rotating screws confined in a barrel to knead, mix and flow material through in a continuous method.

It is an exhilarating time to be part of the mechanochemical community. By all indications, this field is poised to flourish further, with new discoveries on the horizon. The mechanochemist's ability to comprehend the fundamentals of these reactions and predict reactivity compared with conventional solvothermal methods will be pivotal for unlocking the field's full potential. Although mechanochemistry appears to be gaining momentum, many chemists remain unfamiliar with the equipment and methodologies involved. Just as paradigm-shifting ideas and innovations of the past have become integrated into the educational landscape, future generations will incorporate mechanochemistry as a standard topic in chemical education²²⁸.

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Author contributions

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