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Review

Mechanochemistry: Looking back and ahead

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https://doi.org/10.1016/j.chempr.2025.102880

THE BIGGER PICTURE Mechanochemistry leads to the discovery of new chemical transformations, materials with advanced properties, and the degradation of complex chemical wastes. These discoveries come with environmental and economic benefits, such as decreasing greenhouse gas emissions and processing costs. As mechanochemistry becomes more widespread across academic laboratories, transferring this technology to industry is key to designing more sustainable chemical production processes. Using digital tools and artificial intelligence will expedite the optimization of mechanochemical processes, and powering them with renewable energy sources will result in a greater industrial appeal. As a result, pilot and industrial plants based on innovative mechanochemical technologies will emerge, forming the basis of the next-generation chemical industry.

SUMMARY

Starting with the discovery of fire and the preparation of food in prehistoric times, mechanochemistry is the oldest form of chemistry that humans have controlled. Mechanochemical practices, such as grinding with a mortar and pestle, continued into the Middle Ages until dedicated scientific studies began in the 19th century. Since then, research in mechanochemistry has shown that many chemical reactions can be performed via mechanical force without or with small amounts of solvent. Besides being time, material, and energy efficient, mechanochemical reactions often yield products that differ from those obtained in solution. Therefore, not only is mechanochemistry greener and more sustainable than conventional solution chemistry, but it also has the added value of providing new reactivity and selectivity. This is especially important today, when chemists need to invent high-performance materials, intermediates, and products with the use of sustainable feedstocks and develop environmental remediation pathways. At the same time, time-resolved *in situ* monitoring and computational modeling are necessary for addressing fundamental questions about the atomistic, molecular, and electronic nature of mechanochemical reactivity. Integrating digitalization, robotics, and artificial intelligence tools promises to increase the reproducibility and scalability of mechanochemical processes. Further evolution of mechanochemistry is expected to have a transformative effect on the chemical industry.

INTRODUCTION

Using shear and friction to create fire by rubbing stones together can be considered the very beginnings of mechanochemistry. However, the first written documents that describe mechanochemical processes come from the Greek philosopher Theophrastus and his book *On Stones* in the 4th century BC. In this book, Theophrastus described the extraction of mercury via the grinding of cinnabar (HgS) with vinegar in a copper mortar and pestle.[1] Despite being known for millennia, the mechanism of this reaction was only recently elucidated by Marchini et al., who demonstrated that it leads to chalcocite (Cu_2S).[2]

After the ancient Greek alchemists, no explicit references to mechanochemistry appeared for more than a millennium. Yet, it was common knowledge to use a mortar and pestle for the processing and extraction of food, pharmaceuticals, and minerals. This remained the status quo until the 16th century, when the works of Georgius Agricola described machinery for crushing mineral ores as part of their processing,[3] and the 17th century, when Francis Bacon defined milling as a critical treatment step for activating solids.[4] In the 19th century, Michael Faraday reduced silver chloride to elemental silver through a mechanochemical approach,[5] and Carey Lea subsequently showed that silver chloride decomposes into its elements when pressed but sublimes if heated.[6]

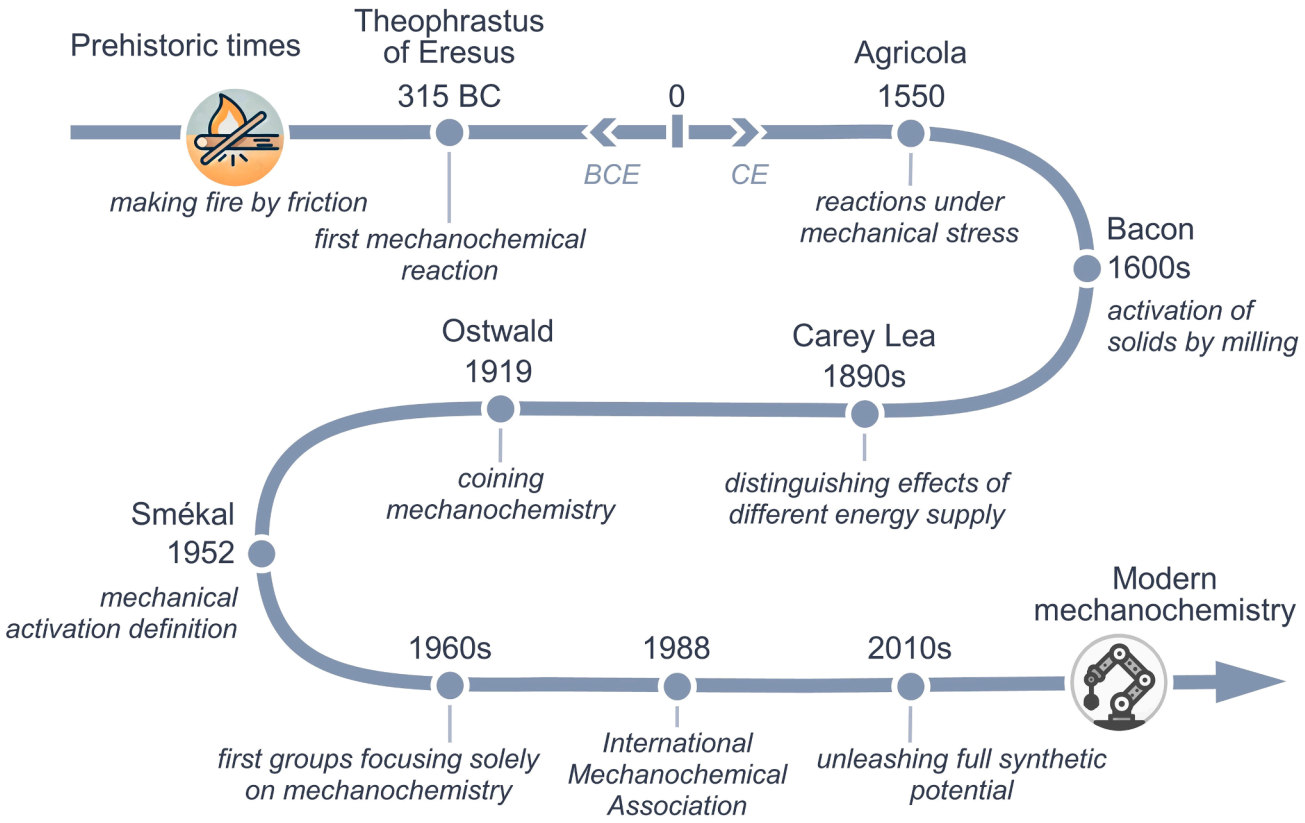

Figure 1. Selected milestones from the history of mechanochemistry

In the 20th century, mechanochemistry was used more frequently, especially by Flavian Mikhailovich Flavitsky[7] and Wilhelm Ostwald, who coined the term "mechanochemistry" to describe "reactions in any state of aggregation, initiated by mechanical action."[8] Furthermore, Adolf Smékal introduced mechanical activation as a process that describes the action of increasing the ability of a substance to react without chemically changing the substance.[9] Throughout the 20th century, the most active areas of research in mechanochemistry involved the synthesis of inorganic materials[10] and polymer chemistry.[11,12] In the second half of the 20th century, many new research groups emerged with a focus on mechanochemistry.[13,14] Building off the pioneering work of the late V.V. Boldyrev, the International Mechanochemical Association was formed in 1988, and an official definition for mechanochemistry appeared from the International Union of Pure and Applied Chemistry in 1997.[15] Selected milestones from mechanochemical history are provided in Figure 1.

Today, mechanochemical transformations are conducted in a wide variety of ball mills, extruders, and resonant acoustic mixers (Figure 2A), among other devices.[16–36] The use of a particular instrument depends on the desired intensity of the mechanical loading,[37] the specific type of mechanochemical action that one aims to exert on the reaction mixture (impact, shear, friction, etc.), the aggregate states of the reagents (solids, liquids, and gases), and the scale of the reaction.

The progress of a mechanochemical reaction typically involves an induction period (comminution and reduction of solid particle sizes), the reaction period (amorphization, crystallization, formation of intermediates, etc.), and the product period (reaching a steady state with no observable changes) (Figure 2B). Mechanochemical conditions enable efficient chemical reactions by providing activation energy and inducing frequent molecular collisions. As a result of mechanical stress, reagents can be driven into higher-energy, "metastable" states, thereby reducing the activation barriers for subsequent reactions or transformations (Figure 2C). Mechanochemistry also aligns with the principles of green chemistry[38] and the United Nations Sustainable Development Goals (Figure 2D),[39] providing a more resource-efficient route for conducting chemistry with enhanced environmental benefits, such as the reduction of greenhouse gases.[40]

Here, we want to emphasize that many of the topics in our review do overlap those in other perspectives or reviews. This is deliberate because our aim is to contextualize the evolving field as broadly as possible. In this respect, our review should not be seen as an attempt to provide a detailed description of all aspects of mechanochemistry but rather as an up-to-date bird's-eye view of the field. From this vantage point, we intentionally direct readers to more specific review articles.

We begin this review by introducing time-resolved *in situ* (TRIS) monitoring methods that enable mechanistic and kinetic understanding and provide inputs for computational modeling studies, which in turn provide atomistic detail of mechanochemical reactivity. We then demonstrate how coupling

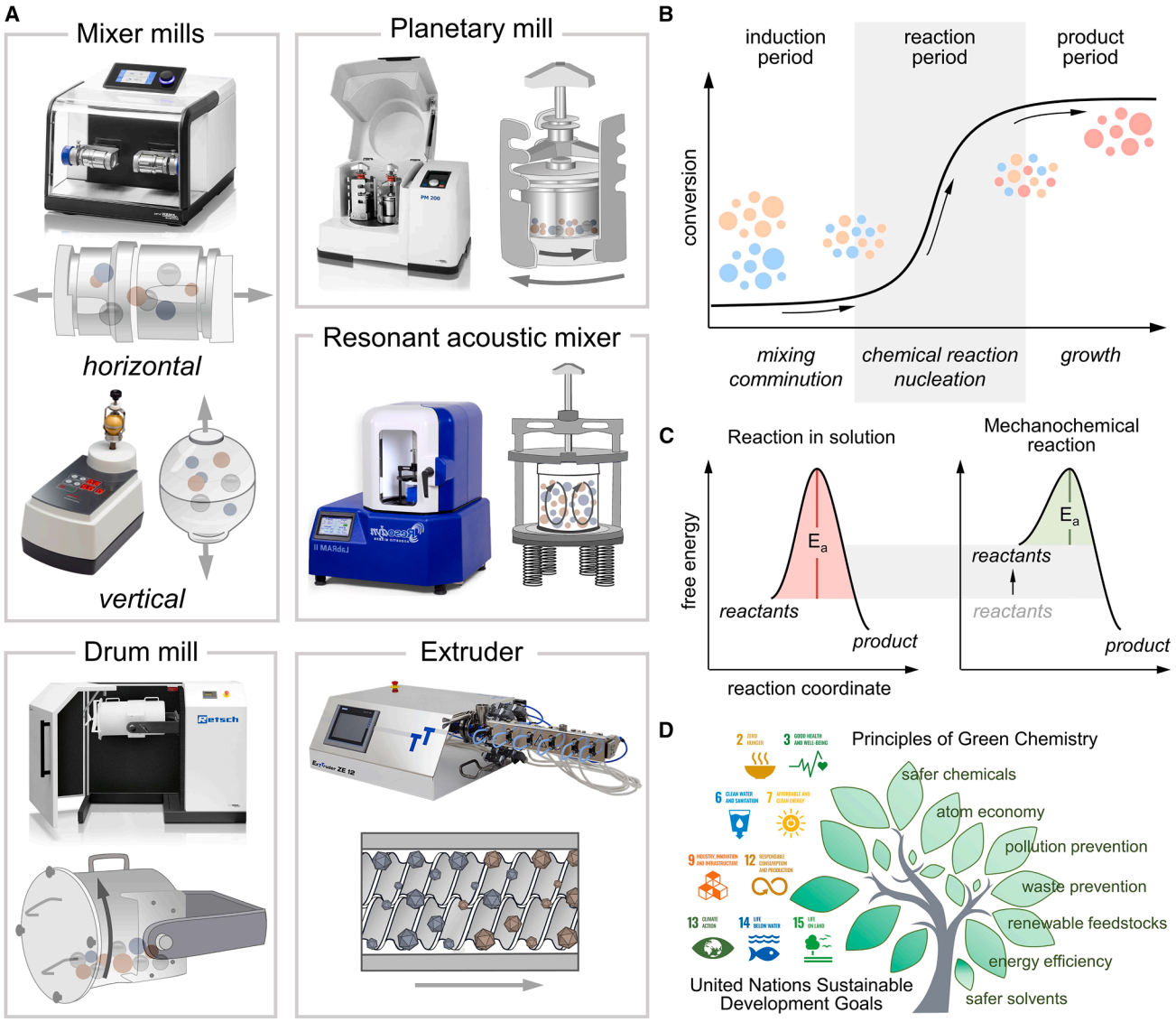

Figure 2. The equipment, working principles, and benefits of mechanochemistry

(A) Typical instruments used for performing mechanochemical reactions. Images are used with permission from Fritsch (vertical mixer mill), Retsch (horizontal, planetary, and drum mills), Resodyn (resonant acoustic mixer), and Three-Tec (extruder).

(B) Progress of mechanochemical reactions.

(C) Concept for the reduction of activation barriers by mechanochemical action.

(D) Sustainability aspects and benefits of mechanochemistry.

mechanochemistry with other energy sources via thermo-, photo-, electro-, and sono-mechanochemical approaches provides added value and opens new chemical reaction spaces. After that, we highlight selected emerging case studies in mechanochemical research, including origin-of-life research, the role of supramolecular structures as intermediates in organic synthetic reactions, and the applications of direct mechanocatalysis. We subsequently discuss how mechanochemistry is being upscaled, a key step in enabling the sustainable transformation of industrial chemistry. Finally, we offer a perspective of mechanochemistry by drawing links to developments in digitalization, artificial intelligence (AI), and robotics.

TRIS METHODS IN MECHANOCHEMICAL RESEARCH

The increasing use of mechanochemistry confronted the mechanochemical community with its biggest limitation, namely, the poor mechanistic understanding of the chemical transformations that occur during milling. The large gap in mechanistic understanding hindered the development of this methodology because these reactions can unpredictably occur outside the kinetic and thermodynamic rules of conventional solution chemistry.

The first attempts to obtain mechanistic insights relied on stepwise *ex situ* analysis,[41] which can provide reliable

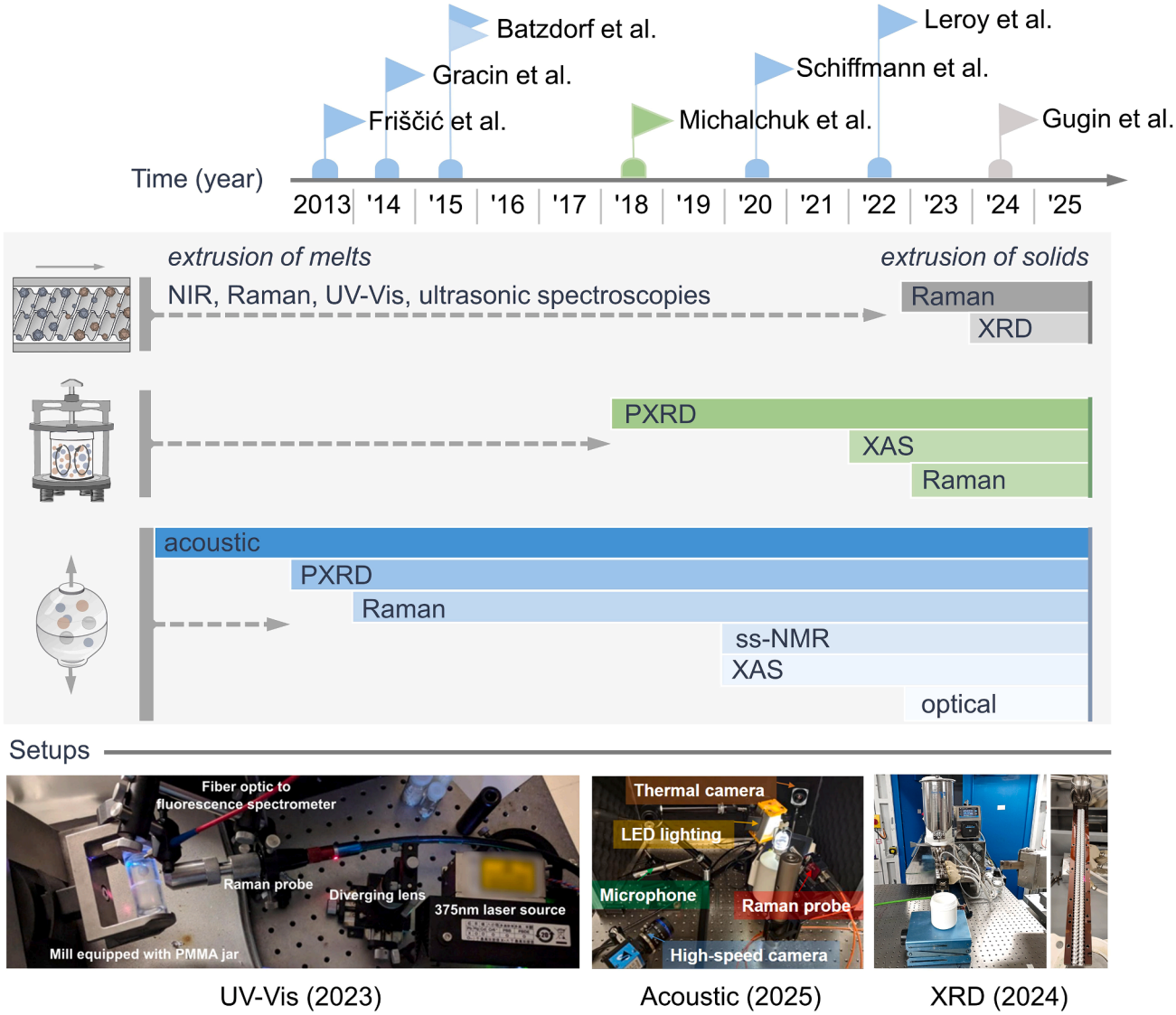

Figure 3. Timeline prospect of TRIS monitoring through direct methods across the three main mechanochemical methodologies
Adapted with permission from Julien et al. (UV-vis),[46] copyright 2023 Royal Society of Chemistry; Parlier et al. (acoustic),[47] copyright 2025 American Chemical Society; and Gugin et al. (X-ray diffraction),[48] copyright 2024 Elsevier.

information only in the presence of robust intermediates or non-self-sustaining reactions. Interrupting and resuming a mechanochemical reaction can provide misleading results because the products formed can differ from those obtained through continuous milling, and air exposure or solvent evaporation can alter the reaction kinetics. As a result, the pursuit of monitoring mechanochemical reactions without disrupting the milling processes led to the development of TRIS methods (Figure 3).[42–45]

Early *in situ* approaches relied on indirect methods of monitoring variations in temperature and pressure along with the progress of the mechanochemical hydrogenation reactions.[49] Given the rising interest in reactions occurring at solid-liquid-gas and gas-gas interfaces, which might achieve notable enhancements in reactivity and selectivity,[50] these methods have recently been further developed and adapted for investigating various systems and experimental setups.[51–53]

Meanwhile, other methods for directly monitoring mechanochemical reactions have been developed.[54] However, it was not until the work of Friščić et al. that synchrotron powder X-ray diffraction (PXRD) was first used for TRIS studies of ball-milling mechanosyntheses,[55] marking a significant milestone in the field. By taking the mechanosyntheses of zeolitic imidazolate frameworks (ZIFs) as benchmark systems, Friščić et al. highlighted the benefits of *in situ* methods, which allow real-time monitoring of the reaction path at the crystalline level, as well as the reaction kinetics. This publication was subsequently followed by others that sought to enhance and expand upon the findings by providing instructions for improved strategies for

data collection and treatment.[56–58] To complement synchrotron-based X-ray diffraction techniques, de Oliveira et al. recently demonstrated that milling transformations can also be tracked by X-ray absorption spectroscopy (XAS).[59] Through X-ray fluorescence, they measured X-ray absorption near-edge spectra at the Au-L_{III} edge during the bottom-up mechanochemical synthesis of Au nanoparticles. This approach enabled them to monitor the mechanochemical redox reaction at the local atomic level before crystalline phases became detectable by TRIS PXRD.

Along with the fact that PXRD is not a suitable method for characterizing reaction mechanisms at a molecular level or amorphous phases that can occur during milling, the limited access to a synchrotron radiation source is challenging. Therefore, the introduction of *in situ* laboratory techniques based on Raman spectroscopy represented a pivotal step.[60] By studying the mechanochemical syntheses of coordination polymers and organic cocrystals, Lukin et al. demonstrated their method's ability to monitor mechanochemical transformations at the molecular level.[61] Quite recently, a new customized Raman system yielded 30% higher spectral resolution and 5-fold faster time resolution than previous fiber-probe Raman systems.[62] Moreover, Borchers et al. recently showed the potential of low-frequency Raman spectroscopy to reveal even crystalline intermediates and polymorphs and thus facilitate the detection of crystalline transformations through spectroscopic methods.[63]

A key advancement in the TRIS monitoring of ball-milling mechanosyntheses was the combination of PXRD and Raman spectroscopy, exemplified by the investigation of four archetypical model compounds ranging from 3D frameworks through layered structures to organic molecular compounds.[64] The results demonstrated the distinct advantage of combining TRIS PXRD and Raman spectroscopy because it enabled a comprehensive analysis of milling processes at both the molecular and crystalline levels and thereby delivered reliable data for mechanistic studies. Moreover, by introducing thermography to complement the experimental setup, Emmerling and co-workers investigated the correlation of structural evolution with temperature data,[65,66] which is essential for understanding reaction thermodynamics and kinetics. Trends in temperature development during milling were indeed identified and related to events such as crystallization and water release.

In the context of tandem methods, a recent publication showed TRIS monitoring of ball-milling transformations through a combination of fluorescence emission and Raman spectroscopy.[46] This proof-of-principle work presented an accessible dual-spectroscopy technique capable of observing mechanochemically induced changes to the polymorph transformation and cocrystallization of indomethacin. The use of UV-visible (UV-vis) methods was also highlighted in TRIS mechanochemical measurements for UV-vis reflectance and photoluminescence measurements with millisecond time resolution for optical TRIS mechanochemical studies on metal halide perovskite systems.[67]

A further step in the development of methods for TRIS monitoring relies on the use of solid-state nuclear magnetic resonance (NMR), which has been significantly developed and optimized in recent years. The first attempt to study mechanochemical reactions by incorporating a ball mill into an NMR probe investigated the formation of zinc phenylphosphonate from zinc acetate and phenylphosphonic acid.[68] A subsequent study showed how magic-angle spinning solid-state NMR *in situ* analyses can also reveal the formation of unexpected intermediates occurring in solid-solid organic reactions.[69] Finally, by tracking the formation of the metal-organic framework (MOF) materials Zn-MOF-74 and ZIF-8, a recent work introduced a novel approach for monitoring mechanochemical transformations by using the T1-T2 relaxation correlation plots derived from magnetic resonance methods.[70] Moreover, building upon the concept of *in situ* analyses, generally confined to the environment where the chemical transformations take place, an NMR-based *ex situ* and *in operando* monitoring system was developed to monitor mechanochemically accelerated sublimations under a constant flow of carrier gas.[71]

Ultimately, a recently presented novel approach is a TRIS technique based on the analysis of sound variations during milling. Although the acoustic approach has already been used for the characterization of mills[72] and the reactions occurring inside,[73] it was demonstrated that changes in sound are directly linked to the (physico)chemical transformations occurring in the reactor.[74] The investigation was then successfully extended to polymorphic transitions that display similar Raman spectra between the reagents, intermediates, and products or a low crystallinity.[47]

The findings obtained through TRIS monitoring have demonstrated the complexity of the ball-milling reactions, revealing the significant influence that experimental parameters, such as liquid additives[75,76] and milling frequency,[77] have on the reaction pathway. These insights underscore the delicate interplay between reaction conditions and mechanochemical outcomes, emphasizing the need for precise control and optimization to achieve reproducible results. The continuous advancements in elucidating the underlying mechanisms have paved the way for the scale-up of mechanochemical processes, bridging the gap between laboratory-scale experiments and industrial applications.

The first example of *in situ* monitoring of reactions performed in a scaled-up reactor was reported by Michalchuk et al.[78] TRIS monitoring via PXRD was used to investigate a cocrystallization reaction performed via resonant acoustic mixing (RAM), a technology designed for intensive mixing of powders with minimal damage to particles. For the first time, the rate of RAM-induced mechanochemical cocrystallization has been tracked, showing that higher acceleration enhances reaction rates by improving mixing and increasing reactive interfaces. Notably, these reactions occur without milling bodies, demonstrating that such tools are not always necessary if thorough mixing and reactive interface formation are achieved, highlighting the versatility and appeal of mechanochemistry. Further studies showed how both TRIS XAS[79] and Raman[80,81] were successfully used to get unprecedented details of mechanochemical syntheses performed via RAM, thus proving that the use of TRIS methods is no longer a prerogative of ball-milling reactions.

Very recently, new findings concerning the TRIS monitoring of reactions performed via extrusion were presented. A work from Gugin et al. showed the possibility of monitoring extruded

reactions by *in situ* X-ray diffraction.[48] Although the effectiveness of *in situ* Raman spectroscopy in providing molecular-level information has been demonstrated, first in the extrusion of melts[82,83] and recently also of solids,[84] this study used energy-dispersive X-ray diffraction to monitor reactive extrusion in real time at the crystalline level through the investigation of four benchmark systems. The results provided previously unavailable control over the reactive extrusion process, promoting its perception as an industrially feasible green alternative to traditional solvent-based syntheses.

COMPUTATIONAL MODELING IN MECHANOCHEMICAL RESEARCH

We can learn a lot about mechanochemical processes by using TRIS methods (see section above). However, these experimental techniques are limited by their spatial and temporal resolution and must be supplemented to achieve a more detailed view of the physical and chemical processes that occur under mechanochemical conditions. One way to achieve this is through detailed experiments of model reactions under well-controlled force conditions, for example, using an atomic force microscope,[85–87] high-pressure cells,[88] or other related tribological devices.[89] An emerging approach is to supplement mechanochemical study with computational modeling, the type of which will depend on the scale of the processes that one aims to study.

At the largest scale are methods that aim to develop mathematic descriptions for microkinetic processes, such as mixing,[90,91] often with the aim of analytically describing the overall macrokinetics of a mechanochemical reaction and fitting reaction kinetic profiles for data obtained through high-quality TRIS experiments.[77,92–94] Importantly, these microkinetic models are only as good as (1) the TRIS data being fed in and (2) the robustness and validity of the models being used. Unsurprisingly, just as experimentalists are continually developing TRIS technologies, the models upon which analytical equations are developed are also an area of active research.

An exceptionally promising microkinetic model being used broadly to model TRIS data is that pioneered by Delogu et al.[95] In their microkinetic models, the team accounts for the multitude of unique physical phenomena that contribute to the reaction rates of mechanochemical transformations, including macroscopic mixing, particle surface (re)generation, the probability and frequency of milling media striking unreacted powder, and a qualitative factor describing the probability of a discrete mechanical loading event having enough energy to initiate a reaction in the affected volume, the critical loading threshold.[96,97] Using this model to fit TRIS Raman spectroscopy data obtained for the mechanochemically induced hydrogen isotope exchange between solid benzoic acid and liquid heavy water,[93] the team was able to propose reaction rates as being limited by the energy of the volume of material included in the impact zone and the impact energy. This has been a recurring theme extracted from microkinetic models, which consistently indicate linear scaling of reaction rates with impact energy, suggesting that other factors such as macroscopic mixing are rarely the rate-limiting step in ball-milling setups.[77] In another study based on TRIS PXRD data for the cocrystallization of ibuprofen and nicotinamide,[94] macroscopic kinetic models were used to determine the amount of material that exists within a given impact volume. When coupled with thermal analysis, this critical insight led to convincing evidence of surface melting at impacted interfaces as being responsible for the onset of mechanochemical cocrystallization. Similar microkinetic models have also been explored (again for the interpretation of TRIS PXRD data) for studying the metathesis of NaI + KCl and suggest that local pressures at the impact zones are essential for driving the reaction forward.[98] A similar proposition was earlier suggested for other inorganic mechanochemical transformations.[99] As a recent approach to bridging microkinetic models with quantum chemical insight, there have been attempts to study mechanochemical reaction kinetics from a more traditional perspective by using *ab initio* modeling to probe the potential energy surface for the reactivity of isolated molecules and approximating the effects of the solid-state environment through dielectric screening corrections.[100] These simulated gas-phase energy surfaces provide effective energy barriers and rate constants that can be used within analytical models of mechanochemical kinetics. Such approaches have so far been found to offer promising comparisons to experimental reaction profiles.

It quickly becomes clear from the above discussion on microkinetic modeling that much can be learned about the physical processes that account for the overall kinetics of a mechanochemical reaction. However, existing TRIS and microkinetic models hit a roadblock once deeper details become of interest, namely the elementary chemical processes that underpin the reaction once the macroscopic parameters are met (e.g., the critical loading threshold). It is here that atomistic models have proved particularly promising. At the larger scale of atomistic modeling efforts, molecular dynamics simulations have been used for investigating what happens when two particles collide under conditions approximating those in a ball mill. Focusing on the collision of rough surfaces of crystalline Ni, Delogu used classical molecular dynamics simulations to explore how particle collisions influence the dynamics of particle surfaces and facilitate the exchange of material across the particle-particle boundary.[101] His studies found that the collision of interfaces leads to the formation of a non-crystalline interfacial layer that allowed the exchange of material between the parent surfaces. Similar, more recent studies extended the use of classical molecular dynamics simulation to study collisions between particles of organic crystals by using the mechanochemical cocrystallization of meloxicam and aspirin as a model system.[102] Again, the results of these simulations indicated the formation of a mobile non-crystalline intermediate at the interfacial boundary after collision, which facilitated the exchange of bulky organic molecules between the particles, consistent with findings of surface melting coming from microkinetic models.[94] More detailed studies also suggest that the orientation of particle impacts could be important for determining the efficacy of material transfer, akin to a "collision geometry" parameter from classical kinetics.[103] Though still limited, these emerging studies do provide a mechanistic view of the important role of mechanical energy in generating mobile, "fluid" interfacial regions upon impact, which allows for the intimate mixing needed to facilitate chemistry.

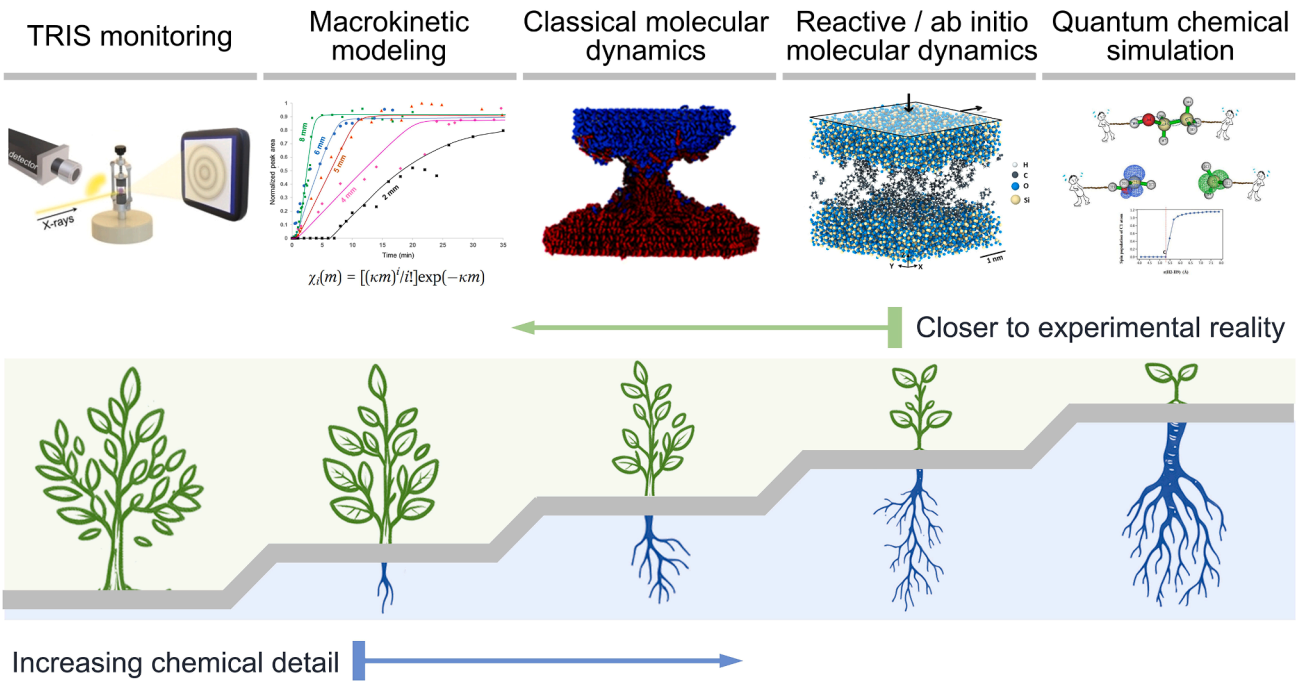

Figure 4. Hierarchy of scale for the use of computational modeling in the study of mechanochemical reactions

Models closer to experimental reality are necessarily more phenomenological and omit information of atomic and electronic structure. As models move further from experimental conditions, they become chemically more accurate and include details of atomic and molecular structure and insight into the electronic origins of chemical reactivity. Adapted with permission from de Oliveira et al. (TRIS monitoring),[59] copyright 2020 Royal Society of Chemistry; Martins et al. (macrokinetic modeling),[92] copyright 2021 American Chemical Society; Ferguson et al. (classical molecular dynamics),[102] copyright 2019 Royal Society of Chemistry; Bhuiyan et al. (reactive and *ab initio* molecular dynamics),[104] copyright 2024 Springer Nature; and Wang and Wang (quantum chemical simulation),[108] copyright 2024 American Chemical Society.

Models at this scale provide extremely useful information about macroscopic aspects of mass transfer while also providing insight into the conditions felt by material at surfaces after a particle-particle collision. They do not, however, offer information at the chemical level about how and why a given reaction takes place. This has been the aim of simulation using reactive force fields or *ab initio* molecular dynamics (AIMD) simulations of sliding interfaces.[104,105] Note that reactive force fields allow for chemical bonds to be broken or formed at the same cost of a classical molecular dynamics simulation. An excellent example of using reactive force fields to study mechanochemical reactions with molecular dynamics was reported by Martini and colleagues, who explored the effects of interfacial shear on the oligomerization of cyclohexene.[104] In their study, a "bath" of 50 cyclohexene molecules was placed between two large, roughly surfaced silica slabs. The slabs were slid atop each other (300 K at a 4 GPa normal stress), and the formation of oligomeric cyclohexene was found to occur competitively with the oxidation of cyclohexene through chemisorption to the silica surfaces. Similarly, a molecular dynamics study using a quantum-based force evaluator (density functional tight binding [DFTB]) prepared an *in silico* rotational diamond anvil cell to explore the effects of compression and shear on the oligomerization of the amino acid glycine.[106] Exciting reactivity was observed in these simulations, in which a range of oligomeric and cyclic molecules were prepared, demonstrating the potential of mechanochemistry for biologically related chemistry with implications for origin-of-life research (see section "mechanochemistry in origin-of-life studies").

Although parameterized methods do provide useful insight into chemical aspects of mechanochemical reactivity, they are limited to the accuracy of the parameterized model and cannot accurately inform on the electronic processes that underpin the transformation. In these respects, the much more expensive method, AIMD, has been explored. Akin to classical molecular dynamics, discussed above, AIMD calculates the electronic structure and atomic forces from a quantum mechanical foundation (e.g., by using density functional theory [DFT]), which in principle allows any chemical system to be studied in full electronic detail. The extra cost associated with AIMD calculations has greatly limited its use in mechanochemistry research of extended solids (typically restricted to studying tribological activation on solid surfaces[107]). Within our "hierarchy" of reactivity (Figure 4), AIMD simulations of isolated molecules are regularly explored to provide the link between the scale of particles and the elementary processes that underpin the *chemistry* itself.

It has been this elementary detail where *ab initio* quantum chemical simulations have been essential. Studies of slow (or static) mechanical strains commonly use methods based on the selective application of mechanical force to molecular bonds, namely the external force explicitly included (EFEI) method[109] or the constrained geometries simulate external force

(CoGEF) method.[110] Both are equivalent in principle (related through a Legendre transform),[111] but broadly, the former explicitly includes a force vector within the geometry optimization and the evaluation of the energy, whereas the latter fixes a molecule in a constrained geometry before conducting the optimization and energy evaluation. These computational methods have aided the exploration of force-modified reaction pathways,[112,113] revealing novel reaction mechanisms,[114,115] mechanically altered reaction kinetics,[87] and even access to novel chemical reactivity.[116] Moreover, these methods have become essential for the study of mechanophores, where the optical response of mechanically strained molecules can be directly probed *in silico*. EFEI has become particularly popular as a tool for exploring the force-modified potential reactivity of small molecules, including understanding the transduction of energy through mechanically stressed molecules,[117,118] probing the nature of mechanical transition states,[119] and probing or even designing the behavior of mechanophores.[120] CoGEF, though also applied to small-molecule force-induced reactivity (e.g., the mechanical dissociation of furan-maleimide adducts[115]), has found particular application in polymer mechanochemistry for the study of bond-breaking dynamics under mechanical strain.[121,122]

More recent methods have applied a hydrostatic "pressure" to isolated molecules, allowing for the consideration of whole-molecule distortion in response to external strains.[123] This approach has proved to be extremely useful for isolating how small supramolecular complexes respond to various mechanical forces[124] or probing how molecular geometry (e.g., when isolated in solution rather than in an extended solid) responds to extremes of pressure.[125] These concepts are akin to more common approaches to applying bulk mechanical strain to crystal geometries within quantum chemical simulations[126–128] to simulate how slow compression or tension affects molecular geometry and the associated electronic structure (and chemical reactivity).

In the more specific case of the high strain-rate initiation of reactions in crystalline systems, models based on kinetic energy transfer via vibrational coherence (phonon scattering) are emerging.[129–132] In these models, a high-velocity mechanical impact is modeled as an injection of energy into the acoustic modes of a crystalline reagent.[133] Through processes of anharmonic phonon scattering, this energy redistributes from the acoustic modes, through intermediate vibration modes, and into localized molecular vibrations. Once sufficient energy reaches molecular vibrations, distortion of the molecular geometry causes the onset of a chemical reaction, akin to an inverse Jahn-Teller effect.[134] To date, this model has been developed to describe successfully the mechanochemical initiation of explosive materials.[131,135]

Beyond studying the mechanism of mechanochemical reactivity across scales of length, simulation has found important use to rationalize the products that are obtained from experiment. Most frequently, this takes the form of calculating the relative stability of the molecular or crystalline products that are obtainable from the given reaction.[136–138] However, these concepts of product stability have also been extended to include unique aspects of the solid state, wherein phase stability not only is a bulk property of the crystal but also must include additional terms relating to crystal surface energy and its size dependence.[139] This is particularly important for mechanochemical reactions because the crystal sizes obtained by ball milling are often on the order of tens of nanometers,[58,140,141] and surface-energy contributions play a major role in the overall stability of the product phase. The inclusion of size-dependent surface energy, as well as their modification with solvents, into quantum chemical models for polymorph stability has been essential for rationalizing the unique polymorphic outcomes obtained under ball-milling conditions for model organic crystals[141,142] and has even been shown to determine the re-emergence of the famously "disappearing" Ritonavir polymorph enabled by mechanochemical methods.[143]

COUPLING MECHANICAL ENERGY WITH OTHER ENERGY SOURCES

Integrating external energy sources, such as heat, light, ultrasound, and electricity, into mechanochemical processes has led to significant advancements in chemical reactivity (see Figure 5). These synergies have not only addressed the limitations of traditional mechanochemistry, but they have also unlocked new possibilities for chemical transformations. Furthermore, this integration has enhanced our understanding of fundamental variables that affect reactivity in mechanochemical processes. The following sections highlight foundational works in these fields and focus on the most recent developments published after the review by Martinez et al.[144]

When discussing the integration of mechanochemistry with other energy sources, thermo-mechanochemistry stands out as the oldest and the most extensively researched subfield. The first documented example of combining thermal and mechanical energy in organic synthesis occurred at the end of the 20th century when Kaupp et al. used a cooling fluid circulating around a milling jar to investigate gas-solid and solid-solid reactions of iminium salts.[146] Given the sensitivity of iminium salts to hydrolysis, their traditional preparation and chemical conversion necessitate the use of dry solvents, followed by purification by chromatography or crystallization. Cryo-milling, however, eliminates moisture and liquid phases, creates fresh reactive surfaces, and results in crystalline products with quantitative yields. In addition to sub-ambient milling, milling under high-temperature conditions is crucial for triggering reactions with high activation energies, as well as obtaining selectivity and satisfactory conversions. The first demonstration of milling at elevated temperatures occurred in 1993 when Fu and Johnson studied the structural characteristics of supersaturated solid solutions prepared by mechanical alloying.[147] The authors used the SuperMISUNI NEV-MA8 milling device, which used an adjacent heating element and temperature controller to reach temperatures of up to 300°C. This study revealed the significant importance of temperature in mechanical alloying, leading to distinct microstructural characteristics, closer equilibrium state positions, and enhanced thermal stability in samples milled at elevated temperatures. Furthermore, a setup developed by Cindro et al. demonstrated the significance of rapid, stable, and precise temperature control in mechanochemical organic reactions,

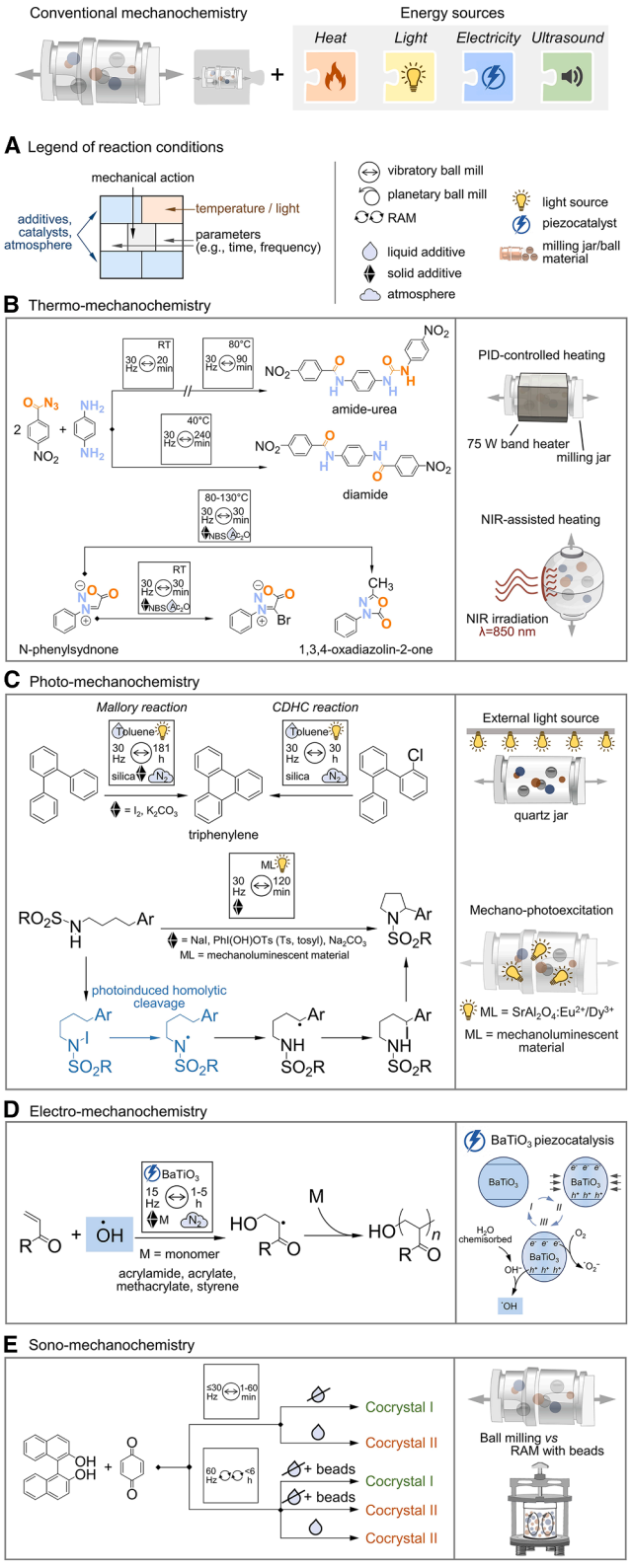

Figure 5. Coupling mechanical energy with other energy sources

(A) Mechanochemical reaction conditions described in Michalchuk et al.[28] We acknowledge other symbols for representing ball-milling reactions, such as the three-ball triangle introduced by Rightmire and Hanusa.[145]

(B–E) Examples of merging mechanochemistry with other external energy sources.

where the bulk milling temperature has a strong impact on chemical reactivity.[148] Compared with conventional milling, the thermally controlled milling reactor has been demonstrated to significantly accelerate and simplify the mechanochemical formation of C–C, C=N, and C–N bonds, as well as, in some cases, alter reaction mechanisms. In 2022, Linberg et al. reported the first TRIS measurements of polymorphic transitions at elevated temperature conditions, demonstrating the effectiveness of thermo-mechanochemistry in facilitating polymorphic transitions at bulk temperatures lower than those required with heating alone.[149] Furthermore, Alić et al. presented a setup for the direct measurement of onset and completion temperatures of polymorphic transitions under programmable heating rates, akin to controlled heating in a differential scanning calorimetry (DSC).[150] Thermo-mechanochemical polymorphic transition temperature in 1-adamantyl-1-diamantyl ether was determined to be 31°C lower than the transition temperature determined by DSC.

In the past few years, new setups have been developed for simultaneous heating and milling, including the use of a simple heat gun,[151] induction-assisted heating,[152] heating using near-infrared (NIR) irradiation,[153] or combined pressurizing and heating using lithium-ion battery packs.[154] Induction heating uses electromagnetic fields to generate heat within a conductive material, offering a rapid heating rate (80°C in 15 min) and the possibility of heating the reaction medium internally by using beads made of conductive material.[152] By contrast, previously reported milling systems only allowed heating of the external walls of the milling vessel. In addition, the contactless heating mode is adaptable to standard milling equipment and enables temperature-controlled *in situ* studies. However, the requirement of conductive materials, such as stainless steel, limits the application of the induction heating system and can infiltrate metal particles into the reaction media. This was circumvented by developing an epoxy resin milling jar doped with a NIR-absorbing dye, which, upon irradiation at 850 nm, releases energy as heat (Figure 5A).[153] The authors tested their approach in Diels-Alder reactions, where heat is needed to compensate energy for overcoming activation barriers, and in the rearrangement of a sydnone into the corresponding 1,3,4-oxadiazolin-2-one.

The pioneering work on combining light and mechanical energy[155] was presented in 1987 when Toda et al. observed the formation of host-guest complexes in a stereoselective manner upon mixing and irradiating several diols with carbonyl compounds in the solid state.[156] The reactions were performed with a test-tube shaker and a visible-light-emitting high-pressure mercury lamp. Twenty-five years later, Stojaković et al. developed an automated method for simultaneous UV irradiation and agitation on the basis of a vortex mixer and UV lamp.[157] Their setup enabled [2 + 2] photodimerization of *trans*-1,2-bis-(4-pyridyl)-ethylene to *rctt*-tetrakis-1,2,3,4-(4-pyridyl)cyclobutene by

using 4,6-dichlororesorcinol as a catalyst in a manner that was four times faster than the same reaction carried out through grinding the reactants in mortar and pestle and subsequent exposure to UV light.[158] After these, various modifications of milling equipment, including the use of a rotating glass rod placed inside a test tube[159] or the adoption of commercially available ball mills and the use of Duran glass jars[160] or poly(methyl methacrylate) (PMMA) milling jars,[161] allowed simultaneous execution of different mechano-photocatalytic reactions. The reported examples show equipment development for simultaneous photo-mechanochemical reactions but also emphasize certain drawbacks and difficulties limiting their performance. Some limitations include low mechanical impact, sluggish reaction kinetics, poor resistance to mechanical shocks, impermeability to UV light, and limited chemical resistance of the milling vessel to organic solvents. However, further progress in the field was achieved in the last 2 years. First, in 2023, Baier et al. employed Mallory and cyclodehydrochlorination (CDHC) reactions to synthesize various polycyclic aromatic compounds by using a custom-built UV-emitting photochemical reactor coupled with a vibrational ball mill (Figure 5B).[162] The newly designed milling vessel consisted of a quartz glass tube with caps made of perfluoroalkoxy alkane and two polytetrafluoroethylene (PTFE) balls, ensuring UV transparency and equipment protection against breakage. With the newly developed approach, they demonstrated a regioselective synthesis of nanographenes, whose production, when performed via traditional Scholl reaction, was unsuccessful or led to a mixture of randomly linked oligomers. After this, Spula et al. proposed the first C–X functionalization of aryl halides to C–B, C–P, and C–S bonds in the absence of metal or organic catalysts by using the same photo-mechanochemical setup.[163] By using a low-pressure Hg fluorescence lamp, they achieved six times higher light efficiency and significantly enhanced reaction kinetics. Afterward, Millward and Zysman-Colman demonstrated the general applicability of the photo-mechanochemical approach on four archetypal photocatalytic reactions traditionally performed in the solution state.[164] Their work highlights valuable advantages of merging photonic and mechanical energies and, among the most important, eliminating or minimizing toxic solvent use, typically used in large volumes in liquid-state conditions. The latest findings by Cvrtila et al. represent the next step in advancing photo-mechanochemistry by demonstrating simultaneous light irradiation and ball milling combined with TRIS Raman monitoring.[165] The authors employed the E/Z isomerization of azobenzenes and the photolysis of adamantane diazirine as model reactions to explore new possibilities for understanding the mechanisms behind photo-mechanochemical transformations in the solid state. By applying alternating UV and blue light irradiation, the researchers showed that multiple reversible photo-switching cycles of 4-methoxyazobenzene can be achieved during ball milling. Additionally, their findings indicate that photo-mechanochemistry offers product selectivity distinct from that observed in traditional photochemical reactions conducted in solution. Importantly, it also prevents the formation of unwanted byproducts that typically arise from interactions between photoreactive species and solvents. Other advantages of applying photo-mechanochemistry include improving reaction rates, overcoming solubility issues, and avoiding the need for an oxygen-free environment. Finally, Xin et al. introduced a new avenue of research that implements *in situ* generation of photons through mechanical force application to mechanoluminescent (ML) materials (Figure 5B).[166] In their innovative mechano-photoexcitation strategy, the authors used $SrAl_2O_4:Eu^{2+}/Dy^{3+}$, a commercially available ML material, to perform a Hofmann-Löffler-Freytag reaction to create N-heterocycles and sulfonylation reactions without the need for external light sources or a transparent milling vessel.

In the field of electro-mechanochemistry, examples in which an external electric source is used for initiating chemical reactions are scarce and led by the groundbreaking paper in 2002 by Calka and Wexler.[167] The authors developed an electrical-discharge-assisted mechanical milling (EDAMM) method by using magneto and vibrational ball mills with an external high-voltage generator that enables electrical discharges during milling. Merging those two fields was demonstrated to play an essential role in accelerating mechanical alloying processes and enabled new reaction pathways that could not be achieved by simple mechanical milling. On a similar note, Wang et al. developed an electromagnetic milling one-step Barbier reaction for carboxylic acid synthesis by utilizing gaseous CO_2 at ambient pressure with ferromagnetic rods as grinding media.[168] The protocol showed strong substrate tolerance by converting aryl bromides with electron-donating groups (e.g., methoxy and methyl) to acids in 55%–92% yields, whereas those with halogens or electron-withdrawing groups yielded 46%–77%, and alkyl bromides achieved 77%–90%. Mechanistic experiments suggest that the reaction involves the direct carboxylation of a transient organomagnesium species and that electromagnetic milling enhances efficiency by crushing Mg to increase surface area and, compared with planetary ball milling, minimizes homo-coupling. The approach extends to ^{13}C-labeling, producing ^{13}C-labeled carboxylic acids in 48%–68% yields from various bromides.

Very recently, Mokhtar et al. introduced a novel two-electrode mechano-electrochemical cell (MEC) connected to an external power source.[169] The authors optimized electrode material, interelectrode gap, solvent volume, and milling frequency to facilitate electrochemically driven reactions under slurry or minimal-solvent conditions. For example, electrochemical reduction of aromatic bromides achieved up to 64% conversion for 4-bromobenzophenone at optimized low milling frequencies (1–4 Hz), and the oxidative coupling of thiols and amines for sulfonamide synthesis with yields up to 76% under acidic conditions. Mixing facilitated by low milling frequencies (1–4 Hz) played a crucial role in enhancing mass transport, diffusion of electroactive species to the electrodes, and maintaining consistent electrode-electrolyte contact, whereas higher frequencies (9–23 Hz) and ball impacts reduced efficiency as a result of excessive agitation and splashing, which hindered contact and reaction progress. Vibrational motion of the mill alone sufficed for mixing, and the primary energy source remained electrical rather than mechanical, hence defining the process as mechanochemically assisted. Overall, the method improved sustainability by achieving a process mass intensity (PMI) of 17 g/g (a 64%–75% solvent reduction over prior electrochemical

approaches), high atom economy (100%), and reaction mass efficiency (46%), highlighting its potential for eco-friendly organic transformations.

Moreover, Zhu et al. developed a dielectric barrier-discharge plasma (DBDP) milling method that generated plasma by applying an alternating current to the mill vials, which functioned as electrodes. The synergic effects of ball milling, high-energy plasma, and electron bombardment led to particle deformation, fracture, heating, and stress, resulting in powders with unique morphologies.[170] More recently, Marrero et al. introduced a new experimental configuration featuring a milling vial connected to an external piezoelectric module made of polyvinylidene fluoride (PVDF).[171] In this design, a reaction mixture, separated from the piezoelectric material by a set of mechanically and electrically connected electronic elements, was placed in the milling vial. The authors used the reduction of methylene blue to leucomethylene blue as a reversible redox system to study the currents generated by the piezoelectric effect. Up to this point, piezo-assisted redox reactions have focused on irreversible systems. This new configuration not only prevents contamination of the reaction mixture with toxic metals commonly found in piezoelectric materials, such as barium or lead, but also allows for the easy reuse of the piezoelectric material without requiring isolation or regeneration from the reaction media.

Although not directly part of electro-mechanochemistry, piezo-assisted mechanochemistry integrates mechanochemistry with electricity generated internally by using piezoelectric materials in chemical reduction and oxidation processes. In 2019, Kubota et al. reported the first example of redox activation of small organic molecules by grinding them with a piezoelectric material in a ball mill.[172] The authors demonstrated that electric potential generated upon agitation of $BaTiO_3$ can be used for arylation and borylation reactions of aryl diazonium salts. Soon afterward, the same authors tested the performance of other piezoelectric materials as well as the influence of liquid-assisted grinding (LAG) conditions on mechanoredox processes during the generation of trifluoromethyl radical, a species important for the incorporation of CF_3 group into new pharmaceuticals.[173] Several studies followed, including the implementation of $BaTiO_3$ or $PbTiO_3$ for activating copper-based catalysis during mechanochemical atom-transfer radical cyclization reactions,[174] regioselective chloro sulfoximidations of allenes,[175] or the synthesis of oxindoles and α-arylacylamides, where the regioselectivity can be tuned through the choice of piezoelectric material.[176] Furthermore, piezo-assisted mechanochemistry enabled controlled radical polymerization of (meth)acrylates through a reversible addition-fragmentation chain transfer (RAFT) process, typically conducted in solution and involving specialized reagents.[177] A parallel study highlighted the significant role of atmospheric molecules, such as water and oxygen, in generating hydroxyl and superoxide radicals upon interacting with mechano-polarized $BaTiO_3$ surface (Figure 5C). These highly reactive radical species can initiate solid-state free radical polymerization of various monomers, leading to inter-chain covalent crosslinking without additional crosslinker.[178] In all the above examples, a change in the electric polarization of the piezoelectric material is a response to mechanical stimuli during a ball-milling process. Interestingly, a recent study demonstrated the possibility of activating piezoelectric material without using milling media in a RAM process.[179]

The earliest instances of incorporating sound waves into mechanochemical processing appeared in 2004, when Mordyuk and Prokopenko introduced the first ultrasonic grinding mill to address challenges in the mechanical alloying of powders.[180] Traditionally, mechanical alloying of powders conducted in planetary ball milling often requires excessively long processing times and frequently results in powder contamination, structural irregularities, and phase inconsistencies. The new device comprised an ultrasonic generator, a magnetostrictive vibrator, and an ultrasonic horn immersed in a reaction container filled with powders and stainless-steel balls. The combination of ultrasonic vibrations and ball attrition greatly enhanced the specific surface energy and defect structure of the powders, enabling the production of pseudo-alloys from immiscible components. Compared with traditional milling processes in planetary ball mills, this led to a notably faster transformation from face-centered cubic to hexagonal close-packed phases in Fe_4N and the significantly accelerated formation of metastable solid solutions, such as Cu + Ni + Fe or Fe + C. Six years later, Chen and Xiao represented the solid-liquid medium ultrasonic ball mill and demonstrated the critical role of ultrasonic waves in the preparation of single-phase nanocrystalline ZnO through sono-mechanochemical reaction between Zn and H_2O.[181] Their efforts to produce a single phase of ZnO via pure ball milling resulted in a mixture of ZnO and $Zn(OH)_2$ or yielded only a single $Zn(OH)_2$ phase. On this basis, the authors proposed that the facilitated transformation of $Zn(OH)_2$ to ZnO in ultrasound-assisted ball milling results from decreased pH value of reaction medium through water sonolysis and generation of H_2O_2. According to the widely accepted hot-spot theory, the sonochemical effects arise when ultrasonic waves create cavitation microbubbles that, upon collapsing, generate localized hot spots of high pressures and temperatures, triggering chemical transformations.[182] Cavitation effects initiate the formation of OH· and H· radicals, which recombine to form H_2O_2 and H_2, acidify solution, and promote the formation of single-phase ZnO nanoparticles. In the following studies, ultrasound-assisted ball milling was mainly used for enhancing the synthesis and structural transformations of distinct inorganic materials[183,184] and investigating the effects of from such processing.[185] Despite the close interconnection of sonochemistry and mechanochemistry,[186] the reported literature findings undoubtedly demonstrate the superiority of combined sono-mechanochemical approach against the only mechanochemical approach in achieving new reactivity, faster reaction kinetics, and product selectivity. In a recent study, Zeitler et al. demonstrated the first example of metal-free mehanoredox polymerization by using a combination of ultrasonic waves or ball milling with piezoelectric materials.[187] The authors compared low-frequency ultrasonic irradiation and ball milling as methods for initiating electron transfer from piezoelectric materials to diaryliodonium salts, which served as radical reaction initiators for the polymerization of (meth)acrylate monomers. Both approaches turned out to be efficient in metal-free mechanoredox polymerizations, albeit the ball-milling approach showed superior reaction kinetics and more dependence on the reactivity

of the applied piezoelectric material. In parallel, RAM is a mechanochemical technique that employs low-frequency, high-intensity acoustic fields to mix powders. In recent years, RAM has emerged as a promising method for the large-scale synthesis of low-impact-resistant materials because it allows for the contactless transfer of mechanical energy. Additionally, incorporating small amounts of solvents is crucial for achieving large-scale synthesis of variable stoichiometry cocrystals and their polymorphs.[188] However, although the core principle of RAM is the contactless mixing of reagents, recent research indicates the potential benefits of combining RAM with ball milling.[189] In this study, the authors investigated the formation of racemic binaphthol-benzoquinone cocrystals I and II under both neat and liquid-assisted (LA) conditions by using ball milling, RAM, and RAM with the addition of ZrO_2 beads (Figure 5D). The results showed that LA-RAM produced cocrystal II, which was also observed under LA-ball-milling conditions. By contrast, RAM under neat conditions did not yield cocrystal I, a product obtained from the neat ball-milling reaction. Interestingly, the inclusion of milling balls in RAM led to the formation of cocrystal II, which transitioned to cocrystal I upon further mixing. These findings represent the first successful synthesis of cocrystal II of racemic binaphthol-benzoquinone under solventless mechanochemical conditions.

Recently, Kong et al. developed a photo-mechanochemical platform that combines visible-light photocatalysis and RAM to address limitations in traditional photocatalysis by facilitating solvent-minimized reactions in glass vials without milling media.[190] After optimization, nickel/photoredox-catalyzed C–X cross-couplings yielded quantitative results for model substrates, such as 4-bromobenzonitrile and aniline, in 30 min at 90 g acceleration under 90 W aqua blue light-emitting diodes (LEDs). The substrate scope encompasses diverse aryl and heteroaryl bromides and chlorides with electron-withdrawing and -donating groups and various N-, O-, P-, and S-nucleophiles, including pharmaceuticals, with yields of 50%–99% and adaptations for low-reactivity cases using narrower-wavelength LEDs. Scalability was demonstrated up to 300 mmol (1,500-fold increase) with minimal catalyst (0.01 mol %), achieving turnover numbers up to 9,800, and comparisons to solution-based approaches showed superior performance in yields (up to 100% vs. 12%–49%), shorter times (20–90 min vs. 48 h), and sustainability metrics. The platform's broad applicability was further confirmed by its successful extension to other photoinduced reactions, such as decarboxylative $C(sp^2)$–$C(sp^3)$ couplings (78% yield), Ullmann C–N couplings (73% yield), [2 + 2] dimerizations (99% yield), α-C–H phosphonylations (70% yield), and electron-donor-acceptor-mediated decarboxylative alkylations (92% yield), all under solvent-minimized conditions. Soon after, Spula et al. reported a photo-mechanochemical RAM platform for two model reactions.[191] For the C–P bond formation between iodobenzene and triethyl phosphite, optimization revealed that LAG with acetonitrile (η = 0.5 μL/mg) and solid NaCl additives (20 wt %) enhanced rheology and yielded up to 94% in 60 min under UVA irradiation, and RAM outperformed ball mills by providing better light penetration and scalability. A second model [2 + 2] cycloaddition of 2,3-dimethylmaleic anhydride achieved 82% yield under similar conditions, confirming the versatility of the approach. Two photoreactor designs were evaluated: a robust acrylic box with internal LEDs for small-scale reactions and a flexible LED strip for larger vessels, the latter of which allowed 10-fold upscaling to 2 mmol with maintained efficiency.

CASE STUDIES

Mechanochemistry in origin-of-life studies

How life appeared on Earth is one of the most fundamental questions in science. Because Earth's surface has been altered over time by geological processes, the origin of life "cannot be 'discovered', it has to be 're-invented.'"[192] The onset of studies in the chemistry leading to life began with the famous Miller-Urey experiment, which showed that organic building blocks could be formed from the mixture of simple gases, such as CH_4, NH_3, H_2O, and H_2.[193] Among the proposed sites for the origin of life on Earth, hot springs or land-based pools are a popular choice.[194] Although dry land on an early Earth might have been scarce, some land was most likely available near volcanoes and on the emerging continents. Dry land is considered to play an important role in prebiotic chemistry because of its ability to concentrate and transform organic building blocks. Besides electrical discharges, other primordial energy sources included UV irradiation, thermal energy, and mechanical energy.[195]

Mechanical forces might have been available on different energy scales and frequencies of occurrence. Although sporadic, extraterrestrial impactors (such as meteorites, asteroids, and comets) are known to have delivered extraterrestrial organic building blocks to Earth, especially during the late heavy bombardment ca. 4 billion years ago.[196] In impact-shock experiments of gas mixtures, Sagan et al. showed that they could produce organic molecules, such as α-amino acids.[197] McKay and Borucki demonstrated that nitrogen-containing molecules could be synthesized in a similar manner starting from gas mixtures.[198] Furthermore, Goldman and Tamblyn used quantum molecular dynamics simulations to show that impact shocks of simple ices produce organic molecules.[199] Moreover, Blank et al. obtained linear dipeptides and tripeptides after exposing aqueous mixtures of amino acids to hypervelocity impacts (up to 1.4 km s^{-1}, 25.8 GPa, at 77 K).[200] Collectively, these studies showed that impacts on the atmospheric entry of comets and meteorites might be beneficial for delivering and producing organic molecules.

Less energetic and more frequent mechanical forces included geomorphological processes, such as erosion and weathering. Importantly, these are known to transform matter even on extraterrestrial planetary surfaces, such as on Mars.[201] The first example of the role of mechanical impacts in the m/s range in origin-of-life studies was demonstrated by Bolm and Hernández for the activation of iron cyanide complexes (Figure 6A).[202] By milling potassium ferricyanide (III) with SiO_2, the authors observed an *in situ* production of HCN that was subsequently incorporated into the corresponding α-aminonitriles in a Strecker-type reaction. Further milling resulted in the hydrolysis of α-aminonitriles into amino amides, showing that mechanochemical activation can lead to amino acids, which are the key building blocks of proteins. This hypothesis was further

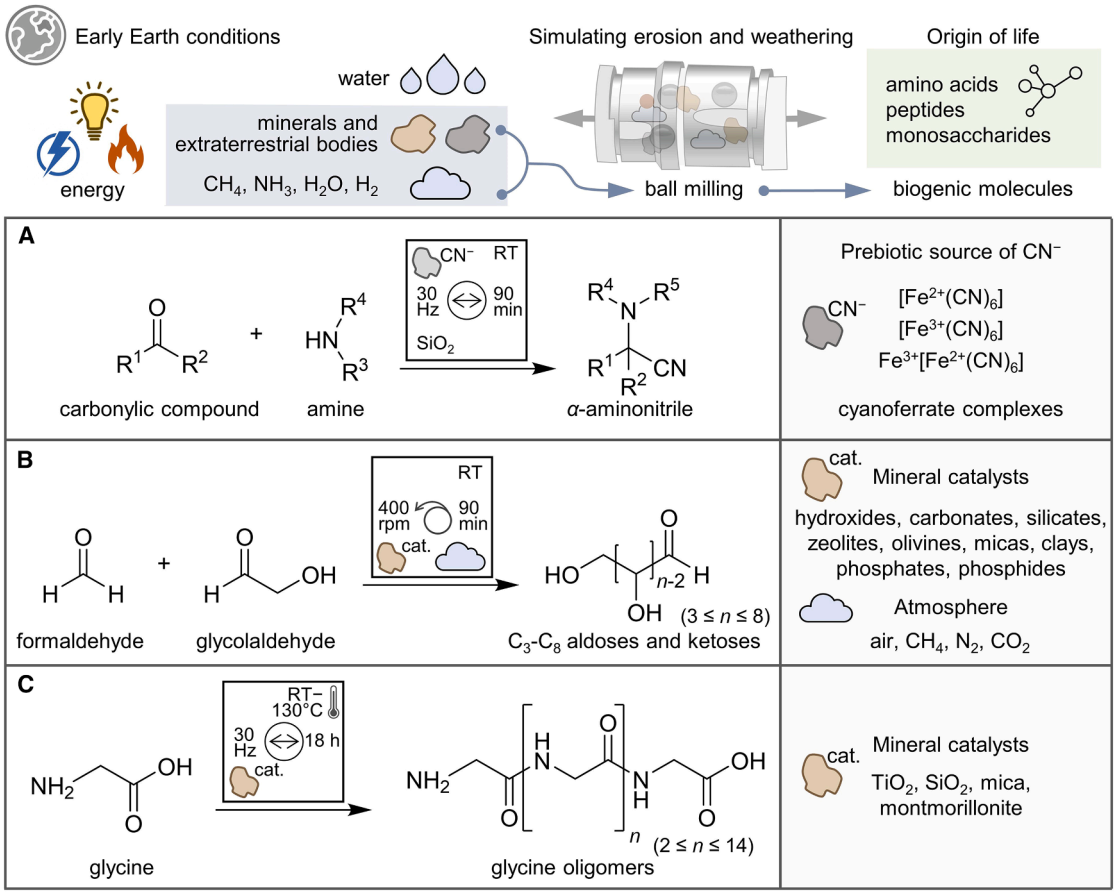

Figure 6. The role of mechanochemistry and examples in origin-of-life studies

supported by a different study where the ball-milling processing of iron meteorites resulted in the formation of amino acids.[203]

Another example of using mechanochemistry in an origin-of-life study was the synthesis of monosaccharides via the formose reaction by the Trapp group (Figure 6B).[204] Ball milling formaldehyde, glycolaldehyde, and glyceraldehyde by using real minerals as catalysts resulted in linear and branched monosaccharides, including ribose. The formose reaction route to sugars was kinetically accelerated under solid-state reaction conditions devoid of aqueous media and enriched monosaccharides over time. The selectivity toward specific sugars could be fine-tuned with a particular mineral catalyst. This is in stark contrast to the aqueous formose reaction pathway, which is notoriously unselective and yields decomposition products. Importantly, the mechanochemical formose pathway is independent of atmospheric conditions and proceeds under cryogenic conditions, thereby having implications for both terrestrial and extraterrestrial prebiotic routes toward sugars.

In addition, Stolar et al. showed that mechanochemistry is useful even for the prebiotic synthesis of larger biomolecules, such as peptides (Figure 6C).[205] Ball milling glycine together with TiO_2, SiO_2, montmorillonite, or mica resulted in different lengths of glycine oligopeptides. Simultaneous heating and milling helped to form longer oligopeptides, but the selectivity favored the formation of a cyclic glycine dimer. The latter has also been shown as a productive intermediate for peptide synthesis, and mechanochemical peptide bond formation tolerates the presence of moisture. Importantly, the length of glycine oligomers obtained by ball milling makes them suitable for establishing a 3D structure, which is the basis of the catalytic properties associated with peptides and proteins. Moreover, milling glycine and alanine results in the formation of their heterooligopeptides and demonstrates that other amino acids can be incorporated into a growing peptide chain.

Although water is essential for life, it is not necessarily desirable for the synthesis of life's building blocks given that the formation of biological polymers is thermodynamically unfavorable in water media.[206] For that reason, wet-dry cycles have been proposed to connect the conditions required for the synthesis of biological polymers with the plausible early Earth environment.[194] The wet phase enables combinatorial selection through compartmentalization, whereas the dry phase allows the formation of covalent bonds. Wet-dry cycles should closely resemble the hydration (due to precipitation) and dehydration (evaporation due to heating) cycles in land-based pools on an early Earth. One of the drawbacks of wet-dry cycles is the poor diffusion of solid reactants in the dry phase, which can be overcome by mechanochemical approaches to simulating environmental conditions in

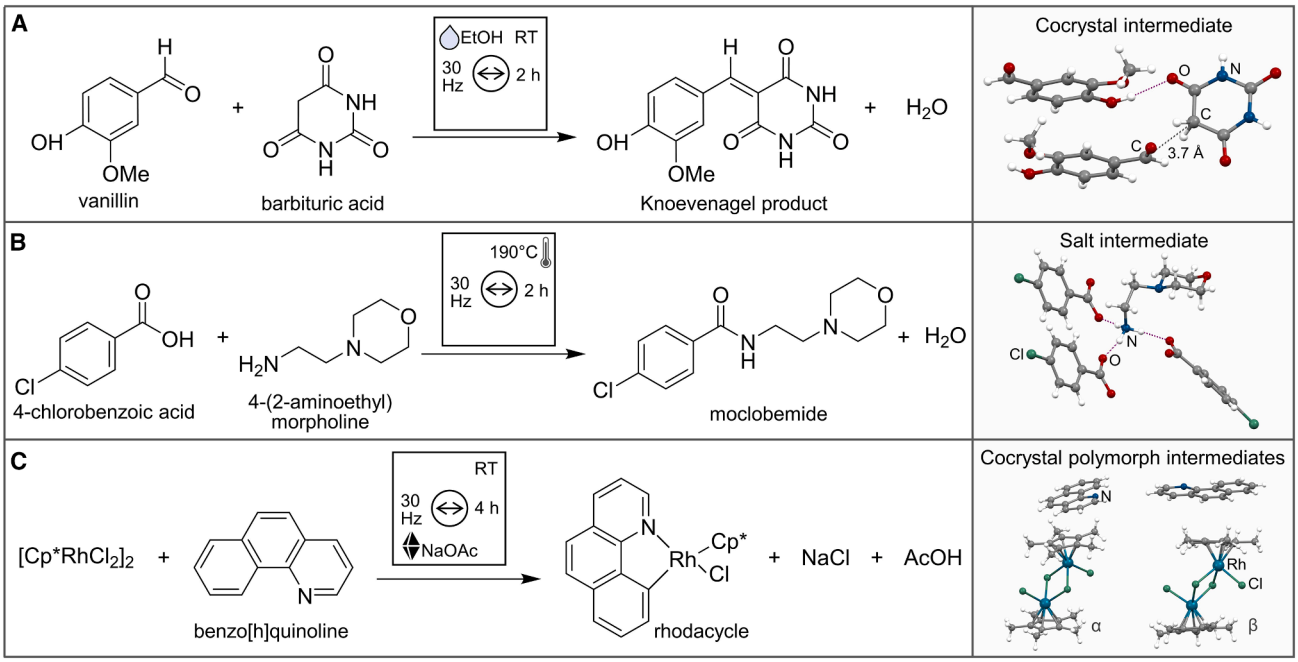

Figure 7. Selected examples of supramolecular intermediates in mechanochemical covalent-bond-forming reactions

a prebiotic scenario. The selected examples show that mechanochemistry enables the evolution of simple organic molecules into more complex ones under solventless and other plausible prebiotic conditions to elucidate prebiotic chemistry.[207] Furthermore, using mechanochemical reaction conditions to mimic natural events that perturb planetary surfaces and deliver mechanical energy has implications for extraterrestrial planetary missions and the search for potential biosignatures.[208]

Non-covalent interactions guiding covalent bond formation

One of the features of mechanochemistry is performing chemical reactions in a concentrated reaction environment. Under such conditions, reagents are in close contact and non-covalent interactions can arise among them. This is obvious in crystal-engineering-type mechanochemical reactions but is also a growing realization in mechanochemical organic synthetic reactions.[209–211] Such non-covalent interactions can result in stable supramolecular complexes that act as reaction intermediates between reactants. Isolating and characterizing these complexes can elucidate how the covalent-bond-forming reactions proceed under mechanochemical conditions and why their mechanisms oftentimes differ from those of solution reactions. In comparison, observing such supramolecular intermediates in solution is difficult because of dilution effects, and their formation might even be hindered by the competing effects of solvent molecules.

The first case of a cocrystal intermediate in mechanochemical organic reaction was reported in 2018 by Lukin et al. (Figure 7A).[209] *In situ* monitoring of ball milling barbituric acid and vanillin by Raman spectroscopy enabled the observation of an intermediate before a Knoevenagel product. After isolation and crystal structure solution, the stable crystalline compound was shown to be a cocrystal of barbituric acid and vanillin. In the cocrystal, the carbon atom from the methylene group of barbituric acid is distanced ca. 3.7 Å from the carbon atom of the aldehyde group of vanillin, and the reactive centers are oriented favorably for the subsequent C–C bond formation. The complete conversion to the condensation product requires 14 h of neat grinding but only 2 h under LAG conditions with ethanol.

Recently, Stolar et al. reported on supramolecular intermediates in thermo-mechanochemical direct amidations between carboxylic acids and amines (Figure 7B).[210] For example, neat grinding of benzoic acid and *p*-toluidine results in the formation of their ammonium carboxylate cocrystal salt with one ionic molecule of benzoic acid and *p*-toluidine and an additional neutral molecule of *p*-toluidine in the asymmetric unit. Further two-step milling of the cocrystal salt at 190°C results in the elimination of the water molecule and a complete conversion to the amide product. Furthermore, neat grinding of 4-chlorobenzoic acid and 4-(2-aminoethyl)morpholine results in the formation of their ammonium carboxylate salt, which quantitatively transforms to the commercially important active pharmaceutical ingredient (API) moclobemide upon two-step milling of the salt at 190°C. The observed cocrystal salt of benzoic acid and *p*-toluidine and a salt of 4-chlorobenzoic acid and 4-(2-aminoethyl) morpholine both exhibit the same R_4^4 (12) and R_4^2 (8) hydrogen-bonded motifs with hydrogen-bonded ammonium and carboxylate groups. The role of milling under high temperatures is to overcome the activation barrier for eliminating water molecules from these crystalline supramolecular complexes. Interestingly, the amide products could be formed without activators or additives, thus achieving almost ideal green chemistry metrics.

Furthermore, Hernández and co-workers reported on non-covalent interactions among reagents involved in mechanochemical organometallic reactions (Figure 7C).[211] *In situ* synchrotron PXRD monitoring of neat grinding of $[Cp^*RhCl_2]_2$ with benzo[h]quinoline revealed the formation of their cocrystal polymorph α, which transforms to polymorph β upon continued grinding.[212] The subsequent acetate-assisted C–H bond activation and the formation of the corresponding rhodacycle have also been monitored *in situ* by synchrotron PXRD and showed that polymorph β is the reactive cocrystal form. Computational investigation using different methodologies and basic variables revealed that the reactive polymorph β is higher in energy than polymorph α, has a more favorable spatial and energetic distribution of the frontier orbitals, has a more fragile crystal structure, and exhibits two electrophilic rhodium centers.[213]

The consequence of the supramolecular intermediates seems to be the close positioning and favorable orientation of the reactive centers and fine-tuning of their electronic nature within the multicomponent crystals. Collectively, supramolecular intermediates have the potential to stabilize and direct specific reaction pathways and enable more efficient and selective mechanochemical organic reactions. Traditionally, the fields of crystal engineering and organic synthesis are separated in training and practice. However, it becomes clear that integrating crystal engineering concepts in mechanochemical organic reactions has the potential to unlock new levels of reactivity and reaction control.

Direct mechanocatalysis

The synergy of mechanochemistry and catalysis provides a powerful synthetic approach not limited by solubility issues. Typically, solid catalysts are added to the reaction mixture and subsequently milled.[214–216] Although this approach is efficient, separating the catalyst from the product mixture and reusing it become challenging. In 2009, the Mack group pioneered a direct mechanocatalytic copper-catalyzed Sonogashira coupling of *para*-substituted aryl halides with trimethylsilylacetylene by using copper milling equipment (Figure 8A).[217] The same reaction can also be performed in stainless-steel equipment with copper iodide as a catalyst, but using milling equipment as the catalyst source greatly simplifies workup without harming the reaction yields.

The first report on using palladium (Pd) balls as the catalyst for a mechanochemical Suzuki polymerization of 4-bromo- or 4-iodophenylboronic acid yielding poly(para-phenylene) was reported in 2019 (Figure 8B).[218] Borchardt and co-workers showed that the main driving force for the Suzuki polymerization was the heterogeneous reaction occurring on the surface of Pd balls despite their minor abrasion. Interestingly, switching from hard zirconia to soft PMMA jar resulted in decreased abrasion and increased degrees of polymerization as a result of the less energetic Pd ball collisions. In the same work, the authors coined the term "direct mechanocatalysis," i.e., by using milling equipment as the only catalyst source, and further expanded the concept in a review article.[219]

The abrasion of Pd balls can be avoided if polymer milling jars are used with the LAG approach.[220] For example, the latter combination has been used in Pd-ball-catalyzed Suzuki coupling of aryl halides and phenylboronic acid in perfluoralkoxy alkane jars. Inductively coupled plasma optical emission spectroscopy measurements confirm below 1 ppm of Pd after 60 min of mechanochemical reaction. Mechanistically, this work also shows that the LAG approach is highly efficient as a result of the catalytic reaction on a thin film or multilayers around the Pd ball's impact points. The role of the liquid additive is to enable the formation of such a thin film on the Pd ball. Alternatively, the reaction works well for liquid substrates without the additional liquid additives.

One of the downsides of the highly efficient direct catalysis by Pd balls is their high market price, especially when considering the scale-up of such protocols. However, this has been circumvented by exploiting the fact that mechanocatalytic reactions occur on the surface of Pd balls. Specifically, Borchardt and co-workers recently reported the galvanostatic coating protocol, which significantly reduces the costs of the direct mechanocatalytic approach.[221] For example, multiple metals can be coated onto stainless-steel balls with different coating thickness levels. Importantly, such coated milling balls perform comparably to pure Pd balls and show minimum levels of abrasion. Such observations have been demonstrated on direct mechanocatalytic Suzuki and Glaser coupling reactions.

Besides copper and palladium, different metals could further broaden the scope of direct mechanocatalytic reactions. For example, the Borchardt group reported the gold-catalyzed direct mechanocatalytic oxidation of alcohols (Figure 8C).[222] Their protocol used gold-coated milling jars and soft polymer milling balls and air as the oxidation agent, resulting in minimal gold abrasion and enabling high aldehyde conversion with a turnover number and turnover frequency as high as 8,200 and a 0.77 s^{-1}, respectively. Furthermore, the Vollmer group exploited zirconia milling balls for the mechanocatalytic depolymerization of polypropylene (Figure 8D).[223] Milling polypropylene by using tungsten carbide milling jars and zirconia milling balls yields C_{1-10} hydrocarbons and is based on radical chemistry. Specifically, the authors demonstrated that the homolytic backbone cleavage of polypropylene chains leads to the formation of mechano-radicals. Thus, a more efficient and selective mechanocatalytic approach based on radicals is fundamentally different from a low-yielding and unselective thermocatalytic approach governed by cations. The performance of the mechanocatalytic approach was optimized by sulfating and tungstating zirconia balls, leading to 45% of C_{1-10} hydrocarbons from polypropylene within 1 h at ambient temperature. The authors also rationalized that Zr^{3+} ions on the surface of zirconia balls act as catalytic sites and stabilize carbon-centered mechano-radical intermediates.

A growing body of evidence clearly shows that the direct mechanocatalytic approach offers many benefits over traditional solution metal-catalyzed and thermo-catalyzed protocols and unlocks new levels of reactivity while at the same time respecting sustainability aspects.

UPSCALING MECHANOCHEMICAL PROCESSES

Mechanochemistry has emerged as a sustainable approach to chemical synthesis and materials processing, offering significant benefits such as reduced solvent use, minimized energy consumption, and reduced waste generation across a range of

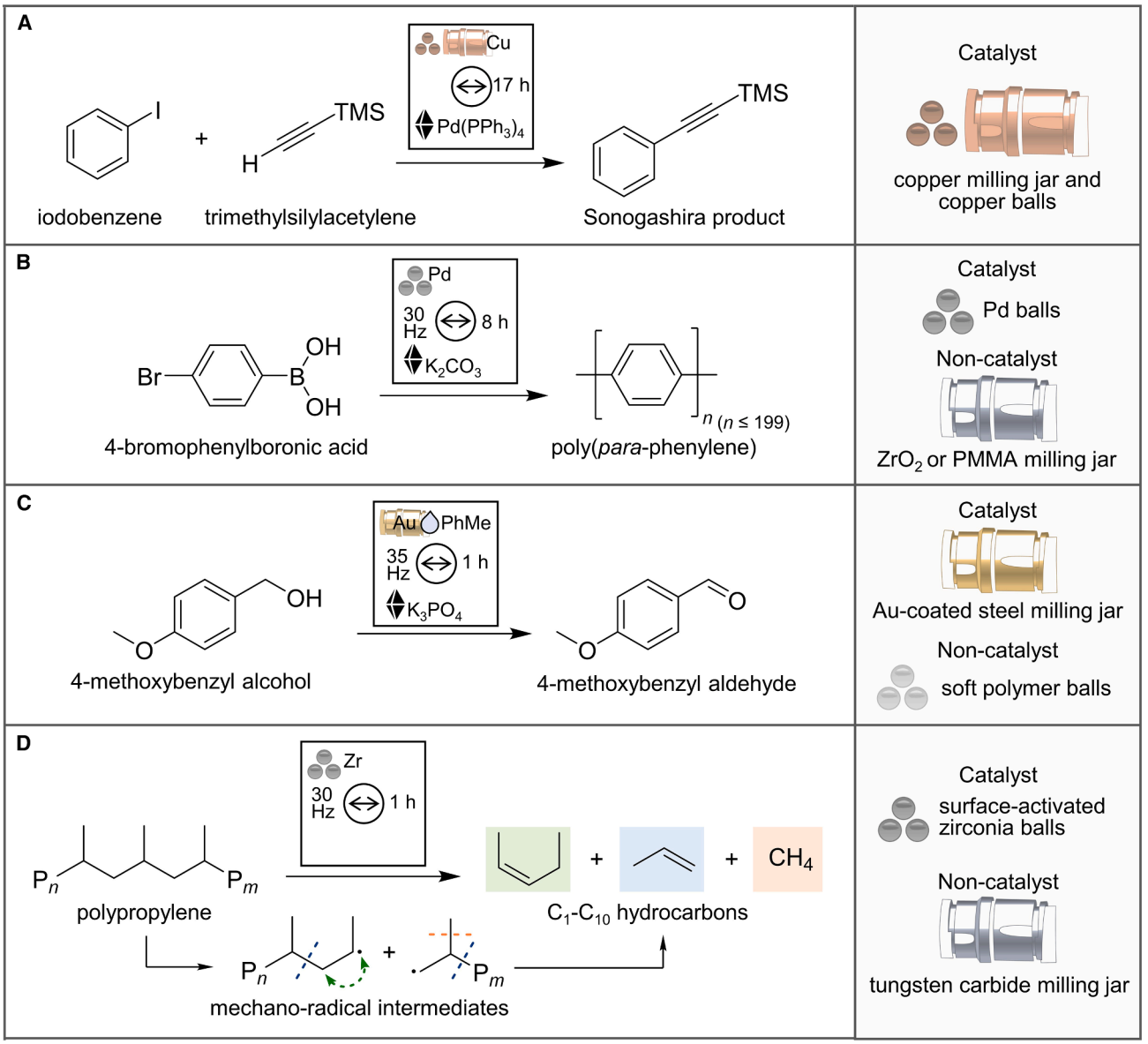

Figure 8. Selected examples of direct mechanocatalytic reactions

industries, including pharmaceuticals, materials science, and chemical manufacturing. As environmental sustainability and cost-efficiency become key drivers for industrial adoption, mechanochemistry's potential to simplify downstream processing makes it an attractive option for companies seeking to reduce their carbon footprint and comply with stringent environmental regulations. Mechanochemistry also enables the use of alternative feedstocks and contributes to a circular economy.[39] Despite the growing body of research demonstrating the benefits of mechanochemistry at laboratory scales, the transition to industrial-scale applications remains a challenge.[224,225] One of the primary obstacles in upscaling mechanochemical processes is the lack of standardization. Unlike solution-based chemistry, which has well-established protocols and equipment for large-scale production, mechanochemical processes are still in their infancy when it comes to industrial implementation. This lack of standardization makes it difficult to directly translate laboratory-scale successes into industrial settings, necessitating innovative approaches and new technologies for effective upscaling.[224]

In the upscaling of mechanochemical processes, there are two main types (see Figure 9): dry processes (with no liquids involved) or wet processes (with various degrees of liquids present). Planetary ball mills with capacities up to 4 × 500 mL jars per batch offer higher production volumes than traditional small ball mills and are suitable for wet processes, whereas drum mills with volumes up to 150 L are designed for dry processes. Traditionally, most horizontal or drum mills have been used for dry processes, such as the comminution of mineral ores in the

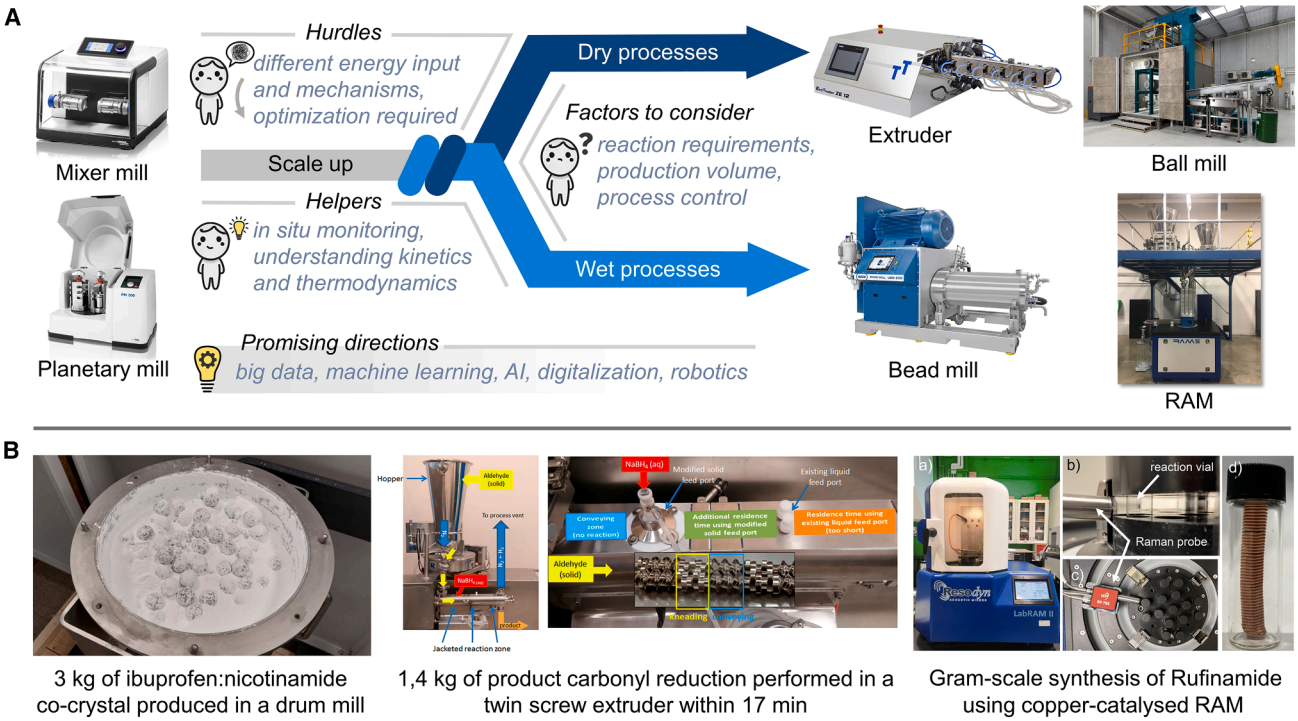

Figure 9. Continuous approaches for scaling up mechanochemical processes: TSE, ball milling, bead milling, and RAM

(A) Conceptual framework for upscaling mechanochemical reactions. Instrument images are used with permission from Retsch (mixer and planetary mills), Three-Tec (continuous TSE), Environmental Decontamination (NZ) Limited (continuous mechanochemical destruction ball-mill reactor), WAB-GROUP (continuous mechanochemical bead-mill reactor), and Resodyn (continuous RAM).

(B) Examples of published upscaling studies. Reprinted with permission from Schöbel et al. (Max-Planck-Institut für Kohlenforschung, left)[227] and adapted with permission from Isoni et al. (middle),[228] copyright 2017 American Chemical Society; and Lennox et al. (right),[80] copyright 2023 Royal Society of Chemistry.

mining industry or the grinding of clinker and gypsum in the cement industry. Various milling devices cater to different scale requirements, from laboratory to industrial production. At the lab scale, mixer mills are ideal for gram-scale experiments, whereas planetary mills of various sizes bridge the gap between small-scale lab work and larger production needs. In a seminal work, Stolle et al. showed that the mechanochemical Knoevenagel condensation between vanillin and barbituric acid is scalable from 20 to 300 mmol in a planetary mill and produces 80 g scales after short reaction times.[226] The transition from mixer mills to larger planetary or drum mills could require additional optimization because of the differences in energy input and operating mechanisms.[37] However, planetary mills do not possess the potential for further scale-up to the industrial scale.

Continuous processing is a key point for industrial-scale applications. One technology with this potential is eccentric vibratory milling (or similar horizontal ball mills), given that more mills can be connected in parallel to a full pilot plant unit.[229] The reagents can be introduced from the top side of the mill, and there is an outlet for products at the back side, which connects to the other unit. The continuous mode is applied in industry. In the laboratory, Baláž et al. applied the batch-mode satellite chamber of the eccentric vibratory mill (mirroring the events going on inside the mill volume) to degrade the polyvinyl chloride waste by using eggshell[230] or produce metal chalcogenides suitable for energy-conversion applications (e.g., thermoelectrics) to demonstrate the potential scalability.[231] Kilogram-scale synthesis using this mill in batch mode was successfully applied for copper sulfide and, more recently, a selected API.[52,232]

Recent studies have investigated continuous ball milling by using DYNO-MILL equipment, highlighting its effectiveness in various wet-milling applications. This technique has shown promise in areas such as catalyst preparation, nanoparticle synthesis, and pharmaceutical processing. Compared with batch processes, continuous ball milling in a DYNO-MILL offers advantages such as improved particle-size reduction, enhanced mixing capabilities, and increased production efficiency. Pérez-Merchán et al. were able to significantly reduce the synthesis time for hydrocalumite to just 5 min under mild conditions while also enabling efficient glucose-to-fructose conversion with high productivity (0.50 kg fructose LH_2O^{-1} h^{-1}) in a short reaction time.[233] Martín-Perales et al. established the preparation of Ag- and Cu-modified ZIF-8 materials through a sustainable, bead-assisted flow reaction.[234] In a recent publication, Nguyen et al. used impact-continuous heated mechanochemical technology to prepare deep eutectic solvents (DESs) through a continuous-flow process. This method allowed for the synthesis of various DESs, such as choline chloride-urea and choline chloride-glycerol, without the need for external heating, achieving impressive productivity rates ranging from 4.8 to 254 g/min.[235]

These studies demonstrate the versatility and potential of continuous ball milling as a scalable and efficient approach to materials processing.

For pilot and manufacturing scales, different types of continuous ball mills, including devices handling operations up to 2 t/h, come into play (Figure 9).

Another technology that efficiently incorporates continuous dry processing is twin-screw extrusion (TSE), which has shown great promise for industrial-scale mechanochemistry (TSE can also accommodate some liquids; Figure 9). The ability to fine-tune process parameters, such as temperature, screw speed, and residence time, provides unprecedented control over reaction conditions, resulting in optimized product quality and yield. This versatility extends to a wide range of applications, from organic synthesis to polymer processing and biomass conversion, making TSE a valuable tool in a variety of industries. Compared with batch processes, TSE allows uninterrupted production, fine-tuning of process parameters, and significantly higher space-time yields. For example, TSE has been successfully applied to the synthesis of ZIF-8 with throughput rates of several kg/h and space-time yields of up to 144,000 kg/m^3/day.[84] TSE represents a significant leap forward in sustainable manufacturing. In addition, TSE's enhanced mass-transfer capabilities contribute to more efficient mechanochemical reactions, potentially leading to improved product properties and reduced processing times. Several studies have demonstrated the potential of extrusion for upscaling mechanochemical processes. James et al.[236] and Karadeniz et al.[237] reported the use of TSE for the continuous synthesis of MOFs and achieved exceptional space-time yields several orders of magnitude greater than those produced by conventional solvothermal methods. More recently, Isoni et al. demonstrated the effectiveness of LAG in overcoming the mass-transfer issues associated with insoluble aromatic aldehydes in aqueous media for exothermic carbonyl reduction. By employing a TSE under LAG conditions, they achieved continuous production at a kilogram scale by generating up to 1.41 kg of product in just 17 min.[228]

This approach not only resolved the challenges of traditional fed-batch methods but also significantly accelerated the reaction, effectively completing it in seconds. As research in this field continues to progress, it is likely that extrusion will play an increasingly important role in bridging the gap between laboratory-scale mechanochemistry and industrial-scale production. Gugin et al. introduced energy-dispersive X-ray diffraction as an advanced *in situ* monitoring technique for reactive extrusion, enabling real-time control and optimization of the extrusion process.[48]

RAM has emerged as a promising alternative for scaling up dry and wet mechanochemical transformations and can be used in a continuous mode (Figure 9). This technique employs pressure waves to induce chemical and morphological changes, offering a gentler approach than traditional ball-milling methods. RAM uniquely eliminates the need for both bulk solvents and milling media, making it an environmentally friendly and scalable option for mechanochemical synthesis. One of the key benefits of RAM is its ability to achieve reactivity through low-frequency acoustic vibrations (around 60 Hz) with energy input modulated by changes in the vertical acceleration of the reaction vessel. Two successful examples of RAM application include the synthesis of halogen-bonded cocrystals and the direct mechanocatalysis of copper-catalyzed alkyne-azide click-coupling (CuAAC) reactions.[80,238] In the first case, RAM efficiently produced eleven halogen-bonded cocrystalline architectures, demonstrating its effectiveness in cocrystal engineering.[238] For the CuAAC reactions, a simple copper coil was used as a catalyst, showcasing RAM's ability to perform direct mechanocatalysis in an impact-free environment.[80] These examples highlight the versatility and potential of RAM in advancing mechanochemical synthesis and catalysis. RAM also allows for better control over reaction stoichiometry than solution-based methods or conventional catalysts.[80] However, there are limitations to overcome, such as the need for a better understanding of the energy-input characterization and the development of more comprehensive theoretical frameworks for mechanochemistry.

Understanding the reaction kinetics and thermodynamics of mechanochemical processes is crucial for successful upscaling because these factors significantly influence the efficiency and feasibility of large-scale operations. Unlike solution-based reactions, where heat transfer and mixing are relatively well understood, mechanochemical reactions involve complex interactions between mechanical energy, heat generation, and chemical transformations. Deciphering these relationships is crucial for optimizing reaction conditions and designing efficient large-scale processes. Advanced characterization techniques and *in situ* monitoring methods have been applied to elucidate the fundamental mechanisms underlying mechanochemical reactions (see section "TRIS methods in mechanochemical research"). These tools not only aid in process optimization but also contribute to the fundamental understanding of mechanochemical transformations, which is essential for effective upscaling.

Integrating mechanochemistry with other emerging technologies offers exciting opportunities for industrial applications. Furthermore, the latest developments in powering mechanochemical devices with renewable energy sources will help in further decreasing processing costs and having a greater industrial appeal.[239] In addition, the use of AI and machine-learning algorithms for process optimization and predictive modeling could significantly accelerate the development of industrial-scale mechanochemical processes. The convergence of mechanochemistry, digitalization, and robotics offers unprecedented opportunities to advance chemical processes. Robotics automates mechanochemical syntheses, ensuring consistent force application and precise reaction control. Digitalization enables real-time monitoring and analysis, enabling rapid process optimization. The integration of big data, machine learning, and AI enhances this synergy through the analysis of vast datasets, the recognition of patterns, and the prediction of optimal reaction conditions. This technological integration promotes standardization, improves reproducibility, and facilitates industrial scale-up. Case studies have demonstrated its potential for the development of sustainable chemical processes. However, challenges remain, including system compatibility, data management, and infrastructure costs.

PROSPECTS AND POSSIBILITIES OF MECHANOCHEMICAL TECHNOLOGIES

Mechanochemistry has emerged as a powerful and sustainable approach to chemical and materials synthesis, as well as to the degradation of complex chemical wastes and upcycling. As research in these fields continues to advance, several exciting prospects and opportunities for mechanochemical technologies are on the horizon.

Sustainable manufacturing is one of the most promising areas for mechanochemistry. The reduction or elimination of solvents, lower energy requirements, and minimized waste generation are well in line with the principles of green chemistry and sustainable development.[39] As industries come under increasing pressure to reduce their environmental impact, mechanochemical technologies could play a crucial role in the development of greener industrial processes.

The pharmaceutical industry stands to benefit greatly from mechanochemical advances. Solvent-free synthesis of APIs, improved formulation techniques, and the ability to access novel polymorphs and cocrystals could revolutionize drug development and manufacturing processes. In addition, mechanochemistry could offer new approaches to addressing drug delivery and bioavailability challenges. Unique reaction conditions provided by mechanochemistry often lead to the discovery of novel materials and chemical transformations that are difficult or impossible to achieve through traditional solution-based methods. One often-overlooked aspect is how the use of solid reagents influences activation energy and reaction selectivity. Unlike dissolved reagents in conventional solution chemistry, solid crystalline reagents possess inherent crystal-lattice energies. Furthermore, higher concentration of the reagents promotes complementary intermolecular non-covalent interactions. These might stabilize certain reaction intermediates and steer the reaction toward previously unexplored pathways.

Continued exploration of mechanochemical synthesis could lead to new compounds with applications in pharmaceuticals, catalysis, energy storage, and advanced materials. Leveraging the benefits of mechanochemistry makes it an excellent choice for innovative recycling solutions within a circular economy. Mechano-sensitive polymers that dynamically respond to force could find applications in soft robotics. Furthermore, hybrid systems could integrate enzymes with mechanophores for *in vivo* catalysis, such as force-triggered drug activation within cells. Quantum mechanochemistry might emerge, where precisely calibrated mechanical forces entangle molecular qubits or manipulate spin states in nanomaterials, enabling quantum sensors. Looking beyond Earth-bound laboratories, mechanochemistry could pioneer extraterrestrial chemistry in microgravity environments on space stations, where minimizing waste and resources and increasing efficiency are of utmost importance.

The combination of mechanochemistry with AI and machine learning could accelerate the optimization of mechanochemical processes, predict reaction outcomes, simulate reactor dynamics and surface interactions, and guide the discovery of new materials. Adapting mechanochemical reactions to continuous flow systems could improve scalability and process control for industrial applications.

One key challenge in applying mechanochemical technologies in industrial settings is the lack of a universal upscaling method, which stems from the numerous factors that govern and influence mechanochemical reactions. Instead, each process must be scaled up individually on the basis of its specific underlying mechanism and kinetics. This requirement complicates repurposing existing pilot plants. For example, a facility equipped for RAM might not accommodate a process needing ball milling or extrusion. This ultimately increases capital and operational expenditures for transferring research to commercial production.

In summary, our goal was to present the evolving field of mechanochemistry as broadly as possible by offering an up-to-date bird's-eye view. We hope that the aspects of mechanochemistry discussed here clearly illustrate its underlying chemical complexity and highlight the unique and intriguing challenges it poses to chemists. Those prepared to tackle these challenges will most likely require broader chemical and interdisciplinary training than traditionally expected, though this comes with the potential for disruptive and transformative innovation.

ACKNOWLEDGMENTS

T.S. is supported by the Add-on Fellowship of the Joachim Herz Foundation. J.A. is supported by the Postdoctoral Fellowship of the Alexander von Humboldt Foundation. M.B. is grateful to the Slovak Research and Development Agency (contract no. APVV-24-0353) and the Slovak Grant Agency VEGA (project 2/0039/26).

AUTHOR CONTRIBUTIONS

Conceptualization, T.S. and F.E.; writing – original draft, T.S., J.A., L.C., N.G., A.A.L.M., M.B., and F.E.; writing – review & editing, T.S., J.A., L.C., N.G., A.A.L.M., M.B., and F.E.; supervision, T.S. and F.E.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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