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Mechanochemistry: A Force of Synthesis

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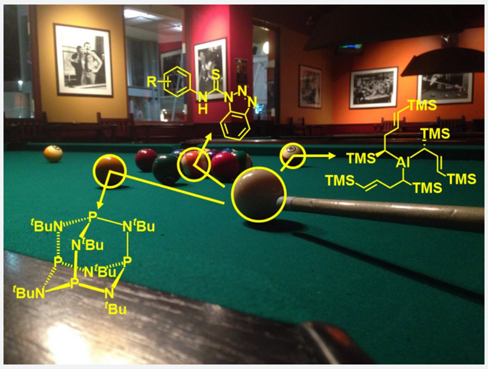
ABSTRACT: The past decade has seen a reawakening of solid-state approaches to chemical synthesis, driven by the search for new, cleaner synthetic methodologies. Mechanochemistry, i.e., chemical transformations initiated or sustained by mechanical force, has been advancing particularly rapidly, from a laboratory curiosity to a widely applicable technique that not only enables a cleaner route to chemical transformations but offers completely new opportunities in making and screening for molecules and materials. This Outlook provides a brief overview of the recent achievements and opportunities created by mechanochemistry, including access to materials, molecular targets, and synthetic strategies that are hard or even impossible to access by conventional means.



Mechanochemistry,[1,2] i.e., chemical synthesis enabled or sustained by mechanical force, is undergoing an exciting period of rediscovery,[3−9] enabled by new synthetic techniques[10] and tools for real-time mechanistic studies.[11] This Outlook highlights several aspects of this renaissance, especially the emergent synthetic advantages of mechanochemistry, notably access to molecules and materials thought impossible to reach, and reactivity that is novel or difficult to achieve in solution.[12−16]

■ MECHANOCHEMISTRY: WHY AND HOW?

The major inspiration behind the rediscovery of mechanochemistry is green chemistry,[17] specifically the need of pharmaceutical and chemical industries for cleaner, safer, and more efficient transformations.[18,19] The hallmark of mechanochemistry is achieving chemical transformations by milling or grinding, without the need for bulk dissolution of reactants. Such procedures are different from conventional laboratory work, as stirrers and heaters are replaced by automated ball mills, and beakers and flasks by jars (Figure 1a) containing milling media. In contrast to manual grinding, which is open and susceptible to a range of environmental factors,[20] ball milling offers an enclosed solvent-free reaction environment with well-defined parameters for optimizing reactivity, such as frequency, medium-to-sample weight ratio, etc.[21,22] Among different mill designs,[23,24] shaker and planetary mill ones are the most popular. In the former, jars swing back and forth with a frequency that determines the milling intensity. Shaker mills are often used for small samples, e.g., in screening of pharmaceutical solids. In a planetary mill, the jar rotates around a central axis, while spinning around its own axis. Such "planetary" motion creates centrifugal forces which emulate the effect of gravity in industrial-scale roller mills, offering a direct connection to scale-up.[21,23,24] Milling balls and jars are usually made of stainless steel, zirconia, tungsten carbide, or polytetrafluoroethylene (Teflon). Jars of transparent poly(methyl)methacrylate (PMMA) are also used (Figure 1a)[25] to facilitate *in situ* monitoring. Steel (density ≈7.5 g/mL) is the most commonly used material, but upon lengthy milling it can lead to metal contamination.[26] This can be avoided by using zirconia, which exhibits a similar density (≈5.6 g/mL) and, therefore, comparable impact to steel.

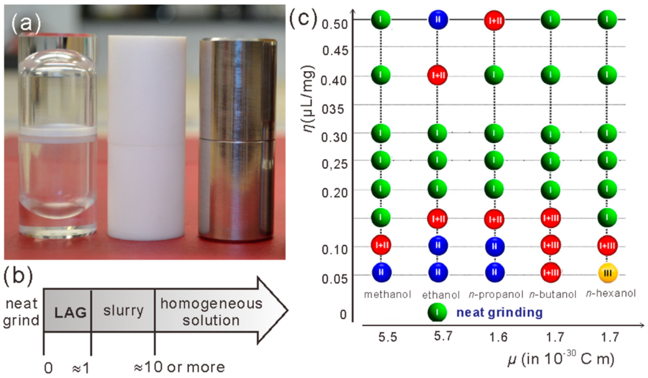


Figure 1. (a) Milling jars of (left to right) PMMA, polytetrafluoroethylene (Teflon), and stainless steel. (b) The η-scale[35] expressed in μL/mg. (c) Effect of η and liquid dipole moment (μ) on appearance of cocrystal polymorphs I, II, and III in LAG cocrystallization of caffeine and anthranilic acid. Adapted with permission from ref 48. Copyright 2016 American Chemical Society.

Key to the success of mechanochemistry are new techniques which use catalytic additives to control reactivity. Of these, liquid-assisted grinding (LAG)[10] is particularly important for expanding mechanochemistry into a viable alternative to solution synthesis, as illustrated by the demonstrated concept of a solvent-free research laboratory,[27,28] or elaborate multistep mechanochemical routes to pharmaceutically and biologically relevant targets.[29−34] LAG uses a small amount of a liquid to accelerate reactions, as well as to enable and direct transformations that do

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not take place by neat grinding. The empirical definition of LAG is based on how mechanochemical reactivity is affected by the ratio of the liquid additive to the weight of reactants (η, Figure 1b).[35] A value of $\eta = 0$ corresponds to neat grinding, $\eta > 10$ μL/mg corresponds to a typical solution reaction, while LAG lies in the range of $\approx$0–1 μL/mg. In that range, reactivity appears independent of reactant solubility, distinguishing LAG from slurry reactions ($\eta > 1$ μL/mg) in which low solubility does hinder reactivity.[35]

High efficiency of LAG was shown in screening for inclusion compounds,[36] cocrystals,[37] salts,[38] solvates,[39] and polymorphs[40] and in organic mechanochemistry.[41,42] Changing the liquid additive in LAG is a simple, powerful route to control mechanochemical reactions,[43] which is especially attractive in screening for solid forms of drugs.[40,44,45] Solubility-independent reactivity in LAG has been explained in different ways, e.g., by formation of mobile surface layers, or the fact that the amount of liquid is sufficiently small to be continuously saturated with reactants.[35] The origin of the structure-directing effect in LAG is unclear, with recent studies pointing to liquid polarity, η, and specific interactions between the liquid and the reactants (Figure 1c).[46−48]

MECHANISTIC STUDIES: REACTION MONITORING IN REAL TIME

Until recently, mechanistic studies of milling reactions have been limited by the inability to directly monitor transformations taking place in rapidly moving milling jars, under continuous impact of milling media. These limitations are circumvented by recently introduced *in situ* techniques which permit reaction monitoring in real time. The first such technique used highly penetrating synchrotron radiation to monitor mechanochemical transformations by X-ray powder diffraction (XRPD) through the walls of the milling jar,[49] and was followed by a more laboratory-friendly Raman spectroscopy technique[50] and a combined synchrotron XRPD/Raman approach (Figure 3a).[51]

In situ monitoring permits the investigation of fundamental aspects of reactivity that are well understood in solution, but have remained largely unexplored in mechanochemistry, e.g., reaction kinetics or the effect of temperature on reactivity. Real-time kinetic studies on model MOF syntheses unexpectedly revealed that reactions follow a first order rate law.[52] Solution-like kinetics was also observed by the James group through *ex situ* Raman monitoring, and was explained by a "pseudofluid" model in which the reaction rate depends on mechanically induced encounters of reactant particles and, therefore, milling frequency.[53] A variable-temperature *in situ* diffraction study revealed that mechanochemical mechanisms can readily change with a modest temperature change,[54] and that reaction rates can be strongly temperature-dependent. This is consistent with *ex situ* studies of Knoevenagel condensation by milling,[22] challenging the view that mechanochemical reactions require localized "hot spots" with temperatures exceeding 1000 °C.[55] Indeed, observed thermal sensitivity suggests that such high-energy environments may not be critical for mechanochemical reactions, at least not of organic and metal−organic solids.

So far, most *in situ* studies have focused on mechanosynthesis of MOFs and coordination polymers. As a result, common aspects of their synthesis have begun to emerge, in particular the propensity for stepwise mechanisms in which a low density or a highly solvated product is often formed first and then transforms into increasingly dense, less solvated materials.[56,57] Such behavior, resembling Ostwald's rule of stages, is particularly notable in mechanochemistry of zeolitic imidazolate frameworks (ZIFs, Figure 2a,b).[49,56] A so far unique *in situ* study of a LAG organic reaction revealed that the rate of a nucleophilic substitution may be correlated to the Gutmann donor number of the liquid additive.[58] *In situ* studies are also a valuable tool for materials discovery, as illustrated by a MOF with a novel katsenite (kat) topology (Figure 2c), observed for the first time as an intermediate in the synthesis of the popular ZIF-8 framework.[14] The kat phase rearranges to the more densely packed diamondoid (dia) polymorph upon exposure to temperature, solvent, and further milling, suggesting that mechanochemistry may be the only route for its synthesis.

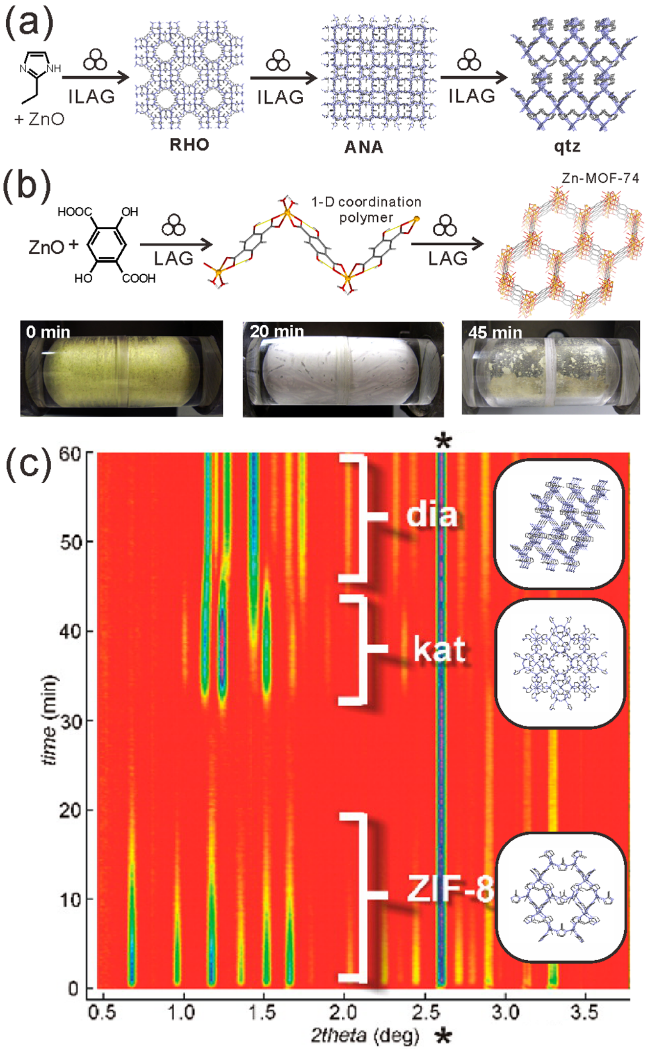
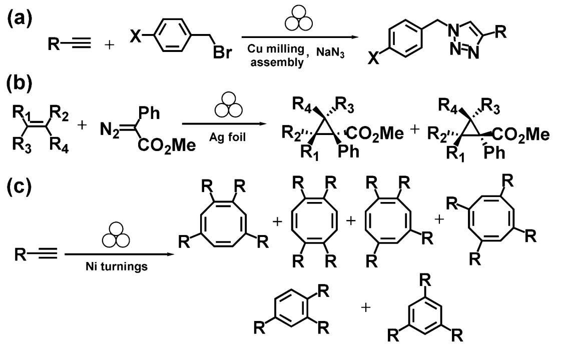


Figure 2. Stepwise MOF formation observed *in situ*. (a) Synthesis of ZIFs[49,56] and (b) Zn-MOF-74, with images of the milling jar for each step.[57] (c) Discovery of katsenite phase: time-resolved diffractogram with highlighted periods of existence of ZIF-8, kat, and dia frameworks.[14] Symbol for mechanochemical reactivity in panels a and b proposed by Rightmire et al.[5]

CATALYSIS IN MECHANOCHEMICAL REACTIONS

Mechanochemistry is a versatile platform for organocatalytic and metal-catalyzed transformations,[59−62] such as the Suzuki−Miyaura coupling[63−65] Huisgen cycloaddition,[66] olefin metathesis,[67] C−H activation, and more.[68−79] Most examples of catalytic mechanochemistry rely on catalysts developed for solution chemistry. However, mechanochemistry offers a very different reaction environment, which can sustain other catalytic designs, and perhaps make previously challenging reactions simpler and more accessible. This was shown by the Mack group, who replaced conventional catalysts with metal surfaces. Using, for example, a milling setup made entirely out of copper enabled efficient Sonogashira coupling without a CuI cocatalyst[71] (Scheme 1). There was no appreciable change in mass of the milling assembly, indicating that its surfaces are acting as a catalyst. The same approach was successfully used for Huisgen coupling[72] (Scheme 1a), and for silver-catalyzed[73] [2 + 1] cyclopropanation of alkenes (Scheme 1b) where a silver foil was used as a readily removable and recyclable catalyst. Attempted alkyne [2 + 2 + 2] cycloaddition by milling with nickel metal, rather that Ni(0) complexes used in solution, led to unexpected [2 + 2 + 2 + 2] cycloaddition to form cyclooctatetraenes (Scheme 1c),[74] demonstrating a mechanochemical catalytic strategy with a selectivity very different than in solution.

Scheme 1. Mechanochemical Reactions Catalyzed by Metal Surfaces[a]



[a](a) Huisgen coupling without a copper cocatalyst;[72] (b) mechanochemical [2 + 1] cyclopropanation of alkenes catalyzed by silver foil;[73] and (c) nickel-catalyzed [2 + 2 + 2 + 2] cycloaddition.[74] Symbol for mechanochemical reactivity proposed by Rightmire et al.[5].

METAL–ORGANIC MATERIALS

Mechanochemistry has been particularly fertile in synthesizing MOFs and other metal–organic materials. Short reaction times and quantitative conversion, coupled with lack of solvent,[75,76] allow mechanochemistry to provide MOFs in a faster, simpler way than conventional routes.

Importantly, conventional syntheses are often solvothermal and require soluble metal reagents, e.g., nitrates or chlorides, whose explosive or toxic nature is a challenge for industrial synthesis.[19] This provides particular importance to the ability of mechanochemistry to use poorly soluble sulfates, oxides, or carbonates[77,78] as reactants. Although MOF synthesis from oxides is possible by neat grinding,[79] liquid-assisted mechanochemistry is much faster. Besides facilitating the reaction, the liquid often acts as a structure-directing and space-filling agent, meaning that quantitative synthesis requires sufficient additive to occupy MOF pores.[78] Central techniques in MOF mechanochemistry are LAG and ion- and liquid-assisted grinding (ILAG),[80] a method akin to LAG, but which also utilizes catalytic salts for activation of metal oxides. These techniques have enabled rapid, quantitative assembly of almost all major MOF families, including MOF-5,[81] ZIFs,[56] UiO-66 systems,[82] pillared MOFs,[78] MOF-74,[57] and HKUST-1. A solvent-free approach to MIL-101(Cr) was reported,[83] as well as a process for continuous mechanosynthesis[84] of aluminum fumarate MOF. Mechanochemistry also permits clean, quantitative synthesis of other metal–organic targets, e.g., bismuth subsalicylate (active ingredient of Pepto-Bismol)[85] and light-emitting diode (LED) material aluminum 8-hydroxyquinolinate (**Alq$_3$**).[86]

NEW SYNTHETIC OPPORTUNITIES

There is a growing realization that mechanochemistry is not just a means of making known chemistry "greener" but can also be a tool for discovery, enabling access to products or processes not encountered in solution. For example, whereas the syntheses of monodisperse metal nanoparticles are normally conducted at high dilution in order to maintain control over particle growth and aggregation, it was recently demonstrated that milling with capping agents permits the solvent-free synthesis of monodisperse gold nanoparticles with sizes between 1 and 2 nm.[87] Moreover, mechanochemistry was used for solvent-free exchange of hydrophobic to hydrophilic ligands on 8 nm superparamagnetic iron oxide nanoparticles, without affecting their size or magnetic behavior.[88] This ability to synthesize and modify monodisperse nanoparticle systems in a solvent-free environment is a clear illustration of unexpected synthetic opportunities offered by mechanochemistry.

STOICHIOMETRIC CONTROL

A surprising quality of mechanochemical reactions is excellent control over the stoichiometry of the reaction, allowing the precise, targeted synthesis of stoichiometrically different cocrystals and coordination polymers by simply controlling the reaction mixture composition.[27,44,89−91] In all cases, control over reaction stoichiometry was remarkably superior to that of analogous solution- or melt-based experiments, where product selectivity was difficult to control and required a large excess of a reactant. Such stoichiometric control is also observed for covalent reactions, where it has been used as an efficient route for desymmetrization. For example, milling of aromatic diamines with one or two equivalents of an aryl isothiocyanate gave cleanly and selectively mono- or bis(thioureas),[12] while milling of mesitylene with different amounts of Oxone and a sodium halide led to its selective mono-, di-, or trihalogenation.[92]

REACTION DISCOVERY

There is a small but steadily growing number of reports of chemical transformations that take place by mechanochemistry, but are accessible with difficulty or not at all in solution. A striking and early demonstration of these is the dimerization of C_{60} by milling with KCN which, instead of expected hydrocyanation, gave the dumbbell-shaped C_{120}.[15] Similarly, isomers of trimeric C_{180} are obtained by milling C_{60} with 4-dimethylaminopyridine.[93] Recently, the Wang group reported that milling enables a novel $FeCl_3$-mediated C–N bond cleavage reaction that was used to generate C_{60}-fused indanes.[94] Mechanochemistry was used to discover and develop a novel C–N coupling of arylsulfonamides and carbodiimides,[16] which readily took place by LAG, but in solution either failed or gave poor conversions, demonstrating how mechanochemistry allows access to novel reactions which, although not impossible, are of low efficiency in solution.

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■ "IMPOSSIBLE" MOLECULES

An exciting aspect of mechanochemistry is access to molecules whose isolation has so far been perceived impossible. In 2014, Rightmire et al. reported the synthesis of a tris(allyl)aluminum complex based on the sterically hindered bis(trimethylsilyl)allyl ligand (Figure 3a).[95] Solution synthesis of such complexes is challenging, and they are often isolated as solvates and adducts. With the bis(trimethylsilyl)allyl ligand, all attempts to prepare and isolate the complex in solution failed. However, milling of $AlCl_3$ with the potassium salt of bis(trimethylsilyl)allyl anion readily gave this elusive compound as an off-white powder. Once dissolved, the product forms oily mixtures of compounds, consistent with its inaccessibility from solution.

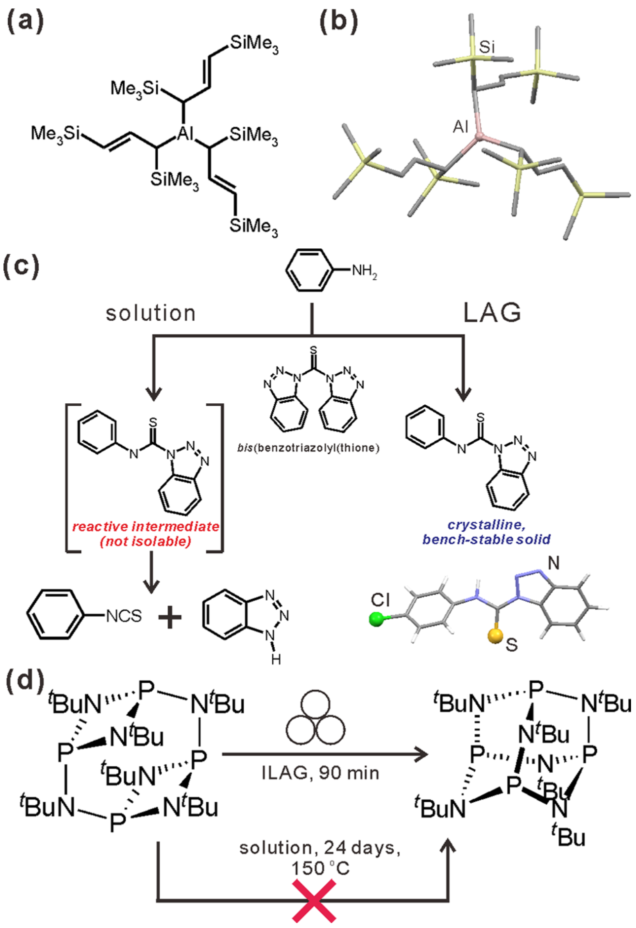

Figure 3. Elusive molecules achieved by mechanochemistry: (a, b) the tris(allyl) aluminum complex prepared by the Hanusa group;[95] (c) mechanochemically enabled synthesis of aryl *N*-thiocarbamoyltriazoles;[97] and (d) synthesis of the "sterically inaccessible" adamantoid cyclophosphazene.[13] Symbol for mechanochemical reactivity in panel d proposed by Rightmire et al.[5]

Aryl *N*-thiocarbamoyltriazoles have been proposed as reaction intermediates in the syntheses of thioureas by thiocarbamoylation of anilines, but were never isolated due to rapid dissociation into isothiocyanates (Figure 3b).[96] Conducting the thiocarbamoylation by LAG revealed transient reaction intermediates which could even be synthesized quantitatively, allowing their identification as the elusive aryl *N*-thiocarbamoyltriazoles (Figure 3b).[97] Structural characterization was possible only in the solid state: although stable upon storage for >1 year, the *N*-thiocarbamoyltriazoles immediately dissociated upon dissolution.

Another "impossible" molecule made by mechanochemistry is the adamantoid P_4N_6-phosphazane substituted by *tert*-butyl groups.[13] Whereas the syntheses of differently substituted adamantoid phosphazanes have been reported, this derivative has remained elusive, and quoted as an example of a sterically inaccessible target.[98] In 2016, the Garcia group demonstrated rapid, quantitative synthesis of this compound by ILAG (Figure 3c).[13] Theoretical calculations show that the reaction is thermodynamically favorable, suggesting that its failure in solution is not due to steric hindrance, but solvation effects.

■ ENERGETICS OF MECHANOCHEMISTRY

There is growing evidence that ball milling also offers an energy advantage over solution reactivity. For example, exploration of mechanochemical Suzuki–Miyaura coupling or of *p*-toluidine oxidation by $KMnO_4$ revealed orders of magnitude higher energy efficiency compared to conventional or microwave heating methods.[65,99] This may seem at odds with high energy demands of ball mills in materials processing.[100] However, such processing is focused on particle comminution which requires overcoming very high lattice energies. In contrast, mechanosynthesis appears to depend largely on particle mixing and surface activation,[23] and does not require particle size reduction to nanometer scale.[101] Understanding and techniques for evaluating energy input in mechanochemical reactions are still in their infancy. A study of Diels–Alder reactivity by McKissic et al.[102] estimated that the maximum energy delivered by milling is between 95 kJ mol^{-1} and 112 kJ mol^{-1}, with reaction mixture compositions indicating conditions analogous to solutions at 90 °C. An elegant approach to evaluate mechanical energy input needed for a reaction was reported by Tumanov et al., who described a setup for exposing reaction mixtures to tunable mechanical pulses of known energy.[103]

■ OUTLOOK

Modern mechanochemistry is rapidly expanding into almost every area of chemistry and materials science, changing its focus from alloying and inorganic materials[104] to catalysis, self-assembly,[105] and synthesis of molecular structures.[106] While mechanochemistry offers a cleaner, more efficient alternative to a majority of conventional transformations, the field is still in its infancy, perhaps at a similar stage as that of organic chemistry at the turn of the 19th century, before the emergence of mechanistic insights of physical organic chemistry. The principal challenge of mechanochemistry today is not in demonstrating synthetic scope, as this is now being shown to match and, indeed, exceed that of known solution and materials chemistry. In our opinion, the true and immediate challenge of mechanochemistry is in divesting itself from qualitative, often only intuitive interpretations of mechanochemical reactivity, and becoming a quantitative, mechanistically well-understood area of chemistry. This can be achieved only through developing new, specialized instrumentation, precise theoretical models, and extensive systematic studies, and integrating these into a general, quantitative model of the mechanochemical reaction environment. This must include understanding the distributions of materials and energy under different regimes of mechanical impact and shearing, and learning how these can be used to control reactivity. Recent progress in this area has been done by the Boldyreva group,[107] who demonstrated that different types of mechanical motion can lead to different products and reaction kinetics in the same milling vessel. Undoubtedly, more surprises will arise with the development of theoretical methods to explain and distinguish thermodynamic and kinetic effects in mechanochemistry, an area recently addressed by the Day group,[105,108] coupled with advances in instrumentation and introduction of new experimental techniques.[109] We strongly hope this Outlook will stimulate and accelerate such development.

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Notes

The authors declare no competing financial interest.

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