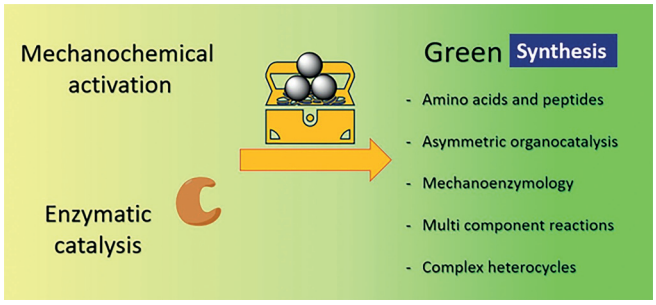
Synthesis E. Juaristi, C. G. Avila-Ortiz Short Review

Salient Achievements in Synthetic Organic Chemistry Enabled by Mechanochemical Activation

Eusebio Juaristi *[a,b]
C. Gabriela Avila-Ortiz[a]

[a] Departamento de Química, Centro de Investigación y de Estudios Avanzados, 07360 Ciudad de México, Mexico
ejuarist@cinvestav.mx
[b] El Colegio Nacional, Donceles # 104, Centro Histórico, 06020 Ciudad de México, Mexico



Received: 07.02.2023
Accepted after revision: 03.05.2023
Published online: 03.05.2023 (Accepted Manuscript), 12.06.2023 (Version of Record)
DOI: 10.1055/a-2085-3410; Art ID: SS-2023-02-0057-SR

Abstract Although known for millennia, it is only recently that mechanochemistry has received serious attention by chemists. Indeed, during the past 15 years an extraordinary number of reports concerning solid-state chemical transformations through grinding and milling techniques have been recorded. This short review discusses the circumstances that led this renaissance, highlighting the present intense interest in so-called green chemistry, the enabling capacity of mechanochemistry to handle insoluble substrates, and the identification of the profound influence that additives can have on mechanochemically activated reactions. The core of this account focuses on salient developments in synthetic organic chemistry, especially in amino acid and peptide mechanosynthesis, the successful employment of mechanochemical activation in combination with asymmetric organocatalysis, the promising combination of mechanochemical activation with enzymatic and whole cell biocatalysis, the remarkable achievement of multicomponent selective reactions via complex, multistep reaction pathways, and the mechanosynthesis of representative heterocycles. The final section comments on some pending tasks in the area, such as scaling-up of milling processes to be of practical use in the chemical industry, the requirement of easier and more efficient control of reaction parameters and monitoring devices, and consequently the careful analysis of additional procedures for a proper understanding of mechanochemical phenomena.

Key words green chemistry, mechanochemistry, solid-state synthesis, synthetic organic chemistry, mechanoenzymology, sustainable chemistry, ball milling

1 Introduction

Mechanochemistry, that is chemical transformations initiated or sustained by mechanical grinding or milling, or alternatively by twin-screw extrusion (TSE), with no or minimal solvent usage, has expanded from a laboratory curiosity to a useful, rapidly developing strategy for the preparation of molecules and amplification of their chemical reactivity. Basically, mechanochemistry deals with physicochemical transformations induced by mechanical energy that originates from impact, shear, compression, extension, etc. Indeed, during the past 15 years a remarkable number of reports on novel solid-state chemical transformations via grinding and milling have been recorded, especially across organic and inorganic chemistry,[1] with special applications such as metal- and metal-organic-catalyzed mechanochemical reactions,[2a–c] mechanochemically induced molecular rearrangements,[2d] preparation of active pharmaceutical ingredients (API),[2e–g] supramolecular chemistry,[2h] mechanosynthesis of heterocyclic rings,[2i] poly-

Eusebio Juaristi studied chemistry at Tecnológico de Monterrey (B.Sc., 1972) and at the University of North Carolina at Chapel Hill (Ph.D., 1977). Juaristi became a postdoctoral associate at the University of California in Berkeley (1977–1978) and research associate at Syntex, Palo Alto, California (1978–1979) before returning to Mexico where he is now Professor of Chemistry at CINVESTAV-IPN. Juaristi was Visiting Professor at the E.T.H.-Zurich, 1985–1986 and 1992–1993, at the University of California in Berkeley (1999–2000), and at RWTH-Aachen, Germany (May–July 2013).
Scientific contributions: Physical organic chemistry with emphasis in conformational analysis and stereochemistry, for example in the study of the *anomeric effect*. Juaristi has also worked in the areas of asymmetric synthesis, in particular on enantioselective synthesis of β-amino acids. Other chemistry areas where Juaristi has had influence include applications of computational chemistry, asymmetric organocatalysis, and sustainable ('green') chemistry.
Awards: Medal of the Mexican Academy of Sciences for Young Scientists in 1988; National Chemistry Award granted by the Mexican Chemical Society in 1994; and the Presidential Medal in Sciences and Arts in 1998. In February of 2006 he became a member of 'El Colegio Nacional', highest academic distinction in Mexico.

mer chemistry,[2j,k] nanomaterials,[2l] valorization of biomass,[2m] and medicinal mechanochemistry,[2n] among others.[2o,p] Remarkably, a range of reactions previously not accessible in solution, can be carried out by means of mechanochemical activation.

Focusing on organic synthesis, this short review presents illustrative examples of salient developments in this exciting field, with the aim to demonstrate its potential as an efficient and clean approach in chemical synthesis, enabled by synthetic procedures that are based on solid state transformations rather than traditional chemistry in solution.

Even though mechanochemical transformations were first recorded several millennia ago,[3] they went mostly unnoticed until recently. Presumably, Aristotle's statement in the 4th century B.C. that 'no reaction takes place in the absence of solvent' led to an erroneous chemistry paradigm which dictates that chemical substrates must be dissolved in a solution to get close to each other through diffusion, so that their functional groups can interact properly.

Importantly, mechanochemistry is now seen as an excellent method of green chemistry, that greatly reduces or even totally avoids solvent use. Indeed, mechanochemistry has been recognized by IUPAC as one of the 10 most promising technologies in the 21st century.[4] In this regard, a now widely accepted representation consisting of three balls arranged triangularly was proposed in 2016 by Rightmire and Hanusa for mechanochemistry in chemical equations (Figure 1a).[5]

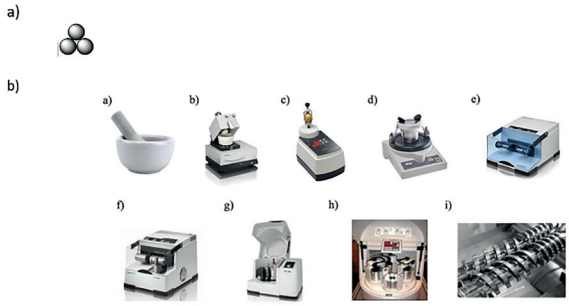


Figure 1 (a) Representation of mechanochemical activation advanced by Hanusa. (b) Typical grinding and milling equipment. (**a**) Mortar and pestle. (**b**) Retsch automated mortar. (**c**) Fritsch vertical shaker mill. (**d**) Fritsch vibrational mill. (**e**) Retsch vibrational ball mill. (**f**) Retsch vibrational ball mill with controlled temperature (Cryomill). (**g**) Retsch planetary ball mill. (**h**) Multiple-sample mill (Automaxion). (**i**) Twin-screw used for continuous mechanochemical extrusion. Reproduced with permission from ref 2e. Copyright 2020 The American Chemical Society.

Mechanochemical reactions can be carried out in various types of instruments, either in batch (vibrational or planetary mills) or continuous manner (twin screw extrusion, TSE), that are often available in larger sizes. Both pieces of equipment are usually operated with the addition of milling balls. The most commonly used instruments are shaker and planetary mills, with increasing attention being paid to TSE (Figure 1b).[6] These instruments are commercially available, and their advantages and limitations have been discussed by several experts.[7] In shaker (vibrational) mills, reactor jars swing back and forth at the chosen frequency (high-speed ball milling, HSBM). By contrast, in a planetary mill the jar spins around a central axis, while rotating around its own axis in the opposite direction (ball milling). Milling equipment (jars and balls) are usually made of stainless steel, minerals (such as agate, zirconia, tungsten carbide), or polytetrafluoroethylene (Teflon). On the other hand, jars of transparent material such as poly(methyl)methacrylate are used to enable *in situ* monitoring (see Section 6.3).

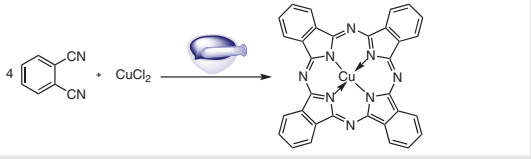
Importantly, in addition to the choice of equipment, a variety of additives can affect mechanochemical reactions. In fact, modified mechanochemical procedures with different additives have resulted in improved reactivity (see Section 4.3).

2 Brief History of Mechanochemistry

One of the earliest recorded applications of mechanochemistry dates back to the 4th century B.C. referring that grinding cinnabar with acetic acid afforded elemental mercury.[3] Importantly, Takacs also pointed out that the addition of small amounts of vinegar helps accelerate the process, apparently 'lubricating' the reaction.[3a] Indeed, a small amount of liquid helps induce a permanent mobile surface layer that facilitated contact between the solid reagents.

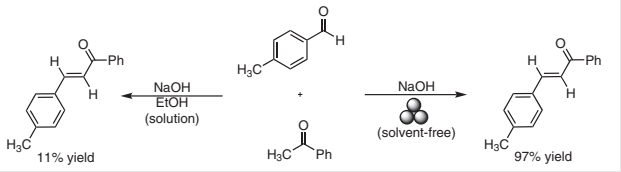
This application of a liquid additive to accelerate the desired reaction between solid reagents in the milling process is presently used in the modern mechanochemical technique of liquid-assisted grinding (LAG), which is discussed in Section 4.3.

As already discussed, during the period between the 3rd century B.C. and the 18th century A.D. reports concerning the use of mechanochemical grinding for the activation of chemical reactions were very rare. However, during the 19th century the German chemical industry developed rather big mills that were employed to grind materials in the preparation of synthetic organic dyes. In an illustrative example, heliogen blue is an intense sapphire dye that was prepared in these mechanical devices by milling phthalonitrile and copper chloride (Scheme 1).[8]



Scheme 1 Mechanochemical (mortar and pestle) preparation of heliogen blue by grinding copper chloride and phthalonitrile[8]

Even after its formal introduction by Ostwald at the end of the 1800s, mechanochemistry continued to be considered as anecdotic rather than reproducible chemistry. Thus, this synthetic strategy was ignored while solution-based methods were well accepted. This situation began to change when Toda and co-workers reported the intriguing observation that neat grinding of an aromatic aldehyde and acetophenone in the presence of NaOH under neat conditions gave the aldol condensation product (the anticipated chalcone) in excellent yield, whereas the reaction performed in 50% aq EtOH afforded the chalcone product in rather low yield (Scheme 2).[9]



Scheme 2 Contrasting behavior in the aldol condensation reaction between *p*-methylbenzaldehyde and acetophenone; left-hand side, in 50% aq EtOH; right-hand side, in the absence of solvent[9]

Subsequently, several applications of solvent-free, mortar and pestle enabled reactions for chemical synthesis were reported by Chimni and co-workers.[10] Nevertheless, manual grinding by means of a mortar and pestle presents several inconveniences, such as lack of reproducibility from lab to lab and even safety concerns. These practical disadvantages motivated the development of automated ball-milling equipment that enable the control of parameters such as frequency (intensity) of milling, securing higher reproducibility in the process.[11] Furthermore, regarding experimental safety issues milling devices incorporate closed containers, minimizing the exposure to potentially toxic or dangerous chemicals. Simultaneously, automated mechanical milling, unlike hand grinding, allows for longer reaction times, which are sometimes needed to attain very small particle sizes for the concomitant activation of reagents in the solvent-free process.

3 Milling Equipment and Reaction Parameters

The reactor jars and balls used for the milling process are generally made from inert materials such as stainless steel, agate, zirconia, tungsten carbide, Teflon, etc. Of course, these materials vary in their hardness and therefore can have an influence on the amount of energy transferred to the reactants and thus their reactivity. For instance, stainless steel and agate milling balls convey greater energy during the milling process than Teflon. Milling media also differ in their chemical resistance, and this fact must be taken into account when dealing with aggressive substrates.[3e] In this regard, stainless steel milling balls and containers may corrode in contact with strong acids. Furthermore, wear of the milling container and milling balls during the milling process can result in metal contamination, and this could impact the reaction outcome.

In this context, while interference of the milling material with reaction substrates is usually undesirable and therefore chemically inert milling materials, such as agate, tungsten carbide, or zirconia, are frequently employed, a novel strategy is being explored in which interaction of the milling jar and balls with the reagents is actually desired.[3e] In particular, the milling tools may be able to act as the catalyst, facilitating catalyst separation and reusability.[12] For example, milling jars and balls made of Cu, Ni, or Pd have been used for mechanochemically catalyzed cross-coupling reactions.[13]

In relevant work in 2014, Borchardt and co-workers[14] devised a galvanostatic procedure for coating inert milling balls with a layer of Pd. The modified milling balls were then successfully used as an *in situ* catalyst in the mechanochemically activated Suzuki reaction. Reaction yields higher than 80% were achieved and the milling balls could be recycled several times.

Nevertheless, the phenomenon of leaching can be a serious handicap of mechanochemistry. In 2023, Friščić and coworkers reported a remarkable contribution in this area using state-of-the-art mills without balls.[15] Specifically, these researchers demonstrated the feasibility of direct mechanocatalysis by resonant acoustic mixing (RAM), an emerging mechanochemical strategy that actually avoids the use of milling media. The proof of concept of this pioneering concept was accomplished by the effective synthesis of triazoles by means of copper-catalyzed alkyne-azide click-coupling (CuAAC) activated by RAM.[15a]

In this regard, the modification of mechanochemical reactions by the presence of additives has resulted in beneficial effects such as increased reactivity (see Section 4.3).

Another way to control a ball-milling reaction involves adjustment of the frequency of milling, which has a direct effect on the motion and beating strength of the balls, which in turn influence the progress of the reaction and therefore the structure of the final products.[16]

As the result of its remarkable attributes, the area of mechanochemistry is presently receiving significant attention.[1,17–20] Accordingly, the potential of mechanochemistry has been highlighted in numerous review articles.[1i,21]

In this short review, we highlight some of the most relevant topics in current mechanochemically enabled synthesis of organic compounds: (1) amino acid and peptide mechanosynthesis, (2) asymmetric organic synthesis and asymmetric organocatalysis under mechanochemical activation, (3) mechanoenzymology, (4) multicomponent reactions activated by mechanochemistry, and (5) mechanosynthesis of representative heterocycles.

4 Attributes of Mechanochemistry That Propelled Its Present Renaissance

4.1 Enormous Attention Being Presently Paid to Sustainable Chemistry

Following the seminal 1998 monograph *'Green Chemistry: Theory and Practice'*, where Anastas and Warner advance the guiding principles of green chemistry,[22] an enormous amount of attention has been paid by the chemical community to the implementation of more sustainable chemical procedures. In this regard, the increasing popularity and success of mechanosynthesis can be ascribed in great measure to the fact that mechanochemical reactions are usually carried out under solvent-free conditions or with minimal volumes of organic solvents [liquid-assisted grinding (LAG); see Section 4.3].[23] This technique drastically minimizes waste production and therefore improves the *E* factor of chemical transformations.[24] In particular, synthetic chemists now have access to mechanochemical equipment that enables solvent-free synthesis.[25] Grinding reactions under solvent-free conditions are usually faster than solution-based reactions owing largely to the increase in the surface area of contact on the solid reactants, as a consequence of smaller particles being generated in the milling process.

Thus, mechanochemical processes are 'greener' since they avoid the usage of excess solvent and concomitant purification protocols. In fact, 'the best solvent is no solvent'[26] and solvent-free mechanochemical techniques are therefore most convenient to eliminate or greatly reduce waste production. Furthermore, the mechanochemical solvent-free environment enables the synthesis of otherwise elusive non-solvated compounds, as well as rapid formation of products that in solution form slowly or not at all.

Furthermore, mechanochemical processes involve low energy consumption (see Section 4.2). Indeed, mechanochemical techniques have been commended for their convenient application in ecologically friendly synthesis, fulfilling the principles of green chemistry.[27]

The mechanochemical solvent-free environment enables the synthesis of otherwise elusive non-solvated compounds, as well as rapid formation of products that in solution form slowly or not at all.

As it was already mentioned, a major motivation for the present renaissance of mechanochemistry is the attention paid to so-called green chemistry, with the concomitant need for transformations that are cleaner, more efficient and safer.[22,26,28] The practical convenience of such development has been endorsed by the pharmaceutical and food industries.[29] As already said, one way to develop more sustainable synthetic methods is by avoiding or minimizing the use of solvents, which is a salient characteristic of solid-state mechanochemical methodologies. Furthermore, solid state grinding usually requires reduced reaction times, and in some instances provide products that are not accessible in solution (see Section 4.5).[3e,30]

In this context, solvents are usually the major components in chemical processes, frequently representing more than 90% of the reactant mixture.[29a,b] Furthermore, many solvents used in chemical reactions are potentially harmful to human health and the environment.[31]

In summary, although the use of solvents in chemical reactions is by far the most common practice,[32] solid-state mechanochemical transformations have demonstrated the feasibility to induce chemical reactivity in the absence of bulk solvents.[33] Mechanochemical methods are therefore rather attractive for both academic and commercial endeavors seeking more sustainable processes. This capacity is especially significant in the present times, when environmental issues, pollution, and climate change are most pressing.[34]

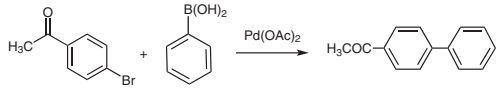
4.2 Reduced Energy Consumption

As already discussed, solid-state and solvent-free organic synthesis will become increasingly important with regard to green or sustainable chemistry. Most important, energy consumption is reduced significantly since used solvents do not have to be recovered and purified for additional use or disposal.

While non-conventional energy sources for chemical reactions such as ultrasound and microwave irradiation continue to attract the interest of many synthetic chemists,[35] mechanical milling can offer an energy advantage over their solution counterparts.[36] For instance, several studies by Ondruschka and co-workers of the energetics of the Suzuki–Miyaura coupling showed significantly higher energy efficiency in a milling process, as compared to traditional heating or microwave irradiation.[37]

In particular, Suzuki–Miyaura coupling of phenylboronic acid with 4-acetylphenyl bromide affording 4-acetylbiphenyl was used as model reaction to evaluate the energy cost of different activation techniques: microwave irradiation, planetary ball milling, and vibrational ball milling. Results of these experiments are summarized in Table 1 revealing lowest energy consumption under mechanochemical activation.[37b]

Table 1 Comparison of Amounts of Electrical Energy Necessary for the Performance of the Suzuki–Miyaura reaction of 4-Acetylphenyl Bromide with Phenylboronic Acid[37b]



Activation mode	Yield (%)	*E* (kW)
microwave	80	40.0
planetary ball mill	89	1.7
vibrating mill	85	1.0

Generally, ball mills are rather efficient regarding energy consumption. For example, a laboratory vibrational mill, such as the one depicted in Figure 1e, requires amounts of energy that are rather convenient, especially when considering the typically short reaction times needed in mechanosynthesis.[38]

It is also worthwhile to recall that solvation frequently suppresses reactivity as a consequence of the stabilization of the reagents. Thus, in addition to minimizing the negative environmental impact of solvents, mechanochemistry may improve the reagent's reactivity, leading to reduced energy demand when solvation is prevented.[2f]

On the other hand, Yang, Chen, and co-workers have stressed the fact that ball-milling activation transfers a rather significant amount of mechanical energy into the treated materials, simultaneously ensuring a large surface area and intimate mixing between reactants. This substantially reduces the energy barriers, and thus a smaller activation energy is needed to initiate the reactions in thermal processes.[39]

4.3 Additive-Based Mechanochemistry

The usual way to carry out a mechanochemical reaction is by 'neat grinding', implying that no additional substances (that is, inert solids or unreactive liquids) have been added to the reactants. Nevertheless, the beneficial effect of added solvent on mechanochemical reactions was reported in 2002.[40a] This method was eventually named 'liquid-assisted grinding' (LAG) by Friščić and co-workers.[40b,c] The term 'kneading' is used when referring to manual grinding with a mortar and pestle.[40d]

In this regard, mechanochemistry helps overcome solubility restrictions (see Section 4.4). LAG protocols use only minute amounts of solvents that function as catalytic additives.[41]

In organic synthesis Eckert-Maksić, Friščić, and coworkers reported LAG for the high-yield mechanosynthesis of more than 50 thioureas.[42] Regarding reaction selectivity, Browne and co-workers reported LAG-activated selective fluorinations (mono- *vis-a-vis* difluorination).[43]

Thus, mechanochemical reactions are accelerated by the addition of small amounts of organic solvents.[44] Apparently LAG facilitates more molecular mobility relative to neat grinding. Usually, the choice of the appropriate additive is based on a process of trial and error. The most commonly used solvents as for LAG include methanol, ethanol, propan-1-ol, ethyl acetate, acetonitrile, and some ethers, such as THF and methyl-*tert*-butyl ether. The LAG process is characterized by the parameter η, that corresponds to the volume of solvent in μL divided by the weight of sample weight in mg. Recommended values for LAG fall in the η range of 0–2 μL mg^{-1}. Higher η values are characteristic in the formation of slurries. By contrast, η = 0 for neat grinding.

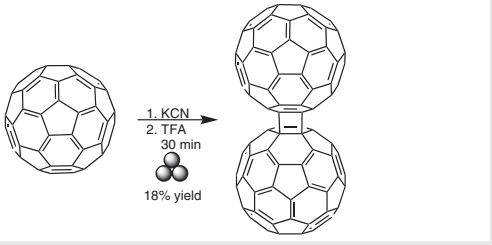
Importantly, the addition of chemically inert milling auxiliaries such as silica, sand, sodium chloride, or sodium sulfate salts can be used as a means of supplying the mechanochemical reactants from an inert support and facilitating the reaction.[1i,3e] Upon the addition of these milling auxiliaries, a more 'dilute' mixture of the milling components can be formed, improving molecular contact and reactivity. It is worthwhile mentioning that removal of inert additives, such as sand and silica, is easily carried out during the workup procedure *via* filtration or centrifugation. In an interesting recent development, hydrotalcite or hydroxyapatite minerals have also been used as additives fulfilling two functions, as activating bases and as supporting material in ball-milling mechanosynthesis of peptides.[45]

4.4 Handling of Insoluble Reactants

Solvent-free mechanochemical activation enables the manipulation of substrates exhibiting poor or negligible solubility. Indeed, insoluble materials can react with no problem under solvent-free reaction conditions. For example, James, Vyle, and co-workers have reported that biomolecules, such as sugars and nucleosides, that are known to exhibit low solubility in organic solvents are readily modified via ball-milling procedures.[46] More generally, reactions between solids that are not soluble in the common solvents are well handled by means of mechanochemistry. Thus, mechanochemistry is frequently able to overcome poor reactant solubility issues in reactions involving reactants with poor solubility, enabling chemical reactions that otherwise would not be possible in solution.

A salient example is the use of amino acids, peptides, and enzymes in synthetic organic chemistry. These biomolecules generally present low solubility in organic solvents, which limits their chemical manipulation and use in synthesis. Recently, however, the use of mechanochemical techniques has helped overcome solubility limitations in the synthesis and application of amino acids and peptides (see Section 5.1). Furthermore, biocatalysts such as enzymes have recently been shown to perform well under ball-milling conditions (see Section 5.3).

Emblematic here is the success achieved in reactions of fullerenes (notoriously insoluble molecules in organic solvents) under ball-milling conditions. In particular, Komatsu and co-workers found that a dimer of C_{120} is readily formed in reactions carried out under high-speed ball milling in the absence of solvent (Scheme 3).[47]



Scheme 3 Dimerization of fullerene C_{120} by means of solvent-free ball milling[47]

The possibility of overcoming solubility limitations in chemical synthesis has encouraged the utilization of ball-milling techniques to enable chemical reactions that are challenging or impossible under solution-based conditions.[48]

In this regard, Ito, Kubota, and co-workers[49] reported in 2021 a high-temperature ball-milling technique for solid-state palladium-catalyzed Suzuki–Miyaura cross-coupling reactions *via* a high-temperature ball-milling technique. This 'heat and beat' strategy enabled, among others, the reaction of insoluble aryl halides with polyaromatic compounds that present extremely low solubility and are therefore scarcely reactive under conventional solution-based conditions. Thus, induction-heated ball milling provides a practical mechanochemical method for performing molecular transformations of insoluble organic compounds that cannot be carried out by any other approach.[21g]

4.5 'Impossible' Reactions That Are Successful by Milling

The grinding, beating, and shearing forces involved in solid-state mechanochemical processes can give rise to chemical reactivity that is not possible in thermal processes.[3a] Indeed, when mechanical forces rather than energy transferred by heat, activate reactions, the mechanism of a reaction inside a ball mill can be different and sometimes can lead to unexpected products.[8] Thus, mechanochemical activation has occasionally resulted in the discovery of new chemical reactivity, expanding the scope of synthetic chemistry.[30,50,51] As for the explanation, it has been advanced that the locally high-energetic mechanical process shifts the reactant's atoms away from their equilibrium position, promoting the irreversible and efficient formation of the reaction solid-state product.[52] Another attractive feature of mechanochemical protocols is the absence of laborious workup protocols.

In an illustrative example showing pronounced differences between thermo- and mechanochemistry in organic chemistry, Gomollón-Bell reported how the structure of copper complexes depends on how they are made. In particular, copper derivatives form square-planar complexes in solution, while ball milling provides octahedral structures, as discovered by D. E. Crawford.[8]

4.6 Successful Handling of Air- and Water-Sensitive Reagents by Ball Milling

Mechanochemical techniques often overcome the need for inert environments when handling air/moisture sensitive reagents. For instance, influential papers by Ito and co-workers[53a,b] and Browne and co-workers[53c–e] revealed that mechanochemistry allows carrying out reactions with sensitive organometallic compounds in air. Indeed, the synthesis of palladium and zinc sensitive complexes, that usually requires the use of a glove box and Schlenk lines, was efficiently accomplished under simple ball-milling conditions.

In this regard, it is worthwhile mentioning that expensive protocols involving the use of degassed and anhydrous solvents can be avoided through the use of mechanochemical techniques.[53,54]

In this context, especially relevant is the mechanochemical activation of zero-valent metals. Indeed, activating zero-valent metals is an important process in many synthetic and catalytic chemical processes. In particular, the

combination of ball milling and chemical synthesis mediated by zero-valent metals provides a timely sustainable platform for chemical synthesis, and catalysis.[55]

In this context, Grignard's reaction is a classical, most helpful synthetic tool for preparing valuable intermediates in the total synthesis of natural products, among many other molecules. Nevertheless, the preparation of Grignard's reagents is often difficult to implement, requiring inert and anhydrous atmospheres. In this regard, the groups of Harrowfield, Birke, Hanusa, Bolm, and Ito have independently reported the mechanochemical activation of magnesium metal for the synthesis of Grignard reagents via the insertion of magnesium metal into organic halides without the need for carefully dried solvents.[56]

As can be anticipated, subsequent reaction of Grignard reagents with carbon dioxide provides the corresponding carboxylic acids in moderate to good yields. Nevertheless, this methodology works well with liquid bromide reagents, but rather poorly when the halides are solid, insoluble substrates. Since neither prolonged time nor various additives or LAG species afforded better results, increasing the temperature was considered. Importantly, Ito and co-workers achieved that goal by means of a heat gun to reach higher temperatures.[57] Such 'heat and beat' mechanochemical procedure has been successfully extended to other mechanochemical processes.[58]

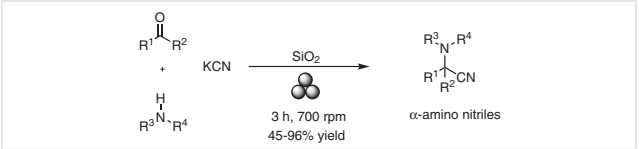
5 Salient Developments in the Mechanochemical Activation of Synthetic Organic Chemistry

This short review aims to highlight salient achievements of mechanochemical activation in (1) amino acid and peptide mechanosynthesis, (2) asymmetric organic synthesis and asymmetric organocatalysis under ball-milling conditions, (3) mechanoenzymology, (4) multicomponent mechanochemical reactions, and (5) mechanosynthesis of representative heterocycles.

5.1 Amino Acid and Peptide Mechanosynthesis

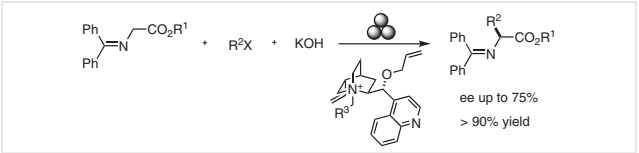
Amino acids are essential components of relevant biomolecules such as peptides and proteins, which in recent years have also been successfully used as organocatalysts in asymmetric synthesis.[59]

Typically, the synthesis of α-amino acids in solution can be carried out by means of the Strecker reaction[60] between amines, cyanides, and carbonyl compounds to afford *rac*-α-aminonitriles, which are then converted into *rac*-α-amino acids *via* hydrolysis.[61] In 2016, Bolm, Hernández, and co-workers described a mechanochemical procedure for the corresponding mechanosynthesis, employing SiO_2 as inert milling additive (Scheme 4).[62]



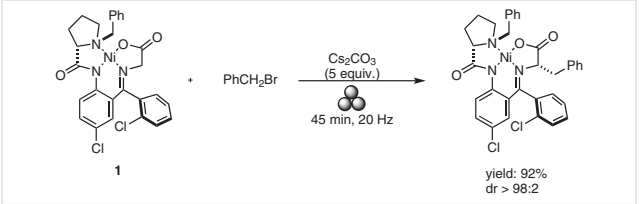
Scheme 4 Mechanochemical Strecker reaction of α-aminonitriles from aldehydes, amines, and cyanides[62]

On the other hand, in 2012 Lamaty and co-workers developed an enantioselective synthesis of α-amino ester derivatives by asymmetric phase-transfer catalyzed alkylation of precursor Schiff bases in a ball mill in the presence of a chiral cinchonidinium ammonium salt (Scheme 5).[63]



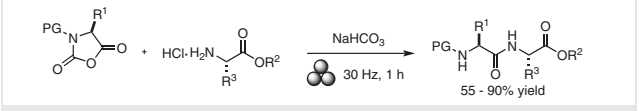
Scheme 5 Enantioselective alkylation of Schiff bases under solvent-free ball-milling conditions[63]

In 2015, Bolm, Soloshonok, and co-workers reported the asymmetric alkylation of glycine residues by means of nickel(II) complex **1** (Scheme 6).[17a]



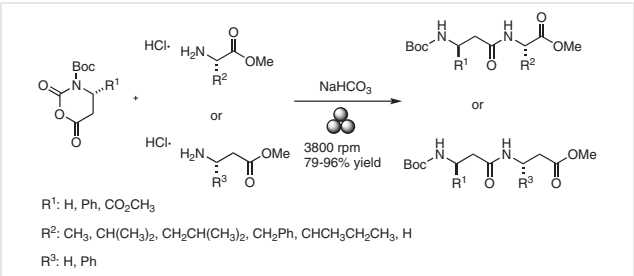
Scheme 6 Mechanochemical asymmetric alkylation of chiral nickel(II) complex **1**[17a]

A relevant challenge in peptide synthesis is to reduce the amount of solvent used; hence mechanochemistry can play an essential role for optimizing peptide synthesis. In this regard, in 2009 Lamaty and co-workers reported that the opening of α-amino acid *N*-carboxy anhydrides with α-amino acid esters under solvent-free conditions in a ball mill affords α-peptides in good yield (Scheme 7).[64,65] With base in this work and motivated by the significant interest in the chemistry of β-amino acids and β-peptides,[66] Hernández and Juaristi reported the synthesis of α,β- and β,β-dipeptides in 2010 (Scheme 8).[67] Importantly, comparison of the specific optical rotations of dipeptides prepared



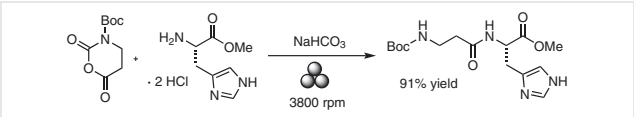
Scheme 7 Solvent-free peptide synthesis[64,65]

in this work with data reported in the literature showed total agreement, indicating that no significant racemization took place.



Scheme 8 Mechanosynthesis of α,β- and β,β-dipeptides[67]

The efficiency of this methodology was further confirmed through the mechanosynthesis of the sweetener aspartame by milling of a mixture of the *N*-carboxy anhydride of aspartic acid and alanine methyl ester for 1 h at 30 Hz. The desired dipeptide was obtained in 97% yield and removal of the protecting groups afforded aspartame hydrochloride.[67] On the other hand, Hernández and Juaristi reported the mechanosynthesis of a protected derivative of the pharmacologically active dipeptide (*S*)-carnosine in the ball mill (Scheme 9).[67]

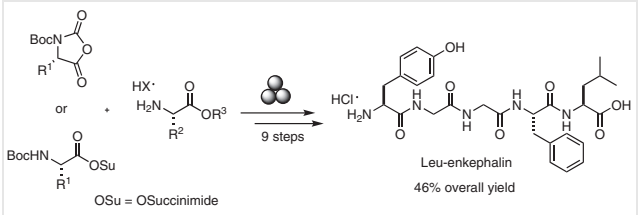


Scheme 9 Mechanosynthesis of protected dipeptide (*S*)-carnosine under solvent-free conditions[67]

In 2017, Landeros and Juaristi reported the high-yielding mechanosynthesis of various α,α-, α,β-, and β,β-dipeptides from *N*-protected amino acids and amino acid methyl ester hydrochlorides in the presence of HOBt and EDC as coupling reagents, and using Mg-Al hydrotalcite (HT) mineral as green activating agent. The mechanochemical protocol offers important advantages, such as easy workup, recovery and recyclability of the hydrotalcite activator, and short reaction times.[45a]

The mechanosynthesis of long peptide chains is a challenging goal since coupling and deprotection reactions become less efficient as the peptide chain length becomes longer.[68] The synthesis of Leu-enkephalin represents one of the most complex mechanosyntheses registered to this date (Scheme 10).[69]

The risk of epimerization represents a severe hurdle in amide coupling.[70] In this regard, Lamaty, Métro, and co-workers[71] examined the potential of ball milling to eliminate epimerization during peptide coupling. In the process, it was observed that the mechanochemical procedure required only one-third of this reaction time, probably as



Scheme 10 Solvent-free mechanosynthesis of Leu-enkephalin[69]

consequence of higher concentration of the reagents in the ball mill, which shortens reaction times relative to the corresponding reaction in solution.

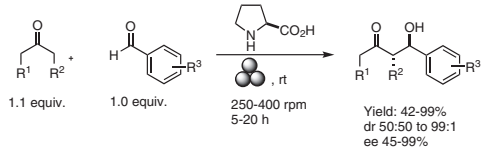
In this context, carbodiimide-activated coupling of amino acid residues has been carried out conveniently by means of mechanochemistry.[72] On the other hand, Lamaty, Laconde, Colacino, and co-workers reported the use of activated α-aminoacyl benzotriazole derivatives in peptide mechanosynthesis.[73]

Also relevantly, Užarević, Hernández, and co-workers reported the oligomerization of glycine promoted by TiO_2 (a mineral likely to be present in earth during prebiotic times) under mechanochemical activation.[74]

5.2 Asymmetric Organic Synthesis and Asymmetric Organocatalysis under Ball-Milling Conditions

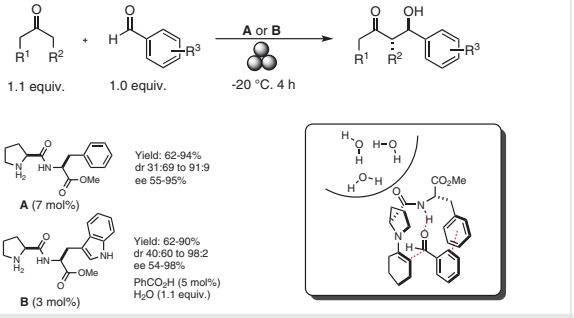
During the 21st century, asymmetric organocatalysis has become a rather efficient and attractive way to prepare chiral compounds in enantiomerically enriched form. The catalytic nature of this strategy fulfills some of the principles of so-called 'green chemistry', which is a major topic associated with the progress of chemistry in the 21st century. Importantly, two papers published in 2012 advance the idea that organocatalysis can be made even more sustainable when in combination with mechanochemistry.[10a,75]

From the beginning of asymmetric organocatalysis,[76] aldol reactions have been used as test reaction of the efficiency of novel organocatalysts.[77] In this context, the remarkable performance of (*S*)-proline as organocatalyst in asymmetric aldol reactions[76a] motivated the examination of the reaction under solvent-free conditions. Indeed, Bolm and co-workers reported the successful asymmetric aldol reaction organocatalyzed by (*S*)-proline under high-speed ball milling (HSBM).[78] Different aldehydes and ketones were used as substrates and the expected aldol products were obtained in 42–99% yield, up to 99:1 diastereoselectivity, and 45–99% ee (Scheme 11). Relative to traditional reactions in solution, HSBM resulted in shorter reaction times and cleaner reactions. Soon thereafter, (S_a)-Binam-(*S*)-prolinamide was successfully employed by Nájera and co-workers as a chiral organocatalyst in the asymmetric aldol reaction under ball-milling conditions.[79]



Scheme 11 Solvent-free enantioselective aldol reaction organocatalyzed by (*S*)-proline in a ball mill[78]

Subsequently, the use of peptidic organocatalysts derived from (*S*)-proline was examined. In particular, dipeptidic organocatalysts (*S*,*S*)-Pro-Phe (**A**) and (*S*,*S*)-Pro-Trp (**B**) were tested by Juaristi and co-workers in the intermolecular aldol reaction under ball milling activation (Scheme 12).[80] These organocatalysts afforded the desired aldol product in high yield and excellent diastereo- and enantioselectivity. Interestingly, the presence of water molecules as additive apparently induces the formation of chiral micelles as consequence of a hydrophobic effect, leading to a more rigid transition state and then high stereoselectivities (see inset in Scheme 12).[80]

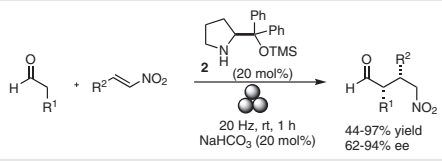


Scheme 12 Enantioselective intermolecular aldol reaction organocatalyzed by dipeptidic organocatalysts (*S*,*S*)-Pro-Phe and (*S*,*S*)-Pro-Trp by HSBM in the presence of water and benzoic acid as additives[80]

Considering that potential role that π–π stacking interactions could play in the robustness of the transition state for the aldol reaction (cf. short distance between the aromatic rings, see inset in Scheme 12), it was reasoned that the replacement of the carbonyl amide segment by a thiocarbonyl in organocatalysts **A** and **B** would afford more acidic N–H protons and consequently stronger hydrogen bonds between the substrate and the organocatalyst; that is, a more rigid transition state. Accordingly, the corresponding (*S*,*S*)-thiodipeptides were synthesized and evaluated in the same aldol reaction under similar reaction conditions. As it turned out, thiopeptidic organocatalysts led indeed to the formation of aldol products with higher diastereoselectivity, up to 98:2 *anti*/*syn* ratio.[81]

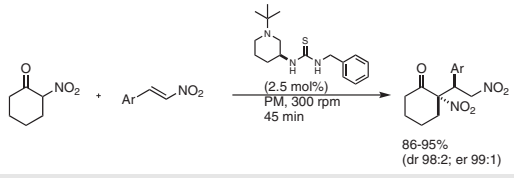
Machuca and Juaristi investigated further the putative stabilizing effect by π–π stacking interactions in the suggested transition state. Specifically, the electron density on the aromatic ring in the substrate aldehydes was systematically varied by the incorporation of substituents with different electron-donating or electron-withdrawing capacity. As anticipated, electron-deficient aldehydes afforded the aldol product in better yields and with higher stereoselectivity relative to electron-rich analogues. This observation is in line with the hypothesis that π–π stacking interactions play a significant role in the resulting yields and stereoselectivities. Furthermore, the solvent-free mechanochemical conditions are expected to enhance the rigidity of the transition state leading to more selective reactions.[82a] Relevantly, when the reaction was evaluated under contrasting experimental protocols, specifically, in solution, neat conditions with stirring, and solvent-free HSBM activation, the highest selectivity (90:10 *anti*/*syn* ratio and 91:9 enantiomeric ratio) was achieved after 0.5 h of reaction under mechanical activation in a ball mill. In the course of this work it was also established that the stereogenic center in the (*S*)-proline residue is primarily responsible for the observed enantioinduction.[82b]

In 2004, Wang and co-workers reported the first example of Michael reactions performed under HSBM solvent-free conditions, employing K_2CO_3, an achiral inorganic base, as catalyst. This mechanochemical reaction required less than 1 h, and provided the expected racemic adducts in good yields and good *anti*/*syn* diastereoselectivity.[83] As it could have been anticipated, this report motivated the examination of chiral organocatalysts that could lead to enantiomerically enriched products. In particular, Michael additions organocatalyzed by chiral thioureas were deemed a particularly attractive subject of study. Indeed, Toma, Šebesta, and co-workers investigated the effectiveness of chiral pyrrolidine derivatives as organocatalysts in the asymmetric Michael reaction between aldehydes and β-nitrostyrene.[84] As it turned out, α,α-diphenylprolinol derivative **2** afforded the enantioenriched Michael products in 44–97% yields, up to 95:5 diastereomeric ratios, and up to 94% ee (Scheme 13).



Scheme 13 Enantioselective Michael addition organocatalyzed by silylated α,α-diphenylprolinol **2** activated by ball milling[84]

Subsequently, Xu and co-workers evaluated the potential of chiral squaramide derivatives as H-bond donor catalysts in the solvent-free Michael addition of 1,3-dicarbonyl nucleophiles to 1-aryl-2-nitroalkenes employing a planetary ball mill.[85] On the other hand, Bolm and co-workers employed thiourea-based organocatalysts in an organocatalytic asymmetric version for the Michael addition, under planetary-milling conditions. For instance, α-nitrocyclohexanone added to various nitroalkene derivatives to give the desired product in up to 95% yield, with a diastereomer-

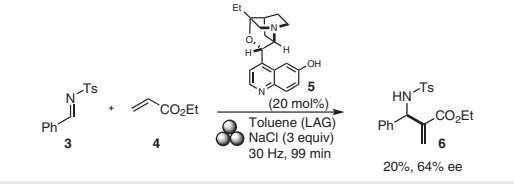


Scheme 14 Mechanochemically activated organocatalyzed asymmetric Michael addition reaction[86]

ic ratio of 98:2 and up to 98% ee. The reaction took place within 30 min (Scheme 14).[86]

In 2020, Šebesta and co-workers reported an organocatalyzed mechanochemically activated sequential asymmetric Mannich addition and diastereoselective fluorination sequence. This reaction was catalyzed by chiral squaramide catalysts affording the desired products as a single diastereomer in good yields and excellent enantiomeric purities.[87]

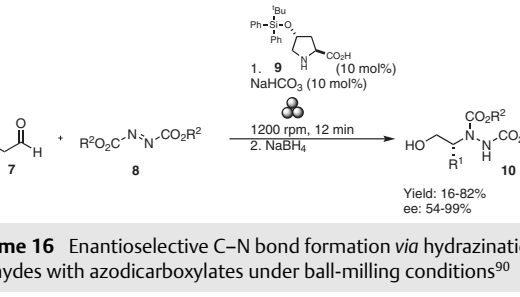
In this context, Mack and Shumba described the efficient activation of the Morita–Baylis–Hillman (MBH) reaction by ball milling.[88] In this regard, chiral tertiary amines were explored as organocatalysts in the MBH reaction of imine **3** with Michael acceptor ethyl acrylate (**4**). Best results were achieved with organocatalyst β-isocupreidine (**5**) delivering the aza-MBH product **6** with 64% ee (Scheme 15).[89]



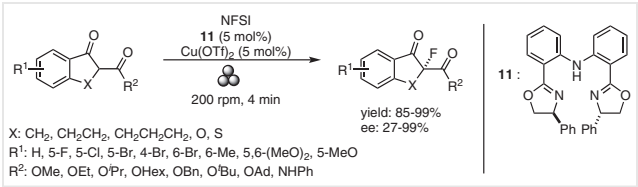
Scheme 15 Organocatalytic aza-Morita–Baylis–Hillman reaction using ball-milling technique[89]

With respect to enantioselective C-amination under solvent-free ball-milling conditions, (*S*)-proline derivative **9** organocatalyzed the reaction of aldehydes **7** with azodicarboxylate **8** to give amine precursors **10** in good yields and high enantioselectivities (Scheme 16).[90]

Highly enantioselective fluorination of β-keto esters employing a planetary ball mill under solvent-free conditions was also accomplished by Xu and co-workers using supported bis(azoline)-Cu(OTf)$_2$ complexes **11** (Scheme 17).[91]



Scheme 16 Enantioselective C–N bond formation *via* hydrazination of aldehydes with azodicarboxylates under ball-milling conditions[90]



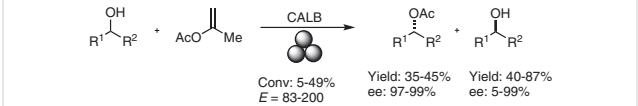
Scheme 17 Enantioselective fluorination of β-keto esters[91]

In 2022, Šebesta and co-workers reported the high yielding, highly enantioselective oxa-Diels–Alder reaction by using either a bifunctional aminothiourea or a monofunctional quinine organocatalyst under LAG ball-milling conditions.[92]

5.3 Mechanoenzymology

The successful mechanosynthesis of amino acids and peptides (see Section 5.1) gave evidence of the resilience of these biomolecules to the stressful conditions prevailing in the milling process. The remarkable stability of amino acids and peptides under mechanic stress was further evidenced by the remarkable degree of stereoselectivity achieved in mechanochemical asymmetric reactions (see Section 5.2). These observations paved the way for the use of mechanochemistry in combination with enzymic catalysis. Indeed, in 2015 Gross and co-workers described the mechanochemical ring-opening polymerization of ω-pentadecalactone catalyzed by immobilized *Candida antarctica* lipase B (CALB).[93] This development demonstrated that enzymic activity does prevail under stressful mechanical milling.

Soon thereafter, seminal experiments of Hernández, Frings, and Bolm established the catalytic capacity of biocatalyst *Candida antarctica* lipase B (CALB) to perform the kinetic resolution of racemic secondary alcohols under mechanical milling. Again, this observation confirms the significant resistance of peptide bonds in biomolecules to mechanical stress (Scheme 18).[21h,94]



Scheme 18 Enzymatic kinetic resolution of racemic secondary alcohols catalyzed by immobilized CALB under mechanochemical conditions;[21h,94] *E* = enantioselectivity

These reports set the basis for the transition from synthesis and manipulation of amino acids and peptides under mechanochemical activation to the application of biocatalysis together with mechanochemistry to perform useful, enantioselective tasks. The new field of *mechanoenzymology* was born (Figure 2).[95]

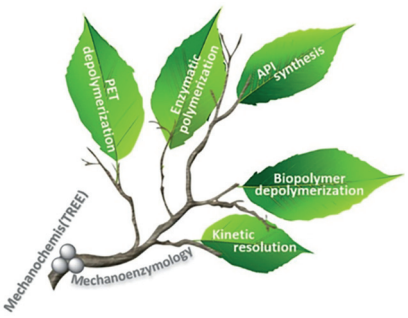


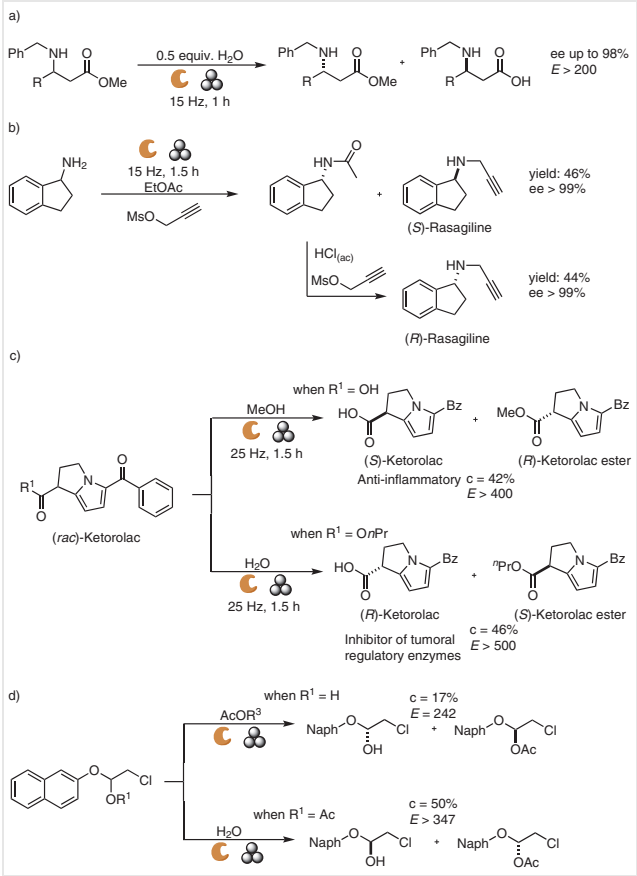
Figure 2 Mechanoenzymology as a new branch of mechanochemistry. Reproduced with permission from ref 95. Copyright 2021 Wiley-VCH.

Systematic studies involving mechanoenzymology with specific emphasis in the area of sustainable medicinal mechanochemistry were then carried out by Juaristi and co-workers using immobilized CALB as catalyst.[96] In particular, CALB enzyme was then used in the kinetic resolution of racemic β-amino esters, β-amino alcohols, amines, and carboxylic acids (Scheme 19); one of the driving forces in these studies being the difference of pharmaceutical activity between enantiomers.[97]

Thus, these mechanoenzymatic strategies (Schemes 18 and 19) allowed, under appropriate conditions (reaction time and frequency, additives, milling jar/balls material), the preparation of enantioenriched and enantiopure active pharmaceutical ingredients or their precursors, with superior results when compared with the same processes in solution. These developments encourage the future examination of even more complex enzymes such as transaminases, reductases, and monooxygenases, among other important enzymes.

In this context, the polymerization of ω-pentadecalactone was reported to afford high-molecular-weight polymers.[98] Furthermore, non-immobilized enzymes have also been used together with mechanochemical activation to carry out peptide bond formation. For instance, the mechanoenzymatic oligomerization of α-amino acids was accomplished by means of protease papain.[99] Oligomerization of α-amino acids by means of a twin-screw extrusion has also been recorded.[68b,99]

Recently, the effectiveness of enzymes in mechanochemical depolymerization of biomaterials has been actively explored by Auclair, Friščić, and co-workers.[100] Most interesting is the successful use of hydrolases, such as cellulases and chitinases, in the depolymerization of feedstocks that are normally considered as biowaste (Figure 3).[100] For the implementation of this work, and aiming to increase the degree of depolymerization, the authors developed the 'reactive aging' technique, which consists of cycles of milling followed by aging.[100c] This protocol reduces mechanical



Scheme 19 Bioactive chiral compounds prepared in enantiomerically pure form *via* mechanoenzymatic kinetic resolution using immobilized CALB. (a) Resolution of *N*-benzylated β^3-amino esters.[96a] (b) Synthesis of enantiomerically pure (*R*)-rasagiline.[96b] (c) Resolution of *rac*-ketorolac.[96c] (d) Resolution of β-blocker propranolol.[96d] *E* = enantioselectivity. *c* = conversion.

stress on the biocatalyst and facilitates contact between the enzyme and the substrate. This strategy offers great potential in the depolymerization of plastic materials such as polyethylene terephthalate (PET).[101]

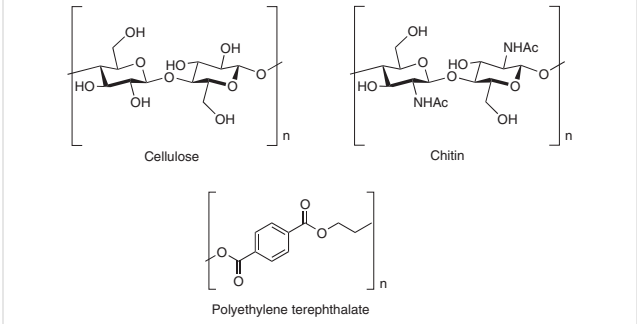
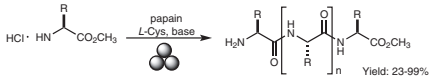


Figure 3 Some polymeric molecules suitable for mechanoenzymatic depolymerization[100]

On the other hand, lipases and proteases can also be employed in mechanoenzymatic protocols to catalyze the polymerization of amino acids.[102] In a salient example, Hernández and co-workers[99] developed a mechanochemical papain-catalyzed polypeptide formation by means of a chemoenzymatic protocol that overcame the low degree of polymerization found in traditional solution procedures, as a consequence of premature precipitation of the oligopeptides (Scheme 20).

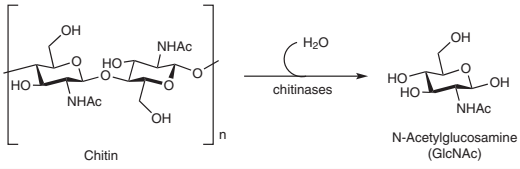


Scheme 20 Mechanoenzymatic papain-catalyzed oligopeptide formation by ball milling[99]

On the other hand, Arciszewski and Auclair focused on mechanoenzymatic reactions involving polymers either as substrates or products.[103] Representative biopolymers were various proteins, DNA, and cellulose, or synthetic polymers such as plastics.

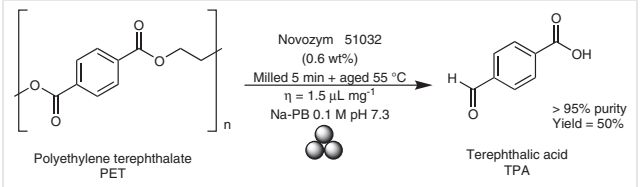
Regarding mechanoenzymatic breakdown of natural polymers, it is worthwhile to emphasize that there is an enormous interest in finding renewable, non-fossil-based feedstocks to satisfy present and future needs for energy and basic chemicals. In particular, natural polymers, such as cellulose, hemicellulose, and chitin, could provide suitable abundant sources of clean energy if they can be broken down into useful products. Particularly pertinent, biomass depolymerization is a challenging issue owing to the poor solubility of the constituent polymers. This limitation can in principle be overcome by means of solvent-free solid-state mechanochemical techniques (see Section 4.4).

In this context, chitinous biomass, that has been recorded as the most abundant nitrogen-containing biopolymer on earth, is an attractive chemical feedstock for the production of useful drugs and agrochemicals (Scheme 21). In 2019, Friščić, Auclair, and co-workers reported the efficient mechanoenzymatic breakdown of chitin to *N*-acetylglucosamine (GlcNAc) by a commercial chitinase (Scheme 21).[100b]



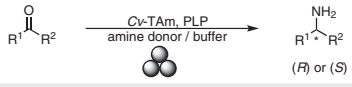
Scheme 21 The mechanoenzymatic hydrolysis of chitin to generate *N*-acetylglucosamine[100b]

Mechanoenzymatic hydrolysis of synthetic polymers. Presently, only one tenth of the global annual plastic production (ca. 370 million tons in 2019) is recycled after use, and the rest represents a serious problem, polluting land, sea, and rivers. Thus, depolymerization is urgently needed for recycling plastics in order to turn them into valuable materials. In this direction, Friščić, Auclair, and co-workers recently reported that mechanoenzymatic procedures enable the direct depolymerization of polyethylene terephthalate (PET) plastics by means of commercially available *Humicola insolens* cutinase (Scheme 22).[101a,104] This process was also efficient in the depolymerization of other plastics such as terephthalates and polycarbonates, with better results relative to the corresponding procedures in solution.



Scheme 22 Mechanoenzymatic procedure for the depolymerization of PET hydrolysis to give chemically useful terephthalic acid[101a,104]

Mechanoenzymatic reactions with whole cell transaminases. In their 'concept' article in 2021 on mechanoenzymatic chemistry, Pérez-Venegas and Juaristi wondered whether whole cells would be sufficiently stable to function properly under milling conditions.[95] As it turns out, in 2022 Hailes and co-workers described the enantioselective amination of various carbonyl substrates catalyzed by whole cell transaminases under mechanochemical activation.[105] Relevantly, the transaminase-catalyzed conversion of prochiral aldehydes and ketones into amino derivatives is totally enantioselective (Scheme 23).



Scheme 23 Enantioselective mechanoenzymatic reductive amination of aldehydes and ketones with transaminases[105]

When compared with traditional conditions in solution, the mechanoenzymatic whole cell reactions afforded significantly higher yields of the products, despite hostile conditions during ball milling; that is, high energy impacts, points of high local temperature, and sites of high pressure inside the reactor jar.

In short, biocatalysts are closely linked to the future of organic synthesis, and enzymatic processes may represent an important avenue in the future of mechanochemistry. Here, one can envision a variety of relevant upcoming developments of mechanoenzymology, for example making use of the many new enzymes that are being discovered by means of modern tools such as protein engineering and bioinformatics. Indeed, one can expect that the performance of engineered enzymes will exceed the efficiency of catalysts traditionally used up to now in organic synthesis.[106] Nevertheless, as it was recently pointed out by Cossy,[107] present day synthetic chemists are better advised

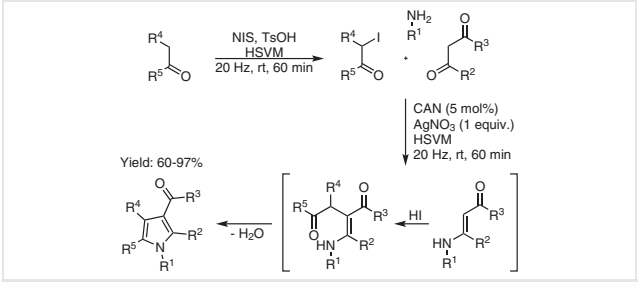
to learn molecular biology and/or to strengthen their collaborations with molecular biologists.

In this context, the possibility of carrying out enzymatic cascades under milling activation for the rapid production of complex compounds should be rather attractive both at laboratory and industrial scale.[108,109]

5.4 Multicomponent Reactions Activated by Mechanochemistry

Multicomponent reactions are a powerful strategy for the synthesis of complex molecular structures. Whereas in solution these reactions usually proceed through a series of reversible processes under thermodynamic control, mechanochemical multicomponent reactions are kinetically controlled.[110]

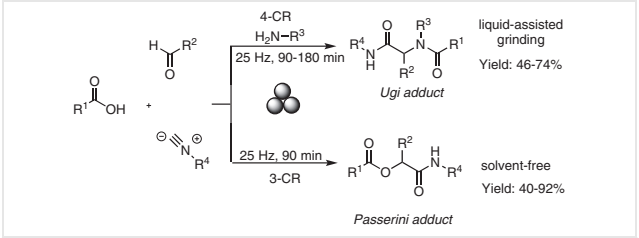
In a relevant contribution in the area of mechanochemistry, Menéndez and co-workers reported that the three-component Hantzsch pyrrole synthesis proceeds efficiently under ball-milling conditions (Scheme 24).[111]



Scheme 24 Mechanochemically activated three-component Hantzsch pyrrole synthesis[111]

In this context, isocyanide-based multicomponent reactions have been well-studied under traditional reaction conditions in solution.[112] By contrast, in 2016 Polindara and Juaristi revealed that Ugi 4-component reactions (4-CR) employing *tert*-butyl isocyanide, aromatic aldehyde, chloroacetic acid, and propargylamine in the presence of 2 mol% $InCl_3$ proceeded satisfactorily in a ball mill (Scheme 25).[113] The same team also disclosed a mechanochemical Passerini 3-component reaction (3-CR) (Scheme 25).[113]

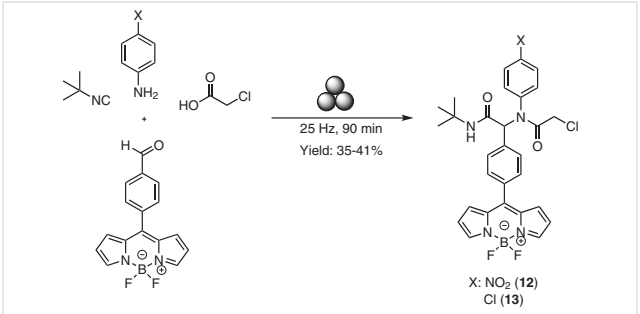
Boron dipyrromethene (BODIPY) dyes have attracted significant interest in view of their useful photophysical



Scheme 25 Mechanosynthesis of Ugi 4-CR and Passerini 3-CR adducts[113]

properties.[114] Indeed, among many biological and medical applications BODIPY dyes have been employed as emitting tags in bioimaging.[115] Accordingly, various synthetic routes have been developed to incorporate BODIPY moieties in their structure. In particular, the Liebeskind–Srogl coupling reaction[116] is a rather convenient means for the preparation of BODIPY derivatives.

In this regard, the Polindara–Juaristi mechanochemical procedure described above,[113] was recently applied for the mechanosynthesis of several BODIPY dyes, including BODIPY-Ugi adducts **12** and **13** (Scheme 26).[117] Figure 4 depicts the X-ray diffraction structure and conformation of BODIPY-Ugi adduct **12**.[117b]



Scheme 26 Ugi reaction in the mechanochemical preparation of BODIPY adducts **12** and **13**[117]

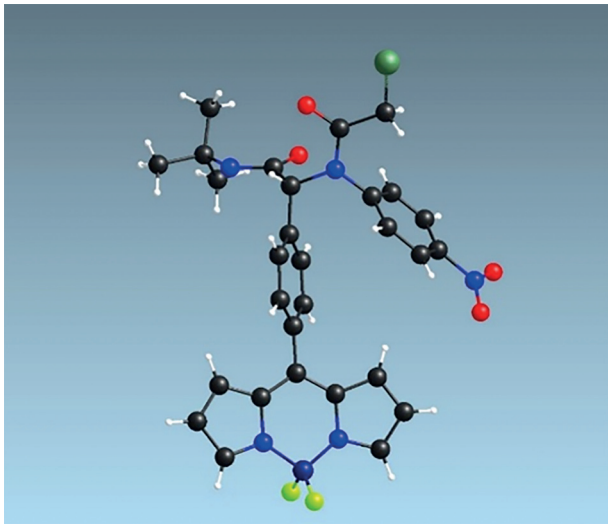
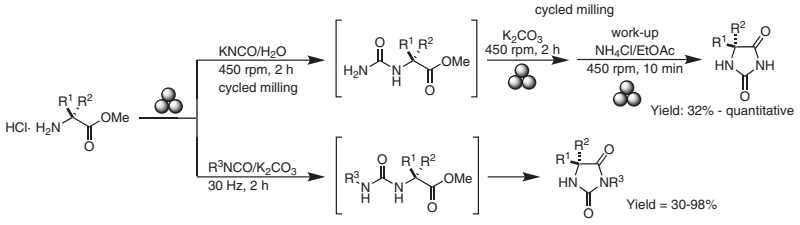


Figure 4 X-ray diffraction structure and conformation of BODIPY-Ugi adduct **12**. Reproduced with permission from ref 117b. Copyright 2022 Wiley-VCH.

On the other hand, the multicomponent Strecker reaction is an emblematic procedure for the synthesis of α-aminonitriles *via* condensation of aldehydes, ammonia, and hydrogen cyanide.[118] In 2016, Bolm, Hernández, and co-workers described a mechanochemical synthesis of α-aminonitriles using representative starting materials and



Scheme 27 Mechanochemical preparation of substituted hydantoins[121]

the milling auxiliary SiO_2 (see Scheme 4); the expected α-aminonitriles were obtained in 70–97% yields.[62] In 2021, Bolm and co-workers reported Biginelli-type multicomponent reactions (MCRs) with NH-free sulfonimidamides that gave 2,3-dihydro-1,2,6-thiadiazine 1-oxides in high yields. The couplings are performed in a planetary ball mill under solvent-free mechanochemical conditions. Acetic acid or ytterbium triflate are used as catalysts.[119]

5.5 Mechanosynthesis of Heterocycles and Modification of Heterocycles

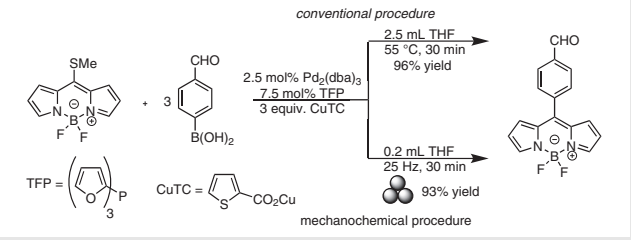
The remarkable pharmacological activity of imidazolidine-2,4-diones, so called hydantoins, motivated Porcheddu, Colacino, and co-workers to develop its efficient mechanochemical preparation, which constitutes a representative example of the ecofriendly preparation of pharmacologically active ingredients.[120]

A systematic investigation of hydantoin synthesis by mechanochemistry starting from a large variety of α-amino acid methyl ester hydrochlorides led to two general approaches using potassium cyanate or isocyanates (Scheme 27).[121]

Compared with solution synthesis, the reaction conditions are simpler, the yields are significantly better, and the workup procedure is more simple.

Boron-dipyrromethenes (BODIPYs) are highly fluorescent compounds that are valuable agents in photodynamic therapy, with further extensive applications in imaging and ion sensing or as components of organic solar cells. A significant number of substituted BODIPYs have been prepared *via* the cross-coupling reaction known as the Liebeskind–Srogl (L-S) protocol.[122] In 2020, Peña-Cabrera, Juaristi, and co-workers reported the effective L-S cross-coupling reaction mediated by mechanical activation, eliminating the use of special reaction conditions (Scheme 28).[123]

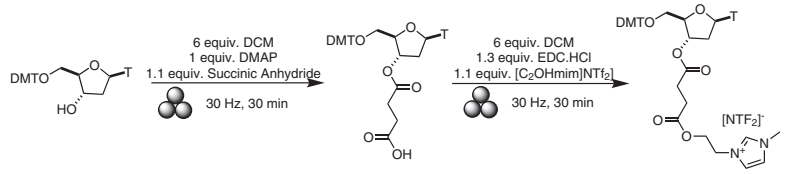
The standard methodology for oligonucleotide synthesis with polymeric supports,[124] requires the use of large volumes of solvents for solubilization of the non-immobilized reagents and for washing the solid support following reactions. In order to reduce solvent usage, in 2021 Migaud and co-workers demonstrated the concept of using an ionic liquid support in combination with liquid-assisted mechanochemistry for various aspects of oligonucleotide synthesis (Scheme 29).[125]



Scheme 28 L-S Cross-coupling reaction under traditional reaction conditions (upper reaction) and under mechanochemical activation (lower reaction)[123]

6 Future Directions

The number of mechanochemical applications has grown enormously in the last two decades; nevertheless, mechanochemistry is still in a phase of study and development before it can become the technique of choice in organic synthesis.[4,8] In this regard, the following sections discuss several areas of opportunity that once fulfilled should help consolidate mechanochemistry as a practical strategy



Scheme 29 One-pot mechanochemical preparation of a nucleoside on an ionic liquid support[125]

both in academic and industrial settings. In this process, mechanochemistry will become a synthetic approach fully supported on a robust conceptual basis.

6.1 Scaling-Up Mechanochemical Protocols

Mechanochemistry is increasingly adopted in academic laboratories in part because it relies on essentially simple techniques involving grinding of substrates under solvent-free conditions, avoiding high temperatures and bulk solvent usage. Thus, mechanochemistry offers economic and environmentally friendly alternatives to synthetic procedures in solution. Nevertheless, the milling technology developed in academic settings confronts significant challenges before it can be fully adopted by industry. For instance, chemical companies will need to replace traditional equipment with, for example, ball mills and extruders satisfying requirements necessary for large-scale production of the compounds and materials of interest.

In this regard, the vibrational mixer mill can handle grams of reactants, which is suitable for most laboratory work, whereas planetary mills are available for larger scales up to charges in the order of kilograms. For instance, the mechanochemical Knoevenagel condensation between vanillin and barbituric acid was carried out in 80-g batches by Stolle and co-workers by means of a planetary mill.[7c]

A convenient strategy for larger chemical reactions consists in modifying the process from batch to continuous. In mechanochemistry, extruders are reactors where the reaction substrates are ground together in a continuous manner through restricted spaces, so that shear and compression forces provide the mechanical energy needed for activation (Figure 5). Thus, twin-screw extrusion (TSE) can be seen as a solid-state equivalent to solution-based flow-reactors. Importantly, extruders operate under controlled reaction conditions (reaction temperature, reagent feed-rate, and screw rotating speed) throughout the process.

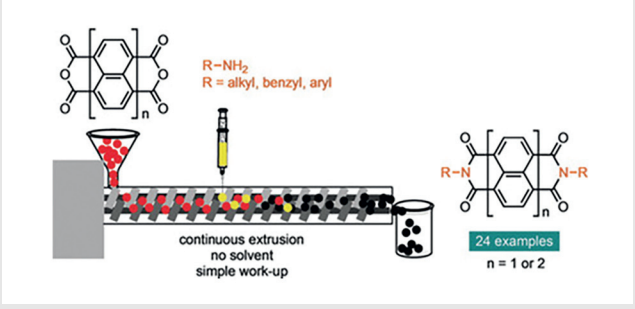


Figure 5 Continuous, solvent-free synthesis of perylene dyes by twin-screw extrusion. Reproduced with permission from ref 126b. Copyright 2020 Wiley-VCH.

In this regard, James and co-workers have prepared metal organic frameworks at rates of kilograms per hour.[126a] Similarly, James and co-workers reported the synthesis of various commercially relevant perylene diimide dyes using TSE (Figure 5).[126b] These dyes were obtained quantitatively without the need for product purification with a throughput rate of about 1.5 kg per day, which is up to two orders of magnitude greater than attained in solvent-based batch methods.

In another relevant development, scaling-up of the mechanoenzymatic oligomerization of amino acids could be accomplished by extrusion techniques.[127] Furthermore, the potential of TSE methodology has been demonstrated for the continuous manufacturing of various pharmaceutically active ingredients.[128] Similarly, Zhang, Niu, and co-workers have recently applied mechanochemical extrusion for the conversion of poly(ethylene terephthalate) (PET) into porous carbon materials.[129] By contrast, in the area of peptide mechanosynthesis, Métro and co-workers developed a continuous solvent-free synthesis of di- and tripeptides *via* extrusion.[130]

6.2 Temperature-Controlled Mechanochemistry

One limitation of present-day ball-milling methods is that the reaction temperature in the milling jar is usually uncontrolled, and then subject to variations in sample heating as the result of beating and friction.[126b] Indeed, Boldyreva, Browne, and others have pointed out that the amount of kinetic energy present in the colliding milling ball(s) determines the maximum amount of energy that can be transferred to the reagents per collision, and eventually dictates whether or not a reaction takes place.[25,131]

The desirable goal to perform mechanochemical procedures at specific temperatures, both above or below ambient temperature, is particularly challenging. Nevertheless, as early as 2003, Kaupp and co-workers described double wall milling jars provided with fittings that permitted the circulation of cooled or heated liquid during the milling process. This equipment was successfully employed in the mechanochemical preparation of heat-sensitive arylboronic esters.[132] Along similar lines, Kumar and Biswas[133] described cryo-mills that were used in combination with programmed pauses in the grinding process to cool the jars with liquid nitrogen.

Presently, the challenging task for manufacturers of milling equipment is the production and commercialization of milling apparatus with the capacity to control thermal energy input between –100 °C and +100 °C. Advancing in this direction, the 'GlenMills' company offers 'Retsch' 'Cryogenic Milling' apparatus where the grinding jar is continually cooled with liquid nitrogen.[134]

In this context, different investigations have shown that increments in the temperature of ball-milling reactions can result in significant acceleration of the mechanochemical transformations, reducing the milling times from hours to minutes. In this regard, Kubota, Ito, and co-workers recently reported the application of temperature-controlled mecha-

nochemistry to enable the mechanochemical nickel-catalyzed Suzuki–Miyaura coupling. The temperature was controlled by means of a programmable jar heater.[16,135,136]

6.3 Understanding Mechanochemical Transformations

Despite the experimental simplicity of mechanochemical protocols, mechanochemistry involves significant degrees of complexity. Indeed, milling containers are opaque, 'black boxes' that render it difficult to experimentally monitor reaction progress and the concomitant molecular transformations. Furthermore, the profound differences between conventional solution chemistry and solid-state chemistry render mechanochemical transformations difficult to understand. In particular, the progress of mechanochemically activated reactions involving two or more solid substrates depends on the generation of interfaces between them, replacing the mediating role of the solvent.[137] Whereas in solution-based reactions the reactant molecules are able to approach each other in order to react, in solid reactants the molecules are fixed, so that displacement of the reactant molecules to the product phase is necessary. A suitable mechanism is likely to involve the formation of a vapor or liquid bulk phase that allows for mobility of the reacting molecules.[2c,138]

On the other hand, several spectroscopic and radiation diffraction techniques have recently facilitated *in situ* monitoring of mechanochemical mechanisms, helping augment our understanding of solid-state chemistry.[3e,139] In particular, the characterization of crystalline powders by means of powder X-ray diffraction is feasible by comparison of the reagent and previously collected product diffractograms, for instance from data deposited in the 'Cambridge Structural Database'.

In cases where grinding results in sample amorphization, leading to a loss of diffraction signals, FT infrared spectroscopy and Raman spectroscopy are suitable techniques that do not depend on compound crystallinity. FT-IR and Raman spectroscopy help assess changes in covalent bonding interactions (that is, bond scission or bond formation).

Further characterization analytical techniques such as solid-state NMR spectroscopy, UV and visible light spectroscopy, and Mössbauer spectroscopy are also useful to monitor and analyze mechanochemical reactions. In general, these measurements are carried out *ex situ*, meaning that the milling process is stopped before isolation of aliquots of the jar content for analysis.

6.4 Emerging Mechanochemical Techniques

Recently, mechanochemical activation is being combined with other energy sources that are traditionally used in solution-based chemistry. In particular, newly developed instrumental setups allow reactions that are not achievable by conventional mechanochemical techniques. Salient areas of opportunity are photo-mechanochemistry, sonomechanochemistry, and electro-mechanochemistry. Advances in these areas are rather promising and represent the future of solid-state reactivity through mechanochemistry.[140]

Regarding photo-mechanochemistry, the synergistic combination of photo- and mechanical activations in organic synthesis offers an enormous potential. Nevertheless, mechanochemical milling is usually conducted in non-translucent containers (e.g., agate, ceramics, steels, and tungsten carbide), which poses an obstacle for light-irradiation procedures. Recently, however, the monitoring of mechanochemical transformations have been accomplished in translucent milling vessels (see Section 6.3) that have been used to carry out photo-mechanochemical reactions.

In an illustrative example, Hernández designed a translucent milling vessel made of poly(methyl methacrylate) (PMMA) to enable the photoborylation of arenediazonium salts with bis(pinacolato)diboron (B_2pin_2) in the presence of the organic photocatalyst eosin Y, while having simultaneously high-speed ball-milling activation.[141]

In this context, the synergistic combination of electrochemistry and mechanochemistry can lead to new areas of opportunity in catalysis. For instance, Schumacher, Hernández, and Bolm reported that mechanical forces transduced by ball milling can induce electrical polarization in piezoelectric materials, thereby enabling chemical reactions influenced by mechanical force and electric fields.[142] In particular, mechanical activation of piezoelectric $BaTiO_3$ nanoparticles by ball milling enabled precise control over the oxidation state of ligand-stabilized metal complexes, and its application in mechanically induced copper-catalyzed atom transfer radical cyclizations. This strategy allowed for the efficient conversion of monobromoacetamides into the corresponding lactams.[142]

In this context, photoredox catalysis is most useful in harnessing light energy to accelerate bond-forming reactions. In 2019, Kubota and co-workers developed a method for the redox-activation of small organic molecules in response to applied mechanical energy through the piezoelectric effect. In particular, the milling of piezoelectric materials via ball milling reduces arenediazonium salts in arylation and borylation reactions.[143]

On the other hand, mechanochemical activation with simultaneous ultrasound irradiation is also a rather attractive area of research. Actually, both techniques share some striking similarities, and numerous sonochemical reactions can be rationalized in purely mechanical terms. Cintas, Cravotto, and Calcio Gaudino examined potential synergistic effects of tribochemical and sonochemical reactivity and demonstrated how strengthened cavitation phenomena can determine the final molecular transformation.[144]

In this context, mechanochemical techniques are presently being applied in the rehabilitation of old reagents. An illustrative example is the application of calcium-based heavy Grignard reagents (R-CaX) in organic synthesis. In contrast with the ready application of traditional Grignard reagents, the use of calcium 'heavy Grignard reagents' has remained essentially unexplored as consequence of the lack of experimental procedures to access such organocalcium under mild conditions.

Recently, it has been demonstrated that mechanochemical ball milling allows the generation of organocalcium reagents from aryl halides and commercially available calcium metal. Importantly, all experimental operations can be carried out in air. This operationally simple protocol enables the development of novel cross-coupling reactions mediated by arylcalcium nucleophiles. This method will allow synthetic chemists to readily access the novel and unique reactivity of organocalcium nucleophiles.[145]

7 Conclusions

The present active search for cleaner and more economic 'green' processes in chemical synthesis has propelled interest in solvent-free solid state synthetic procedures using mechanochemistry. As this short review clearly demonstrates, the success recorded in the field of organic mechanosynthesis during the last two or three decades has been spectacular. Indeed, traditional organic synthesis, asymmetric organocatalysis, multicomponent reactions, metal- and organometal-catalyzed processes, and techniques combining mechanochemical activation with enzymatic catalysis can be conveniently carried out in milling apparatus and extruders, in the absence of bulk solvent and many times in faster and simpler ways, for example when handling air and water sensitive substances or insoluble substrates.

Challenging developments such as implementation of large-scale industrial processes, more efficient control of reaction parameters, and a better understanding of the mechanisms involved in solid state mechanochemical transformations are occupying the attention of chemists and chemical engineers involved in the area. Regarding scaling-up, better control of the reaction's parameters and reaction monitoring issues, manufacturers of laboratory and industrial mills are advancing rapidly to satisfy such needs. It is reasonable to anticipate that as the application of mechanochemistry in synthetic goals increases, so will the employment of reliable techniques for monitoring mechanochemical pathways, and with this the ability to explore successfully unchartered territories and even more innovative applications.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

We are grateful to Consejo Nacional de Ciencia y Tecnología (CONACYT, Mexico) for financial support via grants 220945, 3240029, and A1-S-44097. We are also grateful to the Secretaría de Educación Pública-Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (SEP-CINVESTAV) Fund via grant 126.

References

(1) See, for example: (a) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. *Chem. Soc. Rev.* **2012**, *41*, 413. (b) Baig, R. B. N.; Varma, R. S. *Chem. Soc. Rev.* **2012**, *41*, 1559. (c) Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7668. (d) Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. *Chem. Soc. Rev.* **2011**, *40*, 2317. (e) Boldyreva, E. *Chem. Soc. Rev.* **2013**, *42*, 7719. (f) Mottillo, C.; Friščić, T. *Molecules* **2017**, *22*, 144. (g) Lazuen Garay, A.; Pichon, A.; James, S. L. *Chem. Soc. Rev.* **2007**, *36*, 846. (h) Do, J.-L.; Friščić, T. *Synlett* **2017**, *28*, 2066. (i) Friščić, T.; Mottillo, C.; Titi, H. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 1018. (j) Porcheddu, A.; Colacino, E.; de Luca, L.; Delogu, F. *ACS Catal.* **2020**, *10*, 8344.

(2) (a) Hernández, J. G.; Macdonald, N. A. J.; Mottillo, C.; Butler, I.; Friščić, T. *Green Chem.* **2014**, *16*, 1087. (b) Hernández, J. G.; Friščić, T. *Tetrahedron Lett.* **2015**, *56*, 4253. (c) Baláž, P.; Achimovičová, M.; Baláž, M.; Billik, P.; Cherkezova-Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutková, E.; Gaffet, E.; Gotor, F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Streletskii, A.; Wieczorek-Ciurowa, K. *Chem. Soc. Rev.* **2013**, *42*, 7571. (d) Virieux, D.; Delogu, F.; Porcheddu, A.; García, F.; Colacino, E. *J. Org. Chem.* **2021**, *86*, 13885. (e) Pérez-Venegas, M.; Juaristi, E. *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881. (f) Galant, O.; Cerfeda, G.; McCalmont, A. S.; James, S. L.; Porcheddu, A.; Delogu, F.; Crawford, D. E.; Colacino, E.; Spatari, S. *ACS Sustainable Chem. Eng.* **2022**, *10*, 1430. (g) Bento, O.; Luttringer, F.; El Dine, T. M.; Pétry, N.; Bantreil, X.; Lamaty, F. *Eur. J. Org. Chem.* **2022**, e202101516. (h) Friščić, T. *Chem. Soc. Rev.* **2012**, *41*, 3493. (i) Achar, T. K.; Bose, A.; Mal, P. *Beilstein J. Org. Chem.* **2017**, *13*, 1907. (j) Grätz, S.; Borchardt, L. *RSC Adv.* **2016**, *6*, 64799. (k) Willis-Fox, N.; Rognin, E.; Aljohani, T. A.; Daly, R. *Chem* **2018**, *4*, 2499. (l) Muñoz-Batista, M. J.; Rodriguez-Padron, D.; Puente-Santiago, A. R.; Luque, R. *ACS Sustainable Chem. Eng.* **2018**, *6*, 9530. (m) Dabral, S.; Wotruba, H.; Hernández, J. G.; Bolm, C. *ACS Sustainable Chem. Eng.* **2018**, *6*, 3242. (n) Tan, D.; Loots, L.; Friščić, T. *Chem. Commun.* **2016**, *52*, 7760. (o) Malca, M. Y.; Bao, H.; Bastaille, T.; Saadÿ, N. K.; Kinsella, J. M.; Friščić, T.; Moores, A. *Chem. Mater.* **2017**, *29*, 7766. (p) Métro, T.-X.; Gervais, C.; Martinez, A.; Bonhomme, C.; Laurencin, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 6803.

(3) (a) Takacs, L. *Chem. Soc. Rev.* **2013**, *42*, 7649. See also: (b) Andersen, J.; Mack, J. *Green Chem.* **2018**, *20*, 1435. (c) Xu, C.; De, S.; Balu, A. M.; Ojeda, M.; Luque, R. *Chem. Commun.* **2015**, *51*, 6698. (d) Crawford, D. E.; Miskimmin, C. K. G.; Albadarin, A. B.; Walker, G.; James, S. L. *Green Chem.* **2017**, *19*, 1507. (e) Tan, D.; García, F. *Chem. Soc. Rev.* **2019**, *48*, 2274.

(4) Gomollón-Bell, F. *Chem. Int.* **2019**, *41*, 12.
(5) Rightmire, N. R.; Hanusa, T. P. *Dalton Trans.* **2016**, *45*, 2352.
(6) See, for example: Ávila-Ortiz, C. G.; Juaristi, E. *Molecules* **2020**, *25*, 3579.
(7) (a) Hasa, D.; Jones, W. *Adv. Drug Delivery Rev.* **2017**, *117*, 147. (b) Crawford, D. E.; Casaban, J. *Adv. Mater.* **2016**, *28*, 5747. (c) Stolle, A.; Schmidt, R.; Jacob, K. *Faraday Discuss.* **2014**, *170*, 267. (d) Baláž, P. *Mechanochemistry in Nanoscience and Minerals Engineering*; Springer: Berlin, **2008**. (e) Burmeister, C. F.; Kwade, A. *Chem. Soc. Rev.* **2013**, *42*, 7660. (f) Halasz, I.; Kimber, S. A. J.; Beldon, P. J.; Belenguer, A. M.; Adams, F.; Honkimäki, V.; Nightingale, R. C.; Dinnebier, R. E.; Friščić, T. *Nat. Protoc.* **2013**, *8*, 1718. (g) For safety considerations for laboratory-scale chemical synthesis by ball milling, see: Priestley, I.; Battilocchio, C.; Iosub, A. V.; Barreteau, F.; Bluck, G. W.; Ling, K. B.; Ingram, K.; Ciaccia, M.; Leitch, J. A.; Browne, D. L. *Org. Process Res. Dev.* **2023**, *27*, 269.
(8) Gomollón-Bell, F. *Chem. Eng. News* **2022**, *100*, 21.
(9) Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207.
(10) (a) Chauhan, P.; Chimni, S. S. *Beilstein J. Org. Chem.* **2012**, *8*, 2132. (b) Chauhan, P.; Chimni, S. S. *Asian J. Org. Chem.* **2012**, *1*, 138. (c) Kaur, J.; Chauhan, P.; Singh, S.; Chimni, S. S. *Chem. Rec.* **2017**, *18*, 137.
(11) Thorwirth, R.; Bernhardt, F.; Stolle, A.; Ondruschka, B.; Asghari, J. *Chem. Eur. J.* **2010**, *16*, 13236; and references therein.
(12) Hwang, S.; Grätz, S.; Borchardt, L. *Chem. Commun.* **2022**, *58*, 1661.
(13) (a) Fulmer, D. A.; Shearouse, W. C.; Medonza, S. T.; Mack, J. *Green Chem.* **2009**, *11*, 1821. (b) Pickhardt, W.; Beaković, C.; Mayer, M.; Wohlgemuth, M.; Kraus, F. J. L.; Etter, M.; Grätz, S.; Borchardt, L. *Angew. Chem. Int. Ed.* **2022**, *61*, e202205003; and references cited therein.
(14) (a) Wohlgemuth, M.; Mayer, M.; Rappen, M.; Schmidt, F.; Saure, R.; Grätz, S.; Borchardt, L. *Angew. Chem. Int. Ed.* **2022**, *61*, e202212694. See, also (b) Pickhardt, W.; Siegfried, E.; Fabig, S.; Rappen, M. F.; Etter, M.; Wohlgemuth, M.; Graetz, S.; Borchardt, L. *Angew. Chem. Int. Ed.* **2023**, *62*, e202301490.
(15) (a) Lennox, C. B.; Borchers, T. H.; Gonnet, L.; Barrett, C. J.; Koenig, S. G.; Nagapudi, K.; Friščić, T. *Chem. Sci.* **2023**, in press DOI: org/10.1039/D3SC01591B. See, also (b) Effaty, F.; Gonnet, L.; Koenig, S. G.; Nagapudi, K.; Ottenwaelder, X.; Friščić, T. *Chem. Commun.* **2023**, *59*, 1010.
(16) Andersen, J. M.; Mack, J. *Chem. Sci.* **2017**, *8*, 5447.
(17) (a) Jörres, M.; Aceña, J. L.; Soloshonok, V. A.; Bolm, C. *ChemCatChem* **2015**, *7*, 1265. (b) Jacob, K.; Schmidt, R.; Stolle, A. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**, 34–57.
(18) (a) Tan, D.; Mottillo, C.; Katsenis, A. D.; Štrukil, V.; Friščić, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 9321. (b) Ranu, B. C.; Chatterjee, T.; Mukherjee, N. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**, 1–33.
(19) Friščić, T. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**, 151–189.
(20) Saunders, G. C.; Wehr-Candler, T. T. *J. Fluorine Chem.* **2013**, *153*, 162.
(21) See, for example: (a) *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**. (b) Margetić, D.; Štrukil, V. *Mechanochemical Organic Synthesis*; Elsevier: Oxford, **2016**. (c) O'Neill, R. T.; Boulatov, R. *Nat. Chem. Rev.* **2021**, *5*, 148. (d) Ying, P.; Yu, J.; Su, W. *Adv. Synth. Catal.* **2021**, *363*, 1246. (e) Amrute, A. P.; De Bellis, J.; Felderhoff, M.; Schüth, F. *Chem. Eur. J.* **2021**, *27*, 6819. (f) Egorov, I. N.; Santra, S.; Kopchuk, D. S.; Kovalev, I. S.; Zyryanov, G. V.; Majee, A.; Ranu, B. C.; Rusinov, V. L.; Chupakhin, O. N. *Green Chem.* **2020**, *22*, 302. (g) Bolm, C.; Hernández, J. G. *Angew. Chem. Int. Ed.* **2019**, *58*, 3285. (h) Bolm, C.; Hernandez, J. G. *ChemSusChem* **2018**, *11*, 1410. (i) Štrukil, V. *Synlett* **2018**, *29*, 1281. (j) Machuca, E.; Juaristi, E. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**, 81–95. (k) Kubota, K.; Ito, H. *Trends Chem.* **2020**, *2*, 1066. (l) Leitch, J. A.; Browne, D. L. *Chem. Eur. J.* **2021**, *27*, 9721. (m) Leonardi, M.; Villacampa, M.; Menéndez, J. C. *Chem. Sci.* **2018**, *9*, 2042. (n) Boldyreva, E. *Faraday Discuss.* **2022**, *241*, 9. (o) Margetić, D. *Pure Appl. Chem.* **2023**, *95*, 315.
(22) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**.
(23) Friščić, T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. *CrystEngComm* **2009**, *11*, 418.
(24) Sheldon, R. A. *Green Chem.* **2017**, *19*, 18.
(25) Howard, J. L.; Cao, Q.; Browne, D. L. *Chem. Sci.* **2018**, *9*, 3080.
(26) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
(27) Ardila-Fierro, K. J.; Hernández, J. G. *ChemSusChem* **2021**, *14*, 2145.
(28) (a) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301. (b) Hernández, J. G.; Avila-Ortiz, C. G.; Juaristi, E. *Useful Chemical Activation Alternatives in Solvent-Free Organic Reactions*, In *Comprehensive Organic Synthesis, 2nd ed., Vol. 9*; Molander, G. A.; Knochel, P., Ed.; Elsevier: Oxford, **2014**, 287–314.
(29) (a) Constable, D. J. C.; Jiménez-González, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133. (b) Jiménez-González, C.; Constable, D. J. C.; Ponder, C. S. *Chem. Soc. Rev.* **2012**, *41*, 1485. (c) Dunn, P. J. *Chem. Soc. Rev.* **2012**, *41*, 1452. (d) Leitch, J. A.; Smallman, H. R.; Browne, D. L. *J. Org. Chem.* **2021**, *86*, 14095.
(30) (a) Hernández, J. G.; Bolm, C. *J. Org. Chem.* **2017**, *82*, 4007. See also: (b) Wollenhaupt, M.; Krupička, M.; Marx, D. *ChemPhysChem* **2015**, *16*, 1593.
(31) (a) Krenz, J.; Simcox, N.; Tepe, J. S.; Simpson, C. D. *ACS Sustainable Chem. Eng.* **2016**, *4*, 4021. (b) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. *Chem. Rev.* **2018**, *118*, 747.
(32) (a) Reichardt, C. *Org. Process Res. Dev.* **2007**, *11*, 105. (b) Reichardt, C. *J. Org. Chem.* **2022**, *87*, 1616.
(33) (a) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (b) Metzger, J. O. *Angew. Chem. Int. Ed.* **1998**, *37*, 2975. (c) Kaupp, G. *Organic Solid-State Reactions*, In *Encyclopedia of Physical Organic Chemistry*; Wang, Z.; Wille, U.; Juaristi, E., Ed.; John Wiley & Sons: Hoboken NJ, **2017**, 737–816.
(34) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.
(35) O'Brien, M.; Denton, R.; Ley, S. V. *Synthesis* **2011**, 1157.
(36) Stolle, A. In *Ball Milling Towards Green Synthesis: Applications Projects Challenges*; Stolle, A.; Ranu, B. C., Ed.; RSC: Cambridge, **2015**, 241–270.
(37) (a) Schneider, F.; Ondruschka, B. *ChemSusChem* **2008**, *1*, 622. (b) Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. *Green Chem.* **2009**, *11*, 1894. (c) Schneider, F.; Stolle, A.; Ondruschka, B.; Hopf, H. *Org. Process Res. Dev.* **2009**, *13*, 44.
(38) (a) Yuan, W.; Lazuen-Garay, A.; Pichon, A.; Clowes, R.; Wood, C. D.; Cooper, A. I.; James, S. L. *CrystEngComm* **2010**, *12*, 4063. (b) Trotzki, R.; Hoffmann, M. M.; Ondruschka, B. *Green Chem.* **2008**, *10*, 767.
(39) Mateti, S.; Mathesh, M.; Liu, Z.; Tao, T.; Ramireddy, T.; Glushenkov, A. M.; Yang, W.; Chen, Y. I. *Chem. Commun.* **2021**, *57*, 1080.

(40) (a) Shan, N.; Toda, F.; Jones, W. *Chem. Commun.* **2002**, 2372. (b) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Chem. Commun.* **2004**, 890. (c) Friščić, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 7546. (d) Braga, D.; Curzi, M.; Johansson, A.; Polito, M.; Rubini, K.; Grepioni, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 142.

(41) Liquid-assisted grinding (LAG): (a) Friščić, T.; Jones, W. *Cryst. Growth. Des.* **2009**, *9*, 1621. Kneading: (b) Braga, D.; Giaffreda, S. L.; Grepioni, F.; Pettersen, A.; Maini, L.; Curzi, M.; Polito, M. *Dalton Trans.* **2006**, 1249. Ion- and liquid-assisted grinding (ILAG): (c) Friščić, T.; Reid, D. G.; Halasz, I.; Stein, R. S.; Dinnebier, R. E.; Duer, M. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 712. Polymer-assisted grinding (POLAG): (d) Hasa, D.; Schneider Rauber, G.; Voinovich, D.; Jones, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 7371. Seeding-assisted grinding (SEAG): (e) Cinčić, D.; Brekalo, I.; Kaitner, B. *Cryst. Growth Des.* **2012**, *12*, 44.

(42) Štrukil, V.; Igrc, M. D.; Fábián, L.; Eckert-Maksić, M.; Childs, S. L.; Reid, D. G.; Duer, M. J.; Halasz, I.; Mottillo, C.; Friščić, T. *Green Chem.* **2012**, *14*, 2462.

(43) Howard, J. L.; Sagatov, Y.; Repusseau, L.; Schotten, C.; Browne, D. L. *Green Chem.* **2017**, *19*, 2798.

(44) Bowmaker, G. A. *Chem. Commun.* **2013**, *49*, 334.

(45) (a) Landeros, J. M.; Juaristi, E. *Eur. J. Org. Chem.* **2017**, 687. (b) Anselmi, M.; Stavole, P.; Boanini, E.; Bigi, A.; Juaristi, E.; Gentilucci, L. *Future Med. Chem.* **2020**, *12*, 479.

(46) Giri, N.; Bowen, C.; Vyle, J. S.; James, S. L. *Green Chem.* **2008**, *10*, 627.

(47) Wang, G.-W.; Komatsu, K.; Murata, Y.; Shiro, M. *Nature* **1997**, *387*, 583.

(48) Tanaka, K. *Solvent-Free Organic Synthesis, 2nd ed*; Wiley-VCH: Weinheim, **2008**.

(49) Seo, T.; Toyoshima, N.; Kubota, K.; Ito, H. *J. Am. Chem. Soc.* **2021**, *143*, 6165.

(50) (a) Do, J.-L.; Friščić, T. *ACS Cent. Sci.* **2017**, *3*, 13. (b) Cuccu, F.; De Luca, L.; Delogu, F.; Colacino, E.; Solin, N.; Mocci, R.; Porcheddu, A. *ChemSusChem* **2022**, *15*, e202200362.

(51) See also: Bettens, T.; Alonso, M.; Geerlings, P.; De Proft, F. *J. Org. Chem.* **2023**, *88*, 2046.

(52) Beedle, A. E. M.; Mora, M.; Davis, C. T.; Snijders, A. P.; Stirnemann, G.; Garcia-Manyes, S. *Nat. Commun.* **2018**, *9*, 3155.

(53) (a) Kubota, K.; Takahashi, R.; Ito, H. *Chem. Sci.* **2019**, *10*, 5837. (b) Kubota, K.; Takahashi, R.; Uesugi, M.; Ito, H. *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577. (c) Cao, Q.; Howard, J. L.; Wheatley, E.; Browne, D. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 11339. (d) Cao, Q.; Stark, R. T.; Fallis, I. A.; Browne, D. L. *ChemSusChem* **2019**, *12*, 2554. (e) Yin, J.; Stark, R. T.; Fallis, I. A.; Browne, D. L. *J. Org. Chem.* **2020**, *85*, 2347.

(54) (a) Shao, Q.-L.; Jiang, Z.-J.; Su, W.-K. *Tetrahedron Lett.* **2018**, *59*, 2277. (b) Waddell, D. C.; Clark, T. D.; Mack, J. *Tetrahedron Lett.* **2012**, *53*, 4510.

(55) (a) Jones, A. C.; Leitch, J. A.; Raby-Buck, S. E.; Browne, D. L. *Nat. Synth.* **2022**, *1*, 763. For recent work on Negishi cross-coupling under mechanochemical conditions, see: (b) Čarný, T.; Peňaška, T.; Andrejčák, S.; Šebesta, R. *Chem. Eur. J.* **2022**, *28*, e202202040.

(56) (a) Harrowfield, J. M.; Hart, R. J.; Whitaker, C. R. *Aust. J. Chem.* **2001**, *54*, 423. (b) Birke, V.; Schütt, C.; Burmeier, H.; Ruck, W. K. L. *Fresenius Environ. Bull.* **2011**, *20*, 2794. (c) Speight, I. R.; Hanusa, T. P. *Molecules* **2020**, *25*, 570. (d) Takahashi, R.; Hu, A.; Gao, P.; Gao, Y.; Pang, Y.; Seo, T.; Jiang, J.; Maeda, S.; Takaya, H.; Kubota, K.; Ito, H. *Nat. Commun.* **2021**, *12*, 6691. (e) Pfennig, V. S.; Villella, R. C.; Nikodemus, J.; Bolm, C. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116514. See also: (f) O'Brien, C. J.; Nicewicz, D. S. *Synlett* **2021**, *32*, 814. (g) Gao, Y.; Kubota, K.; Ito, H. *Angew. Chem. Int. Ed.* **2023**, *62*, e202217723.

(57) (a) Takahashi, R.; Seo, T.; Kubota, K.; Ito, H. *ACS Catal.* **2021**, *11*, 14803. (b) Seo, T.; Kubota, K.; Ito, H. *J. Am. Chem. Soc.* **2020**, *142*, 9884. (c) Seo, T.; Ishiyama, T.; Kubota, K.; Ito, H. *Chem. Sci.* **2019**, *10*, 8202.

(58) For some examples of induction-heated ball milling as a promising asset for mechanochemical reactions, see: (a) Andersen, J.; Starbuck, H.; Current, T.; Martin, S.; Mack, J. *Green Chem.* **2021**, *23*, 8501. (b) Bolt, R. R. A.; Raby-Buck, S. E.; Ingram, K.; Leitch, J. A.; Browne, D. L. *Angew. Chem. Int. Ed.* **2022**, *61*, e202210508.

(59) For salient reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (c) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036. (d) Avila-Ortiz, C. G.; Pérez-Venegas, M.; Vargas-Caporali, J.; Juaristi, E. *Tetrahedron Lett.* **2019**, *60*, 1749. (e) Triandafillidi, I.; Voutyritsa, E.; Kokotos, C. G. *Phys. Sci. Rev.* **2020**, *5*, 20180086. (f) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. *Chem. Rev.* **2020**, *120*, 11479.

(60) Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27.

(61) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

(62) Hernández, J. G.; Turberg, M.; Schiffers, I.; Bolm, C. *Chem. Eur. J.* **2016**, *22*, 14513.

(63) Nun, P.; Pérez, V.; Calmés, M.; Martinez, J.; Lamaty, F. *Chem. Eur. J.* **2012**, *18*, 3773.

(64) Declerck, V.; Nun, P.; Martinez, J.; Lamaty, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 9318.

(65) (a) Métro, T.-X.; Colacino, E.; Martinez, J.; Lamaty, F. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B.; Stolle, A., Ed.; RSC: Cambridge, **2015**, 114–150. (b) Maurin, O.; Verdié, P.; Subra, G.; Lamaty, F.; Martinez, J.; Métro, T.-X. *Beilstein J. Org. Chem.* **2017**, *13*, 2087.

(66) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (b) *Enantioselective Synthesis of β-Amino Acids, 2nd ed*; Juaristi, E.; Soloshonok, V., Ed.; Wiley: New York, **2005**.

(67) Hernández, J. G.; Juaristi, E. *J. Org. Chem.* **2010**, *75*, 7107.

(68) (a) Yang, Y. In *Side Reactions in Peptide Synthesis*; Elsevier: Amsterdam, **2016**, 257–292. (b) Hernández, J. G.; Ardila-Fierro, K. J.; Crawford, D.; James, S. L.; Bolm, C. *Green Chem.* **2017**, *19*, 2620. (c) Gómez-Carpintero, J.; Sánchez, J. D.; González, J. F.; Menéndez, J. C. *J. Org. Chem.* **2021**, *86*, 14232.

(69) (a) Bonnamour, J.; Métro, T.-X.; Martinez, J.; Lamaty, F. *Green Chem.* **2013**, *15*, 1116. See also: (b) Lavayssiere, M.; Lamaty, F. *Chem. Commun.* **2023**, *59*, 3442.

(70) Popovic, S.; Bieraugel, H.; Detz, R. J.; Kluwer, A. M.; Koole, J. A. A.; Streefkerk, D. E.; Hiemstra, H.; van Maarseveen, J. H. *Chem. Eur. J.* **2013**, *19*, 16934.

(71) (a) Yeboue, Y.; Jean, M.; Subra, G.; Martinez, J.; Lamaty, F.; Métro, T.-X. *Org. Lett.* **2021**, *23*, 631. (b) Yeboue, Y.; Rguioueg, N.; Subra, G.; Martinez, J.; Lamaty, F.; Metro, T.-X. *Eur. J. Org. Chem.* **2022**, e202100839.

(72) Štrukil, V.; Bartolec, B.; Portada, T.; Dilović, I.; Halasz, I.; Margetić, D. *Chem. Commun.* **2012**, *48*, 12100.

(73) Gonnet, L.; Tintillier, T.; Venturini, N.; Konnert, L.; Hernandez, J.-F.; Lamaty, F.; Laconde, G.; Martinez, J.; Colacino, E. *ACS Sustainable Chem. Eng.* **2017**, *5*, 2936.

(74) Stolar, T.; Grubešić, S.; Cindro, N.; Meštrović, E.; Užarević, K.; Hernández, J. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 12727.

(75) Hernández, J. G.; Juaristi, E. *Chem. Commun.* **2012**, *48*, 5396.

(76) (a) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. For a recent review, see: (c) Juaristi, E. *Tetrahedron* **2021**, *88*, 132143.
(77) See, for example: Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.
(78) (a) Rodríguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 6924. (b) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710.
(79) Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F. *Tetrahedron: Asymmetry* **2007**, *18*, 2300.
(80) (a) Hernández, J. G.; Juaristi, E. *J. Org. Chem.* **2011**, *76*, 1464. (b) Hernández, J. G.; Juaristi, E. *Tetrahedron* **2011**, *67*, 6953.
(81) Hernández, J. G.; García-López, V.; Juaristi, E. *Tetrahedron* **2012**, *68*, 92.
(82) (a) Machuca, E.; Juaristi, E. *Tetrahedron Lett.* **2015**, *56*, 1144. (b) Machuca, E.; Rojas, Y.; Juaristi, E. *Asian J. Org. Chem.* **2015**, *4*, 46.
(83) Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* **2004**, 61.
(84) Veverková, E.; Poláčková, V.; Liptáková, L.; Kázmerová, E.; Mečiarová, M.; Toma, Š.; Šebesta, R. *ChemCatChem* **2012**, *4*, 1013.
(85) Wang, Y.-F.; Chen, R.-X.; Wang, K.; Zhang, B.-B.; Li, Z.-B.; Xu, D.-Q. *Green Chem.* **2012**, *14*, 893.
(86) Jörres, M.; Mersmann, S.; Raabe, G.; Bolm, C. *Green Chem.* **2013**, *15*, 612.
(87) (a) Krištofíková, D.; Mečiarová, M.; Rakovský, E.; Šebesta, R. *ACS Sustainable Chem. Eng.* **2020**, *8*, 14417. (b) Némethová, V.; Krištofíková, D.; Mečiarová, M.; Šebesta, R. *Chem. Rec.* **2023**, *23*, e202200283.
(88) Mack, J.; Shumba, M. *Green Chem.* **2007**, *9*, 328.
(89) Williams, M. T. J.; Morrill, L. C.; Browne, D. L. *ACS Sustainable Chem. Eng.* **2020**, *8*, 17876.
(90) Veverková, E.; Modrocká, V.; Šebesta, R. *Eur. J. Org. Chem.* **2017**, 1191.
(91) Wang, Y.; Wang, H.; Jiang, Y.; Zhang, C.; Shao, J.; Xu, D. *Green Chem.* **2017**, *19*, 1674.
(92) Peňaška, T.; Modrocká, V.; Stankovianska, K.; Mečiarová, M.; Rakovský, E.; Šebesta, R. *ChemSusChem* **2022**, *15*, e202200028.
(93) Spinella, S.; Ganesh, M.; Lo Re, G.; Zhang, S.; Raquez, J.-M.; Dubois, P.; Gross, R. A. *Green Chem.* **2015**, *17*, 4146.
(94) Hernández, J. G.; Frings, M.; Bolm, C. *ChemCatChem* **2016**, *8*, 1769.
(95) Pérez-Venegas, M.; Juaristi, E. *ChemSusChem* **2021**, *14*, 2682.
(96) (a) Pérez-Venegas, M.; Reyes-Rangel, G.; Neri, A.; Escalante, J.; Juaristi, E. *Beilstein J. Org. Chem.* **2017**, *13*, 1728. (b) Pérez-Venegas, M.; Juaristi, E. *Tetrahedron* **2018**, *74*, 6453. (c) Pérez-Venegas, M.; Rodríguez-Treviño, A. M.; Juaristi, E. *ChemCatChem* **2020**, *12*, 1782. (d) Gamboa-Velázquez, G.; Juaristi, E. *ACS Org. Inorg. Au* **2022**, *2*, 343. (e) Shahmohammadi, S.; Faragó, T.; Palkó, M.; Forró, E. Molecules **2022**, *27*, 2600.
(97) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis, Chap. 7*; Wiley: New York, **1991**, See, for example: 106–128.
(98) (a) Weißbach, U.; Dabral, S.; Konert, L.; Bolm, C.; Hernández, J. G. *Beilstein J. Org. Chem.* **2017**, *13*, 1788. (b) Jiang, L.; Ye, L.-d.; Gu, J.-l.; Su, W.-k.; Ye, W.-t. *J. Chem. Technol. Biotechnol.* **2019**, *94*, 2555.
(99) Ardila-Fierro, K. J.; Crawford, D. E.; Körner, A.; James, S. L.; Bolm, C.; Hernández, J. G. *Green Chem.* **2018**, *20*, 1262.
(100) (a) Hammerer, F.; Loots, L.; Do, J.-L.; Therien, J. P. D.; Nickels, C. W.; Friščić, T.; Auclair, K. *Angew. Chem. Int. Ed.* **2018**, *57*, 2621. (b) Therien, J. P. D.; Hammerer, F.; Friščić, T.; Auclair, K. *ChemSusChem* **2019**, *12*, 3481. (c) Hammerer, F.; Ostadjoo, S.; Friščić, T.; Auclair, K. *ChemSusChem* **2020**, *13*, 106. (d) Hammerer, F.; Ostadjoo, S.; Dietrich, K.; Dumont, M.-J.; Del Rio, L. F.; Friščić, T.; Auclair, K. *Green Chem.* **2020**, *22*, 3877.
(101) (a) Kaabel, S.; Therien, J. P. D.; Deschênes, C. E.; Duncan, D.; Friščić, T.; Auclair, K. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2026452118. See also: (b) Kaabel, S.; Arciszewski, J.; Borchers, T. H.; Therien, J. P. D.; Friščić, T.; Auclair, K. *ChemSusChem* **2023**, *16*, e202201613.
(102) Shoda, S.-I.; Uyama, H.; Kadokawa, J.-I.; Kimura, S.; Kobayashi, S. *Chem. Rev.* **2016**, *116*, 2307; and references therein.
(103) Arciszewski, J.; Auclair, K. *ChemSusChem* **2022**, *15*, e202102084.
(104) See also: (a) Ambrose-Dempster, E.; Leipold, L.; Dobrijevic, D.; Bawn, M.; Carter, E. M.; Stojanovski, G.; Sheppard, T. D.; Jeffries, J.; Ward, J. M.; Hailes, H. C. *RSC Adv.* **2023**, *13*, 9954. (b) Zhou, J.; Hsu, T.-G.; Wang, J. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300768.
(105) Carter, E. M.; Ambrose-Dempster, E.; Ward, J. M.; Sheppard, T. D.; Hailes, H. C. *Green Chem.* **2022**, *24*, 3662.
(106) For example a recent report on structure-based redesign of the enzymic cavity yielding variants with improved substrate selectivity in the sulfoxidation of prochiral sulfides, see: (a) Kratky, J.; Eggerichs, D.; Heine, T.; Hofmann, S.; Sowa, P.; Weiße, R. H.; Tischler, D.; Sträter, N. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300657. See also: (b) Burke, A. J.; Lister, T. M.; Marshall, J. R.; Brown, M. J. B.; Lloyd, R.; Green, A. P.; Turner, N. J. *ChemCatChem* **2023**, *15*, e202300256.
(107) Cossy, J. *Tetrahedron* **2022**, *123*, 132966.
(108) See, for example: (a) Xia, Y.; Li, F.; Zhang, X.; Balamkundu, S.; Tang, F.; Hu, S.; Lescar, J.; Tam, J. P.; Liu, C.-F. *J. Am. Chem. Soc.* **2023**, *145*, 6838. (b) Wu, R.; Li, F.; Cui, X.; Li, Z.; Ma, C.; Jiang, H.; Zhang, L.; Zhang, Y.-H.; Zhao, T.; Zhang, Y.; Li, Y.; Chen, H.; Zhu, Z. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218387. See, also: (c) González-Granda, S.; Albarrán-Velo, J.; Lavandera, I.; Gotor-Fernández, V. *Chem. Rev.* **2023**, *123*, 5297.
(109) Guo, F.; Berglund, P. *Green Chem.* **2017**, *19*, 333.
(110) Dichtel, W. R.; Miljanić, O. Š.; Zhang, W.; Spruell, J. M.; Patel, K.; Aprahamian, I.; Heath, J. R.; Stoddart, J. F. *Acc. Chem. Res.* **2008**, *41*, 1750.
(111) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun.* **2013**, *49*, 591.
(112) (a) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544. (b) Shaabani, S.; Dömling, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 16266. (c) Contreras-Cruz, D. A.; Sánchez-Carmona, M. A.; Vengoechea-Gómez, F. A.; Peña-Ortiz, D.; Miranda, L. D. *Tetrahedron* **2017**, *73*, 6146. (d) Ricardo, M. G.; Vasco, A. V.; Rivera, D. G.; Wessjohann, L. A. *Org. Lett.* **2019**, *21*, 7307. (e) Flores-Reyes, J. C.; Islas-Jacome, A.; González-Zamora, E. *Org. Chem. Front.* **2021**, *8*, 5460.
(113) Polindara-García, L. A.; Juaristi, E. *Eur. J. Org. Chem.* **2016**, 1095.
(114) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891.
(115) Kolemen, S.; Akkaya, E. U. *Coord. Chem. Rev.* **2018**, *354*, 121.
(116) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.
(117) (a) Pérez-Venegas, M.; Arbeloa, T.; Bañuelos, J.; López-Arbeloa, I.; Lozoya-Pérez, N. E.; Franco, B.; Mora-Montes, H. M.; Belmonte-Vázquez, J. L.; Bautista-Hernández, C. I.; Peña-Cabrera, E.; Juaristi, E. *Eur. J. Org. Chem.* **2021**, 253. (b) Arroyo-Córdoba, I. J.; Gamboa-Velázquez, G.; Avila-Ortiz, C. G.; Leyva-Ramírez, M. A.; Cortez-Picasso, M. T.; García-Revilla, M. A.; Ramírez-Ornelas, D. E.; Peña-Cabrera, E.; Juaristi, E. *ChemistryOpen* **2022**, *11*, e202200197.

(118) (a) Liu, Y.-L.; Zhou, J. *Synthesis* **2015**, *47*, 1210. (b) Sahoo, P. K.; Bose, A.; Mal, P. *Eur. J. Org. Chem.* **2015**, 6994.
(119) Krauskopf, F.; Truong, K.-N.; Rissanen, K.; Bolm, C. *Org. Lett.* **2021**, *23*, 2699.
(120) Colacino, E.; Porcheddu, A.; Charnay, C.; Delogu, F. *React. Chem. Eng.* **2019**, *4*, 1179; and references cited therein.
(121) (a) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, *79*, 10132. (b) Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E. *RSC Adv.* **2016**, *6*, 36978.
(122) Musaev, D. G.; Liebeskind, L. S. *Organometallics* **2009**, *28*, 4639.
(123) Pérez-Venegas, M.; Villanueva-Hernández, M. N.; Peña-Cabrera, E.; Juaristi, E. *Organometallics* **2020**, *39*, 2561.
(124) Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859.
(125) Johnston, C.; Hardacre, C.; Migaud, M. E. *Chem: Methods* **2021**, *1*, 382.
(126) (a) Crawford, D. E.; Casaban, J.; Haydon, R.; Giri, N.; McNally, T.; James, S. L. *Chem. Sci.* **2015**, *6*, 1645. (b) Cao, Q.; Crawford, D. E.; Shi, C.; James, S. L. *Angew. Chem. Int. Ed.* **2020**, *59*, 4478.
(127) Crawford, D. E. *Beilstein J. Org. Chem.* **2017**, *13*, 65.
(128) (a) Crawford, D. E.; Porcheddu, A.; McCalmont, A. S.; Delogu, F.; James, S. L.; Colacino, E. *ACS Sustainable Chem. Eng.* **2020**, *8*, 12230. (b) Sharma, P.; Vetter, C.; Ponnusamy, E.; Colacino, E. *ACS Sustainable Chem. Eng.* **2022**, *10*, 5110.
(129) Xu, J.; Duan, X.; Zhang, P.; Niu, Q.; Dai, S. *ChemSusChem* **2022**, *15*, e202201576.
(130) Yeboue, Y.; Gallard, B.; Le Moigne, N.; Jean, M.; Lamaty, F.; Martinez, J.; Métro, T.-X. *ACS Sustainable Chem. Eng.* **2018**, *6*, 16001.
(131) Michalchuk, A. A. L.; Tumanov, I. A.; Drebushchak, V. A.; Boldyreva, E. V. *Faraday Discuss.* **2014**, *170*, 311.
(132) Kaupp, G.; Naimi-Jamal, M. R.; Stepanenko, V. *Chem. Eur. J.* **2003**, *9*, 4156.
(133) Kumar, N.; Biswas, K. *Rev. Sci. Instrum.* **2015**, *86*, 83903.
(134) http://www.glenmills.com (accessed Jan 2, 2023)
(135) For additional examples of mechanochemical reactions via a high-temperature ball-milling technique using a heat gun, see: Gao, Y.; Feng, C.; Seo, T.; Kubota, K.; Ito, H. *Chem. Sci.* **2022**, *13*, 430.
(136) For salient reports on temperature controlled mechanochemistry, see: (a) Immohr, S.; Felderhoff, M.; Weidenthaler, C.; Schuth, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 12688. (b) Schmidt, R.; Burmeister, C. F.; Balaž, M.; Kwade, A.; Stolle, A. *Org. Process Res. Dev.* **2015**, *19*, 427. (c) Užarević, K.; Štrukil, V.; Mottillo, C.; Julien, P. A.; Puškarić, A.; Friščić, T.; Halasz, I. *Cryst. Growth Des.* **2016**, *16*, 2342. (d) Fischer, F.; Wenzel, K.-J.; Rademann, K.; Emmerling, F. *Phys. Chem. Chem. Phys.* **2016**, *18*, 23320. (e) Cindro, N.; Tireli, M.; Karadeniz, B.; Mrla, T.; Užarević, K. *ACS Sustainable Chem. Eng.* **2019**, *7*, 16301. (f) Andersen, J. M.; Starbuck, H. F. *J. Org. Chem.* **2021**, *86*, 13983.
(137) (a) Carta, M.; Colacino, E.; Delogu, F.; Porcheddu, A. *Phys. Chem. Chem. Phys.* **2020**, *22*, 14489. (b) Traversari, G.; Porcheddu, A.; Pia, G.; Delogu, F.; Cincotti, A. *Phys. Chem. Chem. Phys.* **2021**, *23*, 229.
(138) Cintas, P.; Tagliapietra, S.; Caporaso, M.; Tabasso, S.; Cravotto, G. *Ultrason. Sonochem.* **2015**, *25*, 8.
(139) (a) Lukin, S.; Germann, L. S.; Friščić, T.; Halasz, I. *Acc. Chem. Res.* **2022**, *55*, 1262. (b) Julien, P. A.; Friščić, T. *Cryst. Growth Des.* **2022**, *22*, 5726.
(140) Martinez, V.; Stolar, T.; Karadeniz, B.; Brekalo, I.; Užarević, K. *Nat. Rev. Chem.* **2023**, *7*, 51.
(141) (a) Hernández, J. G. *Beilstein J. Org. Chem.* **2017**, *13*, 1463. (b) Baier, D. M.; Spula, C.; Fanenstich, S.; Graetz, S.; Borchardt, L. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218719.
(142) Schumacher, C.; Hernández, J. G.; Bolm, C. *Angew. Chem. Int. Ed.* **2020**, *59*, 16357.
(143) (a) Kubota, K.; Pang, Y.; Miura, A.; Ito, H. *Science* **2019**, *366*, 1500. (b) Nothling, M. D.; Daniels, J. E.; Fillbrook, L. L.; Vo, Y.; Beves, J. E.; McCamey, D. R.; Stenzel, M. H. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218955. (c) Ding, R.; Liu, Q.; Zheng, L. *Chem. Eur. J.* **2023**, *29*, 20220379.
(144) Cravotto, G.; Calcio Gaudino, E.; Cintas, P. *Chem. Soc. Rev.* **2013**, *42*, 7521.
(145) Gao, P.; Jiang, J.; Maeda, S.; Kubota, K.; Ito, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202207118.