EurJOC
European Journal of Organic Chemistry

Review
doi.org/10.1002/ejoc.202400425

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Mechanochemistry in Organic Synthesis: An Italian Journey through Innovations

Francesco Basoccu,[a] Lidia De Luca,[b] and Andrea Porcheddu*[a]

Mechanochemistry, as an enabling technology, harnesses mechanical force to drive chemical reactions, presenting compelling advantages in organic synthesis within the principles of green chemistry. This review explores how its unique advantages and alignment with sustainable practices have been widely developed in different scientific fields in Italy. As a transformative strategy for organic synthesis, mechanochemistry has been portrayed in this review as a valuable synthetic alternative due to the various advantages, such as solvent reduction and new reaction pathways, that its use brings. Nonetheless, the improvements brought about by its use have also been crucial in other fields of chemistry described by Italian scientists. In this whole context, Italian researchers have analysed both already optimised processes and new feasible pathways, paving the way for new avenues previously hampered by all the limitations that belong to in-solution chemistry.

1. Introduction

The global recognition of sustainability's critical importance has catalyzed the formation of a distinct discipline within chemistry and chemical engineering.[1] Pioneered by a dedicated community of chemists and chemical engineers, this innovative field focuses on minimizing or completely eradicating the production of toxic substances and environmental pollutants.[2] This commitment represents a profound paradigm shift towards practices that prioritize environmental stewardship. The roots of this movement for sustainability go back to the 1930s with the creation of chemurgy, which laid the foundations for environmentally conscious chemical innovation. The concept of chemurgy was first raised by George Washington Carverword due to his research on plant products, which earned him the title '*father of chemurgy*'.[3] The term '*chemurgy*', instead, was later coined by chemist William J. Hale whom reported it in his 1934 book '*The Farm Chemurgic*'.[4] This discipline was essentially based on preparing industrial products from agricultural raw materials and proved its value in the industrial production of automobiles, rubber, and military life jackets.[5] Despite its initial success, in the 1950s, chemurgy began to undergo a rapid decline that led to its almost complete disappearance in the 1970s.[6] There are various reasons for this, but probably one of the most significant was the introduction of fossil fuels, which were cheaper and more adaptable to different processes on an industrial scale.[3a,7] It was not until 1991 that Professor Paul Anastas reconsidered the possible role of natural products in industrial processes and the need to control the impact of humanity on the environment by formally introducing and defining the concept of green chemistry.[8] Anchored by twelve guiding principles developed by Anastas and Warner in 1998, Green Chemistry endeavours to redefine chemical processes to be inherently safer and more aligned with ecological principles (Figure 1).[9] This vision has sparked a transformative revaluation and rejuvenation of conventional chemical methodologies, propelling the development and integration of novel approaches such as electrochemical processes, flow chemistry, and photochemical methods.[10] Each of these innovations marks a pivotal advancement in the quest for sustainable chemical practices, demonstrating a collective stride toward integrating eco-efficiency and safety into the core of chemical engineering and chemistry.[11]

Within the array of groundbreaking techniques that have emerged, mechanochemistry distinguishes itself through its extraordinary ability to facilitate reactions devoid of solvents. Its simplicity in setup and remarkable efficiency has propelled its widespread adoption across the scientific community, making it a favored approach for conducting chemical reactions.[12] The International Union of Pure and Applied Chemistry (IUPAC) has recognized mechanochemistry as one of the most significant emerging technologies in 2021, underscoring its transformative potential in steering chemical synthesis towards a more sustainable and environmentally friendly direction.[13] This endorsement highlights mechanochemistry's role in reshaping the landscape of chemical research, offering a cleaner, greener

Figure 1. *Green Chemistry* principles.

[a] *F. Basoccu, Prof. Dr. A. Porcheddu*
Dipartimento di Scienze Chimiche e Geologiche
Università degli Studi di Cagliari
Cittadella Universitaria, SS554 bivio per Sestu, 09042-Monserrato (CA), Italy
E-mail: porcheddu@unica.it

[b] *Prof. Dr. L. De Luca*
Dipartimento di Scienze Chimiche, Fisiche, Matematiche e Naturali
Università degli Studi di Sassari

alternative to traditional synthesis methods. As mechanochemistry advances, it is set to become a cornerstone in pursuing more sustainable and eco-conscious scientific practices, embodying the principles of *green chemistry* and driving innovation towards minimizing the environmental impact of chemical processes.[14]

Mechanochemical experiments involve the use of specialized equipment called the ball-grinding device.[10e,15] This innovative device utilizes the kinetic energy of balls of varying sizes within a jar to drive chemical transformations in solid-state conditions. The machine can operate in various dynamic modes, including vertical, horizontal, and planetary movements or even patterns that mimic the shape of a figure-eight.[16] These diverse motions force the balls to apply grinding and shredding pressures on the reactant materials, facilitating various chemical transformations.[17]

The choice of materials for the grinding balls and the vessels profoundly influences the efficacy and nature of these transformations. Commonly used materials for grinding balls and jars include stainless steel, zirconia, and Teflon, as well as less conventional choices like tungsten carbide, Erthalyte®, and polyacrylamide (PAM).[18] Each material presents unique densities and properties, providing the flexibility to tailor the mechanochemical process to meet specific experimental setups' nuanced demands (Figure 2).[19] This adaptability underscores the versatility of mechanochemistry in facilitating diverse chemical synthesis, paving the way for innovative discoveries and advancements in the field.

A hallmark of mechanochemical reactions is their execution at ambient temperature, obviating the need for external heating or cooling typically requisite in conventional chemical reactions.[16c,20] This characteristic drastically reduces the energy consumption of maintaining specific reaction conditions, such as temperature or pressure. Furthermore, eliminating solvents diminishes the thermal energy required for heating and circum-

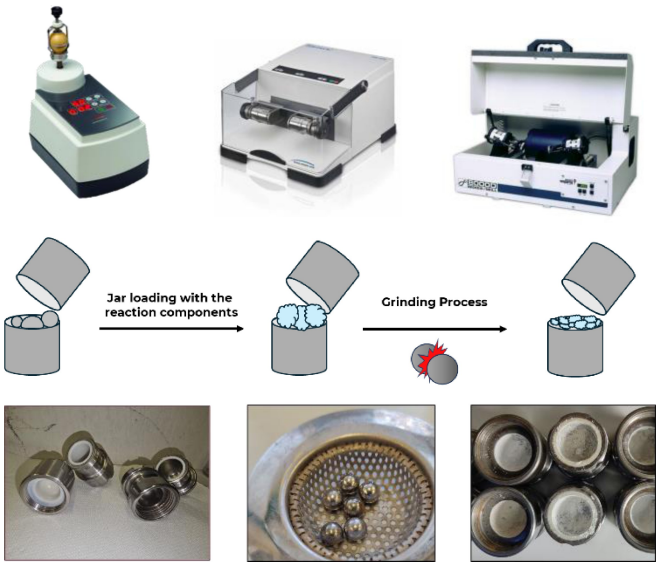


Figure 2. Typical instruments used in mechanochemistry with the description of a typical mechanochemical set-up. The reagents will be added once the chosen jar is loaded with the desired number and type of balls. Then, the jar will be closed, and the grinding process will be run. As it is completed, the ground material can be recovered as itself or employed for further processes.

Francesco Basoccu hails from the coastal city of Cagliari in Italy. He graduated in Medicinal Chemistry from the University of Cagliari in 2021 under the guidance of Professor Maccioni (University of Cagliari) and Professor Vittorio Pace (University of Torino). In 2022, he joined Porcheddu's research group at the University of Cagliari as a PhD student. After spending a brief period in Friscic's group as a visiting Ph.D. student, he is currently spending part of the third year of his Ph.D. at Chiesi Farmaceutici, one of the most prestigious pharmaceutical industries in Italy. He has co-authored 7 papers on the topic of mechanochemistry.

Lidia De Luca obtained a Ph.D. at the University of Sassari under the supervision of Professor Giampaolo Giacomelli. In 2016, she was recruited as associate professor at the University of Sassari. In 2023, she was promoted to full professor at the University of Sassari. Her current research work is mainly focused on the field of green and sustainable chemistry, on the development of new visible-light mediated procedure for oxidations, chlorinations and cross-coupling reaction for C–N and C–O bond formations. Recent interest includes the development of new photocatalysts based on earth abundant metals.

Andrea Porcheddu, distinguished with first-class honors in Chemistry from the University of Sassari (1995), advanced his expertise with a Ph.D. under Prof. Taddei (1999), and post-doctoral research at Louis Pasteur University, Strasbourg (2000). By 2001, he was an Assistant Professor at Sassari, progressing to Full Professor at the University of Cagliari's Chemistry Department (Italy) by 2021. Porcheddu specializes in eco-friendly synthesis, focusing on advanced techniques like Borrowing Hydrogen, Transfer Hydrogenation, and mechanochemistry for developing compounds with intricate molecular structures and applications in industry and pharmaceuticals. He has authored over 135 peer-reviewed papers, achieving an H-index of 42 on Scopus.

vents the energy-intensive processes of solvent recovery and purification.[21]

By bolstering energy efficiency, mechanochemistry aligns with the Green Chemistry principle of minimizing energy usage and curtailing the carbon footprint of chemical manufacturing.[22]

Ensuring safety in chemical processes is crucial, as traditional methods often involve using toxic solvents, reagents, and conditions that pose significant risks to human health and the environment. Mechanochemistry provides a safer alternative by enabling reactions without solvents, eliminating the associated risks. Adopting mechanochemical methods enhances laboratory safety for researchers and extends to industrial applications where robust safety measures are crucial. This shift towards solvent-free reactions signifies a move toward safer chemical manufacturing practices. It aligns with green chemistry principles, promoting more sustainable and health-conscious scientific practices.

Mechanochemistry unlocks innovative avenues for synthesizing compounds and overcoming challenges or inefficiencies inherent in conventional solution-based methodologies.[16c] This field thrives on the unique reaction environments created by mechanical forces, which catalyze distinct reaction dynamics, intermediates, and outcomes not typically observed in traditional chemical processes.[12a] Such a distinctive approach has been crucial in developing novel materials and compounds, including advanced polymers, metal-organic frameworks (MOFs), and co-crystals, thus broadening the horizons of materials science and pharmaceutical research.

These innovative synthetic methods have led to the development of advanced materials with improved properties and pharmaceuticals with enhanced therapeutic effects.[23] Mechanochemistry, which allows the direct manipulation of molecular and material structures without relying on solvent-based reactions,[22a,24] facilitates the design of compounds with specific functionalities, higher stability, and increased biocompatibility.[25]

Mechanochemical reactions are typically more efficient, offer reduced reaction times, and improve selectivity,[26] facilitating the targeted synthesis of desired products with minimal waste.[16c,27] Delving into mechanochemical procedures reveals a rich tapestry of parameters distinctly different from those encountered in traditional solution-based chemistry. This complexity includes variables such as the frequency of oscillations (measured in hertz), the specific type of motion enacted by the milling device, how much of the jar is occupied by materials, and the intrinsic physical properties of the powder reactants (Figure 3).[28]

An incredibly nuanced aspect of mechanochemistry is the potential integration of liquid additives into the process, a technique referred to as liquid-assisted grinding (LAG).[22b,29] Liquid-assisted grinding employs a minimal volume of liquid ($\eta = \mu L/mg$) to enhance reaction rates and facilitate transformations that cannot occur through dry grinding alone. LAG can profoundly impact the reaction's trajectory, enabling modifications in the reaction environment to enhance outcomes (Figure 4).[20c,29c,30]

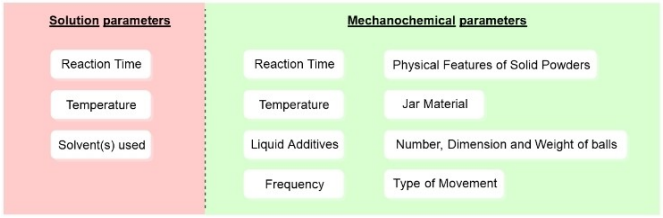


Figure 3. *In-solution* parameters compared with the mechanochemical ones.

This advanced approach significantly broadens the scope and adaptability of mechanochemical methods, highlighting a delicate equilibrium between conducting reactions in solid states and the strategic incorporation of liquid components. Such integration refines the process, allowing for precise adjustments to reaction conditions that can lead to the tailored synthesis of compounds with specific characteristics or properties.

The ability to fine-tune mechanochemical reactions through these variables demonstrates the field's sophistication and potential for innovation, providing a versatile toolkit for scientists aiming to design and execute chemical transformations with increased precision, efficiency, and environmental consideration.[31]

2. Mechanochemistry in Italy

Mechanochemistry has experienced remarkable growth and contributions in Italy, reflecting the country's strong chemical research and innovation tradition.[32] Italian scientists and research groups have been at the forefront of exploring and applying mechanochemical methods across various domains of chemistry, contributing significantly to the global understanding and development of this field. The interest in mechanochemistry within the Italian scientific community is driven by

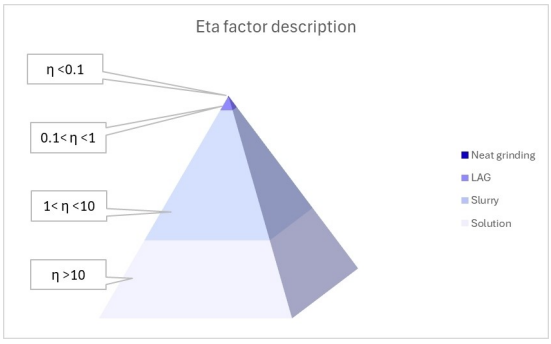


Figure 4. The definition of LAG is based on how the mechanochemical reactivity is dependent on the liquid additive's ratio to the reactants' weight (η = total amount of liquids in μL/total amount of solids in mg). A value of $\eta = 0$ corresponds to pure grinding, whereas when η is between 0.1 and 1 μL/mg, the process can be described as liquid-assisted grinding (LAG). Finally, when $\eta > 1$ μL/mg, the reaction takes place in a slurry state and then can be described as a typical solution approach when $\eta > 10$ μL/mg.

pursuing more sustainable, efficient, and environmentally friendly chemical processes.[33]

The emergence of mechanochemistry in Italy can be traced back to seminal research in 1988, spearheaded by Schiffini and Cocco, whose pioneering efforts set the stage for subsequent developments in this field.[34] Their innovative work applied mechanochemical principles to delve into the properties of the Ni–Ti system, explicitly examining residual crystallinity, crystallite size, and strain content, all of which were elucidated through mechanical alloying. These initial forays primarily concentrated on inorganic systems, with a particular emphasis on metals and metal alloys, thereby establishing a solid foundation for the expansive research that would follow.

This early exploration demonstrated mechanochemistry's potential to unlock new insights into material properties and highlighted its applicability in understanding and manipulating the structural characteristics of various inorganic systems. By pioneering the use of mechanochemical methods to investigate such fundamental aspects of materials science, Schiffini and Cocco's work in Italy has contributed significantly to the broader acceptance and application of mechanochemistry, paving the way for its integration into diverse fields of study and its role in advancing our understanding of material behaviours and properties.[35]

Schiffini and Cocco's exploration of mechanochemistry took a significant turn in 1995 when they expanded their research to encompass organic synthesis.[36] This new direction focused on the catalytic hydrogenation of carbon monoxide, graphite, and ethylene – a venture that marked a notable departure from their previous work. The innovation lay in their application of mechanochemical processes for synthesizing the metal catalyst (Figure 5), followed by the meticulous analysis of the resultant reduced products through a gas chromatographic system intricately connected to specific vessels designed for this purpose.

This innovative approach has turned mechanochemical jars into batch chemical reactors, creating a unique and controlled environment for hydrogenation processes. More importantly, it has allowed for a detailed study of gas-solid interactions in a solvent-free context, providing insights into reaction dynamics that were previously difficult to observe under traditional solvent-based conditions. The work of Schiffini and Cocco in this field highlights the versatility of mechanochemical methods in facilitating organic synthesis. It demonstrates their potential to contribute significantly to the catalysis and reaction engineering field. Their groundbreaking research has opened new avenues for applying mechanochemistry, enriching the scientific community's understanding of chemical processes and interactions.

This significant shift towards applying mechanochemistry in organic synthesis underscored the technique's versatility and potential to revolutionize traditional chemical processes. By eliminating the need for solvents, this approach offered a greener alternative to conventional methods, setting a precedent for future research in mechanochemical organic synthesis within Italy and beyond. Through these pioneering efforts, Italy has contributed significantly to the broader narrative of mechanochemistry, demonstrating its utility in both inorganic and organic contexts and paving the way for its application in sustainable chemical processes.

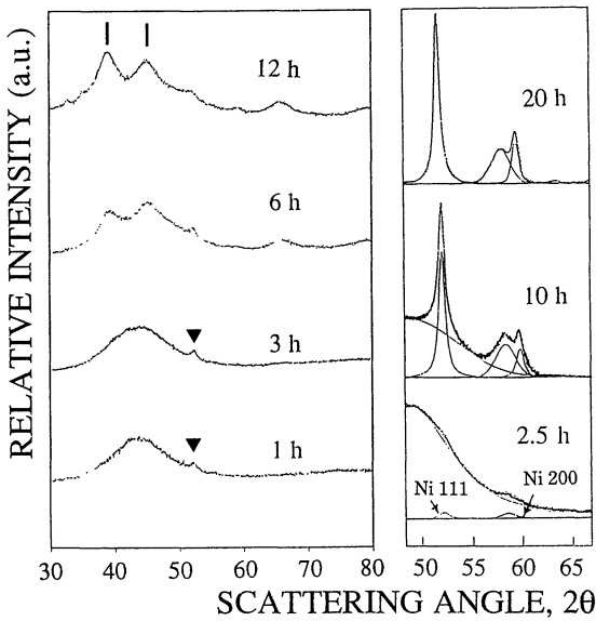


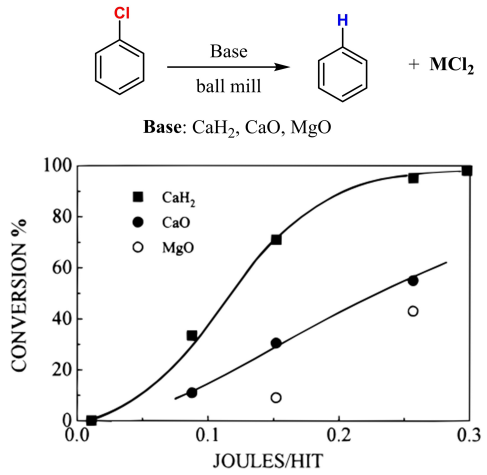
Figure 5. Structural transformation of $Ni_{40}Zr_{60}$ amorphous powders mechanically activated under CO/H_2 atmosphere. Reproduced from ref. [36] from J-Stage (free access).

In the years following Schiffini and Cocco's groundbreaking work, applying organic chemistry under ball milling conditions gained significant momentum. This burgeoning interest in mechanochemistry within the organic chemistry community can be attributed to its numerous advantages, including reducing or eliminating solvent use, enhanced reaction rates, and the potential for increased selectivity. As a result, organic chemistry was substantially enriched, marking the beginning of an era focused on developing synthetic procedures tailored to constructing complex molecular scaffolds through mechanochemical means.

The 1996 study by Cocco *et al.* showed that mechanical treatment could trigger dehalogenation in chlorinated organic compounds when a reactive substrate is present, resulting in distinct reaction products.[37] Using the ball milling technique at low temperatures and atmospheric pressure, the researchers successfully dechlorinated up to 100% of liquid and solid-chlorinated compounds.

The experiments focused on hexachlorobenzene, and chlorobenzene primarily produced benzene and chloride salts. The use of calcium hydride (CaH_2) as a hydrogen source was found to markedly improve both the specificity and the rate of the reaction, offering a significant advantage over calcium oxide (CaO) and magnesium oxide (MgO) substrates in a hydrogen atmosphere (Scheme 1).

The process's effectiveness was closely linked to the amount of mechanical energy introduced and the frequency of collisions. Notably, an explosive-type reaction was observed



Scheme 1. Mechanochemical conversion of chlorobenzene was observed at different ball collision energies over CaH (squares), CaO (full circles), and MgO (open circles) substrates. Conversion values refer to a constant milling time of 12 h. Powder load, 11.2 g; impact frequency, 29 hits/s; ball mass, 1–18 g. Adapted from ref. [37] with permission from the American Chemical Society.

with hexachlorobenzene at specific milling intervals, directly related to the kinetic energy applied.

These innovative synthetic strategies, often inspired by traditional solution chemistry methods, aim to replicate and enhance the efficiency and sustainability of chemical processes.[38] By adopting mechanochemistry, researchers began to explore new possibilities for synthesizing compounds that were previously challenging or inefficient to produce using conventional methods.

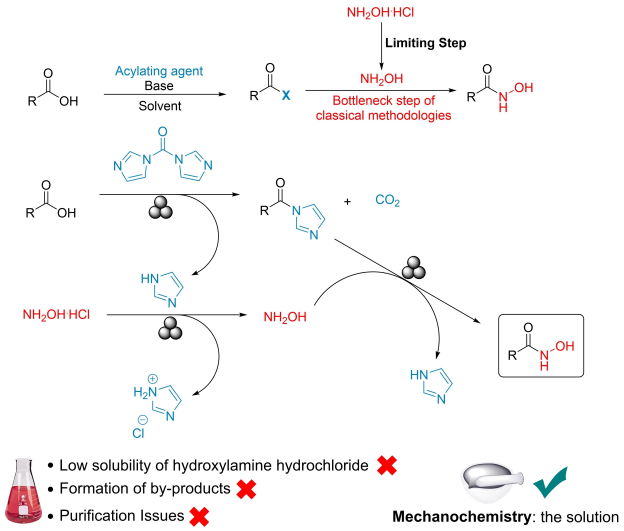
Integrating mechanochemistry into organic synthesis opened up many opportunities for creating complex molecules with precision and environmental consciousness.[39]

This shift towards mechanochemical methods in organic chemistry underlines a broader commitment within the scientific community to adopt practices that are not only technologically advanced but also aligned with the principles of sustainability and environmental stewardship. As mechanochemistry continues to evolve and expand its applications, it promises to revolutionize the field of organic chemistry further, driving the development of novel synthetic procedures that are both innovative and eco-friendly.

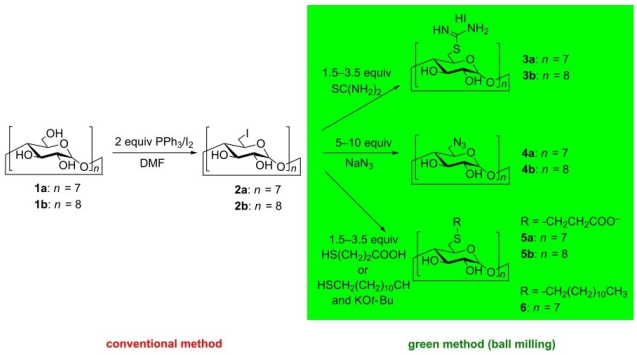
Italian scientific research has been a driving force behind the advancement of mechanochemical methodologies, leading to groundbreaking applications that have significantly impacted the field. One such milestone was the synthesis of hydroxamic acids using carbonyl diimidazole (CDI) as a carboxylic acid activator, a pioneering achievement by Porcheddu in 2016 (Scheme 2).[40] This method employed ball milling techniques to facilitate the use of compounds like hydroxylamine hydrochloride, known for their poor solubility in traditional solvent-based reactions.[41] The approach made these reactions feasible and streamlined the purification process, offering a simpler and more efficient alternative to established methods.

Simultaneously, Cravotto's work on synthesizing cyclodextrins (CDs) showcased the economic and environmental benefits of using a planetary ball mill (Scheme 3).[42] This innovative strategy enabled the production of synthetic thiocyclodextrins **3a**, **3b**, **5a**, **5b**, and **6** without aprotic polar solvents, a common requirement in conventional synthesis that often leads to challenging by-products and impurities.[43] By eliminating these solvents, the mechanochemical approach simplified the synthetic process and significantly reduced the potential environmental impact associated with solvent disposal.

These developments highlight the versatility and potential of mechanochemistry to transform organic synthesis, making it possible to conduct complex reactions more sustainably and cost-effectively. The work of Porcheddu and Cravotto exemplifies the capacity of mechanochemical techniques to overcome traditional chemical synthesis limitations, paving the way for future innovations in the field. As



Scheme 2. Standard route to synthesizing hydroxamic acids by using hydroxylamine hydrochloride along with the mechanism of the mechanochemical procedure based on CDI. Adapted from ref. [40] with permission from Wiley.



Scheme 3. Synthesis of per-6-derivatized CDs. Ball milling conditions: 1500 steel balls of 1 mm diameter and 50 steel balls of 5 mm diameter, sun wheel speed 650 min, 2 h grinding. Reproduced from ref. [42] from Beilstein Journal of Organic Chemistry (open access).

mechanochemistry continues to evolve, its applications in organic chemistry are poised to expand further, offering new pathways for developing environmentally friendly and economically viable synthetic methods.

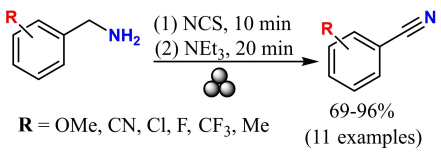
The elimination of solvents in these processes streamlined the synthesis and significantly simplified the isolation and purification phases, marking a leap towards more efficient and environmentally friendly chemical synthesis. These advancements underscore the potential of mechanochemistry to revolutionize traditional chemical processes, offering a sustainable alternative that aligns with the principles of green chemistry. Through these examples, Italian researchers have showcased the versatility and efficiency of mechanochemical approaches, contributing to their growing prominence in the global scientific community.[44]

De Luca's 2017 research marks a significant leap in organic chemistry, highlighting the transformation of primary amines into their aldehyde and ketone counterparts or their direct oxidation to nitriles through C–N bond reactivity.[45] Traditional approaches, typically dependent on metal catalysts or harmful oxidants, have paved the way for a greener alternative utilizing *N*-chlorosuccinimide (NCS). This innovation offers a more environmentally friendly method for oxidizing these substrates (Scheme 4).

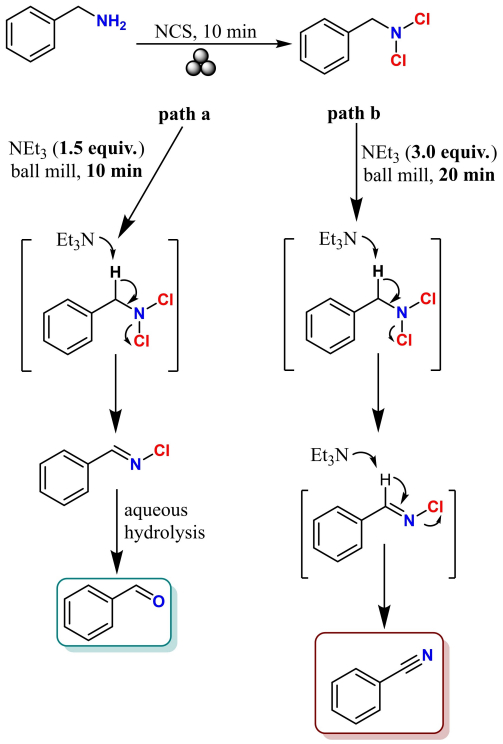
In this innovative approach, the authors treated a benzylic amine with the oxidant, forming the corresponding *N, N*-dichloramine. Afterward, the process was divided into two paths, depending on the use of triethylamine (Scheme 5). This split allowed for the creation of either a nitrile or the *N*-chloroimine. The halo-derivative could then be separated using a diluted HCl solution to obtain the desired carbonyl derivative, demonstrating the method's adaptability in producing diverse chemical compounds.

Studying the kinetics of organic reactions is pivotal in deepening our comprehension of the mechanisms through which these chemical processes occur.[46] This area of research has been extensively explored, with one of the significant contributions being the detailed review by Delogu in 2018.[47] This review meticulously examined the synthesis of 2,3-diphenyl quinazoline and a Knovenagel condensation to elucidate these reactions' underlying kinetics and dynamics (Scheme 6).[48] One of the key insights derived from this analysis was the critical role of grinding frequency in mechanochemical reactions, a parameter that profoundly affects the outcome of the reactions.

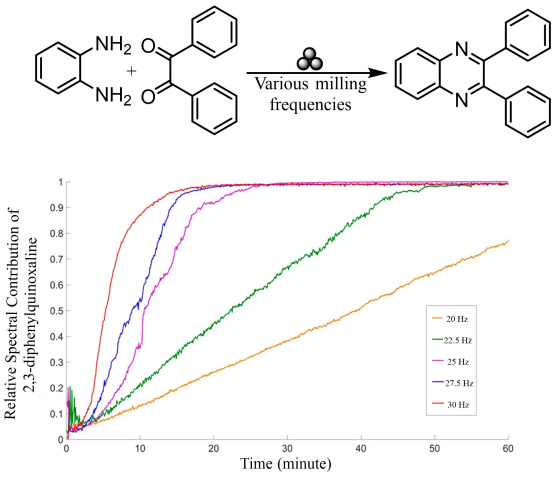
The significance of grinding frequency as a mechanochemical parameter stems from its direct impact on the energy transferred to the reactant powders.[20c,49] The forces of impact and crushing generated within the milling jar, facilitated by the grinding action, are responsible for this energy transfer.[50] These mechanical forces not only initiate the reaction by breaking down the reactant materials but also influence the rate and extent of the reaction, thereby affecting the overall efficiency and selectivity of the process. This discovery underscores the importance of optimizing mechanochemical conditions, such as grinding frequency, to achieve desired reaction outcomes, offering valuable insights into the design and execution of efficient mechanochemical syntheses.



Scheme 4. Oxidation of amines to nitriles.



Scheme 5. Proposed mechanism for the formation of the carbonyl compounds and nitriles. Adapted from ref. [45] with permission from Wiley.



Scheme 6. Analysis of the kinetics of the 2,3-diphenyl quinazoline formation under various reaction frequencies. Adapted from ref. [47] from the American Chemical Society (open access).

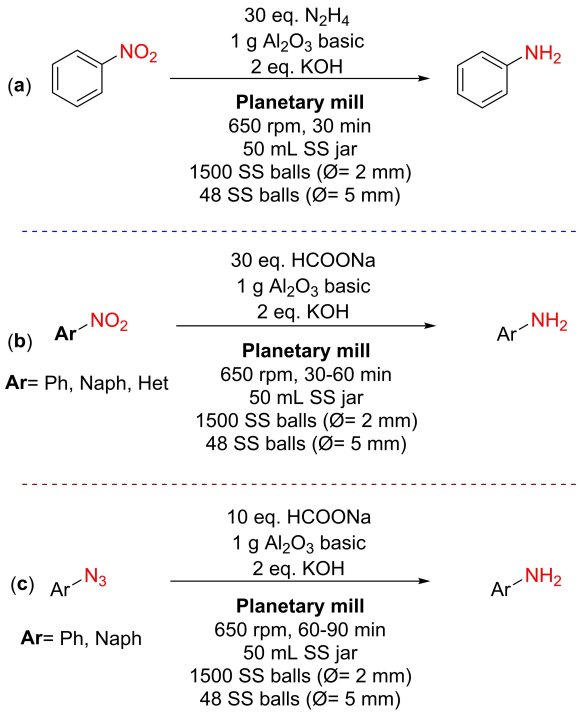
The findings from this comprehensive analysis illuminate the substantial influence that mechanochemical parameters exert on the trajectory and efficiency of chemical reactions. Similarly, comparing the efficacy of liquid-assisted grinding (LAG) and conventional dry grinding in synthesizing non-symmetrical disulfides further accentuates the critical role of mechanochemical conditions.[51] The decision to employ LAG or dry grinding has implications for the reaction mechanism and significantly impacts the yield and purity of the resulting product. These observations highlight the intricate interplay of mechanochemical techniques in driving chemical transformations, underscoring the capacity to fine-tune reaction conditions toward achieving more efficient and sustainable outcomes.

Through such rigorous investigations, the scientific community is progressively demystifying the complexities inherent in mechanochemistry, thereby expanding its utility in organic synthesis. This exploration into the nuanced effects of mechanochemical parameters is instrumental in optimizing synthetic pathways, offering a promising avenue for enhancing reaction selectivity, yield, and environmental compatibility. As research in this field advances, the potential for incorporating mechanochemical strategies into a more comprehensive array of chemical processes grows, signalling a significant stride toward realizing greener and more efficient synthetic methodologies.

The transformation of nitrobenzene derivatives into anilines is a cornerstone process in organic chemistry. It is typically realized through catalytic hydrogenation or within an acidic environment to temper the high reactivity of intermediates.[52] In 2018, Cravotto introduced a groundbreaking methodology that utilizes the mechanical force provided by a planetary ball mill to achieve this conversion.[53] This innovative approach enables the reduction of nitrobenzene and azides under basic conditions, representing a significant shift from traditional methods (Scheme 7).[54]

Adopting mechanochemistry for this reaction circumvents the need for external solvents and harsh chemical conditions and presents a more environmentally friendly and potentially safer alternative. By harnessing the energy of mechanical milling, this technique offers a direct, efficient pathway to achieve the desired transformation, opening new avenues for sustainable chemical synthesis. This method exemplifies the evolving landscape of organic chemistry, where mechanochemical processes are increasingly recognized for facilitating complex reactions more sustainably and straightforwardly.

Employing a planetary ball mill eliminates the need for external solvents, typically required in catalytic hydrogenation, thereby reducing the process's environmental footprint. Furthermore, the ability to conduct the reaction in a basic setting opens new avenues for synthesizing anilines, offering enhanced control over the reaction conditions and selectivity.[55] To gain a deeper understanding of the reaction parameters, both the reaction time and the rotation frequency of the planetary ball mill (rpm, minutes) were adjusted (refer to Figure 1). The model reaction underwent testing at speeds of 650, 500, 400, and 200 rpm for durations of 10 minutes, achieving complete conversion at 650 rpm. This outcome supports the idea that



Scheme 7. Nitrobenzene and alkyl/aryl azide reduction in stainless steel jars without catalyst addition.

increasing kinetic energy facilitates the reduction process and that a higher rotational speed improves conversion rates. Milling durations of 10, 20, and 30 minutes were explored, with complete conversion of nitrobenzene to aniline after 30 minutes. (Figure 6).

Cravotto's work exemplifies the ongoing evolution of synthetic methodologies in organic chemistry, driven by the pursuit of more efficient, greener, and more adaptable reaction processes. This study was innovatively designed to explore the in-situ hydrogen generation through the mechanochemical grinding process, enabling the necessary gaseous-solid interaction for the reduction step without a catalyst.

Initially, they used hydrazine monohydrate as a hydrogen source, which was then compared with safer alternatives, such as ammonium and sodium formate, in search of less toxic options (Scheme 7a). A significant breakthrough was achieved when the reduction process was conducted only in stainless-steel vessels. This discovery highlighted the dual role of stainless-steel vessels in serving as mechanical enclosures and actively contributing to chemical reactions as batch reactors.

This revelation broadens the scope of mechanochemistry, showcasing the potential of specific vessel materials to influence and drive chemical transformations. By acting as an integral component of the reaction, stainless-steel vessels facilitate the reduction of complex organic compounds, indicating a promising avenue for conducting sophisticated organic transformations under mechanochemical conditions.[56]

This advancement builds upon and extends Cocco's foundational work, opening new possibilities for applying mechano-

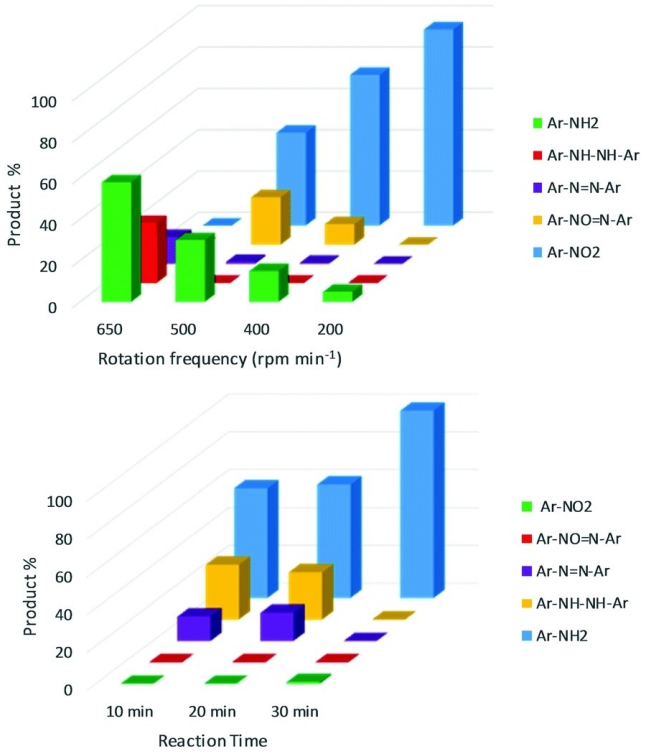
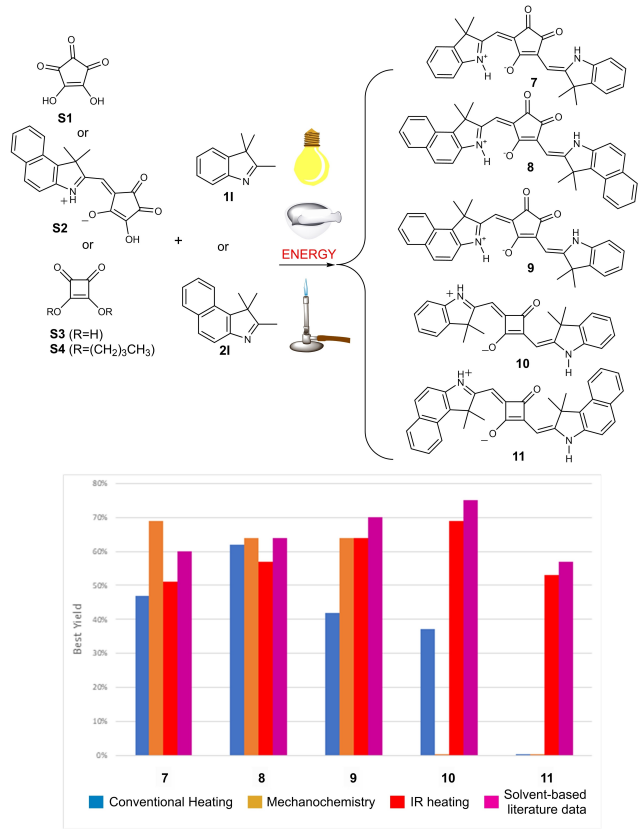


Figure 6. The influence of rotation frequency (top) and milling time (bottom) on conversion to aniline. Reaction conditions: nitrobenzene (0.5 mmol), hydrate hydrazine (30 eq.), KOH (1 mmol), alumina (1 g), stainless steel jar, 1500 balls (∅ = 2 mm), and 48 balls (∅ = 5 mm); rpm and reaction time were varied as described in the graphs. Reproduced from ref. [53] with permission from the Royal Chemical Society.



Scheme 8. Solvent-free reactions for synthesizing indolenine-based squaraines and crocodiles: comparison of thermal heating, mechanochemical milling, and IR irradiation. Adapted from ref. [57] with permission from Wiley.

chemistry in organic synthesis. It signifies a step forward in understanding how reaction vessels' physical properties and materials can play a critical role in the outcome of mechanochemical processes, potentially leading to more efficient and environmentally friendly synthetic pathways.

Further examination into the mechanics of the mechanochemical process revealed a nuanced understanding of the role played by the grinding spheres. It was observed that a synergistic effect arises from using a combination of spheres with small (Ø = 2 mm) and medium (Ø = 5 mm) diameters. This optimal arrangement surpassed the efficiency of using spheres of a single size, attributing the enhanced outcome to the strategic management of the jar's dead volume and the resultant homogeneity of the reaction mixture. Such findings underscore the critical influence of the grinding medium's characteristics on the reaction's success, highlighting the complexity and adaptability of mechanochemical methodologies in organic synthesis.

In 2021, Farinola's research offered a comprehensive analysis that juxtaposed traditional chemical synthesis methods against modern approaches, including mechanochemistry, solvent-free thermal heating, and infrared (IR) light activation.[57] The study specifically scrutinized the synthesis of indoline-based croconaines and squaraines, molecules recognized for their utility across various applications (Scheme 8, top).[58] This investigation highlighted the efficacy of the mechanochemical approach in producing indoline-based croconaines, achieving results that were on par with those reported in the existing literature (Scheme 8, bottom).[59]

A significant revelation from this study was the mechanochemical method's ability to streamline the synthesis process, eliminating the need for additional reagents or catalysts typically required in solution-phase reactions. This simplification is credited to using ball milling techniques, which facilitate chemical transformations through mechanical energy, thereby offering a greener, more efficient alternative to conventional synthesis methods. Farinola's work underscores the potential of mechanochemical synthesis to match and potentially surpass traditional methods in efficiency while also contributing to the advancement of sustainable chemical practices.

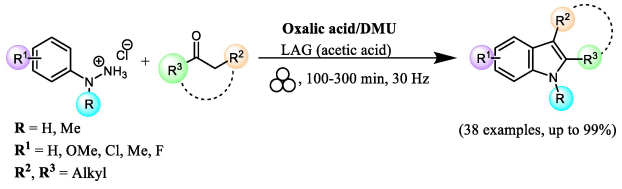
Nonetheless, the study also uncovered a limitation of the mechanochemical method in synthesizing squaraines, highlighting the intricate nuances of mechanochemical reactions (Scheme 8, bottom). In contrast, IR light activation emerged as a remarkably successful method for squaraine synthesis, underscoring the pivotal role that IR irradiation can play in influencing reaction dynamics under solvent-free conditions. This divergence in outcomes between the different techniques emphasizes the importance of selecting an appropriate synthetic approach based on the specific chemical structure and desired reaction pathway. Farinola's work significantly contributes to the broader understanding of how novel

synthetic methodologies, like mechanochemistry and IR activation, can be harnessed to optimize the production of complex organic molecules, thereby advancing the field of chemical synthesis.

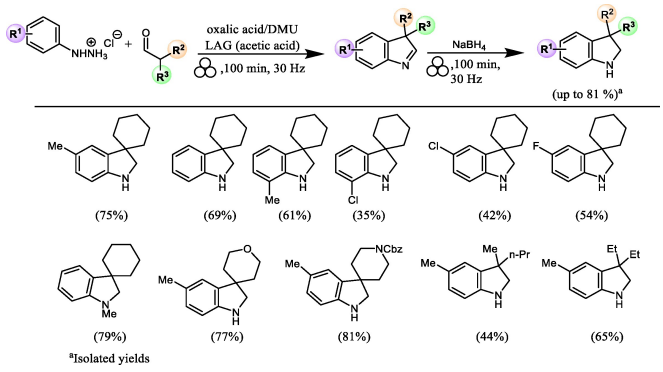
In 2022, D'Auria *et al.* significantly contributed to medicinal chemistry by introducing a novel approach to synthesizing various indoles and indole-like derivatives (Scheme 9).[60] This initiative was driven by the objective of exploiting the bioactive capabilities of these compounds. Indoles, renowned for their pivotal role as heterocyclic structures, boast an extensive range of biological activities. These compounds are integral to various biomolecules, including tryptophan, an essential amino acid, and serotonin, a critical neurotransmitter.[61]

Beyond their occurrence in these biomolecules, indoles and their structural relatives, indolines, are fundamental constituents of a myriad of alkaloids (Scheme 10). This marks them as up-and-coming candidates among azaheterocycles for developing drugs and bio-based products.[62]

The strategic focus on synthesizing indoles and their derivatives underscores the ongoing efforts to unlock the therapeutic potential inherent in these molecules. By tapping into their vast bioactive properties, D'Auria's work aims to pave new pathways for drug discovery and the creation of innovative bio-based products, highlighting the indole motif's versatility and its significant promise in advancing medicinal chemistry and pharmaceutical sciences.



Scheme 9. Mechanochemical Fischer indole synthesis. Reaction conditions: $R^1ArNH(R)NH_3Cl$ (1.0 mmol), ketone (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol), and acetic acid ($\eta = 0.1\ \mu L mg^{-1}$) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls ($\phi = 3$ mm, m_{tot} 6.5 g) of the same material for the given time.

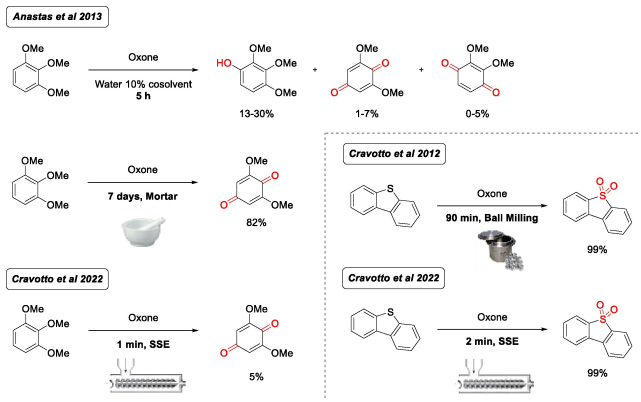


Scheme 10. Mechanochemical interrupted Fischer indole synthesis. Reaction conditions: R^1NHNH_3Cl (1.0 mmol), aldehyde (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol), and acetic acid ($\eta = 0.1\ \mu L mg^{-1}$) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling ball ($\phi = 3$ mm, m_{tot} 6.5 g) of the same material for the given time. Afterward, the jar was opened, and the sodium borohydride (2.0 mmol) was added to the resulting reaction mixture that was further ball-milled for 60 minutes.

A striking feature of D'Auria's approach is the simplified and environmentally friendly purification process, which mainly involves the straightforward precipitation of the product in water. This method streamlines the synthesis of these valuable compounds and significantly reduces the environmental impact associated with traditional purification techniques. Indoles, being a privileged motif, find widespread application across a vast array of bioactive compounds, including alkaloids like Ergot and bisindole alkaloids, known for their potent medicinal and cytotoxic properties.[63] Through this innovative synthesis approach, D'Auria explores and develops new, sustainable pathways for producing complex molecules with high biological and therapeutic relevance, further enriching the toolkit available for drug discovery and development (Scheme 10).

In 2022, Cravotto introduced an innovative study showcasing Reactive Extrusion (REX) as a transformative tool for analyzing various chemical processes on a larger scale, moving beyond the traditional confines of ball milling.[64] The essence of REX lies in its ability to synergize heat and mass transfer with chemical reactions, all occurring within the extruder. This multifaceted approach enables real-time modification of the reacting materials' properties, providing a unique platform for conducting complex chemical transformations. The study paid particular attention to the reactivity of dibenzothiophene and a lignin-like methoxylated substrate, focusing on their oxidation using Oxone® as the oxidizing agent in a solvent-free environment (Scheme 11).

This exploration highlighted the method's efficacy in degrading lignin derivatives and facilitating oxidative desulfurization.[31b,65] Such achievements draw attention to the versatility and environmental benefits of the REX methodology, presenting it as a valuable asset in sustainable chemistry. By offering a cleaner, more efficient pathway for the synthesis and modification of chemical compounds, Cravotto's work on REX represents a significant leap forward in the quest for greener, more scalable chemical processes, potentially revolutionizing the way industrial chemistry addresses environmental challenges and efficiency.



Scheme 11. Reactivity of lignin-like methoxylated substrate and dibenzothiophene under in-solution, ball-milling, and single-screw extruder (SSE) conditions. Adapted from ref. [64] from MDPI (open access).

A year after Cravotto's pioneering work, Selva further expanded the utility of extrusion technology by demonstrating its application in catalysis.[66] The research introduced a novel methodology for synthesizing palladium nanoparticles anchored on an *N*-doped mesoporous carbon matrix through a Pd-based process. This innovative approach commenced with Pd acetate, ethylene glycol, and chitin, followed by a reaction set at 200 °C. After being recovered and dried, the resulting material proved highly effective as a catalyst in a subsequent Suzuki-Miyaura coupling reaction between iodobenzene and phenylboronic acid (Figure 7). A stoichiometric amount of Na_2CO_3 was incorporated into the reaction medium to enhance the catalytic system's efficiency, forming a Pd-chitin-Na_2CO_3 complex designed to optimize the catalyst's performance in this cross-coupling process.

Intriguingly, their study revealed that calcined catalysts exhibited marginally superior performance compared to their non-calcined counterparts, suggesting that the calcination process could enhance the catalyst's effectiveness. However, including the base within the catalyst matrix did not prevent the need to add a specific quantity of K_2CO_3 to the reaction mixture to complete the process efficiently (Table 1).

This insight highlights the nuanced interplay between catalyst composition, preparation, and the reaction environment, underscoring the potential of extrusion technology in synthesizing advanced catalytic materials and facilitating their application in complex chemical reactions. Through Selva's work, extrusion technology reaffirms its versatility and potential as a valuable tool in developing efficient, sustainable catalytic processes.

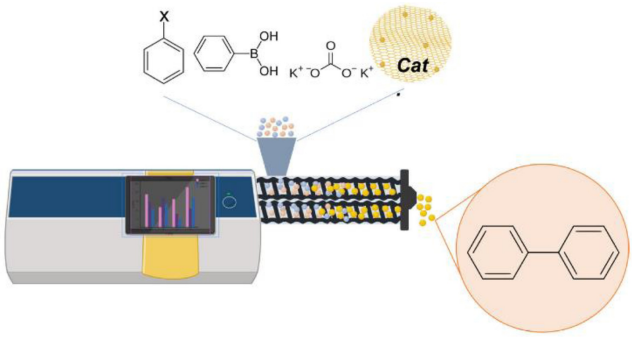
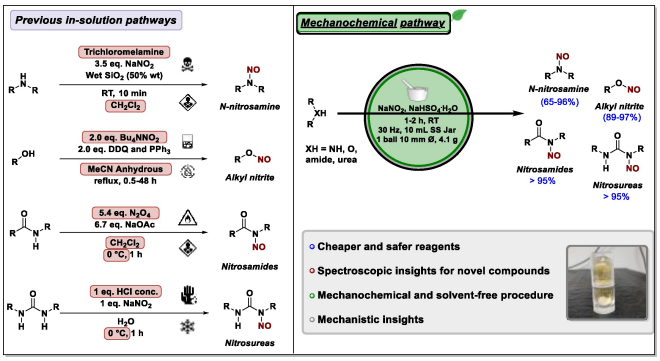


Figure 7. Extruder set-up for the Suzuki coupling. Reproduced from ref. [66].

Table 1. Conversion rate of the Suzuki coupling with different reaction conditions. Adapted from ref. [66].

Entry	Catalyst	Base	Conversion (%)	Selectivity
1	Pd-Chitin-500	/	< 10	> 99
2	Pd-Chitin-Na_2CO_3	/	< 10	> 99
3	Pd-Chitin-Na_2CO_3-500	/	< 10	> 99
4	Pd-Chitin	K_2CO_3	73	> 99
5	**Pd-Chitin-500**	**K_2CO_3**	**81**	**> 99**
6	Pd-Chitin-Na_2CO_3-500	K_2CO_3	78	> 99



Scheme 12. Comparison between traditional solvent-based procedures and mechanochemical methodology. Reproduced from ref. [67] (open access).

As mechanochemistry reached the zenith of its evolution, it began to intertwine with diverse scientific domains, shedding light on how its distinct attributes can profoundly affect chemical reactions. A notable exploration into this domain was conducted by Porcheddu in 2023, focusing on the synthesis of nitroso derivatives (Scheme 12).[67] Notoriously, nitroso compounds, especially nitrosamines, have been linked to high mutagenicity, halting numerous pharmaceutical batches globally due to their unintended presence as impurities.[68] This research aimed to examine their formation in the solid state, offering insights potentially contrasting with those reported by the European Medicines Agency (EMA) for solution-based processes.[69] The experiments demonstrated the formation of nitrous acid and its subsequent decomposition into "*nitrosating*" agents under solvent-free conditions, paving the way for the synthesis of *N*-nitrosamines, as well as alkyl nitrites, nitrosamides, and nitrosoureas (Scheme 12).[70]

Pharmaceutically, the synthesis of nitroso-synephrine stood out, incorporating the pharmacophore of Short-Acting Beta-Agonists (SABA) and Long-Acting Beta-Agonists (LABA) within its structure, marking a significant contribution to medicinal chemistry.[71]

To evaluate the sustainability of the mechanochemical procedure, the authors quantified and compared several key metrics: chemical yield (CY), atom economy (AE), environmental factor (E-factor), and reaction mass efficiency (RME) for compound **12** (depicted in Figure 8).

Furthermore, Porcheddu's study delved into how ball milling characteristics influence chemical reactions, mainly focusing on the interaction between liquid or solid and a gaseous reactant like hydrogen (Scheme 13).[12a] By varying the milling conditions, including the presence or absence of balls and altering their diameters, their study underscored the pivotal role of mechanical deformation in enhancing the selectivity and speed of such reactions. This was particularly evident in the catalytic hydrogenation of liquid and solid olefins, where grinding action was shown to be crucial (Scheme 14). The authors gave a detailed kinetic analysis further illuminating the significant impact of mechanochemical conditions on reaction

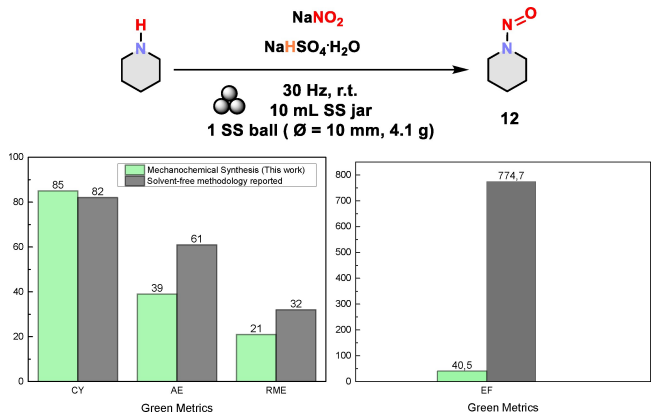
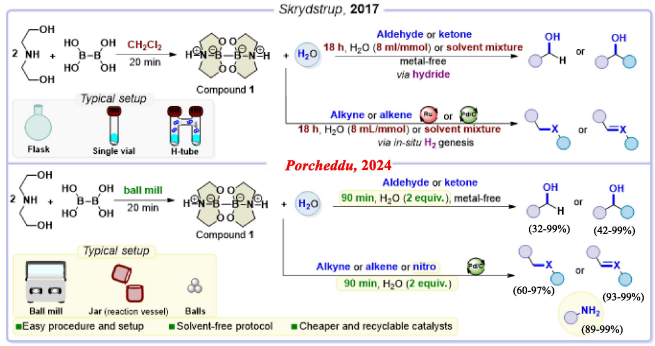
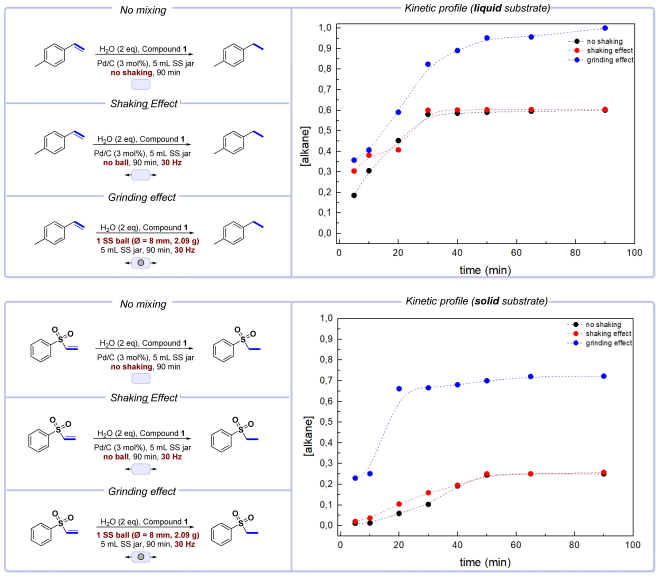


Figure 8. Green metrics for the mechanosynthesis of **12**. Reproduced from ref. [67] (open access).



Scheme 13. Similarities and differences between the reported protocol in solution and Porcheddu's solid-state procedure. Reproduced from ref. [12a] with permission from The Royal Society of Chemistry.



Scheme 14. The control experiments and kinetics for the starting materials of liquid (above) and solid (below). Reproduced from ref. [12a] with permission from The Royal Society of Chemistry.

outcomes, highlighting the intersection of mechanochemistry with other fields and its potential to revolutionize traditional chemical processes.

From the comparative analysis conducted, a hypothesis emerged explaining why the physical state of the starting material significantly impacts the redox process. This influence stems from two main factors: firstly, the varying capacity of hydrogen gas to diffuse through and be adsorbed by the reactant mass, and secondly, the development of a cohesive structure between the reducing agent and the solid starting material. The latter was convincingly demonstrated through Scanning Electron Microscopy (SEM) analysis, which provided visual evidence of the intimate interactions and structural integration between the reactants.

This phenomenon suggests that the physical form of the starting materials dictates how effectively hydrogen gas can interact and react, highlighting the importance of surface area, porosity, and the physical arrangement of molecules in facilitating or hindering chemical reactions. The formation of a cohesive structure further indicates that mechanical forces, such as those applied during ball milling, can induce changes not only on the surface but also in the internal architecture of the materials involved, thereby affecting the overall reaction pathway and efficiency.

This insight illuminates the intricate relationship between reactants' physical states and the dynamics of redox processes, offering valuable considerations for optimizing reaction conditions in mechanochemical syntheses.

3. APIs Synthesis in Italy

Active Pharmaceutical Ingredients (APIs) are the cornerstone of pharmaceutical products, acting as the primary agents responsible for their therapeutic effects.[72] For Contract Manufacturing Organizations (CMOs) and pharmaceutical companies alike, the ultimate goal is to develop a manufacturing process that facilitates the rapid and secure introduction of APIs into the marketplace and adheres to the highest safety, robustness, and efficiency standards. An ideal API production process is characterized by its scalability, safety, and the consistent attainment of high yield and purity levels.[73] These attributes are fundamental to ensuring the API's effectiveness and safety for patient use, which, in turn, guarantees that the resulting pharmaceutical products are both efficacious and safe for consumption. The pharmaceutical industry's commitment to refining and upholding superior production methodologies underscores its unwavering dedication to enhancing patient health and well-being, thereby highlighting the pivotal role of APIs in healthcare and medical treatments.[74]

Despite the broad spectrum of available techniques for synthesizing APIs on an industrial scale, sustainability and operational performance challenges persist. One of the most critical issues is the management of organic solvents within the reaction mixture, particularly their removal and disposal.[75] This process frequently necessitates energy-demanding distillation techniques, and the presence of

impurities often compromises the potential for solvent recovery.[76] Given that solvents seldom offer therapeutic advantages and may, in some instances, provoke adverse reactions, their usage has been scrutinized and regulated. The International Council for Harmonisation (ICH) Q3C(R6) has categorized solvents based on their toxicity, establishing defined limits for the allowable content of residual solvents in pharmaceutical products.[77] This regulatory framework underscores the industry's move towards more sustainable and patient-safe manufacturing practices, mirroring the broader push for environmental responsibility and minimizing adverse health impacts in pharmaceutical production.

Challenges also arise from the insolubility of specific reagents in the reaction medium and the necessity for costly heating systems to facilitate reactions. Given these constraints, the quest for new synthetic methodologies for API production, particularly those that can be applied on a large scale, is relentless.[78] Mechanochemistry has emerged as a promising alternative, offering a solvent-free approach to synthesis.[79] This method has gained traction in Italy, among other places, for synthesizing APIs and their precursors across various classes, including antibiotics, muscle relaxants, histone deacetylase inhibitors, and non-opioid analgesic agents. Adopting mechanochemistry represents a significant stride towards more sustainable, efficient, and safer pharmaceutical manufacturing processes, addressing both environmental and safety concerns associated with conventional methods.

3.1. Antibiotics

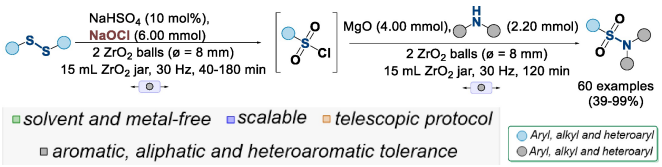
Antibiotics are pivotal in the arsenal against bacterial and certain protozoan infections.[80] They prevent bacterial reproduction (bacteriostatic) or destroy bacteria (bactericidal).[81] While the human immune system, mainly white blood cells and antibodies, form the first line of defense against these pathogens, antibiotics are crucial when the immune response alone is insufficient (Figure 9).

Focusing on specific classes, Sulfamethoxazole (SMZ) and Nitrofurantoin stand out for their unique mechanisms of action and therapeutic applications. SMZ, a sulphonamide, inhibits folic acid synthesis by competitively inhibiting dihydropteroate synthase. Often combined with trimethoprim (TMP) to enhance its efficacy by blocking dihydrofolate reductase, SMZ/TMP is effective against many bacteria.[82]

The synthesis of sulfonamides traditionally involves challenges related to the use of potentially hazardous reagents.[83] However, a safer, more efficient mechanochemical method using $NaOCl{\cdot}5H_2O$ as the oxidizing and halogenating agent has been proposed, significantly reducing the environmental impact of the synthesis process (Scheme 15).[84] This mechanochemical approach, culminating in a one-pot procedure, highlights a green methodology with a low environmental factor (EF), showcasing the synthesis of SMZ precursors with notable efficiency and sustainability.

Nitrofurantoin, belonging to the nitrofurans class, operates through a mechanism believed to involve the alteration of bacterial DNA, possibly through the formation of reactive by-products or reactive oxygen species upon reduction of its nitro moiety.[85]

This antibiotic is typically employed in treating urinary tract infections, with traditional production methods involving rigorous conditions. Remarkably, mechanochemical synthesis offers a room-temperature alternative, enabling rapid production of nitrofurantoin on a gram scale within minutes using milling equipment like the SPEX 8000 mill (Table 2).[19] This method significantly advances antibiotic synthesis, streamlining production while minimizing environmental impact and safety hazards.



Scheme 15. One-pot, two-step sulfonamide mechanosynthesis, including aromatic, aliphatic, secondary, and cyclic amines.

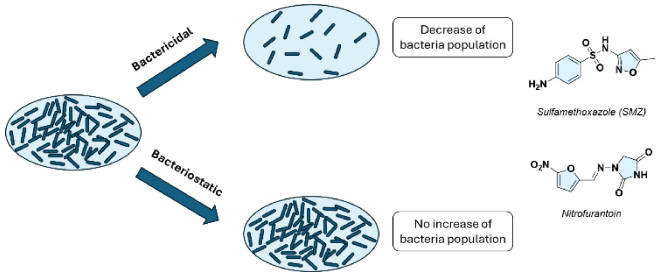
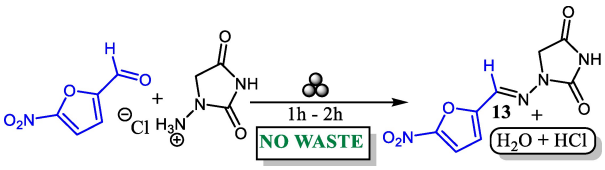


Figure 9. Bactericidal and bacteriostatic action on a population of bacteria. On the right, sulfamethoxazole (bacteriostatic) and nitrofurantoin (bacteriostatic for concentrations <32 μg/mL and bactericidal for concentrations >100 μg/mL).

Table 2. Comparative results for the preparation of nitrofurantoin **13**.[a] Adapted from ref. [19].



Type of Mill	Vibrating[b]	Planetary[c]	Spex [d]
Reaction time	30[e]	120	15
Reaction scale (mmol)	0.84×10^{-3}	13.2	6.6
Yield (%)	85	87	95
Quantity **13** (g)	0.169	2.73	1.49
Jar/ball material	SS[e]	ZrO_2	ZrO_2
Jar volume (mL)	5	12	50

[a] Reaction conditions: 1-Amino hydantoin hydrochloride (1.0 equiv.) and 5-nitro-2-furfural (1.0 equiv.) were ground as follows: [b] 30 Hz, 2 balls (5 mm Ø). [c] 600 rpm, 25 zirconium oxide balls (5 mm Ø). [d] 2 zirconium oxide balls (12 mm Ø). [e] SS stands for stainless steel.

Both examples underline the growing importance of mechanochemistry in pharmaceutical synthesis, providing safer, more sustainable pathways to essential medications. These developments not only enhance the efficiency of drug production but also align with broader environmental and safety goals within the pharmaceutical industry.

3.2. Muscle Relaxants

Muscle relaxants are critical in medical treatment by acting on skeletal muscle function to reduce muscle tone, offering relief from muscle spasms, pain, and hyperreflexia.[86] These therapeutic agents are categorized into two primary groups: neuromuscular blockers and spasmolytics. Neuromuscular blockers, which inhibit transmission at the neuromuscular endplate without affecting the central nervous system (CNS), are predominantly utilized in surgical settings to facilitate temporary paralysis. Conversely, spasmolytics are more commonly recognized as muscle relaxants due to their action on the CNS, where they alleviate musculoskeletal pain and spasticity, making them essential for non-surgical interventions.[87]

Dantrolene, a spasmolytic, is notable for its unique mechanism of action.[88] It involves inhibiting calcium ion release from the sarcoplasmic reticulum by antagonizing ryanodine receptors (Figure 10). This process is crucial for muscle contraction, and by modulating it, dantrolene effectively reduces muscle spasticity and pain.[89]

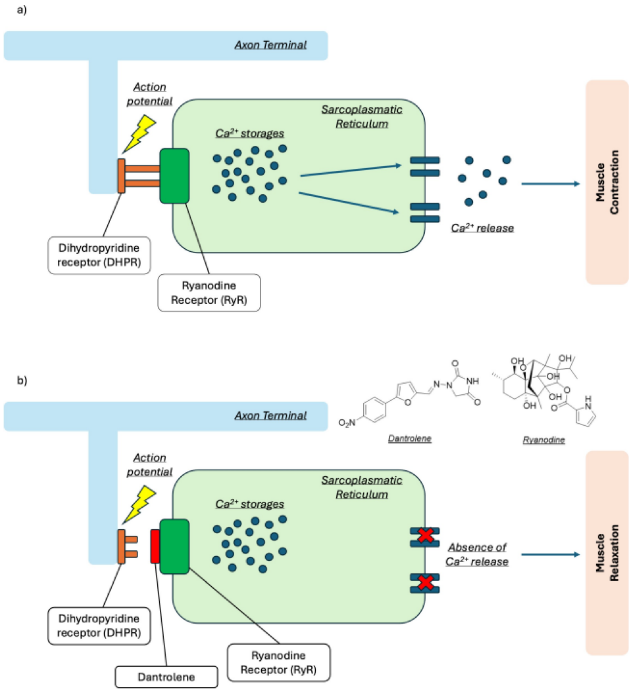


Figure 10. (a) Under normal conditions, the Dihydropyridine Receptor (DHPR) interacts with the Ryanodine Receptor (RyR), causing calcium to be released from the sarcoplasmic reticulum. This event makes muscle contraction possible. (b) Due to the presence of dantrolene bound to RyR subunits, DHPR cannot interact with it, resulting in blocked calcium release. This event blocks myofibril contraction and leads to muscle relaxation.

The synthesis of dantrolene involves a condensation step similar to that used in the production of nitrofurantoin (see Scheme in Table 2). However, leveraging mechanochemistry for this step has shown a path toward a more cost-effective and environmentally friendly approach to synthesizing dantrolene.[19] This method aligns with sustainable pharmaceutical manufacturing practices and underscores the broader potential of mechanochemical techniques in drug synthesis, offering a more sustainable alternative to traditional chemical processes. Through such advancements, mechanochemistry is poised to play a significant role in developing safer, more efficient pathways for producing vital medications like muscle relaxants.

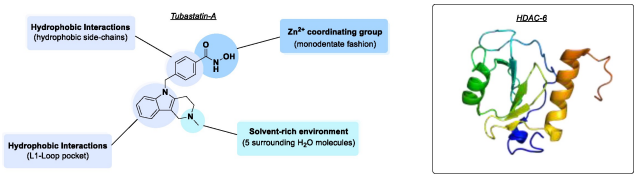
3.3. Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) are crucial enzymes in regulating gene expression, primarily functioning by removing acetyl groups from histones.[90] This action results in the tighter wrapping of DNA around histones, typically suppressing gene expression. Among the various HDACs, HDAC6 is distinguished by its unique structural attributes, which include two deacetylase domains, a C-terminal zinc finger domain capable of binding ubiquitin (ZnF-UBP), and an *N*-terminal domain that binds to microtubules.[91] The enzyme's predominant cytosolic presence and its regulatory effect on specific non-histone cytosolic proteins, such as α-tubulin, highlight its critical role in microtubule-mediated intracellular trafficking and signaling processes, especially within neuronal cells. Thus, HDAC6 has emerged as a crucial target in developing innovative treatments for various neurological conditions.[92]

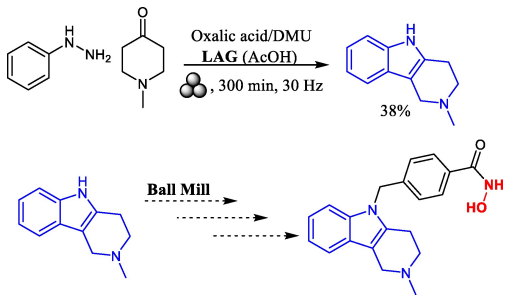
Tubastatin A, recognized as a potent inhibitor of HDAC6, is a derivative of tetrahydro-γ-carboline. It is synthesized through a series of reactions that traditionally involve the use of environmentally and health-damaging reagents, such as H_2SO_4 in dioxane solutions (Scheme 16).[93]

Dioxane, identified as a potential carcinogen, presents significant risks to the central nervous system, while using strong acids like H_2SO_4 raises concerns regarding safety and waste disposal.[94]

In response to these challenges, the synthesis route for Tubastatin A's heterocyclic ring was reimagined through a more sustainable lens. This innovative approach leveraged liquid-assisted grinding (LAG) with acetic acid and a deep eutectic solvent made from oxalic acid and dimethyl urea to forge a greener synthetic pathway (Scheme 17).[60]



Scheme 16. Tubastatin A scaffold with the description of its pharmacophore.



Scheme 17. A greener synthetic approach to Tubastatin A.

This method significantly reduces the reliance on hazardous chemicals and embodies the principles of green chemistry, which emphasizes minimizing the environmental footprint of chemical manufacturing. By adopting such eco-friendly practices, the production of Tubastatin A and analogous compounds becomes more benign, ensuring safer conditions for researchers and minimizing ecological impact. This shift towards sustainable synthesis methods opens new avenues for creating therapeutics and offers promising strategies for reducing the environmental burden of drug development.

3.4. Analgesic Agents

Analgesics, the heart of pain management, are categorized into three principal groups: opioid, non-opioid, and compound analgesics.[95] The accessibility of these medications varies significantly across jurisdictions, with non-opioid analgesics and compound analgesics generally available over the counter. At the same time, opioids and their derivatives are tightly controlled due to their high addiction and overdose risks.[96] Among the non-opioid class, paracetamol (acetaminophen) is a widely used analgesic and antipyretic agent, prized for its efficacy in alleviating fever and mild to moderate pain. Its analgesic mechanism, while not entirely elucidated, is believed to involve selective action on the cyclooxygenases (COX) within the brain and enhancement of endocannabinoid pathways, distinguishing it from other non-steroidal anti-inflammatory drugs (NSAIDs) by its reduced risk of gastrointestinal bleeding, making it a preferred option for managing chronic pain (Figure 11).[97]

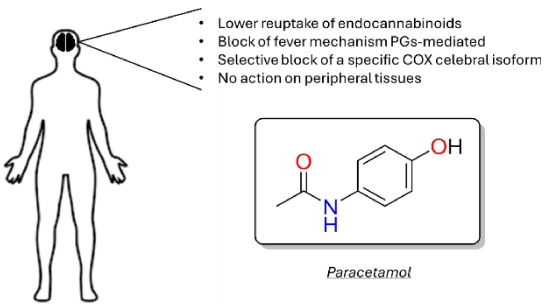


Figure 11. Paracetamol scaffold with its typical effect on the human body.

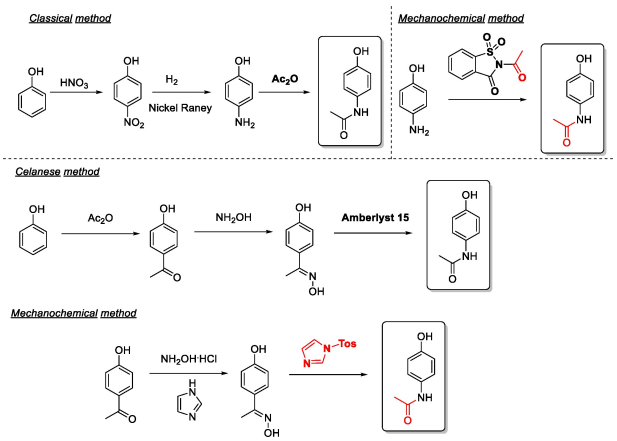
The synthesis of paracetamol has been the subject of considerable research. Traditionally, it employed the acetylation of 4-amino phenol with acetic anhydride or leveraged the Beckmann rearrangement of 4-hydroxyacetophenone oxime.[98]

However, these methods encounter challenges, including the low solubility of starting materials and the reaction's poor selectivity. Innovative solvent-free approaches have been developed to enhance the process in response to these issues. One notable strategy involves using *N*-acetyl saccharin as a safer, non-flammable surrogate for acetic anhydride in acetylation, achieving high selectivity while mitigating safety risks.[99] Similarly, the Beckmann rearrangement has been refined by substituting *p*-tosylimidazole for hazardous reagents like sulfuric acid or halogens, offering a more environmentally benign alternative (Scheme 18).[100]

These advancements in the synthesis of paracetamol underscore a broader shift towards more sustainable, safer chemical processes in pharmaceutical manufacturing. By optimizing traditional reactions and employing greener alternatives, the production of widely used medications like paracetamol can become more efficient, reducing environmental impact and enhancing safety for both manufacturers and consumers. This evolution in drug synthesis aligns with the growing emphasis on green chemistry principles across the pharmaceutical industry, paving the way for developing next-generation analgesics with minimized ecological footprints.

4. Mechanochemistry in Other Chemical Fields in Italy

Mechanochemistry, characterized by its solvent-free approach, has significantly expanded its influence across various fields of chemistry in recent years.[13a,25d,78a,101] This surge in interest is mainly due to the environmental and operational advantages it offers. Below is a brief overview of how mechanochemistry is applied across different domains.



Scheme 18. Paracetamol typical in-solution synthesis compared with the mechanochemical approaches.

The widespread adoption of mechanochemistry across these fields underscores its potential to revolutionize traditional chemical processes. By eliminating the need for solvents, mechanochemistry reduces the environmental impact of chemical syntheses. It offers the possibility of exploring new chemical landscapes, leading to the discovery of innovative materials and reactions. As research in this area continues to grow, mechanochemistry is expected to play an increasingly prominent role in the future of sustainable chemistry.[14a,102]

4.1. Kinetics and Pure Solid-State Studies

Mechanochemistry offers unique insights into reaction kinetics by enabling reactions to occur under solvent-free conditions. This characteristic opens doors to discovering novel reaction pathways often inaccessible in traditional solution-based chemistry, enhancing our understanding of reaction mechanisms and rates.[46a,47]

The investigation into mechanochemical setups reveals a complex interplay of variables, such as the composition of the milling jar and the grinding frequency, each exerting a distinct influence on the progression of chemical reactions.

The seminal research conducted by Delogu in 2004 represents a pivotal advancement in our comprehension of the structural and chemical transformations induced by mechanochemistry.[103] By integrating experimental data with theoretical models, Delogu uncovered the underlying kinetics of mechanochemical processes, revealing that they could be briefly represented through asymptotic trends and sigmoidal curves.

This groundbreaking finding significantly enhances the predictability of mechanochemical reactions and lays the foundation for devising more efficient and selective mechanochemical protocols. An insightful aspect of Delogu's work involved the analysis of the physical states of reactants during mechanochemical reactions, particularly how they relate to the enthalpy of mixing. This led to the formulation of "*mechanochemical activation energy*," which is especially relevant for immiscible systems characterized by a positive enthalpy of mixing.

Traditionally, such systems pose challenges due to their inherent resistance to mixing.[104] However, Delogu's research demonstrated that these systems could undergo significant transformations when subjected to mechanochemical energy, highlighting mechanochemistry's ability to facilitate and catalyze reactions among typically incompatible substances.

By establishing the concept of mechanochemical activation energy and elucidating the kinetic models governing mechanochemical reactions, Delogu's contributions provide a solid foundation for the predictive optimization of mechanochemical processes. This research significantly enriches the field's understanding of mechanochemistry, suggesting that researchers can leverage this methodology to achieve specific chemical transformations with enhanced efficiency and precision through precise control of mechanochemical conditions. As such, Delogu's work heralds new possibilities for applying mechanochemistry across a broad spectrum of chemical disciplines, highlighting its potential as a transformative tool for modern chemistry.

The study of ball milling reactions has dramatically improved thanks to innovative strategies by Paolo Mazzeo et al.[105] Their approach includes optimized data collection techniques, advanced processing algorithms, and miniaturized milling jars.

These advancements have eliminated the limitations and complexities previously associated with in situ diffraction investigations, enabling the acquisition of high-quality *in situ* diffraction data that accurately represents mechanochemical experiments under typical conditions (Figure 12). Sophisticated Rietveld refinements, incorporating innovative functions for peak displacement and shape, have unveiled exceptional details about the reactions under study. This includes the capability to monitor the microstructural evolution of materials undergoing different milling processes with remarkable accuracy, offering unprecedented insights into mechanochemical transformations.

Furthermore, these advancements open new pathways in X-ray-based TRIS methodology, reshaping the future of mechanochemistry and catalyzing novel research directions in this dynamically evolving field.[106]

4.2. Mechanosynthesis of Co-Crystals

Co-crystals are a fascinating area of materials science and pharmaceutical research. They offer a way to improve or modify the physical properties of compounds while maintaining their molecular integrity.[107] These crystalline structures contain two or more distinct molecular entities in a specific ratio and have been found to have better solubility, stability, and mechanical properties than their components. This makes them valuable for developing new materials and refining active pharmaceutical ingredients (APIs), resulting in improved drug delivery, stability, and solubility profiles.[108]

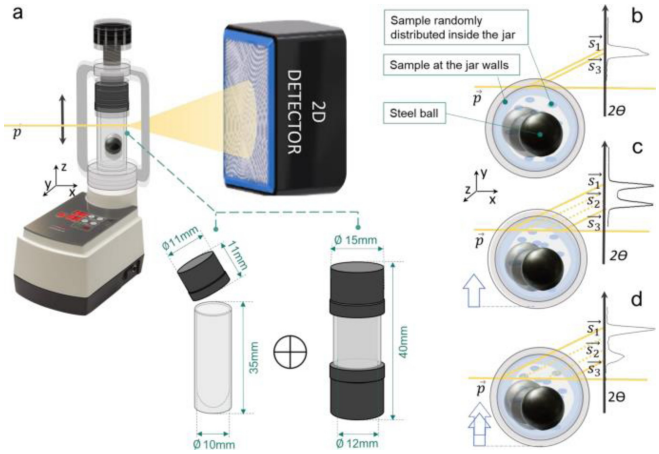


Figure 12. , Schematic representation of the milling setup. Reproduced from ref. [105] (open access).

Mechanochemical synthesis is an effective and adaptable technique for producing co-crystals, mainly ionic co-crystals (ICCs).[109] This process allows the solvent-free mixing of different components, even reactants with completely different solubilities, to create innovative crystalline structures with a hybrid nature. One of the main benefits of mechanochemical synthesis is its precise control over the stoichiometry and polymorphism of the co-crystals produced.[110] Moreover, it is a critical strategy for creating pharmaceutical co-crystals by significantly improving pharmaceutical solubility and membrane diffusivity.[111] Therefore, mechanochemical synthesis is undeniably a promising avenue for co-crystal engineering, offering an efficient, green, and straightforward pathway for material and pharmaceutical development. As the field continues to grow, mechanochemistry is poised to impact the future of co-crystal research significantly, expanding the potential within materials science and pharmaceutical chemistry.

In a recent study, Braga and colleagues have shown that proflavine co-crystals with silver, copper, zinc, and gallium metal complexes exhibit selective efficacy against various bacterial strains and growth states.[112] They explored a series of complexes created through mechanochemical and solution-based co-crystallization of copper and silver salts with the amino acids arginine and histidine, forming novel coordination polymers (Figure 13). Their antibacterial activity was then assessed against prevalent bacterial strains, examining the effects of enantiopure versus racemic amino acids in polymer formation.

The study also investigated the existence of a "*chiral preference*" in the interaction between the polymers and bacteria. Although chirality introduced subtle differences in antibacterial effectiveness, the key finding was that arginine and histidine form coordination polymers with silver and copper that exhibit antimicrobial activities that vary mainly with the type of metal involved.

In the view of studying the interaction between metals and organic derivatives, Grepioni *et al.* conducted a study on the solid-state reactivity between dicyandiamide (DCD) and CuX_2 salts (X=Cl^-, NO_3^-) to explore their agrochemical potential and nitrification challenges.[113] Their research illuminated the influence of milling conditions (such as wet grinding water volume and milling frequency) on the reaction trajectories and the formation of various products (Figure 14), resulting in the identification of two novel crystalline forms: the neutral complexes $[Cu(DCD)_2(OH_2)_2(NO_3)_2]$ (**15**) and $[Cu(DCD)_2(OH_2)Cl_2]\cdot H_2O$ (**17**). The research also highlighted the formation of the salt $[Cu(DCD)_2(OH_2)_2](NO_3)_2\cdot 2H_2O$ (**14**) and, significantly, the compound **16** from the reaction between DCD and $CuCl_2\cdot 2H_2O$, showcasing unique hydrogen-bonded wavy chains stabilized by interactions between chloride anions and coordinated water molecules. By proving the sensitivity of the reactions to water content and milling conditions, this research demonstrates the advantages of the mechanochemical method over traditional solution-based synthesis, setting the stage for applying these findings to broader hydrate metal systems.

Within this framework, investigations into solid formulations of metal complexes with active ingredients were analyzed for antimicrobial applications.[114] This specific co-crystallization process combines organic active molecules such as active pharmaceutical ingredients (APIs) or natural antimicrobials with inorganic metals and complexes. Emerging as a successful strategy for generating diverse new derivatives, these compounds can supplement or replace current antimicrobials that are becoming ineffective due to resistance.[115]

Despite the growing understanding of the macroscopic effects of grinding in forming co-crystals, the microscopic fundamentals driving mechanochemical co-crystallization still need to be discovered. In a pioneering study by Mazzeo *et al.*, the co-crystallization of thymol and hexamethylenetetramine was explored, showcasing a remarkable mechanochemical reaction that progresses solvent-free through an essential metastable low melting eutectic phase (Scheme 19).[116]

The team meticulously tracked this process by employing time-resolved in situ powder X-ray diffraction (PXRD) with a specialized ball-milling setup at the μSpot beamline of the BESSY-II synchrotron facility. Upon mixing, the coformers rapidly initiate a low-melting eutectic phase, as evidenced by changes in the pXRD patterns recorded at half-second intervals. These

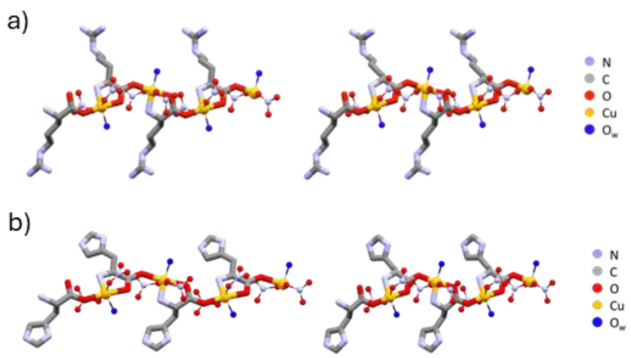


Figure 13. (a) Polymeric chains in L–Arg·Cu (left) and DL–Arg·Cu (right). **(b)** Polymeric chains in L–His·Cu form II (left) and DL–His·Cu (right). Reproduced from ref. [112].

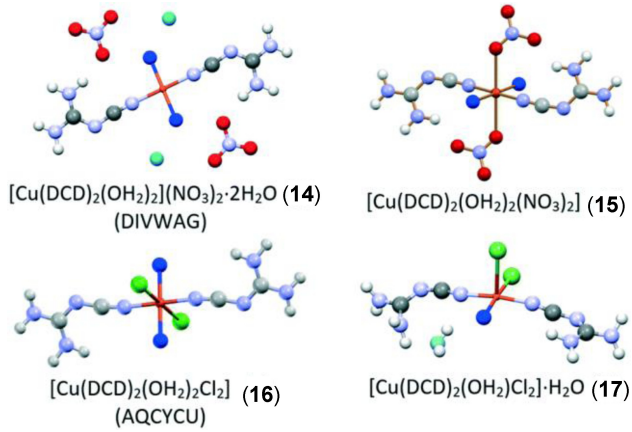
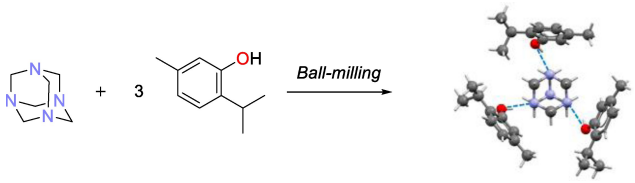


Figure 14. Schematic representation of the neutral complex and salt obtained and reproduced from ref. [113] (open access).



Scheme 19. Corresponding crystalline structures show the assembling of thymol and hexamethylenetetramine. Adapted from ref. [116] (open access).

patterns illustrated a continuous decrease in the coformers' peak intensities alongside an escalating background, signaling the emergence of the liquid phase. Remarkably, the transition from this metastable eutectic state to complete cocrystallization occurs in less than five seconds.,

Naphthalenediimide derivatives, a notable class of π-conjugated molecules, have been extensively studied for their utility as components in metal-organic frameworks (MOFs) and as coformers in hydrogen-bond-based cocrystals.[117] Despite their broad application, exploring their potential to form halogen-bond interactions has been notably limited. Utilizing a crystal engineering methodology, this study unveils four novel cocrystals comprising *N, N*′-di(4-pyridyl)-naphthalene-1,4,5,8-tetracarboxidiimide and diiodo-substituted coformers, synthesized through an efficient mechanochemical process. This detailed analysis, bolstered by energy framework calculations, aimed to elucidate the intricate balance between halogen-bond and π–π interactions in stabilizing these frameworks. Bacchi and Pelagatti's work has decisively demonstrated that *N, N*′-di(4-pyridyl)-naphthalenediimmide, despite its poor solubility, can be adeptly integrated into XB-based cocrystals with various iodo-containing XB donors through a mechanochemical approach (Figure 15).[118]

In-depth structural analysis, complemented by in-silico studies, revealed that π–π solid interactions between stacked molecules of the naphthalenediimmide derivative predominantly stabilize the solid-state frameworks of the newly

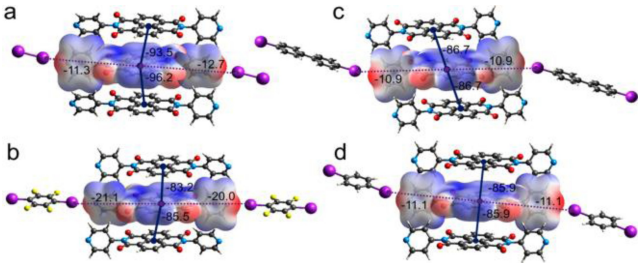


Figure 15. Ability of *N,N*′-di(4-pyridyl)-naphthalene-1,4,5,8-tetracarboxydiimide as an XB acceptor in cocrystal formation. The experiments were performed between **1** and several diiodo-substituted organic molecules, namely molecular iodine (**I_2**), 1,4-diiodotetrafluorobenzene (**DITFB**), 4,4′-diiodobiphenylene (**DIBPH**), 1,4-diiodobenzene (**DIB**). Simplified energy framework and molecular electrostatic potential (MEP) plotted on the electron density surface in **1-I_2** (a), **1-DITFB** (b), **1-DIBPH** (c), **1-DIB** (d) are reported for **1** in all cocrystals. Blue lines represent the dispersive contribution to the energy framework, while dashed purple lines represent the halogen bonds. Stabilizing contributions are reported in kJ/mol. Reproduced from ref. [118] (open access).

synthesized compounds. These interactions, characterized by significant dispersive and Coulombic forces, contribute most substantially to the framework's stability, surpassing the XB interactions' energy contributions. This research advances the understanding of halogen bonding in naphthalene diimide derivatives, laying the ground for further explorations into the design and synthesis of novel crystalline materials with tailored properties.

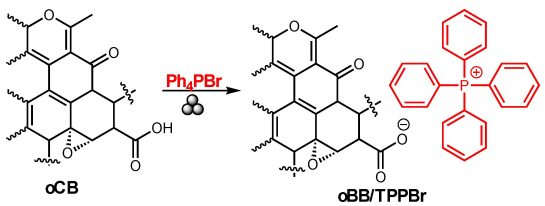
4.3. Materials

Among the various fields of its application, ball-milling has even been proposed for the preparation of different classes of materials, such as functional composite materials.[20b,119] Compared with traditional liquid phase blending, the mechanochemical reactions are based on the kinetic energy generated during milling. This promotes the wear, fracture, and refinement of the microstructure of a chemical system, allowing better blending, coating, and dispersibility.

Carbon black has extensive application across diverse industrial activities, with its chemical and physical traits modifiable through precise functionalization. Especially when used as a filler in nanocomposites, overcoming the hurdles of even dispersion and enhancing its contribution to the nanocomposite's characteristics are achieved via specific modifications to its surface. Acocella's commendable study delves into the capacity of carbon black to form ionic bonds with quaternary phosphonium salts employing a dry ball milling method, thereby creating a distinctive filler endowed with both flame-retardant and anti-bacterial qualities (Scheme 20).[120]

This pioneering mechanochemical technique facilitates chemical alterations in the solid phase, eliminating the need for solvents and marking a significant step towards adopting green chemistry principles and meeting environmental sustainability goals.[119b,121] This method is faster, more effective, and more economical compared to traditional methods that use solutions. The outcomes indicate that this technique can generate new fillers designed to meet particular demands, providing a straightforward and flexible avenue for producing new materials with specific attributes.

Black phosphorus (BP) is the thermodynamically stable form of phosphorus at room temperature and pressure. It is usually synthesized by treating red or white phosphorus under high pressures and heating cycles or recrystallizing it



Scheme 20. Ionic functionalization of **oCB** with **TPPBr** promoted by ball milling under solvent-free conditions.

with toxic or expensive metals. BP can exist in different crystalline phases, and sensors based on this material exhibit several superior qualities compared to traditional materials used in piezoelectric or resistive sensors.[122] Due to its unique lattice structure, its properties ensure high sensitivity and mechanical resilience, making it an attractive candidate for sensor technology.

Mustarelli et al. proposed a possible mechanochemical synthesis of BP in 2019 using a planetary mill to perform a high-energy ball milling (HEBM) approach on commercial red phosphorus.[123] The process was optimized under mechanochemical conditions, demonstrating that the most relevant factor for BP synthesis was the ratio of balls to powder (BtPw ratio). The physical laws underlying a reaction conducted in the planetary ball mill showed how a high BtPw ratio enables quantitative BP synthesis even in short times, such as 15 minutes (Figure 16).

Furthermore, the comparison between the XRD, NMR, and Raman spectroscopy showed how NMR data, less influenced by experimental aspects such as grain size and orientation or degree of crystallinity, can better estimate the overall BP content.

In the same year, Colussi *et al.* analyzed the activation of methane with a solvent-free catalytic process. Methane is a potent greenhouse gas, so numerous efforts are underway to reduce its presence in the atmosphere.[124] In this case, a mechanically prepared Pd-CeO_2 catalyst was proposed. During the various tests, it became evident that specific mechanochemical parameters heavily influenced the decomposition of methane. Running the reactions with a Spex8000 mill made it possible to assess the relevance of the number of grinding balls. Being governed by the kinetic energy of the spheres rather than the almost absent kinetic force of the jar walls, this mechanochemical reaction demonstrated the critical role played by the impacts between spheres. Furthermore, HRTEM analyses showed how these higher energy conditions, caused by a higher number of spheres, implied the palladium to be enclosed within the ceria (Figure 17).

This event resulted in less methane activation, finally allowing an in-depth description of the best reaction conditions

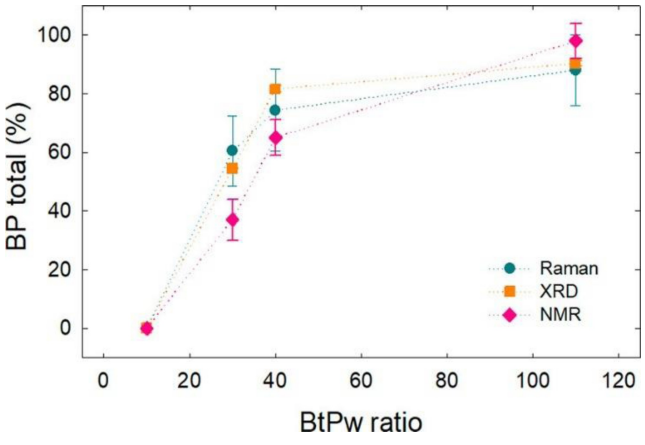


Figure 16. Quantity of total BP as determined using Raman (circle), XRD (square), and NMR (diamond) as a function of the BtPw ratio for a series of samples with a fixed milling time (15 min) and rotation speed (500 rpm). Reproduced from ref. [123] with the permission of the American Chemical Society.

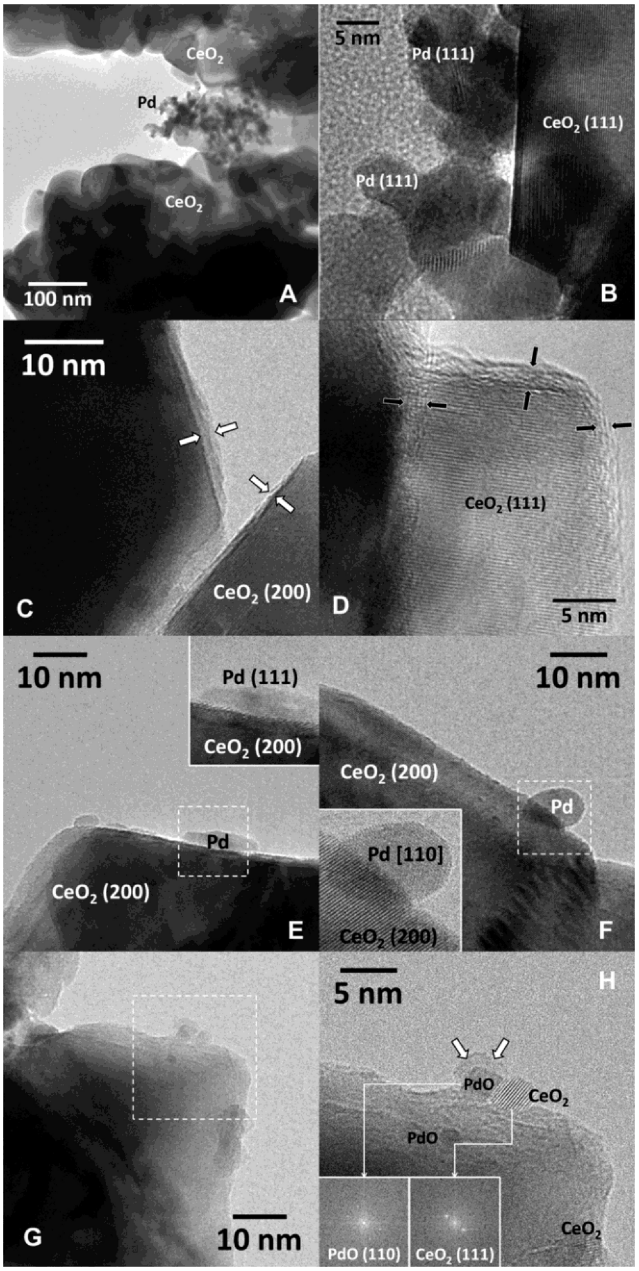


Figure 17. (**A, B**) HRTEM images of the Pd–CeO_2 catalyst synthesized with a Pulverisette 23 Minimill (P23 Minimill) in 10 minutes at a frequency of 15 Hz without loading the jar with any balls. The slight shaking of the powders results in the appearance of Pd aggregates in weak contact with the ceria. (**C, D**) Formation of an amorphous layer with embedded Pd when the grinding process is performed in 10 minutes at a frequency of 15 Hz and a BtPw ratio of 10 in a P23 Minimill (Figure C) or when a mortar is used (Figure D). (**E**, **F**) Well-defined Pd particles in a flattened form or partially embedded in the crystal lattice of CeO_2 when the high-energy ball milling process is exercised for 5 minutes with a Spex8000. (**G**, **H**) Breakage of CeO_2 crystallites and oxidation of Pd to PdO when the high-energy ball milling process is exerted for 8 hours with a Spex8000. Reproduced from ref. [124] with the permission of the Royal Chemical Society.

for the simple and direct synthesis of a Pd–CeO_2 catalyst for methane activation under mild solvent-free conditions.

4.4. Supramolecular Mechanochemistry

The fusion of supramolecular chemistry and mechanochemistry marks a significant breakthrough in chemical sciences, paving the way for groundbreaking discoveries and innovations across numerous scientific fields.[125] Supramolecular chemistry involves assembling molecular units into complex entities through non-covalent forces, such as hydrogen bonds, van der Waals forces, and electrostatic interactions. This exploration extends beyond molecular considerations to create materials and systems with bespoke functionalities, from self-healing materials to highly selective sensors and sophisticated drug delivery systems, thereby transforming materials science and pharmaceuticals.[109d]

Mechanochemistry complements supramolecular chemistry by introducing a solvent-free methodology for triggering chemical reactions via mechanical force. This collaborative effort between these two is expected to lead to significant technological advancements, potentially redefining industries ranging from pharmaceuticals to materials science, showcasing the transformative power of modern chemistry.

A particularly captivating domain within this synergy is the study of complex topologies in co-crystals. They are known for their unique properties and their considerable challenges in design, preparation, and control over self-assembly processes. The innovative work by Metrangolo and colleagues exemplifies this by employing a novel, solvent-free strategy through ball milling to influence the supramolecular trajectory of a three-component crystalline adduct (Figure 18).[126] Their study on a halogen-bonded ionic co-crystal, composed of potassium iodide (KI), 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (crypt-222), and 1,8-diiodohexadecafluorooctane (DIPFO), demonstrates how minor tweaks in mechanochemical conditions can significantly shift the topologies of resulting supramolecular architectures, enabling transitions between non-interpenetrated structures and Borromean-type entanglements.

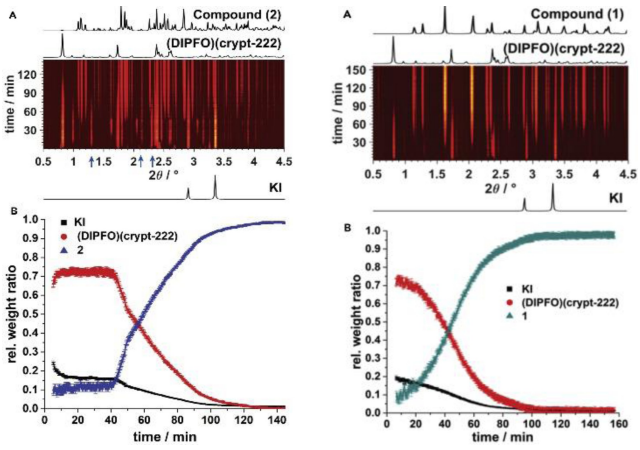


Figure 18. a,b. (a) Real-time in situ monitoring of KI, DIPFO, and Crypt-222 reaction by milling with two stainless-steel balls (1.38 g). This approach implied the formation of the non-interpenetrated halogen-bonded derivative. (b) Real-time in situ monitoring of the KI, DIPFO, and Crypt-222 reaction by milling with a single stainless-steel ball (2.9 g). This approach allowed the formation of the desired Borromean network product. They were reproduced from ref. [126].

This revelation not only showcases the adaptability of mechanochemical synthesis in achieving selective topologies but also emphasizes the importance of finely tuning mechanochemical parameters to master solid-state reactivity and polymorph selection.

Additionally, the pioneering use of synchrotron pXRD for in situ reaction monitoring unveils the dynamic evolution of Zeolitic Imidazolate Frameworks (ZIFs), marking a significant methodological advancement. This convergence expands the boundaries of chemical synthesis and material design by offering a straightforward, sustainable, and cost-effective pathway to discovering novel materials and phenomena, heralding an era of enhanced scientific exploration and technological innovation.

4.5. Mechanosynthesis of Polymers

Mechanochemical treatment emerges as a pioneering green technology with a pivotal role in sustainable biofuels, fine chemicals, and food production. Biopolymers, integral to these processes, aid in the isolation, derivation, and modification of natural compounds. However, mechanochemical processing's inadvertent alteration of biopolymers can introduce subtle yet significant challenges that might not be readily apparent.[127]

In the groundbreaking work by Pedrazzo *et al.*, a novel, environmentally sustainable method for synthesizing cyclodextrin nanosponges (CD–NS) is presented, leveraging the principles of mechanochemistry.[128] Cyclodextrins, with their reactive hydroxy groups capable of acting as multifunctional monomers, traditionally required organic polar aprotic solvents like *N,N*-dimethylformamide, or dimethyl sulfoxide for cross-linking. This conventional method posed potential limitations for biomedical applications due to solvent-associated concerns.[129] The study introduced a green synthetic pathway using ball milling, with 1,1-carbonyldiimidazole as the cross-linker, producing polymers that retain the characteristics of CD-based carbonate NS synthesized in solvents.

The post-synthesis modification involves the nucleophilic reaction of the polymer's carboxylic group with organic dyes such as fluorescein, methyl red, and rhodamine B, utilizing the imidazoyl carbonyl group of the NS for additional chemical transformations. The research demonstrates the method's flexibility by exploring various cyclodextrins (α, β, and γ) and adjusting the molar ratios between the cyclodextrin and the crosslinker (1:2, 1:4, and 1:8). Moreover, nanoparticles achieved through ball milling and high-pressure homogenization were characterized by a mean diameter of less than 200 nm and displayed a negative ζ-potential (Figure 19).

This pioneering study by Pedrazzo et al. shows a significant advancement in the synthesis and functionalization of cyclo-

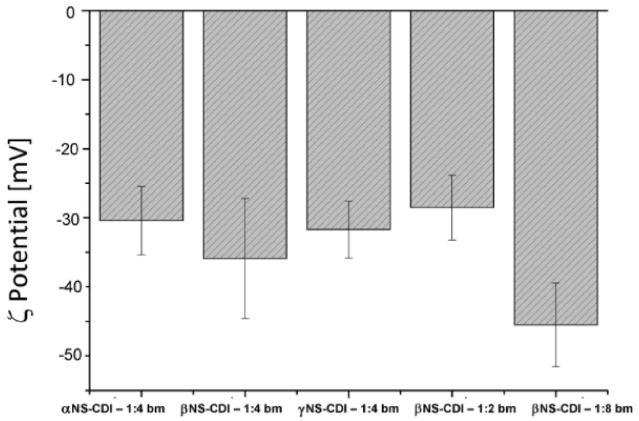


Figure 19. ζ-Potential of bm cyclodextrin nanosponges with relative STDev (mV). Reproduced from ref. [128] (open access).

dextrin-based nanosponges. It offers a green, efficient, and versatile approach that could revolutionize the production and application of these polymers in various fields, especially in biomedical applications.

Vincamine (VIC) is a significant indole alkaloid obtained from Vinca Minor L. it is used to help treat brain sclerosis and aid in the recovery of the central nervous system after surgery.[130] However, its oral bioavailability is limited due to its highly crystalline nature when recrystallized from solvents such as acetone or methanol.[131] Furthermore, VIC's solubility decreases in intestinal fluids, challenging enhancing oral absorption. To address these challenges, Voinovich explored the application of a high mechanical energy to induce physical modifications in VIC.[132] The process disrupts the crystal lattice, yielding disordered structures such as nanocrystalline or amorphous phases or molecular drug dispersion within a carrier. The stabilization of these metastable structures, crucial for improving VIC's bioavailability, was achieved by introducing crosslinked polymers like AcDiSol® and PVP–Cl during the mechanochemical activation.

Detailed characterizations confirmed the intimate mixing of the drug and polymers in the ground mixtures, demonstrating significant improvements in VIC's in vitro and in vivo bioavailability when activated in the presence of these polymers. Systems based on AcDiSol® emerged as superior, showing enhanced drug dissolution rates and physical stability. Among the co-ground samples, two stood out based on dissolution performance analyses (Figure 20). In-depth physicochemical characterization and in vivo studies further delineated the Cog 180 min VIC: AcDiSol® 1:7 wt sample as superior (Formulation number 15 in Figure 20). Conversely, the optimal system for PVP–Cl was identified as the Cog 180 min VIC:PVP–Cl 1:4 wt, with higher concentrations of PVP–Cl adversely affecting performance.

Despite enhancing oral bioavailability, they exhibited distinct plasma profiles. Concerning their stability, the nanocrystalline state of VIC in the AcDiSol® co-ground remained unchanged for one year under ambient conditions, in contrast to the VIC:PVP–Cl systems, which showed signs of recrystallization and consequent dissolution performance variability. This research highlights the potential of mechanochemical activation combined with suitable polymers for improving vincamine's solubility, bioavailability, and stability, offering a promising avenue for optimizing oral drug formulations.

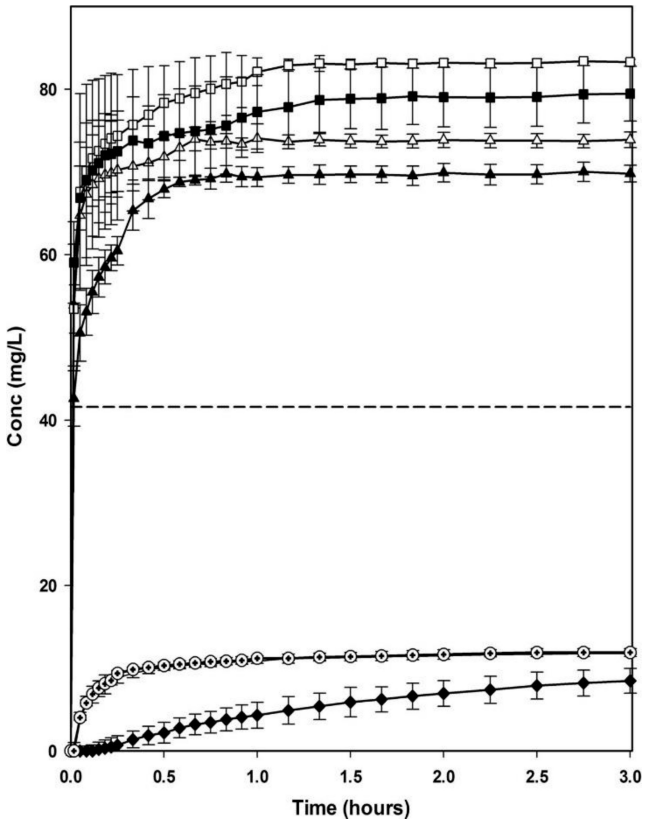


Figure 20. Solubilization kinetics of pure vincamine (♦), Cog formulation number 13 (▲), Cog formulation number 14 (Δ), Cog formulation number 10 (■), and Cog formulation number 15 (□). PMs vincamine:PVP–K30 1:4 wt ratio (+) and 1:7 wt ratio (○) showed superimposable solubilisation kinetics. Pure vincamine solubility at equilibrium (Cs) is indicated by a dotted line. Reproduced from ref. [132] with permission from Elsevier.

5. Summary and Outlook

In conclusion, mechanochemistry is a promising method within green chemistry that can potentially transform the industry.[133] It provides a way to conduct chemical reactions that are both environmentally friendly, safer, and more efficient. However advantageous in different scientific fields, it still needs to overcome challenges that prevent its widespread adoption.[102a,134] These include scaling up reactions for industrial applications and developing a comprehensive understanding of the mechanisms behind mechanochemically driven transformations. If researchers can overcome these challenges, it could lead to breakthroughs that make it a fundamental part of sustainable industrial chemistry. Its potential to significantly reduce the impact of industrial processes aligns perfectly with sustainability and environmental protection goals, which are becoming increasingly important in today's global context.[135]

The engagement with mechanochemistry in Italy showcases a vibrant and forward-thinking research community dedicated to pushing the boundaries of what is achievable in chemical synthesis. With their deep commitment to innovation, sustainability, and cross-disciplinary collaboration, Italian researchers have made notable strides in advancing mechanochemistry. Their work deepens our comprehension of the underlying chemical phenomena and spearheads the development of novel technologies and methodologies to address some of our time's most pressing environmental issues.

As mechanochemistry continues to grow and mature, Italy's contributions are recognized as significant and impactful, marking the country as a critical player in future green chemistry developments. The ongoing evolution of this field promises advancements in chemical synthesis and a broader movement toward sustainable scientific practices that respect and preserve our environment. With continued research and innovation, the potential for mechanochemistry to contribute to a more sustainable future is immense, making it an exciting area of study and application in the years ahead.

Acknowledgements

This research was funded by Fondazione Banco di Sardegna (FDS), "*A Rational Design and Eco-Friendly Synthesis of G-Quadruplex Binders to Attack Viral Nucleic Acids*", grant number F73C23001600007. Open Access publishing facilitated by Università degli Studi di Cagliari, as part of the Wiley - CRUI-CARE agreement.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: Italy · mechanochemistry · enabling technology · Active Pharmaceutical Ingredient · sustainability

[1] a) T. Welton, *Proc. R. Soc. A: Math. Phys. Eng. Sci.* **2015**, *471*, 20150502; b) V. G. Zuin, I. Eilks, M. Elschami, K. Kümmerer, *Green Chem.* **2021**, *23*, 1594–1608; c) I. T. Horváth, P. T. Anastas, *Chem. Rev.* **2007**, *107*, 2169–2173; d) C.-J. Li, P. T. Anastas, *Chem. Soc. Rev.* **2012**, *41*, 1413–1414.
[2] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) J.-I. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331–340.
[3] a) F. Uekötter, *Hist. Technol.* **2021**, *37*, 429–445; b) M. R. Finlay, *J. Ind. Ecol.* **2003**, *7*, 33–46.
[4] W. J. Hale, *The Farm Chemurgic: Farmward the Star of Destiny Lights Our Way*, Stratford Company, **1934**.
[5] a) D. D. Songstad, P. Lakshmanan, J. Chen, W. Gibbons, S. Hughes, R. Nelson, *In Vitro Cell. Dev. Biol. Plant* **2009**, *45*, 189–192; b) can be found under https://www.mlive.com/news/2014/02/a weed goes to war and michiga.html, **2014** (accessed: 12/05/2024).
[6] R. Beeman, *Agric. Hist.* **1994**, *68*, 23–45.
[7] J. P. Clark, in *Kirk-Othmer Encyclopedia of Chemical Technology*, **2000**.
[8] a) H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata, P. T. Anastas, *Green Chem.* **2018**, *20*, 1929–1961; b) M. A. Murphy, *Found. Chem.* **2018**, *20*, 121–165.
[9] a) can be found under https://www.acs.org/greenchemistry/principles/12-principles-of-green-chemistry.html, **1998** (accessed: 12/05/2024); b) P. T. Anastas, J. C. Warner, *Green chemistry: theory and practice*, Oxford university press, **2000**; c) P. G. Jessop, S. Trakhtenberg, J. Warner, ACS Publications, **2009**.
[10] a) C.-J. Li, B. M. Trost, *Proc. Nat. Acad. Sci.* **2008**, *105*, 13197–13202; b) O. V. Kharissova, B. I. Kharisov, C. M. Oliva González, Y. P. Méndez, I. López, *R. Soc. Open Sci.* **2019**, *6*, 191378; c) Y. H. Budnikova, E. L. Dolengovski, M. V. Tarasov, T. V. Gryaznova, *J. Solid State Electrochem.* **2024**, *28*, 659–676; d) S. Głowniak, B. Szczęśniak, J. Choma, M. Jaroniec, *Mater. Today* **2021**, *46*, 109–124; e) F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocci, A. Porcheddu, *ChemSusChem* **2022**, *15*, e202200362.
[11] a) F. Casti, F. Basoccu, R. Mocci, L. De Luca, A. Porcheddu, F. Cuccu, *Molecules* **2022**, *27*, 1988; b) D. Kralisch, D. Ott, D. Gericke, *Green Chem.* **2015**, *17*, 123–145; c) B. Karadeniz, A. J. Howarth, T. Stolar, T. Islamoglu, I. Dejanović, M. Tireli, M. C. Wasson, S.-Y. Moon, O. K. Farha, T. Friščl, *ACS Sustainable Chem. Eng.* **2018**, *6*, 15841–15849; d) B. G. Fiss, L. Hatherly, R. S. Stein, T. Friščić, A. Moore, *ACS Sustainable Chem. Eng.* **2019**, *7*, 7951–7959; e) F. Pancrazzi, G. Castronuovo, G. Maestri, A. M. Constantin, A. Voronov, R. Maggi, P. P. Mazzeo, E. Motti, D. A. Cauzzi, R. Viscardi, N. Della Ca', *Eur. J. Org. Chem.* **2022**, *2022*, e202201315.
[12] a) F. Cuccu, F. Basoccu, C. Fattuoni, A. Porcheddu, *Green Chem.* **2024**, *26*, 1927–1934; b) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13–19; c) J. L. Howard, M. C. Brand, D. L. Browne, *Angew. Chem.* **2018**, *130*, 16336–16340; d) J. Mack, M. Shumba, *Green Chem.* **2007**, *9*, 328–330; e) E. Juaristi, C. G. Avila-Ortiz, *Synthesis* **2023**, *55*, 2439–2459.
[13] a) D. Tan, T. Friščić, *Eur. J. Org. Chem.* **2018**, *2018*, 18–33; b) F. Gomollón-Bel, *Chem. Int.* **2019**, *41*, 12–17.
[14] a) K. J. Ardila-Fierro, J. G. Hernández, *ChemSusChem* **2021**, *14*, 2145–2162; b) F. Puccetti, *Chem* **2023**, *9*, 1066–1068; c) J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435–1443; d) M. Pérez-Venegas, E. Juaristi, *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881–8893.
[15] a) J. F. Reynes, V. Isoni, F. García, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300819; b) D. Tan, F. García, *Chem. Soc. Rev.* **2019**, *48*, 2274–2292.
[16] a) S. Hwang, S. Grätz, L. Borchardt, *Chem. Commun.* **2022**, *58*, 1661–1671; b) L. Vugrin, M. Carta, S. Lukin, E. Meštrović, F. Delogu, I. Halasz, *Farad. Disc.* **2023**, *241*, 217–229; c) N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García, E. Colacino, *Chem. Soc. Rev.* **2023**, *52*, 6680–6714.
[17] G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700.
[18] a) A. Porcheddu, F. Delogu, L. De Luca, C. Fattuoni, E. Colacino, *Beilstein J. Org. Chem.* **2019**, *15*, 1786–1794; b) C. Weidenthaler, *Crystals* **2022**, *12*, 345; c) J.-L. Do, T. Auvray, C. B. Lennox, H. M. Titi, L. A. Cuccia, T. Friščić, *Green Chem.* **2023**, *25*, 5899–5906.
[19] E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, F. Delogu, R. Guerra, J. Fullenwarth, *Green Chem.* **2018**, *20*, 2973–2977.
[20] a) F. H. Bhuiyan, Y.-S. Li, S. H. Kim, A. Martini, *Sci. Rep.* **2024**, *14*, 2992; b) A. L. Sanna, M. Carta, G. Pia, S. Garroni, A. Porcheddu, F. Delogu, *Sci. Rep.* **2022**, *12*, 9445; c) S. Mateti, M. Mathesh, Z. Liu, T. Tao, T. Ramireddy, A. M. Glushenkov, W. Yang, Y. I. Chen, *Chem. Commun.* **2021**, *57*, 1080–1092; d) R. Takahashi, T. Seo, K. Kubota, H. Ito, *ACS Catal.* **2021**, *11*, 14803–14810.
[21] a) J. D. Chea, A. Christon, V. Pierce, J. H. Reilly, M. Russ, M. Savelski, C. S. Slater, K. M. Yenkie, *Comput. Aided Chem. Eng.* **2019**, *47*, 199–204; b) J. Strube, R. Gärtner, M. Schulte, *Chem. Eng. J.* **2002**, *85*, 273–288.
[22] a) R. A. Sheldon, M. L. Bode, S. G. Akakios, *Curr. Opin. Green Sustain. Chem.* **2022**, *33*, 100569; b) R. A. Sheldon, *Green Chem.* **2017**, *19*, 18–43; c) R. A. Sheldon, *Green Chem.* **2016**, *18*, 3180–3183.
[23] a) Y. Zhou, F. Guo, C. E. Hughes, D. L. Browne, T. R. Peskett, K. D. Harris, *Cryst. Growth Des.* **2015**, *15*, 2901–2907; b) A. Bodach, A. Portet, F. Winkelmann, B. Herrmann, F. Gallou, E. Ponnusamy, D. Virieux, E. Colacino, M. Felderhoff, *ChemSusChem* **2023**, *17*, e202301220.
[24] a) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; b) K. L. Mulholland, R. W. Sylvester, J. A. Dyer, *Environ. Prog.* **2000**, *19*, 260–268.
[25] a) Z. Liu, G. Liu, L. Cheng, J. Gu, J. Yang, H. Yuan, Y. Chen, Y. Wu, *Sep. Purif. Tech.* **2024**, *335*, 126174; b) Y. Gao, K. Kubota, H. Ito, *Angew. Chem. Int. Ed.* **2023**, *62*, e202217723; c) R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota, H. Ito,

Nat. Commun. **2021**, *12*, 6691; d) C. Bolm, J. G. Hernández, *Angew. Chem. Int. Ed.* **2019**, *58*, 3285–3299.
[26] a) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007–4019; b) J. M. J. Paulusse, R. P. Sijbesma, *Chem. Commun.* **2008**, 4416–4418; c) C. G. Avila-Ortiz, M. Pérez-Venegas, J. Vargas-Caporali, E. Juaristi, *Tetrahedron Lett.* **2019**, *60*, 1749–1757.
[27] F. Gomollón-Bel, *ACS Cent. Sci.* **2022**, *8*, 1474–1476.
[28] R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan, J. Mack, *ACS Sustainable Chem. Eng.* **2016**, *4*, 2464–2469.
[29] a) P. Ying, J. Yu, W. Su, *Adv. Synth. Catal.* **2021**, *363*, 1246–1271; b) S. Karki, T. Friščić, W. Jones, W. S. Motherwell, *Mol. Pharm.* **2007**, *4*, 347–354; c) Z.-J. Jiang, Z.-H. Li, J.-B. Yu, W.-K. Su, *J. Org. Chem.* **2016**, *81*, 10049–10055.
[30] T. Friščić, D. G. Reid, I. Halasz, R. S. Stein, R. E. Dinnebier, M. J. Duer, *Angew. Chem. Int. Ed.* **2010**, *4*, 712–715.
[31] a) can be found under https://bigthink.com/hard-science/mechano-chemistry-grind-revolutionize-materials-science/, **2023** (accessed: 10/04/2024); b) F. Hajiali, T. Jin, G. Yang, M. Santos, E. Lam, A. Moores, *ChemSusChem* **2022**, *15*, e202102535.
[32] a) G. Papeo, M. Pulici, *Molecules* **2013**, *18*, 10870–10900; b) R. Piria, *Il Cimento* **1846**, *4*, 55–73; c) C. Bertagnini, *Justus Liebigs Ann. Chem.* **1853**, *85*, 179–196.
[33] a) M. Carta, F. Delogu, A. Porcheddu, *Phys. Chem. Chem. Phys.* **2021**, *23*, 14178–14194; b) G. Cravotto, P. Cintas, *Chem. Sci.* **2012**, *3*, 295–307.
[34] L. Battezzati, S. Enzo, L. Schiffini, G. Cocco, *J. Less-Common Met.* **1988**, *145*, 301–308.
[35] a) S. Enzo, L. Schiffini, L. Battezzati, G. Cocco, *J. Less-Common Met.* **1988**, *140*, 129–137; b) G. Cocco, L. Schiffini, I. Soletta, M. Baricco, N. Cowlam, *J. Phys. Colloq.* **1990**, *51*, C4-175-C174-180.
[36] G. Cocco, G. Mulas, L. Schiffini, *Mater. Trans. JIM* **1995**, *36*, 150–160.
[37] S. Loiselle, M. Branca, G. Mulas, G. Cocco, *Environ. Sci. Technol.* **1997**, *31*, 261–265.
[38] a) L. Takacs, V. Šepelák, *J. Mater. Sci.* **2004**, *39*, 5487–5489; b) V. Martinez, T. Stolar, B. Karadeniz, I. Brekalo, K. Užarević, *Nat. Chem. Rev.* **2023**, *7*, 51–65.
[39] a) A. Stolle, T. Szuppa, S. E. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317–2329; b) K. Roy, S. Sahoo, A. Saha, L. Adak, *Curr. Org. Chem.* **2023**, *27*, 153–165.
[40] R. Mocci, L. D. Luca, F. Delogu, A. Porcheddu, *Adv. Synth. Catal.* **2016**, *358*, 3135–3144.
[41] Q. Wei, L. Zhu, Y. Ma, G. Xu, W. Zhao, X. Zhao, Y. Wang, *J. Mol. Liq.* **2022**, *361*, 119620.
[42] L. Jicsinszky, M. Caporaso, K. Martina, E. C. Gaudino, G. Cravotto, *Beilstein J. Org. Chem.* **2016**, *12*, 2364–2371.
[43] a) L. Jicsinszky, G. Cravotto, *Molecules* **2021**, *26*, 5193; b) P. Saokham, C. Muankaew, P. Jansook, T. Loftsson, *Molecules* **2018**, *23*, 1161; c) Z. Lu, B. Cheng, Y. Hu, Y. Zhang, G. Zou, *Food Chem.* **2009**, *113*, 17–20.
[44] a) G. Cravotto, M. Caporaso, L. Jicsinszky, K. Martina, *Beilstein J. Org. Chem.* **2016**, *12*, 278–294; b) A. Porcheddu, F. Delogu, L. De Luca, E. Colacino, *ACS Sustainable Chem. Eng.* **2019**, *7*, 12044–12051.
[45] S. Gaspa, A. Porcheddu, A. Valentoni, S. Garroni, S. Enzo, L. De Luca, *Eur. J. Org. Chem.* **2017**, *2017*, 5519–5526.
[46] a) F. Delogu, L. Takacs, *J. Mater. Sci.* **2018**, *53*, 13331–13342; b) M. Carta, E. Colacino, F. Delogu, A. Porcheddu, *Phys. Chem. Chem. Phys.* **2020**, *22*, 14489–14502; c) C. Hinshelwood, K. Laidler, E. Timm, *J. Chem. Soc.* **1938**, 848–858;d) M. Carta, L. Vugrin, G. Miletić, M. J. Kulcsár, P. C. Ricci, I. Halasz, F. Delogu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308046.
[47] E. Colacino, M. Carta, G. Pia, A. Porcheddu, P. C. Ricci, F. Delogu, *ACS Omega* **2018**, *3*, 9196–9209.
[48] P. A. Julien, I. Malvestiti, T. Friščić, *Beilstein J. Org. Chem.* **2017**, *13*, 2160–2168.
[49] G. Kaupp, *CrystEngComm* **2009**, *11*, 388–403.
[50] a) E. Nwoye, S. Raghuraman, M. Costales, J. Batteas, J. R. Felts, *Phys. Chem. Chem. Phys.* **2023**, *25*, 29088–29097; b) L. Vugrin, M. Carta, S. Lukin, E. Meštrović, F. Delogu, I. Halasz, *Farad. Disc.* **2023**, *241*, 217–229; c) G. Traversari, A. Porcheddu, G. Pia, F. Delogu, A. Cincotti, *Phys. Chem. Chem. Phys.* **2021**, *23*, 229–245.
[51] A. M. Belenguer, G. I. Lampronti, D. J. Wales, J. K. Sanders, *J. Am. Chem. Soc.* **2014**, *136*, 16156–16166.
[52] a) J. Wisniak, M. Klein, *Ind. Eng. Chem. Prod. Res. Dev.* **1984**, *23*, 44–50; b) F. Basoccu, F. Cuccu, P. Caboni, L. De Luca, A. Porcheddu, *Molecules* **2023**, *28*, 2239; c) J. Dong, Y. Zhao, R. Zhao, R. Zhou, *J. Environ. Sci.* **2010**, *22*, 1741–1747; d) C. Liang, Y.-T. Lin, J.-W. Shiu, *J. Hazard. Mater.* **2016**, *302*, 137–143; e) S. Yamabe, S. Yamazaki, *J. Phys. Org. Chem.* **2016**, *29*, 361–367.
[53] K. Martina, F. Baricco, S. Tagliapietra, M. J. Moran, G. Cravotto, P. Cintas, *New J. Chem.* **2018**, *42*, 18881–18888.
[54] a) Z. Hongyue, S. Lei, S. Qi, *Chin. J. Catal.* **2012**, *33*, 1463–1469; b) S. Diao, W. Qian, G. Luo, F. Wei, Y. Wang, *Appl. Catal. A* **2005**, *286*, 30–35.
[55] O. Cope, R. Brown, *Can. J. Chem.* **1961**, *39*, 1695–1710.
[56] W. Pickhardt, E. Siegfried, S. Fabig, M. F. Rappen, M. Etter, M. Wohlgemuth, S. Grätz, L. Borchardt, *Angew. Chem. Int. Ed.* **2023**, *62*, e202301490.
[57] N. Zappimbulso, M. A. M. Capozzi, A. Porcheddu, G. M. Farinola, A. Punzi, *ChemSusChem* **2021**, *14*, 1363–1369.
[58] a) N. Liu, V. Gujrati, J. Malekzadeh-Najafabadi, J. P. F. Werner, U. Klemm, L. Tang, Z. Chen, J. Prakash, Y. Huang, A. Stiel, *Photoacoustics* **2021**, *22*, 100263; b) A. Punzi, M. A. M. Capozzi, V. Fino, C. Carlucci, M. Suriano, E. Mesto, E. Schingaro, E. Orgiu, S. Bonacchi, T. Leydecker, *J. Mater. Chem. C* **2016**, *4*, 3138–3142; c) S. Khopkar, G. Shankarling, *Dyes Pigm.* **2019**, *170*, 107645; d) J. V. Ros-Lis, B. García, D. Jiménez, R. Martínez-Máñez, F. Sancenón, J. Soto, F. Gonzalvo, M. C. Valldecabres, *J. Am. Chem. Soc.* **2004**, *126*, 4064–4065.
[59] M. H. Sleiman, S. Ladame, *Chem. Commun.* **2014**, *50*, 5288–5290.
[60] A. Porcheddu, R. Mocci, M. Brindisi, F. Cuccu, C. Fattuoni, F. Delogu, E. Colacino, M. V. d'Auria, *Green Chem.* **2022**, *24*, 4859–4869.
[61] a) R. J. Melander, M. J. Minvielle, C. Melander, *Tetrahedron* **2014**, *70*, 6363–6372; b) N. N. Biswas, S. K. Kutty, N. Barraud, G. M. Iskander, R. Griffith, S. A. Rice, M. Willcox, D. S. Black, N. Kumar, *Org. Biomol. Chem.* **2015**, *13*, 925–937; c) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195–7210.
[62] a) A. Mauger, M. Jarret, C. Kouklovsky, E. Poupon, L. Evanno, G. Vincent, *Nat. Prod. Rep.* **2021**, *38*, 1852–1886; b) H.-J. Borschberg, *Curr. Org. Chem.* **2005**, *9*, 1465–1491.
[63] a) L. El Kaïm, L. Grimaud, X.-F. Le Goff, M. Menes-Arzate, L. D. Miranda, *Chem. Commun.* **2011**, *47*, 8145–8147; b) X. Wei, W.-G. Wang, Y. Matsuda, *Fungal Biol. Biotech.* **2022**, *9*, 6; c) R. H. Himes, R. N. Kersey, I. Heller-Bettinger, F. E. Samson, *Cancer Res.* **1976**, *36*, 3798–3802; d) K. Fuxe, S. O. Ogren, L. F. Agnati, K. Andersson, H. Hall, C. Köhler, B. Fredholm, *Adv. Biochem. Psychopharmacol.* **1980**, *23*, 41–62.
[64] E. Calcio Gaudino, G. Grillo, M. Manzoli, S. Tabasso, S. Maccagnan, G. Cravotto, *Molecules* **2022**, *27*, 449.
[65] E. Calcio Gaudino, G. Cravotto, M. Manzoli, S. Tabasso, *Chem. Soc. Rev.* **2021**, *50*, 1785–1812.
[66] O. Trentin, D. Polidoro, A. Perosa, E. Rodríguez-Castellon, D. Rodríguez-Padrón, M. Selva, *Chemistry* **2023**, *5*, 1760–1769.
[67] F. Basoccu, F. Cuccu, A. Porcheddu, *ChemSusChem* **2024**, *17*, e202301034.
[68] a) I. Sedlo, T. Kolonić, S. Tomić, *Arch. Ind. Hyg. Toxicol.* **2021**, *72*, 1–5; b) R. Ruepp, R. Frötschl, R. Bream, M. Filancia, T. Girard, A. Spinei, M. Weise, R. Whomsley, *Front. Med.* **2021**, *8*; c) T. Öncü, B. Yüksel, E. Binay, N. Şen, *Ann. Pharm. Fr.* **2024**, *82*, 72–83; d) S. S. Bharate, *J. Med. Chem.* **2021**, *64*, 2923–2936.
[69] EMA, "Nitrosamine impurities in human medicinal products", can be found under https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report en.pdf, **2020** (accessed: 09/06/2023).
[70] E. Kaiser, C. Wu, *J. Phys. Chem.* **1977**, *81*, 1701–1706.
[71] Q. Shi, Z. Liu, Y. Yang, P. Geng, Y.-y. Zhu, Q. Zhang, F. Bai, G. Bai, *Acta Pharmacol. Sin.* **2009**, *30*, 567–575.
[72] a) J. C. McWilliams, A. D. Allian, S. M. Opalka, S. A. May, M. Journet, T. M. Braden, *Org. Process Res. Dev.* **2018**, *22*, 1143–1166; b) M. Blanco, M. Bautista, M. Alcalà, *AAPS PharmSciTech* **2008**, *9*, 1130–1135.
[73] a) M. Berton, J. M. de Souza, I. Abdiaj, D. T. McQuade, D. R. Snead, *J. Flow Chem.* **2020**, *10*, 73–92; b) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194–1219; c) J.-S. Poh, D. L. Browne, S. V. Ley, *React. Chem. Eng.* **2016**, *1*, 101–105.
[74] D. Wieckhusen, *Chimia* **2006**, *60*, 598–598.
[75] a) K. Grodowska, A. Parczewski, *Acta Pol. Pharm. Drug Res.* **2010**, *67*, 3–12; b) S. H. Chang, *Environ. Sci. Pollution Res.* **2020**, *27*, 32371–32388.
[76] J. Geens, B. De Witte, B. Van der Bruggen, *Sep. Sci. Technol.* **2007**, *42*, 2435–2449.
[77] a) D. R. Joshi, N. Adhikari, *J. Pharm. Res. Int.* **2019**, *28*, 1–18; b) J. Connelly, in *ICH Quality Guidelines: An Implementation Guide* (Eds.: A. Teasdale, D. Elder, R. W. Nims), **2017**, pp. 199–232; c) I. H. T. Guideline, "Impurities: Guideline for residual solvents Q3 C (R5)", can be found under http://www.boroyf.com/Private/Files/20180710/636668239029314423785398l.pdf, **2005** (accessed: 10/04/2024).

[78] a) D. E. Crawford, J. Casaban, *Adv. Mater.* **2016**, *28*, 5747–5754; b) D. E. Crawford, *Beilstein J. Org. Chem.* **2017**, *13*, 65–75.
[79] a) M. Li, C. G. Gogos, N. Ioannidis, *Int. J. Pharm.* **2015**, *478*, 103–112; b) R. R. Bolt, J. A. Leitch, A. C. Jones, W. I. Nicholson, D. L. Browne, *Chem. Soc. Rev.* **2022**, *51*, 4243–4260; c) L. Konnert, B. Reneaud, R. M. de Figueiredo, J.-M. Campagne, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 10132–10142; d) M. Pérez-Venegas, E. Juaristi, *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881–8893.
[80] a) M. I. Hutchings, A. W. Truman, B. Wilkinson, *Curr. Opin. Microbiol.* **2019**, *51*, 72–80; b) K. I. Mohr, *History of antibiotics research* **2016**, *398*, 237–272.
[81] J. Nemeth, G. Oesch, S. P. Kuster, *J. Antimicrob. Chemother.* **2015**, *70*, 382–395.
[82] a) B. C. Rudy, B. Z. Senkowski, in *Analytical profiles of drug substances, Vol. 2*, Elsevier, New Jersey, **1973**, pp. 467–486; b) J. D. Smilack, *Mayo Clin. Proc.* **1999**, *74*, 730–734.
[83] a) R. F. Langler, Z. A. Marini, E. S. Spalding, *Can. J. Chem.* **1979**, *57*, 3193–3199; b) A. Nishiguchi, K. Maeda, S. Miki, *Synthesis* **2006**, *2006*, 4131–4134; c) S. Madabhushi, R. Jillella, V. Sriramoju, R. Singh, *Green Chem.* **2014**, *16*, 3125–3131.
[84] F. Cuccu, A. Porcheddu, *Green Chem.* **2024**, *26*, 2684–2691.
[85] a) P. F. D'Arcy, *Drug Intell. Clin. Pharm.* **1985**, *19*, 540–547; b) C. C. McOsker, P. M. Fitzpatrick, *J. Antimicrob. Chemother.* **1994**, *33*, 23–30.
[86] a) S. See, R. Ginzburg, *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **2008**, *28*, 207–213; b) S. Kampe, J. W. Krombach, C. Diefenbach, *Best Pract. Res. Clin. Anaesthesiol.* **2003**, *17*, 137–146; c) S. See, R. Ginzburg, *Am. Fam. Physician* **2008**, *78*, 365–370.
[87] M. G. Larach, T. T. Klumpner, B. W. Brandom, M. T. Vaughn, K. G. Belani, A. Herlich, T. W. Kim, J. Limoncelli, S. Riazi, E. L. Sivak, *Anesthesiology* **2019**, *130*, 41–54.
[88] a) T. Krause, M. Gerbershagen, M. Fiege, R. Weisshorn, F. Wappler, *Anaesthesia* **2004**, *59*, 364–373; b) K. Ellis, A. Castellion, L. Honkomp, F. Wessels, J. Carpenter, R. Halliday, *J. Pharm. Sci.* **1973**, *62*, 948–951.
[89] a) A. Szent-Györgyi, *Biophys. J.* **1975**, *15*, 707–723; b) P. Szentesi, C. Collet, S. Sárközi, C. Szegedi, I. Jona, V. Jacquemond, L. Kovács, L. Csernoch, *J. Gen. Physiol.* **2001**, *118*, 355–376.
[90] a) P. A. Marks, T. Miller, V. M. Richon, *Curr. Opin. Pharmacol.* **2003**, *3*, 344–351; b) N. Sengupta, E. Seto, *J. Cell. Biochem.* **2004**, *93*, 57–67.
[91] T. Liang, H. Fang, *Curr. Top. Med. Chem.* **2018**, *18*, 2429–2447.
[92] a) C. Simões-Pires, V. Zwick, A. Nurisso, E. Schenker, P.-A. Carrupt, M. Cuendet, *Mol. Neurodegener.* **2013**, *8*, 1–16; b) R. Ferreira de Freitas, R. J. Harding, I. Franzoni, M. Ravichandran, M. K. Mann, H. Ouyang, M. Lautens, V. Santhakumar, C. H. Arrowsmith, M. Schapira, *J. Med. Chem.* **2018**, *61*, 4517–4527.
[93] a) K. V. Butler, J. Kalin, C. Brochier, G. Vistoli, B. Langley, A. P. Kozikowski, *J. Am. Chem. Soc.* **2010**, *132*, 10842–10846; b) M. Morgen, R. R. Steimbach, M. Géraldy, L. Hellweg, P. Sehr, J. Ridinger, O. Witt, I. Oehme, C. J. Herbst-Gervasoni, J. D. Osko, *ChemMedChem* **2020**, *15*, 1163–1174.
[94] H. Kano, Y. Umeda, M. Saito, H. Senoh, H. Ohbayashi, S. Aiso, K. Yamazaki, K. Nagano, S. Fukushima, *J. Toxicol. Sci.* **2008**, *33*, 141–153.
[95] a) M. A. Munir, N. Enany, J.-M. Zhang, *Anesthesiol. Clin.* **2007**, *25*, 761–774; b) G. Burgess, D. Williams, *J. Clin. Investig.* **2010**, *120*, 3753–3759.
[96] Y.-I. Hser, E. Evans, C. Grella, W. Ling, D. Anglin, *Harv. Rev. Psychiatry* **2015**, *23*, 76–89.
[97] a) G. G. Graham, K. F. Scott, *Am. J. Ther.* **2005**, *12*, 46–55; b) B. J. Anderson, *Pediatr. Anesth.* **2008**, *18*, 915–921; c) G. G. Graham, K. F. Scott, *Inflammopharmacology* **2003**, *11*, 401–413.
[98] a) F. Garzón-Posse, Y. Quevedo-Acosta, D. Gamba-Sánchez, *J. Chem. Educ.* **2022**, *99*, 2385–2391; b) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233–1246.
[99] F. Cuccu, F. Basoccu, C. Fattuoni, A. Porcheddu, *Molecules* **2022**, *27*, 5450.
[100] R. Mocci, E. Colacino, L. D. Luca, C. Fattuoni, A. Porcheddu, F. Delogu, *ACS Sustainable Chem. Eng.* **2021**, *9*, 2100–2114.
[101] a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. Harris, G. Hyett, W. Jones, *Chem. Soc. Rev.* **2012**, *41*, 413–447; b) A. A. Michalchuk, E. V. Boldyreva, A. M. Belenguer, F. Emmerling, V. V. Boldyrev, *Front. Chem.* **2021**, *9*, 685789; c) T. Kleine, J. Buendia, C. Bolm, *Green Chem.* **2013**, *15*, 160–166; d) F. Cuccu, D. L. Browne, A. Porcheddu, *ChemCatChem* **2023**, *15*, e202300762; e) S. Behera, S. Bera, F. Basoccu, F. Cuccu, P. Caboni, L. De Luca, A. Porcheddu, *Adv. Synth. Catal.* **2024**, *366*, 2035; f) P. Baláž, M. Achimovičová, M. Baláž, P. Billik, Z. Cherkezova-Zheleva, J. M. Criado, F. Delogu, E. Dutková, E. Gaffet, F. J. Gotor, *Chem. Soc. Rev.* **2013**, *42*, 7571–7637.
[102] a) E. Colacino, V. Isoni, D. Crawford, F. García, *Trends Chem.* **2021**, *3*, 335–339; b) M. Pérez-Venegas, E. Juaristi, *ChemSusChem* **2021**, *14*, 2682–2688.
[103] F. Delogu, C. Deidda, G. Mulas, L. Schiffini, G. Cocco, *J. Mater. Sci.* **2004**, *39*, 5121–5124.
[104] a) S. Schmitz, W. Löser, H. Klauß, B. Büchner, *J. Alloys Compd.* **2011**, *509*, S131–S135; b) J. Kyeong, D. Kim, J. Lee, E. Park, *Intermetallics* **2012**, *31*, 9–15.
[105] G. I. Lampronti, A. A. Michalchuk, P. P. Mazzeo, A. M. Belenguer, J. K. Sanders, A. Bacchi, F. Emmerling, *Nat. Commun.* **2021**, *12*, 6134.
[106] a) T. Friščić, I. Halasz, P. J. Beldon, A. M. Belenguer, F. Adams, S. A. Kimber, V. Honkimäki, R. E. Dinnebier, *Nat. Chem.* **2013**, *5*, 66–73; b) D. Gracin, V. Štrukil, T. Friščić, I. Halasz, K. Užarević, *Angew. Chem. Int. Ed.* **2014**, *53*, 6193–6197; c) L. Batzdorf, F. Fischer, M. Wilke, K. J. Wenzel, F. Emmerling, *Angew. Chem.* **2015**, *127*, 1819–1822.
[107] a) J. Ter Horst, M. Deij, P. Cains, *Cryst. Growth Des.* **2009**, *9*, 1531–1537; b) E. Gagnière, D. Mangin, F. Puel, A. Rivoire, O. Monnier, E. Garcia, J.-P. Klein, *J. Cryst. Growth* **2009**, *311*, 2689–2695.
[108] a) P. Vishweshwar, J. A. McMahon, J. A. Bis, M. J. Zaworotko, *J. Pharm. Sci.* **2006**, *95*, 499–516; b) N. Blagden, S. Coles, D. Berry, *CrystEngComm* **2014**, *16*, 5753–5761.
[109] a) M. Solares-Briones, G. Coyote-Dotor, J. C. Páez-Franco, M. R. Zermeño-Ortega, C. M. de la O Contreras, D. Canseco-González, A. Avila-Sorrosa, D. Morales-Morales, J. M. Germán-Acacio, *Pharmaceutica* **2021**, *13*, 790; b) D. R. Weyna, T. Shattock, P. Vishweshwar, M. J. Zaworotko, *Cryst. Growth Des.* **2009**, *9*, 1106–1123; c) D. Braga, L. Maini, F. Grepioni, *Chem. Soc. Rev.* **2013**, *42*, 7638–7648; d) T. Friščić, *Chem. Soc. Rev.* **2012**, *41*, 3493–3510.
[110] a) A. V. Trask, W. Jones, in *Organic Solid State Reaction* (Ed.: F. Toda), Springer Berlin, Heidelberg, **2005**, pp. 41–70; b) Y. Yuan, L. Wang, D. Li, Z. Deng, H. Zhang, *Cryst. Growth Des.* **2018**, *18*, 7244–7247.
[111] M. Banik, S. P. Gopi, S. Ganguly, G. R. Desiraju, *Cryst. Growth Des.* **2016**, *16*, 5418–5428.
[112] C. Fiore, A. Lekhan, S. Bordignon, M. R. Chierotti, R. Gobetto, F. Grepioni, R. J. Turner, D. Braga, *Int. J. Mol. Sci.* **2023**, *24*, 5180.
[113] L. Casali, T. Feiler, M. Heilmann, D. Braga, F. Emmerling, F. Grepioni, *CrystEngComm* **2022**, *24*, 1292–1298.
[114] a) P. K. Bolla, R. S. Kalhapure, V. A. Rodriguez, D. V. Ramos, A. Dahl, J. Renukuntla, *J. Drug Delivery Sci. Technol.* **2019**, *49*, 6–13; b) L. Yang, D. Tao, X. Yang, Y. Li, Y. Guo, *Chem. Pharm. Bull.* **2003**, *51*, 494–498.
[115] a) A. Frei, J. Zuegg, A. G. Elliott, M. Baker, S. Braese, C. Brown, F. Chen, C. G. Dowson, G. Dujardin, N. Jung, *Chem. Sci.* **2020**, *11*, 2627–2639; b) Z. Breijyeh, B. Jubeh, R. Karaman, *Molecules* **2020**, *25*, 1340.
[116] P. P. Mazzeo, M. Prencipe, T. Feiler, F. Emmerling, A. Bacchi, *Cryst. Growth Des.* **2022**, *22*, 4260–4267.
[117] a) J.-J. Liu, T. Liu, S.-B. Xia, C.-X. He, F.-X. Cheng, M.-J. Lin, C.-C. Huang, *Dyes Pigm.* **2018**, *149*, 59–64; b) Y. Ma, L. Luo, C. Yang, W. Wang, X. Liu, J. Zhang, W. Huang, *Macromol. Rapid Comm.* **2021**, *42*, 2000655.
[118] P. P. Mazzeo, M. Pioli, F. Montisci, A. Bacchi, P. Pelagatti, *Cryst. Growth Des.* **2021**, *21*, 5687–5696.
[119] a) M. Kumar, X. Xiong, Z. Wan, Y. Sun, D. C. Tsang, J. Gupta, B. Gao, X. Cao, J. Tang, Y. S. Ok, *Bioresour. Technol.* **2020**, *312*, 123613; b) A. Kiani, E. Lamberti, G. Viscusi, P. Giudicianni, C. M. Grottola, R. Ragucci, G. Gorrasi, M. R. Acocella, *Mater Adv* **2024**, *5*, 695–704; c) M. Danielis, S. Colussi, N. J. Divins, L. Soler, A. Trovarelli, J. Llorca, *Johnson Matthey Tech. Rev.* **2024**, *68*, 2; d) Y. Xu, J. M. Marrett, H. M. Titi, J. P. Darby, A. J. Morris, T. Friscic, M. Arhangelskis, *J. Am. Chem. Soc.* **2023**, *145*, 3515–3525.
[120] A. Kiani, N. Sozio, M. R. Acocella, *Mol. Syst. Des. Eng.* **2023**, *8*, 942–949.
[121] a) F. Shen, X. Xiong, J. Fu, J. Yang, M. Qiu, X. Qi, D. C. Tsang, *Renewable Sustainable Energy Rev.* **2020**, *130*, 109944; b) M. Kumar, X. Xiong, Z. Wan, Y. Sun, D. C. Tsang, J. Gupta, B. Gao, X. Cao, J. Tang, Y. S. Ok, *Bioresour. Technol.* **2020**, *312*, 123613; c) H. Lyu, B. Gao, F. He, A. R. Zimmerman, C. Ding, H. Huang, J. Tang, *Environ. Pollut.* **2018**, *233*, 54–63; d) L. Maini, P. P. Mazzeo, F. Farinella, V. Fattori, D. Braga, *Farad. Disc.* **2014**, *170*, 93–107.
[122] a) X. Du, B. Zhang, *ACS Nano* **2021**, *15*, 16851–16860; b) D. Callegari, S. Colombi, A. Nitti, C. Simari, I. Nicotera, C. Ferrara, P. Mustarelli, D. Pasini, E. Quartarone, *ACS Appl. Mater. Interfaces* **2021**, *13*, 13170–13182.
[123] C. Ferrara, E. Vigo, B. Albini, P. Galinetto, C. Milanese, C. Tealdi, E. Quartarone, S. Passerini, P. Mustarelli, *ACS Appl. Energ. Mater.* **2019**, *2*, 2794–2802.

[124] M. Danielis, S. Colussi, C. de Leitenburg, L. Soler, J. Llorca, A. Trovarelli, *Catal. Sci. Technol.* **2019**, *9*, 4232–4238.
[125] a) J. M. Marrett, H. M. Titi, Y. Teoh, T. Friščić, *Chem. Sci.* **2024**, *15*, 298–306; b) A. Bose, P. Mal, *Beilstein J. Org. Chem.* **2019**, *15*, 881–900; c) D. Braga, S. L. Giaffreda, F. Grepioni, A. Pettersen, L. Maini, M. Curzi, M. Polito, *Dalton Trans.* **2006**, *10*, 1249–1263;d) A. Delori, T. Friščić, W. Jones, *CrystEngComm* **2012**, *14*, 2350–2362.
[126] L. Catalano, L. S. Germann, P. A. Julien, M. Arhangelskis, I. Halasz, K. Užarević, M. Etter, R. E. Dinnebier, M. Ursini, M. Cametti, *Chem* **2021**, *7*, 146–154.
[127] a) J. Li, C. Nagamani, J. S. Moore, *Acc. Chem. Res.* **2015**, *48*, 2181–2190; b) J. N. Brantley, K. M. Wiggins, C. W. Bielawski, *Polym. Int.* **2013**, *62*, 2–12.
[128] A. R. Pedrazzo, F. Caldera, M. Zanetti, S. L. Appleton, N. K. Dhakar, F. Trotta, *Beilstein J. Org. Chem.* **2020**, *16*, 1554–1563.
[129] A. Gescher, *Chemical Res. Toxicol.* **1993**, *6*, 245–251.
[130] a) P. Dhyani, C. Quispe, E. Sharma, A. Bahukhandi, P. Sati, D. C. Attri, A. Szopa, J. Sharifi-Rad, A. O. Docea, I. Mardare, *Cancer Cell Int.* **2022**, *22*, 206; b) P. Fischhof, R. Möslinger-Gehmayr, W. Herrmann, A. Friedmann, D. Ruβmann, *Neuropsychobiology* **1996**, *34*, 29–35.
[131] a) P. Maincent, R. Le Verge, P. Sado, P. Couvreur, J.-P. Devissaguet, *J. Pharm. Sci.* **1986**, *75*, 955–958; b) L. Emara, B. El-Menshawi, M. Estefan, *Drug Dev. Ind. Pharm.* **2000**, *26*, 243–251.
[132] D. Hasa, B. Perissutti, M. R. Chierotti, R. Gobetto, I. Grabnar, A. Bonifacio, S. Dall'Acqua, S. Invernizzi, D. Voinovich, *Int. J. Pharm.* **2012**, *436*, 41–57.
[133] V. Isoni, in *Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing*, CRC Press, Boca Raton, **2023**, pp. 139–150.
[134] R. Boulatov, *ChemPhysChem* **2017**, *18*, 1419–1421.
[135] a) S. S. Kamble, A. Gunasekaran, S. A. Gawankar, *Process Saf. Environ. Prot.* **2018**, *117*, 408–425; b) C. Labuschagne, A. C. Brent, R. P. Van Erck, *J. Cleaner Prod.* **2005**, *13*, 373–385.

Manuscript received: April 16, 2024
Revised manuscript received: May 16, 2024
Accepted manuscript online: May 18, 2024
Version of record online: July 18, 2024