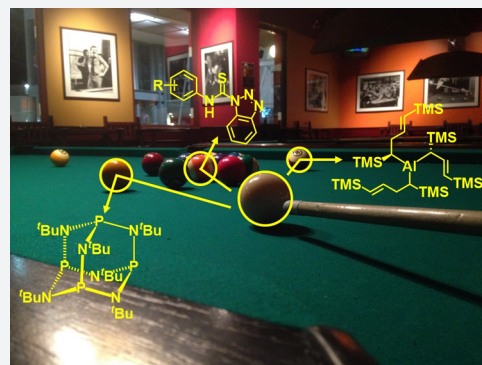


# Mechanochemistry: A Force of Synthesis

Jean-Louis Do and Tomislav Friščić\*<sup>✉</sup>

Department of Chemistry, McGill University, 801 Sherbrooke Street West H3A0B8 Montreal, Canada

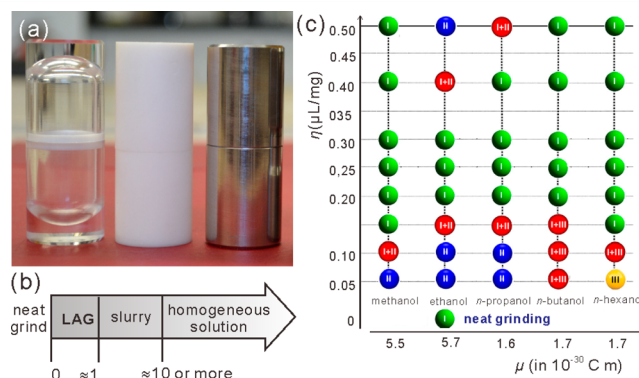
**ABSTRACT:** The past decade has seen a reawakening of solid-state approaches to chemical synthesis, driven by the search for new, cleaner synthetic methodologies. Mechanochemistry, i.e., chemical transformations initiated or sustained by mechanical force, has been advancing particularly rapidly, from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



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

## MECHANOCHEMISTRY: WHY AND HOW?

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



**Figure 1.** (a) Milling jars of (left to right) PMMA, polytetrafluoroethylene (Teflon), and stainless steel. (b) The  $\eta$ -scale<sup>35</sup> expressed in  $\mu\text{L}/\text{mg}$ . (c) Effect of  $\eta$  and liquid dipole moment ( $\mu$ ) on appearance of cocrystal polymorphs I, II, and III in LAG cocrystallization of caffeine and anthranilic acid. Adapted with permission from ref 48. Copyright 2016 American Chemical Society.

most commonly used material, but upon lengthy milling it can lead to metal contamination.<sup>26</sup> This can be avoided by using zirconia, which exhibits a similar density ( $\approx 5.6$  g/mL) and, therefore, comparable impact to steel.

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

Received: September 17, 2016

Published: December 29, 2016

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

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

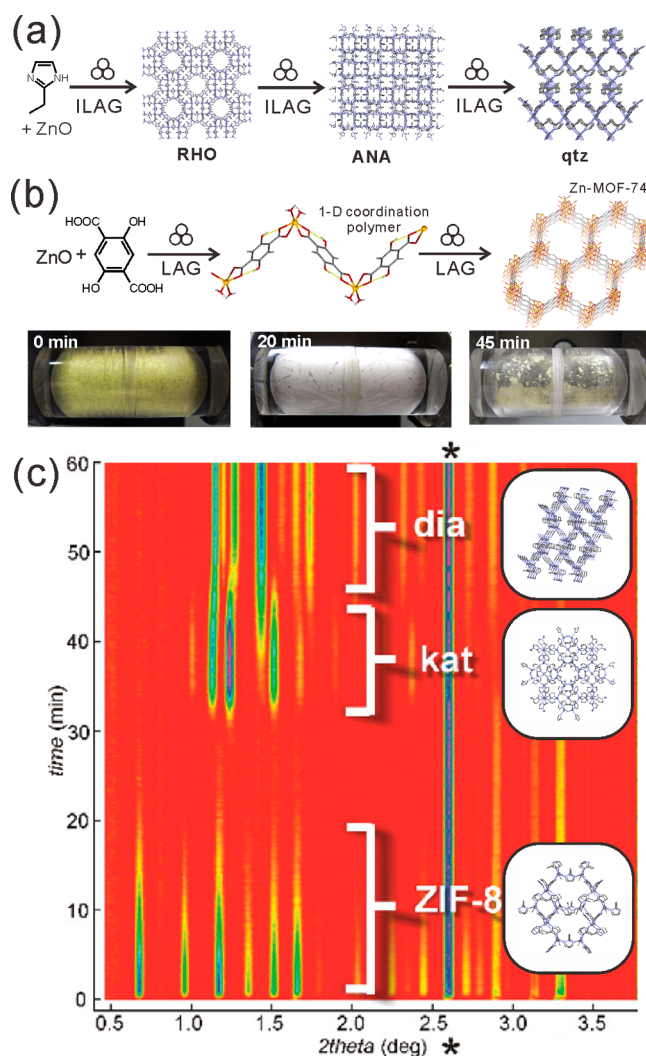
## MECHANISTIC STUDIES: REACTION MONITORING IN REAL TIME

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

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

So far, most *in situ* studies have focused on mechanosynthesis of MOFs and coordination polymers. As a result, common aspects of their synthesis have begun to emerge, in particular the propensity for stepwise mechanisms in which a low density or a highly solvated product is often formed first and then transforms into increasingly dense, less solvated materials.<sup>56,57</sup> Such behavior, resembling Ostwald’s rule of stages, is particularly

notable in mechanochemistry of zeolitic imidazolate frameworks (ZIFs, Figure 2a,b).<sup>49,56</sup> A so far unique *in situ* study of a LAG



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

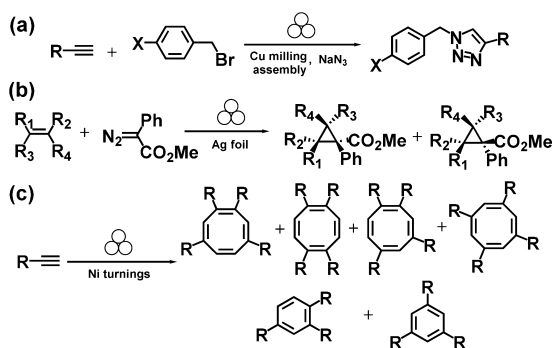
organic reaction revealed that the rate of a nucleophilic substitution may be correlated to the Gutmann donor number of the liquid additive.<sup>58</sup> *In situ* studies are also a valuable tool for materials discovery, as illustrated by a MOF with a novel katesenite (kat) topology (Figure 2c), observed for the first time as an intermediate in the synthesis of the popular ZIF-8 framework.<sup>14</sup> The kat phase rearranges to the more densely packed diamondoid (dia) polymorph upon exposure to temperature, solvent, and further milling, suggesting that mechanochemistry may be the only route for its synthesis.

## CATALYSIS IN MECHANOchemical REACTIONS

Mechanochemistry is a versatile platform for organocatalytic and metal-catalyzed transformations,<sup>59–62</sup> such as the Suzuki–Miyaura coupling<sup>63–65</sup> Huisgen cycloaddition,<sup>66</sup> olefin metathesis,<sup>67</sup> C–H activation, and more.<sup>68–79</sup> Most examples of catalytic mechanochemistry rely on catalysts developed for

solution chemistry. However, mechanochemistry offers a very different reaction environment, which can sustain other catalytic designs, and perhaps make previously challenging reactions simpler and more accessible. This was shown by the Mack group, who replaced conventional catalysts with metal surfaces. Using, for example, a milling setup made entirely out of copper enabled efficient Sonogashira coupling without a CuI cocatalyst<sup>71</sup> (Scheme 1). There was no appreciable change in mass of the

**Scheme 1. Mechanochemical Reactions Catalyzed by Metal Surfaces<sup>a</sup>**



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

milling assembly, indicating that its surfaces are acting as a catalyst. The same approach was successfully used for Huisgen coupling<sup>72</sup> (Scheme 1a), and for silver-catalyzed<sup>73</sup> [2 + 1] cyclopropanation of alkenes (Scheme 1b) where a silver foil was used as a readily removable and recyclable catalyst. Attempted alkyne [2 + 2 + 2] cycloaddition by milling with nickel metal, rather than Ni(0) complexes used in solution, led to unexpected [2 + 2 + 2] cycloaddition to form cyclooctatetraenes (Scheme 1c),<sup>74</sup> demonstrating a mechanochemical catalytic strategy with a selectivity very different than in solution.

## METAL–ORGANIC MATERIALS

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

Importantly, conventional syntheses are often solvothermal and require soluble metal reagents, e.g., nitrates or chlorides, whose explosive or toxic nature is a challenge for industrial synthesis.<sup>19</sup> This provides particular importance to the ability of mechanochemistry to use poorly soluble sulfates, oxides, or carbonates<sup>77,78</sup> as reactants. Although MOF synthesis from oxides is possible by neat grinding,<sup>79</sup> liquid-assisted mechanochemistry is much faster. Besides facilitating the reaction, the liquid often acts as a structure-directing and space-filling agent, meaning that quantitative synthesis requires sufficient additive to occupy MOF pores.<sup>78</sup> Central techniques in MOF mechanochemistry are LAG and ion- and liquid-assisted grinding (ILAG),<sup>80</sup> a method akin to LAG, but which also utilizes catalytic salts for activation of metal oxides. These techniques have enabled rapid, quantitative assembly of almost all major MOF families, including MOF-5,<sup>81</sup> ZIFs,<sup>56</sup> UiO-66 systems,<sup>82</sup> pillared MOFs,<sup>78</sup> MOF-74,<sup>57</sup> and HKUST-1. A solvent-free

approach to MIL-101(Cr) was reported,<sup>83</sup> as well as a process for continuous mechanochemistry<sup>84</sup> of aluminum fumarate MOF. Mechanochemistry also permits clean, quantitative synthesis of other metal–organic targets, e.g., bismuth subsalicylate (active ingredient of Pepto-Bismol)<sup>85</sup> and light-emitting diode (LED) material aluminum 8-hydroxyquinolate (Alq<sub>3</sub>).<sup>86</sup>

## NEW SYNTHETIC OPPORTUNITIES

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

## STOICHIOMETRIC CONTROL

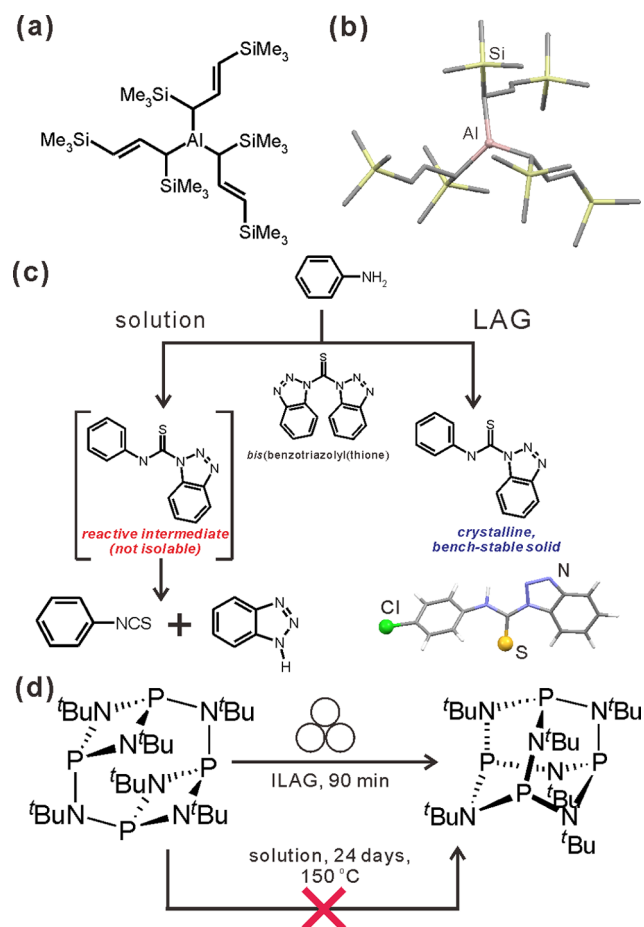
A surprising quality of mechanochemical reactions is excellent control over the stoichiometry of the reaction, allowing the precise, targeted synthesis of stoichiometrically different cocrystals and coordination polymers by simply controlling the reaction mixture composition.<sup>27,44,89–91</sup> In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

## REACTION DISCOVERY

There is a small but steadily growing number of reports of chemical transformations that take place by mechanochemistry, but are accessible with difficulty or not at all in solution. A striking and early demonstration of these is the dimerization of C<sub>60</sub> by milling with KCN which, instead of expected hydrocyanation, gave the dumbbell-shaped C<sub>120</sub>.<sup>15</sup> Similarly, isomers of trimeric C<sub>180</sub> are obtained by milling C<sub>60</sub> with 4-dimethylaminopyridine.<sup>93</sup> Recently, the Wang group reported that milling enables a novel FeCl<sub>3</sub>-mediated C–N bond cleavage reaction that was used to generate C<sub>60</sub>-fused indanes.<sup>94</sup> Mechanochemistry was used to discover and develop a novel C–N coupling of arylsulfonamides and carbodiimides,<sup>16</sup> which readily took place by LAG, but in solution either failed or gave poor conversions, demonstrating how mechanochemistry allows access to novel reactions which, although not impossible, are of low efficiency in solution.

## ■ “IMPOSSIBLE” MOLECULES

An exciting aspect of mechanochemistry is access to molecules whose isolation has so far been perceived impossible. In 2014, Rightmire et al. reported the synthesis of a tris(allyl)aluminum complex based on the sterically hindered bis(trimethylsilyl)allyl ligand (Figure 3a).<sup>95</sup> Solution synthesis of such complexes is



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

challenging, and they are often isolated as solvates and adducts. With the bis(trimethylsilyl)allyl ligand, all attempts to prepare and isolate the complex in solution failed. However, milling of  $\text{AlCl}_3$  with the potassium salt of bis(trimethylsilyl)allyl anion readily gave this elusive compound as an off-white powder. Once dissolved, the product forms oily mixtures of compounds, consistent with its inaccessibility from solution.

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

thiocarbamoyltriazoles immediately dissociated upon dissolution.

Another “impossible” molecule made by mechanochemistry is the adamantoid  $\text{P}_4\text{N}_6$ -phosphazane substituted by *tert*-butyl groups.<sup>13</sup> Whereas the syntheses of differently substituted adamantoid phosphazanes have been reported, this derivative has remained elusive, and quoted as an example of a sterically inaccessible target.<sup>98</sup> In 2016, the Garcia group demonstrated rapid, quantitative synthesis of this compound by ILAG (Figure 3c).<sup>13</sup> Theoretical calculations show that the reaction is thermodynamically favorable, suggesting that its failure in solution is not due to steric hindrance, but solvation effects.

## ■ ENERGETICS OF MECHANOCHEMISTRY

There is growing evidence that ball milling also offers an energy advantage over solution reactivity. For example, exploration of mechanochemical Suzuki–Miyaura coupling or of *p*-toluidine oxidation by  $\text{KMnO}_4$  revealed orders of magnitude higher energy efficiency compared to conventional or microwave heating methods.<sup>65,99</sup> This may seem at odds with high energy demands of ball mills in materials processing.<sup>100</sup> However, such processing is focused on particle comminution which requires overcoming very high lattice energies. In contrast, mechanochemistry appears to depend largely on particle mixing and surface activation,<sup>23</sup> and does not require particle size reduction to nanometer scale.<sup>101</sup> Understanding and techniques for evaluating energy input in mechanochemical reactions are still in their infancy. A study of Diels–Alder reactivity by McKissic et al.<sup>102</sup> estimated that the maximum energy delivered by milling is between  $95 \text{ kJ mol}^{-1}$  and  $112 \text{ kJ mol}^{-1}$ , with reaction mixture compositions indicating conditions analogous to solutions at  $90^\circ\text{C}$ . An elegant approach to evaluate mechanical energy input needed for a reaction was reported by Tumanov et al., who described a setup for exposing reaction mixtures to tunable mechanical pulses of known energy.<sup>103</sup>

## ■ OUTLOOK

Modern mechanochemistry is rapidly expanding into almost every area of chemistry and materials science, changing its focus from alloying and inorganic materials<sup>104</sup> to catalysis, self-assembly,<sup>105</sup> and synthesis of molecular structures.<sup>106</sup> While mechanochemistry offers a cleaner, more efficient alternative to a majority of conventional transformations, the field is still in its infancy, perhaps at a similar stage as that of organic chemistry at the turn of the 19<sup>th</sup> century, before the emergence of mechanistic insights of physical organic chemistry. The principal challenge of mechanochemistry today is not in demonstrating synthetic scope, as this is now being shown to match and, indeed, exceed that of known solution and materials chemistry. In our opinion, the true and immediate challenge of mechanochemistry is in divesting itself from qualitative, often only intuitive interpretations of mechanochemical reactivity, and becoming a quantitative, mechanistically well-understood area of chemistry. This can be achieved only through developing new, specialized instrumentation, precise theoretical models, and extensive systematic studies, and integrating these into a general, quantitative model of the mechanochemical reaction environment. This must include understanding the distributions of materials and energy under different regimes of mechanical impact and shearing, and learning how these can be used to control reactivity. Recent progress in this area has been done by the Boldyreva group,<sup>107</sup> who demonstrated that different types of

mechanical motion can lead to different products and reaction kinetics in the same milling vessel. Undoubtedly, more surprises will arise with the development of theoretical methods to explain and distinguish thermodynamic and kinetic effects in mechanochemistry, an area recently addressed by the Day group,<sup>105,108</sup> coupled with advances in instrumentation and introduction of new experimental techniques.<sup>109</sup> We strongly hope this Outlook will stimulate and accelerate such development.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [tomislav.friscic@mcgill.ca](mailto:tomislav.friscic@mcgill.ca). Tel: +1-514-398-3959.

### ORCID

Tomislav Friščić: 0000-0002-3921-7915

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We acknowledge the financial support of the NSERC Discovery Grant and the McGill University W. J. Dawson Scholarship (T.F.).

## REFERENCES

- (1) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- (2) Takacs, L. The historical development of mechanochemistry. *Chem. Soc. Rev.* **2013**, *42*, 7649–7659.
- (3) Wang, G.-W. Mechanochemical organic synthesis. *Chem. Soc. Rev.* **2013**, *42*, 7668–7700.
- (4) Šepelák, V.; Düvel, A.; Wilkening, M.; Becker, K.-D.; Heitjans, P. Mechanochemical reactions and syntheses of oxides. *Chem. Soc. Rev.* **2013**, *42*, 7507–7520.
- (5) Rightmire, N. R.; Hanusa, T. P. Advances in organometallic synthesis with mechanochemical methods. *Dalton Trans.* **2016**, *45*, 2352–2362.
- (6) Friščić, T. Supramolecular concepts and new techniques in mechanochemistry: cocrystals, cages, rotaxanes, open metal–organic frameworks. *Chem. Soc. Rev.* **2012**, *41*, 3493–3510.
- (7) Delori, A.; Friščić, T.; Jones, W. The role of mechanochemistry and supramolecular design in the development of pharmaceutical materials. *CrystEngComm* **2012**, *14*, 2350–2362.
- (8) Lazuen Garay, A.; Pichon, A.; James, S. L. Solvent-free synthesis of metal complexes. *Chem. Soc. Rev.* **2007**, *36*, 846–855.
- (9) Baláž, P.; Achimovičová, M.; Baláž, M.; Billik, P.; Cherkezova-Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutková, E.; Gaffet, E.; Gotor, F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Streletskii, A.; Wieczorek-Ciurowa, K. Hallmarks of mechanochemistry: from nanoparticles to technology. *Chem. Soc. Rev.* **2013**, *42*, 7571–7637.
- (10) Friščić, T.; Jones, W. Recent advances in understanding the mechanism of cocrystal formation via grinding. *Cryst. Growth Des.* **2009**, *9*, 1621–1637.
- (11) Užarević, K.; Halasz, I.; Friščić, T. Real-time and *in situ* monitoring of mechanochemical reactions: A new playground for all chemists. *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.
- (12) Štrukil, V.; Margetić, D.; Igrc, M. D.; Eckert-Maksić, M.; Friščić, T. Desymmetrisation of aromatic diamines and synthesis of non-symmetrical thiourea derivatives by click-mechanochemistry. *Chem. Commun.* **2012**, *48*, 9705–9707.
- (13) Shi, Y. X.; Xu, K.; Clegg, J. K.; Ganguly, R.; Hirao, H.; Friščić, T.; Garcia, F. The first synthesis of the sterically encumbered adamantoid phosphazane  $P_4((N^t)Bu)_6$ : enabled by mechanochemistry. *Angew. Chem., Int. Ed.* **2016**, *55*, 12736–12740.
- (14) Katsenis, A. D.; Puškarić, A.; Štrukil, V.; Mottillo, C.; Julien, P. A.; Užarević, K.; Pham, M.-H.; Do, T.-O.; Kimber, S. A. J.; Lazić, P.; Magdysyuk, O.; Dinnebier, R. E.; Halasz, I.; Friščić, T. *In situ* X-ray diffraction monitoring of a mechanochemical reaction reveals a unique topology metal-organic framework. *Nat. Commun.* **2015**, *6*, 6662.
- (15) Wang, G.-W.; Komatsu, K.; Murata, Y.; Shiro, M. Synthesis and X-ray structure of dumb-bell-shaped  $C_{120}$ . *Nature* **1997**, *387*, 583–586.
- (16) Tan, D.; Mottillo, C.; Katsenis, A. D.; Štrukil, V.; Friščić, T. Development of C-N coupling using mechanochemistry: catalytic coupling of arylsulfonamides and carbodiimides. *Angew. Chem., Int. Ed.* **2014**, *53*, 9321–9324.
- (17) Baig, R. B. N.; Varma, R. S. *Chem. Soc. Rev.* **2012**, *41*, 1559–1584.
- (18) Jiménez-González, C.; Constable, D. J. C.; Ponder, C. S. *Chem. Soc. Rev.* **2012**, *41*, 1485–1498.
- (19) Czaja, A.; Leung, E.; Trukhan, N.; Müller, U. Industrial MOF synthesis. In *Metal-Organic Frameworks: Applications from Catalysis to Gas Storage*; Farrusseng, D., Ed.; Wiley-VCH Verlag GmbH: Weinheim, 2011.
- (20) Cinčić, D.; Brekalo, I.; Kaitner, B. *Chem. Commun.* **2012**, *48*, 11683–11685.
- (21) Stolle, A.; Schmidt, R.; Jacob, K. Scale-up of organic reactions in ball mills: process intensification with regard to energy efficiency and economy of scale. *Faraday Discuss.* **2014**, *170*, 267–286.
- (22) Schmidt, R.; Burmeister, C. F.; Baláž, M.; Kwade, A.; Stolle, A. Effect of Reaction Parameters on the Synthesis of 5-Arylidene Barbituric Acid Derivatives in Ball Mills. *Org. Process Res. Dev.* **2015**, *19*, 427–436.
- (23) Baláž, P. *Mechanochemistry in Nanoscience and Minerals Engineering*; Springer-Verlag: Berlin, 2008.
- (24) Burmeister, C. F.; Kwade, A. Process engineering with planetary ball mills. *Chem. Soc. Rev.* **2013**, *42*, 7660–7667.
- (25) Halasz, I.; Kimber, S. A. J.; Beldon, P. J.; Belenguer, A. M.; Adams, F.; Honkimäki, V.; Nightingale, R. C.; Dinnebier, R. E.; Friščić, T. *In situ* and real-time monitoring of mechanochemical milling reactions using synchrotron X-ray diffraction. *Nat. Protoc.* **2013**, *8*, 1718–1729.
- (26) Stefančić, G.; Krehula, S.; Stefančić, I. The high impact of a milling atmosphere on steel contamination. *Chem. Commun.* **2013**, *49*, 9245–9247.
- (27) Štrukil, V.; Fábíán, L.; Reid, D. G.; Duer, M. J.; Jackson, G. J.; Eckert-Maksić, M.; Friščić, T. Towards an environmentally-friendly laboratory: dimensionality and reactivity in the mechanosynthesis of metal–organic compounds. *Chem. Commun.* **2010**, *46*, 9191–9193.
- (28) Štrukil, V.; Igrc, M. D.; Fábíán, L.; Eckert-Maksić, M.; Childs, S. L.; Reid, D. G.; Duer, M. J.; Halasz, I.; Mottillo, C.; Friščić, T. A model for a solvent-free synthetic organic research laboratory: click-mechanosynthesis and structural characterization of thioureas without bulk solvents. *Green Chem.* **2012**, *14*, 2462–2473.
- (29) Bonnamour, J.; Métro, T.-X.; Martinez, J.; Lamaty, F. Environmentally benign peptide synthesis using liquid-assisted ball-milling: application to the synthesis of Leu-enkephalin. *Green Chem.* **2013**, *15*, 1116–1120.
- (30) Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E. Poly(ethylene) glycols and mechanochemistry for the preparation of bioactive 3,5-disubstituted hydantoins. *RSC Adv.* **2016**, *6*, 36978–36986.
- (31) Eguaoie, O.; Cooke, L. A.; Martin, P. M. L.; Ravalico, F.; Conway, L. P.; Hodgson, D. R. W.; Law, C. J.; Vyle, J. S. Synthesis of novel pyrophosphorothiolate-linked dinucleoside cap analogues in a ball mill. *Org. Biomol. Chem.* **2016**, *14*, 1201–1205.
- (32) Cummings, A. J.; Ravalico, F.; McColgan-Bannon, K. I. S.; Eguaoie, O.; Elliott, P. A.; Shannon, M. R.; Bermejo, I. A.; Dwyer, A.; Maginty, A. B.; Mack, J.; Vyle, J. S. Nucleoside azide-alkyne cycloaddition reactions under solvothermal conditions or using copper vessels in a ball mill. *Nucleosides, Nucleotides Nucleic Acids* **2015**, *34*, 361–370.
- (33) Tan, D.; Loots, L.; Friščić, T. Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). *Chem. Commun.* **2016**, *52*, 7760–7781.

- (34) Tan, D.; Štrukil, V.; Mottillo, C.; Friščić, T. Mechanochemical synthesis of pharmaceutically relevant sulfonyl-(thio)ureas. *Chem. Commun.* **2014**, *50*, 5248–5250.
- (35) Friščić, T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. The role of solvent in mechanochemical and sonochemical cocrystal formation: a solubility-based approach for predicting cocrystallisation outcome. *CrystEngComm* **2009**, *11*, 418–426.
- (36) Friščić, T.; Meštrović, E.; Škalec Šamec, D.; Kaitner, B.; Fábíán, L. One-Pot mechanochemical synthesis with three levels of molecular self-assembly: coordination bonds, hydrogen bonds and host-guest inclusion. *Chem. - Eur. J.* **2009**, *15*, 12644–12652.
- (37) Weyna, D. R.; Shattock, T.; Vishweshwar, P.; Zaworotko, M. J. Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: mechanochemistry vs slow evaporation from solution. *Cryst. Growth Des.* **2009**, *9*, 1106–1123.
- (38) André, V.; Duarte, M. T.; Braga, D.; Grepioni, F. Polymorphic ammonium salts of the antibiotic 4-aminosalicylic acid. *Cryst. Growth Des.* **2012**, *12*, 3082–3090.
- (39) Stilić, V.; Cinčić, D.; Zbačnik, M.; Kaitner, B. Controlling solvate formation of a Schiff base by combining mechanochemistry with solution synthesis. *Croat. Chem. Acta* **2012**, *85*, 485–493.
- (40) Trask, A. V.; Shan, N.; Motherwell, W. D. S.; Jones, W.; Feng, S.; Tan, R. B. H.; Carpenter, K. J. Selective polymorph transformation via solvent-drop grinding. *Chem. Commun.* **2005**, 880–882.
- (41) Hardacre, C.; Huang, H.; James, S. L.; Migaud, M. E.; Norman, S. E.; Pitner, W. R. Overcoming hydrolytic sensitivity and low solubility of phosphitylation reagents by combining ionic liquids with mechanochemistry. *Chem. Commun.* **2011**, 47, 5846–5848.
- (42) Štrukil, V.; Igrc, M. D.; Eckert-Maksić, M.; Friščić, T. Click mechanochemistry: quantitative synthesis of "Ready to Use" chiral organocatalysts by efficient two-fold thiourea coupling to vicinal diamines. *Chem. - Eur. J.* **2012**, *18*, 8464–8473.
- (43) Hernández, J. G.; Macdonald, N. A. J.; Mottillo, C.; Butler, I. S.; Friščić, T. A mechanochemical strategy for oxidative addition: remarkable yields and stereoselectivity in the halogenation of organometallic Re(I) complexes. *Green Chem.* **2014**, *16*, 1087–1092.
- (44) Trask, A. V.; van de Streek, J.; Motherwell, W. D. S.; Jones, W. Achieving polymorphic and stoichiometric diversity in cocrystal formation: Importance of solid-state grinding, powder X-ray structure determination, and seeding. *Cryst. Growth Des.* **2005**, *5*, 2233–2241.
- (45) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Solvent-drop grinding: green polymorph control of cocrystallisation. *Chem. Commun.* **2004**, 890–891.
- (46) Friščić, T.; Trask, A. V.; Motherwell, W. D. S.; Jones, W. Guest-directed assembly of caffeine and succinic acid into topologically different heteromolecular host networks upon grinding. *Cryst. Growth Des.* **2008**, *8*, 1605–1609.
- (47) Fischer, F.; Scholz, G.; Benemann, S.; Rademann, K.; Emmerling, F. Evaluation of the formation pathways of cocrystal polymorphs in liquid-assisted syntheses. *CrystEngComm* **2014**, *16*, 8272–8278.
- (48) Hasa, D.; Miniussi, E.; Jones, W. Mechanochemical Synthesis of Multicomponent Crystals: One Liquid for One Polymorph? A Myth to Dispel. *Cryst. Growth Des.* **2016**, *16*, 4582–4588.
- (49) Friščić, T.; Halasz, I.; Beldon, P. J.; Belenguer, A. M.; Adams, F.; Kimber, S. A. J.; Honkimäki, V.; Dinnebier, R. E. Real-time and *in situ* monitoring of mechanochemical milling reactions. *Nat. Chem.* **2013**, *5*, 66–73.
- (50) Gracin, D.; Štrukil, V.; Friščić, T.; Halasz, I.; Užarević, K. Laboratory real-time and *in situ* monitoring of mechanochemical milling reactions by Raman spectroscopy. *Angew. Chem., Int. Ed.* **2014**, *53*, 6193–6197.
- (51) Batzdorf, L.; Fischer, F.; Wilke, M.; Wenzel, K.-J.; Emmerling, F. Direct *in situ* investigation of milling reactions using combined X-ray diffraction and Raman spectroscopy. *Angew. Chem., Int. Ed.* **2015**, *54*, 1799–1802.
- (52) Halasz, I.; Friščić, T.; Kimber, S. A. J.; Užarević, K.; Puškarić, A.; Mottillo, C.; Julien, P.; Štrukil, V.; Honkimäki, V.; Dinnebier, R. E. *Faraday Discuss.* **2014**, *170*, 203–221.
- (53) Ma, X.; Yuan, W.; Bell, S. E. J.; James, S. L. Better understanding of mechanochemical reactions: Raman monitoring reveals surprisingly simple 'pseudo-fluid' model for a ball milling reaction. *Chem. Commun.* **2014**, *50*, 1585–1587.
- (54) Užarević, K.; Štrukil, V.; Mottillo, C.; Julien, P. A.; Puškarić, A.; Friščić, T.; Halasz, I. Exploring the effect of temperature on a mechanochemical reaction by *in situ* synchrotron powder X-ray diffraction. *Cryst. Growth Des.* **2016**, *16*, 2342–2347.
- (55) Urakaev, F. K.; Boldyrev, V. V. Mechanism and kinetics of mechanochemical processes in comminuting devices - I. Theory. *Powder Technol.* **2000**, *107*, 93–107.
- (56) Beldon, P. J.; Fábíán, L.; Stein, R. S.; Thirumurugan, A.; Cheetham, A. K.; Friščić, T. Rapid room-temperature synthesis of zeolitic imidazolate frameworks by using mechanochemistry. *Angew. Chem., Int. Ed.* **2010**, *49*, 9640–9643.
- (57) Julien, P. A.; Užarević, K.; Katsenis, A. D.; Kimber, S. A. J.; Wang, T.; Farha, O. K.; Zhang, Y.; Casaban, J.; Germann, L. S.; Etter, M.; Dinnebier, R. E.; James, S. L.; Halasz, I.; Friščić, T. *In situ* monitoring and mechanism of the mechanochemical formation of a microporous MOF-74 framework. *J. Am. Chem. Soc.* **2016**, *138*, 2929–2932.
- (58) Tireli, M.; Juribašić Kulcsár, M.; Cindro, N.; Gracin, D.; Biliškov, N.; Borovina, M.; Čurić, M.; Halasz, I.; Užarević, K. Mechanochemical reactions studied by *in situ* Raman spectroscopy: base catalysis in liquid-assisted grinding. *Chem. Commun.* **2015**, *51*, 8058–8061.
- (59) Hernández, J. G.; Juaristi, E. Recent efforts directed to the development of more sustainable asymmetric organocatalysis. *Chem. Commun.* **2012**, 48, 5396–5409.
- (60) Jörres, M.; Mersmann, S.; Raabe, G.; Bolm, C. Organocatalytic solvent-free hydrogen bonding-mediated asymmetric Michael additions under ball milling conditions. *Green Chem.* **2013**, *15*, 612–616.
- (61) Hernández, J. G.; Friščić, T. Metal-catalyzed organic reactions using mechanochemistry. *Tetrahedron Lett.* **2015**, *56*, 4253–4265.
- (62) Declerck, V.; Colacino, E.; Bantreil, X.; Martinez, J.; Lamaty, F. Poly(ethylene glycol) as reaction medium for mild Mizoroki-Heck reaction in a ball-mill. *Chem. Commun.* **2012**, *48*, 11778–117780.
- (63) Braga, D.; D'Addario, D.; Polito, M. Mechanically induced expeditious and selective preparation of disubstituted pyridine/pyrimidine ferrocenyl complexes. *Organometallics* **2004**, *23*, 2810–2812.
- (64) Cravotto, G.; Garella, D.; Tagliapietra, S.; Stolle, A.; Schöbfler, S.; Leonhardt, S.; Ondruschka, B. Suzuki cross-couplings of (hetero)aryl chlorides in the solid-state. *New J. Chem.* **2012**, *36*, 1304–1307.
- (65) Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. Energetic assessment of the Suzuki-Miyaura reaction: a curate life cycle assessment as an easily understandable and applicable tool for reaction optimization. *Green Chem.* **2009**, *11*, 1894–1899.
- (66) Thorwirth, R.; Stolle, A.; Ondruschka, B.; Wild, A.; Schubert, U. S. Fast, ligand- and solvent-free copper-catalyzed click reactions in a ball mill. *Chem. Commun.* **2011**, 47, 4370–4372.
- (67) Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščić, T. Mechanochemical ruthenium-catalyzed olefin metathesis. *J. Am. Chem. Soc.* **2015**, *137*, 2476–2479.
- (68) Hermann, G. N.; Becker, P.; Bolm, C. Mechanochemical iridium(III)-catalyzed C-H bond amidation of benzamides with sulfonyl azides under solvent-free conditions in a ball mill. *Angew. Chem., Int. Ed.* **2016**, *55*, 3781–3784.
- (69) Hernández, J. G.; Bolm, C. [Cp\*RhCl<sub>2</sub>]<sub>2</sub>: mechanochemical synthesis and applications in C-H bond functionalisations under ball-milling conditions. *Chem. Commun.* **2015**, *51*, 12582–12584.
- (70) Li, L.; Wang, J.-J.; Wang, G.-W. Manganese(III) acetate-promoted cross-coupling reaction of benzothiazole/thiazole derivatives with organophosphorus compounds under ball-milling conditions. *J. Org. Chem.* **2016**, *81*, 5433–5439.
- (71) Fulmer, D. A.; Shearouse, W. C.; Medonza, S. T.; Mack, J. Solvent-free Sonogashira coupling reaction via high speed ball milling. *Green Chem.* **2009**, *11*, 1821–1825.
- (72) Cook, T. L.; Walker, J. A., Jr.; Mack, J. Scratching the catalytic surface of mechanochemistry: a multi-component CuAAC reaction using a copper reaction vial. *Green Chem.* **2013**, *15*, 617–619.

- (73) Chen, L.; Bovee, M. O.; Lemma, B. E.; Keithley, K. S. M.; Pilson, S. L.; Coleman, M. G.; Mack, J. An inexpensive and recyclable silver-foil catalyst for the cyclopropanation of alkenes with diazoacetates under mechanochemical conditions. *Angew. Chem., Int. Ed.* **2015**, *54*, 11084–11087.
- (74) Haley, R. A.; Zellner, A. R.; Krause, J. A.; Guan, H.; Mack, J. Nickel catalysis in a high speed ball mill: A recyclable mechanochemical method for producing substituted cyclooctatetraene compounds *ACS Sustainable Chem. Eng.* **2016**, *4*, 2464–2469.
- (75) Pichon, A.; Lazuen-Garay, A.; James, S. L. Solvent-free synthesis of a microporous metal–organic framework. *CrystEngComm* **2006**, *8*, 211–214.
- (76) Klimakow, M.; Klobes, P.; Thünemann, A. F.; Rademann, K.; Emmerling, F. Mechanochemical synthesis of metal-organic frameworks: A fast and facile approach toward quantitative yields and high specific surface areas. *Chem. Mater.* **2010**, *22*, S216–S221.
- (77) Adams, C. J.; Kurawa, M. A.; Lusi, M.; Orpen, A. G. Solid state synthesis of coordination compounds from basic metal salts. *CrystEngComm* **2008**, *10*, 1790–1795.
- (78) Friščić, T.; Fábíán, L. Mechanochemical conversion of a metal oxide into coordination polymers and porous frameworks using liquid-assisted grinding (LAG). *CrystEngComm* **2009**, *11*, 743–745.
- (79) Tanaka, S.; Kida, K.; Nagaoka, T.; Ota, T.; Miyake, Y. Mechanochemical dry conversion of zinc oxide to zeolitic imidazolate framework. *Chem. Commun.* **2013**, *49*, 7884–7886.
- (80) Friščić, T. New opportunities for materials synthesis using mechanochemistry. *J. Mater. Chem.* **2010**, *20*, 7599–7605.
- (81) Prochowicz, D.; Sokolowski, K.; Justyniak, I.; Kornowicz, A.; Fairen-Jimenez, D.; Friščić, T.; Lewinski, J. A mechanochemical strategy for IRMOF assembly based on pre-designed oxo-zinc precursors. *Chem. Commun.* **2015**, *51*, 4032–4035.
- (82) Užarević, K.; Wang, T. C.; Moon, S.-Y.; Fidelli, A. M.; Hupp, J. T.; Farha, O. K.; Friščić, T. Mechanochemical and solvent-free assembly of zirconium-based metal-organic frameworks. *Chem. Commun.* **2016**, *52*, 2133–2136.
- (83) Leng, K.; Sun, Y.; Li, X.; Sun, S.; Xu, W. Rapid synthesis of metal-organic frameworks MIL-101(Cr) without the addition of solvent and hydrofluoric acid. *Cryst. Growth Des.* **2016**, *16*, 1168–1171.
- (84) Crawford, D.; Casaban, J.; Haydon, R.; Giri, N.; McNally, T.; James, S. L. Synthesis by extrusion: continuous, large-scale preparation of MOFs using little or no solvent. *Chem. Sci.* **2015**, *6*, 1645–1649.
- (85) André, V.; Hardeman, A.; Halasz, I.; Stein, R. S.; Jackson, G. J.; Reid, D. G.; Duer, M. J.; Curfs, C.; Duarte, M. T.; Friščić, T. Mechanochemical synthesis of the metallodrug bismuth subsalicylate from Bi<sub>2</sub>O<sub>3</sub> and structure of bismuth salicylate without auxiliary organic ligands. *Angew. Chem., Int. Ed.* **2011**, *50*, 7858–7861.
- (86) Ma, X.; Lim, G. K.; Harris, K. D. M.; Apperley, D. C.; Horton, P. N.; Hursthouse, M. B.; James, S. L. Efficient, Scalable, and Solvent-free Mechanochemical Synthesis of the OLED Material Alq<sub>3</sub> (q = 8-Hydroxyquinolate). *Cryst. Growth Des.* **2012**, *12*, 5869–5872.
- (87) Rak, M. J.; Saadé, N. K.; Friščić, T.; Moores, A. Mechanochemical synthesis of ultra-small monodisperse amine-stabilized gold nanoparticles with controllable size. *Green Chem.* **2014**, *16*, 86–89.
- (88) Korpany, K.; Mottillo, C.; Bachelder, J.; Dong, P.; Trudel, S.; Friščić, T.; Blum, A. S. One-step ligand exchange and switching from hydrophobic to water-stable hydrophilic superparamagnetic iron oxide nanoparticles by mechanochemical milling. *Chem. Commun.* **2016**, *52*, 3054–3057.
- (89) Mavračić, J.; Cinčić, D.; Kaitner, B. Halogen bonding of N-bromosuccinimide by grinding. *CrystEngComm* **2016**, *18*, 3343–3346.
- (90) Karki, S.; Friščić, T.; Jones, W. Control and interconversion of cocrystal stoichiometry in grinding: stepwise mechanism for the formation of a hydrogen-bonded cocrystal. *CrystEngComm* **2009**, *11*, 470–481.
- (91) Cinčić, D.; Friščić, T.; Jones, W. A stepwise mechanism for the mechanochemical synthesis of halogen-bonded cocrystal architectures. *J. Am. Chem. Soc.* **2008**, *130*, 7524–7525.
- (92) Schmidt, R.; Stolle, A.; Ondruschka, B. Aromatic substitution in ball mills: formation of aryl chlorides and bromides using potassium peroxomonosulfate and NaX. *Green Chem.* **2012**, *14*, 1673–1679.
- (93) Kunitake, M.; Uemura, S.; Ito, O.; Fujiwara, K.; Murata, Y.; Komatsu, K. Structural analysis of C<sub>60</sub> trimers by direct observation with scanning tunneling microscopy. *Angew. Chem., Int. Ed.* **2002**, *41*, 969–972.
- (94) Su, Y.-T.; Wang, G.-W. FeCl<sub>3</sub>-Mediated cyclization of [60]-fullerene with N-benzhydryl sulfonamides under high-speed vibration milling conditions. *Org. Lett.* **2013**, *15*, 3408–3411.
- (95) Rightmire, N. R.; Hanusa, T. P.; Rheingold, A. L. Mechanochemical synthesis of [1,3-(SiMe<sub>3</sub>)<sub>2</sub>C<sub>3</sub>H<sub>3</sub>]<sub>3</sub>(Al,Sc), a base-free tris(allyl)aluminum complex and its scandium analogue. *Organometallics* **2014**, *33*, 5952–5955.
- (96) Katritzky, A. R.; Witek, R. M.; Rodriguez-Garcia, V.; Mohapatra, P. P.; Rogers, J. W.; Cusido, J.; Abdel-Fattah, A. A. A.; Steel, P. J. Benzotriazole-assisted thioacylation. *J. Org. Chem.* **2005**, *70*, 7866–7881.
- (97) Štrukil, V.; Gracin, D.; Magdysyuk, O. V.; Dinnebie, R. E.; Friščić, T. Trapping reactive intermediates by mechanochemistry: elusive aryl N-thiocarbamoylbenzotriazoles as bench-stable reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 8440–8443.
- (98) Scherer, O. J.; Andres, K.; Krüger, C.; Tsay, Y.-H.; Wolmerhäser, G. P<sub>4</sub>(N-i-C<sub>3</sub>H<sub>7</sub>)<sub>6</sub>, a P<sub>4</sub>X<sub>6</sub> molecule with and without adamantane structure. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 571–572.
- (99) Stolle, A. Technical Implications of Organic Synthesis in Ball Mills. In *Ball Milling Towards Green Synthesis – Applications, Projects, Challenges*; Stolle, A., Ranu, B. C., Eds.; RSC Green Chemistry: 2014.
- (100) Breitung-Faes, S.; Kwade, A. Prediction of energy effective grinding conditions. *Miner. Eng.* **2013**, *43–44*, 36–43.
- (101) Ibrahim, A. Y.; Forbes, R. T.; Blagden, N. Spontaneous crystal growth of co-crystals: the contribution of particle size reduction and convection mixing of the co-formers. *CrystEngComm* **2011**, *13*, 1141–1152.
- (102) McKissic, K. S.; Caruso, J. T.; Blair, R. G.; Mack, J. Comparison of shaking versus baking: further understanding the energetics of a mechanochemical reaction. *Green Chem.* **2014**, *16*, 1628–1632.
- (103) Tumanov, I. A.; Achkasov, A. F.; Boldyreva, E. V.; Boldyrev, V. V. Following the products of mechanochemical synthesis step by step. *CrystEngComm* **2011**, *13*, 2213–2216.
- (104) Suryanarayana, C. Mechanical alloying and milling. *Prog. Mater. Sci.* **2001**, *46*, 1–184.
- (105) Belenguer, A. M.; Friščić, T.; Day, G. M.; Sanders, J. K. M. Solid-state dynamic combinatorial chemistry: reversibility and thermodynamic product selection in covalent mechanochemistry. *Chem. Sci.* **2011**, *2*, 696–700.
- (106) Içli, B.; Christinat, N.; Tönnemann, J.; Schüttler, C.; Scopelliti, R.; Severin, K. Synthesis of Molecular Nanostructures by Multi-component Condensation Reactions in a Ball Mill. *J. Am. Chem. Soc.* **2009**, *131*, 3154–3155.
- (107) Michalchuk, A. A. L.; Tumanov, I. A.; Drebushchak, V. A.; Boldyreva, E. V. Advances in elucidating mechanochemical complexities via implementation of a simple organic system. *Faraday Discuss.* **2014**, *170*, 311–335.
- (108) Bygrave, P. J.; Case, D. H.; Day, G. M. Is the equilibrium composition of mechanochemical reactions predictable using computational chemistry? *Faraday Discuss.* **2014**, *170*, 41–57.
- (109) Hasa, D.; Schneider Rauber, G.; Voinovich, D.; Jones, W. Cocrystal formation through mechanochemistry: from neat and liquid-assisted grinding to polymer-assisted grinding. *Angew. Chem., Int. Ed.* **2015**, *54*, 7371–7375.