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Review

Mechanochemical Organic Synthesis—Powerful Tool in Greener Chemistry

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Abstract: Organic chemical reactions are usually promoted by heating the reactants in various organic solvents. Amongst emerging synthetic methods mechanochemistry is recognized as being promising in the reduction of the environmental impact by conducting chemical reactions in solid state. The energy required to promote transformation is obtained by mechanical force commonly by vibrational ball milling. Greener aspects of the mechanochemistry are in the reduction of solvent use, shorter reaction times, room temperature and better reaction yields in comparison to classical thermal solution conditions. This mini-review gives selected examples of eco-sustainable mechanochemical organic reactions.

Keywords**:** organic synthesis, mechanochemistry, green methods

1. Introduction

Development of industrial-scale organic chemical reactions towards more eco-sustainable processes is needed to tackle issues such as greenhouse gas emissions, processing wastewater, waste materials including solvents[1] and their appropriate disposal. Gross solvent consumption in the world is between 20 and 30 million tonnes per annum.[2] It is estimated that solvents comprise about 80% of the mass of chemicals which are used in organic synthesis. Organic synthetic processes (such as fine organic chemicals and pharmaceuticals) are important contributors to the total volume of waste solvents. In addition to environmental issues, organic solvents pose several hazards, these are often flammable or toxic[3] requiring their replacement with alternative sustainable solvents[4] and reduction of their consumption. These sustainability goals could be achieved by re-designing syntheses to use less solvent.[5] One of the emerging synthetic methods which could be applied for such purpose is mechanochemistry, where energy required to promote chemical reaction is obtained from a nonconventional source, by mechanical force. Technical details on various milling equipment are covered in several reviews.[6] Ball-milling mechanochemical reactions are usually carried out in solid state, without solvents or with a minimal amount of solvent, and these conditions were successfully applied to the various types of organic reactions.[7-10] Steps forward were made by the researchers exploring mechanochemical substitutes to the traditional reaction conditions in an attempt to bring this chemistry to applications on industrial scale[11] and the move from batch to continuous process gives promising leads.[12] Selected examples of mechanochemical organic reactions will be presented to illustrate the benefits of improvement of sustainability.[13]

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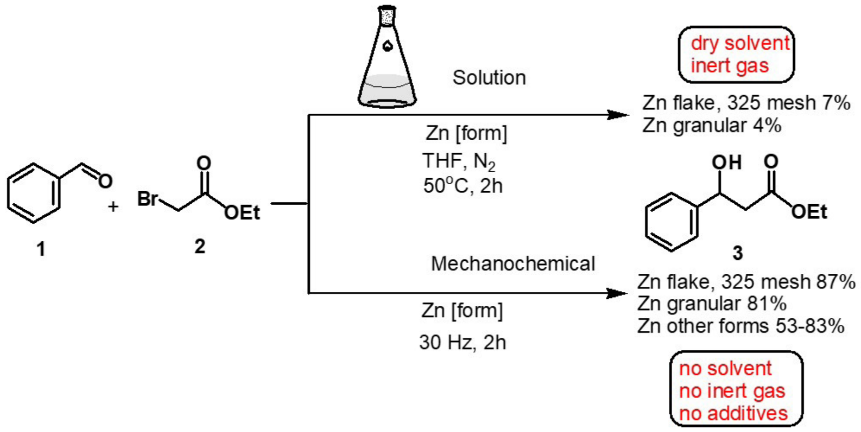
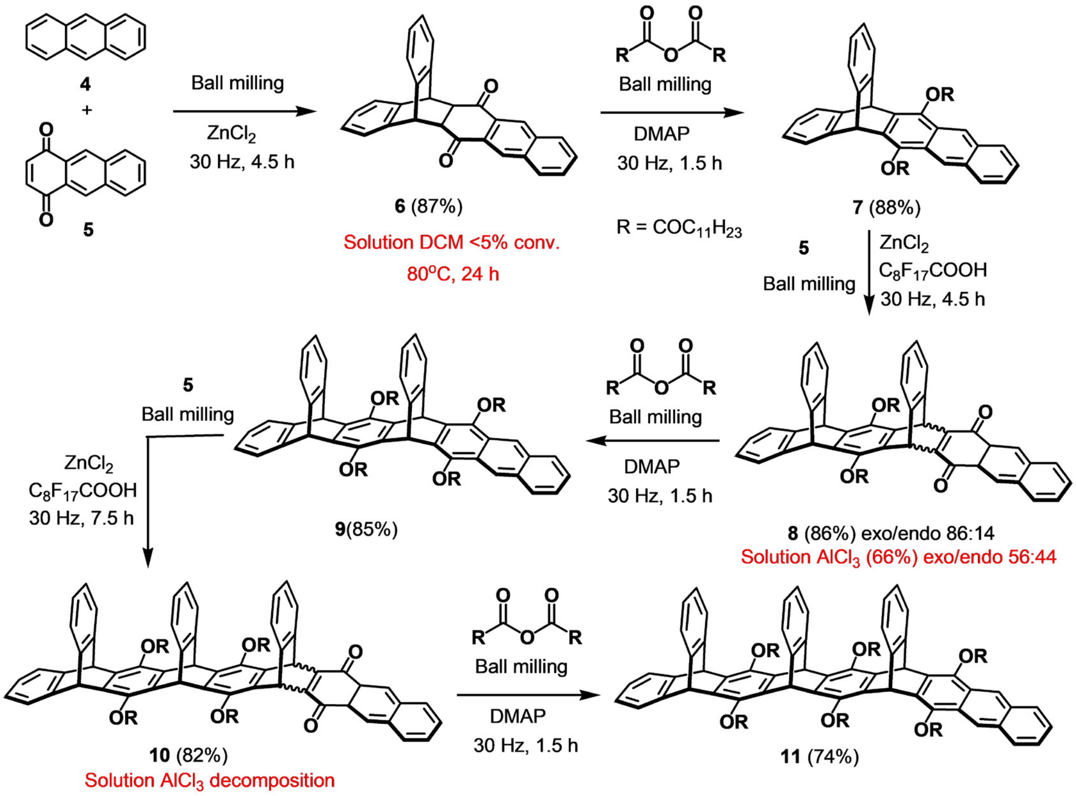
2. Reduction of solvent use

Arguably the most important improvement in sustainablilty of synthesis by mechanochemistry is accomplished by the avoidance of solvent by conducting chemical reactions in solid state conditions. Environmental benefits of such processes are obvious, and could be illustrated by the Reformatsky reaction of benzaldehyde and ethylbromoacetate **2** catalyzed by metallic zinc (Scheme 1).[14] Traditional solution reaction conditions require the use of dry solvent, precaution of moisture, and freshly prepared organozinc reagents. Mechanochemical process is much more plain in execution, simple ball milling of reactants with metallic zinc, without solvent and any measures for protection against moisture. When two reactants were ball-milled for two hours applying various forms of metallic zinc, the β-hydroxyester **3** was obtained in high yields, regardless on the form of zinc used. Traditional heating of reactants in tetrahydrofuran (THF) solution for the same period of time has proven to be much less effective, with very low yields of product **3**.



Scheme 1. Mechanochemical Reformatsky reaction

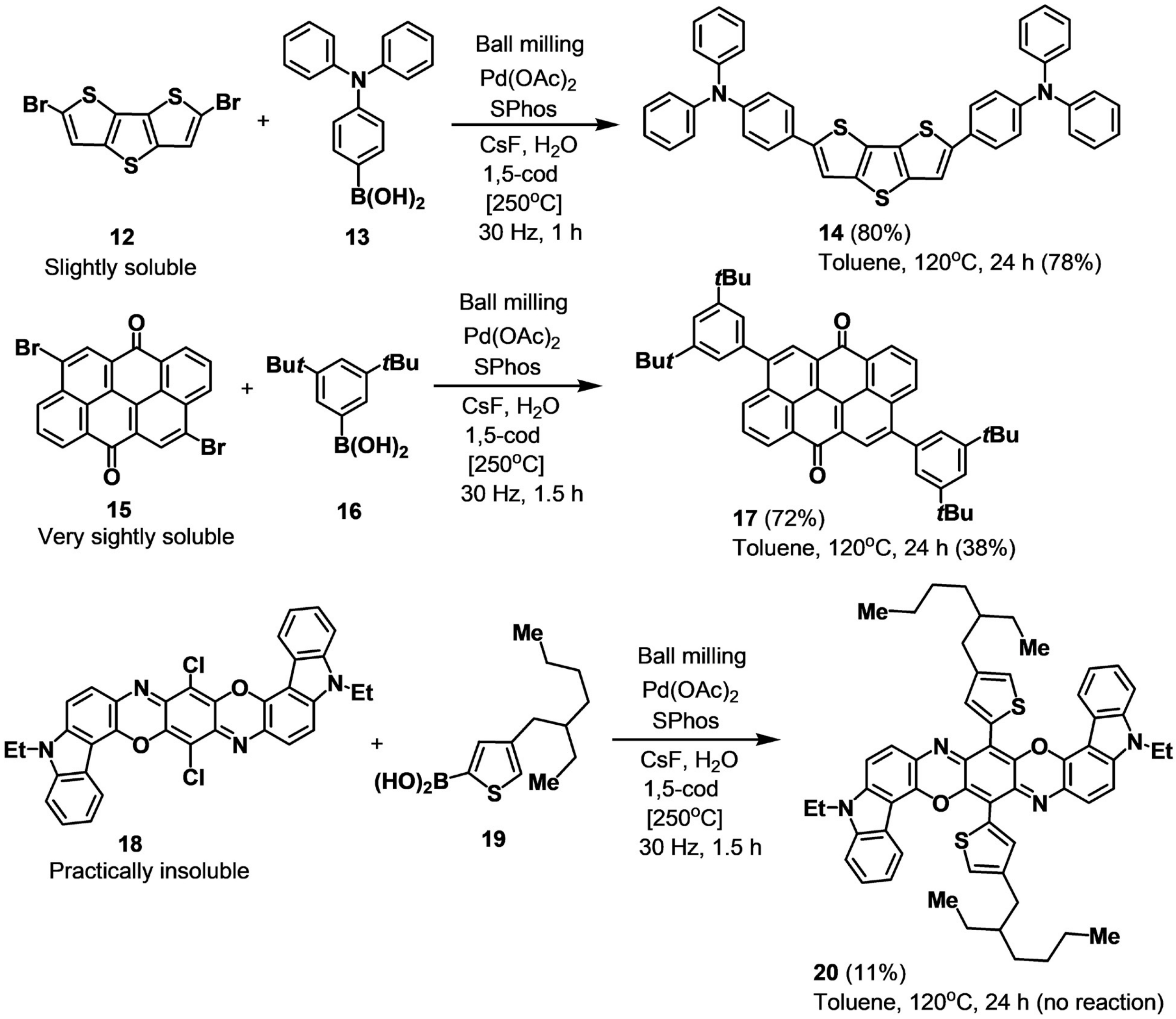
Aside from the greener conditions with reduced use of the solvent, the conduction of chemical reactions by solid state milling has some additional advantages such as the possibility to achieve reaction of molecules with very low solubility in organic solvents. Early precedents are fullerene functionalizations[15] and more recent is a report on the advantageous application in the synthesis of iptycenes. Their low solubility and high temperatures required for the Diels-Alder cycloaddition are usually problematic for their production in solution reactions. However, the preparation of iptycenes in mechanochemical solvent-free conditions was found to be a quite efficient process (Scheme 2).[16] Mechanochemical Diels-Alder reactions of anthracene and 1,4-anthraquinone catalyzed by zinc chloride smoothly led to cycloadduct **6** in high yield (87%). In contrast, the solution conditions required much longer time and heating, and still product **6** was obtained in very low yield. An additional advantage of the ball milling procedure is that the product was obtained in good purity, and chromatography was not needed for purification. Simple extraction with CH_2Cl_2 and washing with water was followed by precipitation from methanol. Next synthetic step, aromatization/functionalization step using lauric anhydride as an acylating agent was also carried out in solvent-free conditions in high yield with added base *N*,*N*-dimethylpyridine (DMAP). The acyl substituent chain added largely improves the solubility of iptycenes. Remarkably, by the iteration of this synthetic sequence, extended iptycenes were prepared in six consecutive mechanochemical reactions. In the case of the second Diels-Alder reaction (synthesis of **8**), perfluorononanoic acid ($C_8F_{17}COOH$) was used as an additive to obtain product in 89% yield. Cycloadduct **8** could be also prepared in a solution employing $AlCl_3$ catalyst, albeit in a lower yield (66%). Furthermore, the stereoselectivity is significantly better in the solid state conditions (*exo*/*endo* ratio, 86:14 vs. 56:44). Usefulness of ball milling conditions is illustrated in synthesis of the cycloadduct **10**, which is obtained in high yield, whereas conventional synthesis in solution employing $AlCl_3$ as Lewis acid failed to provide any product, due to decomposition of iptycene **9**.



Scheme 2. Multistep mechanochemical synthesis of iptycenes

Synthesis of iptycenes presented above also features additional phenomena which are characteristic for solid state reactions: kinetics of reactions is accelerated and reaction yields are higher, which could be ascribed to the maximal possible concentration and non-existence of solvent effects. As such, important sustainability effects are achieved: less energy is required to complete reactions and the amount of remaining waste material is reduced.

Several very low or practically insoluble aromatic compounds were successfully modified by palladium catalyzed Suzuki cross-coupling reaction of aromatic halides with boronic esters. To achieve adequate reactivity, additional energy was introduced to the reaction system by external heating of the milling jars (heat-gun). In practice, with heat-gun preset temperature of 250 °C, the temperature inside the jar was about 120 °C. Although this heating decreases the greenes of the method by larger consumption of energy, it enables that otherwise hardly possible reactions could take place and obtain more soluble products. For example, Suzuki coupling of thiophene **12** (slightly soluble molecule) with boronic acid **13** with the aid of palladium acetate, SPhos, caesium fluoride, water and 1,5-cod afforded product **14** in very high yield, after one hour milling at a preset temperature of 250 °C (Scheme 3).[17] Toluene conducted thermal reaction requires 24 h heating to achieve similar results. When same reaction conditions were applied to very slightly soluble dibromide **15**, the corresponding Suzuki product **17** was obtained in 73% yield. Solution reaction was much less effective, affording **17** in only 38% yield. The full advantage of solid state ball milling method is visible in the case of practically insoluble molecules such as heterocycle **18**. In this case, coupling product **20** was obtained in 11% yield, whereas the reaction in toluene did not produce any material. Other functional derivatives of **20** were obtained mechanochemically in higher yields (30 and 39%).



Scheme 3. Suzuki cross-coupling of low solubility aromatics

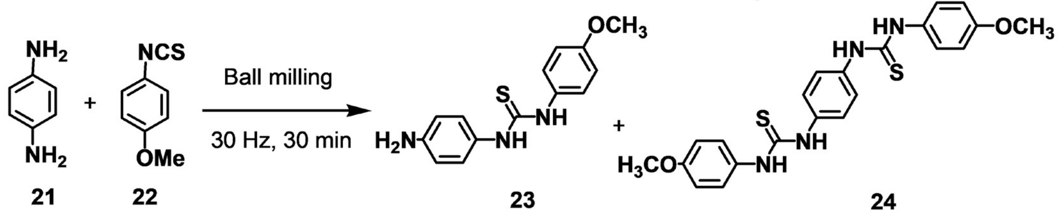
3. Liquid assisted grinding (LAG)

Although full avoidance of organic solvents or their replacement with benign ones such as water is ecologically the most desirable, sometimes the application of very small amounts of solvents greatly enhance the reaction efficacy or even enable the reaction. This method is called liquid assisted grinding (LAG).[18,19] This method was used firstly for mechanochemical cocrystal formation (active pharmaceutical ingredients, APIs) and then subsequently applied for chemical reactions in ball mill.[20] The mechanisms of action of added solvent are not fully understood, however it is thought that the formation of a liquid eutectic phase could be an important mechanistic factor to promote reactions.[21] The employment of LAG could alter reaction pathways by changing liquid polarity[22] and could also change chemoselectivity and reaction kinetics. The amount of added solvent for LAG is quantified by the empirical parameter η (in μL mg^{-1}) defined as the ratio of volume of added solvent (μL) and combined weight of reactants (mg).[23] In LAG conditions η parameter is < 1 μL mg^{-1}, whereas when $1 < \eta < 10$ μL mg^{-1} is considered as slurry reactions (Figure 1).

Figure 1. LAG reactions

In addition to development of LAG method to promote mechanochemical reactions, Ionic Liquid Assisted Grinding (IL-AG)[24,25] was developed in which ionic liquid is an additive Whereas LAG and IL-AG were used in organic synthesis, so far ion- and liquid-assisted grinding (ILAG)[26] and polymer assisted grinding (POLAG)[27] were applied for synthesis of metal-organic frameworks (MOFs) and for formation of cocrystals.

Mechanochemical synthesis of aromatic thioureas by the aid of small amount of solvent (LAG) is illustrated in Scheme 4.[28] The screening of reaction conditions illustrates the profound effect of solvent on the efficiency of ball milling reaction and requirement for its catious selection. The reaction of 4-phenylenediamine **21** with 4-methoxyphenylisocyanate could be achieved in solution within 24 h in high yields. Less effective was neat grinding (with the formation of side bis-product **24**) and the addition of LAG solvent was essential to obtain high yield. In this case, the addition of ethyl acetate for LAG, the same solvent which was used for classical thermal conditions was the most beneficial and yield was increased in comparison to solution reaction. Further improvements in yields to quantitative reaction were achieved by the addition of NaCl as a solid grinding auxiliary. Quantitative yields are the result of full conversion of reagents, as well as a simple workup consisting of washing with water.

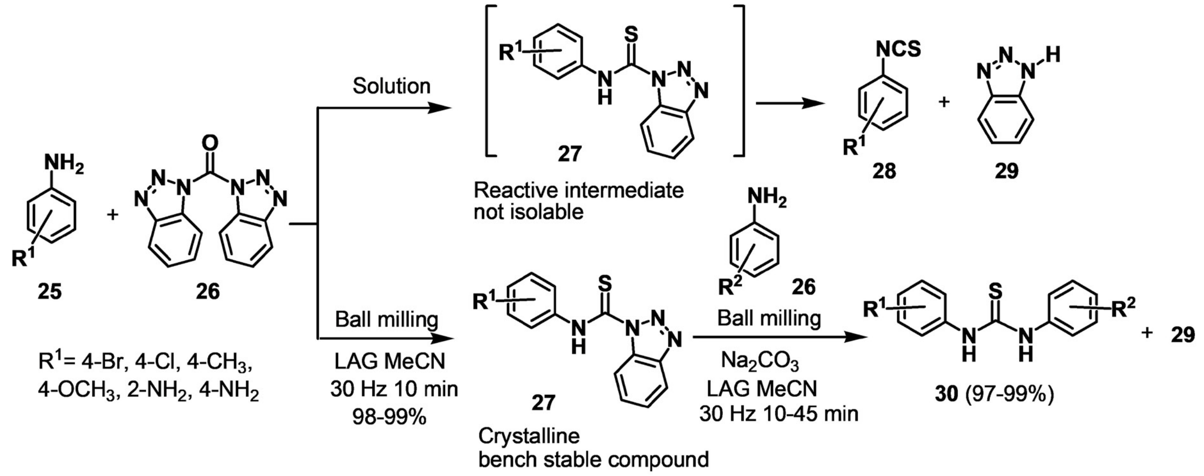


21 **22**

	23	**24**
solution EtOAc 24 h RT	78%	
NG	65%	17%
LAG H_2O	36%	
LAG MeOH	70%	
LAG DMF	70%	
LAG Cyclohexane	74%	
LAG EtOAc	88%(91%)	
Teflon LAG EtOAc	93%	
Teflon LAG EtOAc	95% m(NaCl)=10xm(**9**)	
Teflon LAG EtOAc	97% m(NaCl)=20xm(**9**)	

Scheme 4. Synthesis of aromatic thioureas

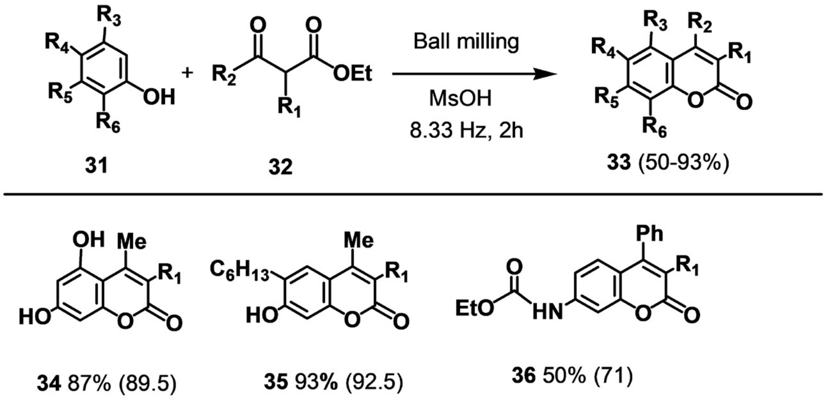
Mechanochemistry in solid state sometimes offers conditions sufficient to prepare stable and isolable reaction intermediates which were previously proposed as intermediates, but unstable to be isolated. When anilines **25** were reacted with bis(benzotriazolyl)methanethione **26** in the solution, aryl isothiocyanates **28** and benzotriazoles were obtained, via intermediate aryl *N*-thiocarbamoylbenzotriazoles **27** (Scheme 5).[29] In variance, ball milling of anilines and **26** afforded almost quantitatively *N*-thiocarbamoylbenzotriazoles **27** as stable solids, which could be fully spectroscopically characterized. The *N*-thiocarbamoylbenzotriazoles **27** could be then employed as bench stable reagents for thiocarbonylation of anilines providing diaryl thioureas **30** in quantitative yields. As a result of quantitative conversion of **27** and **30**, their purification was not required, and products were just scraped off the walls of the milling jar and washed with water.



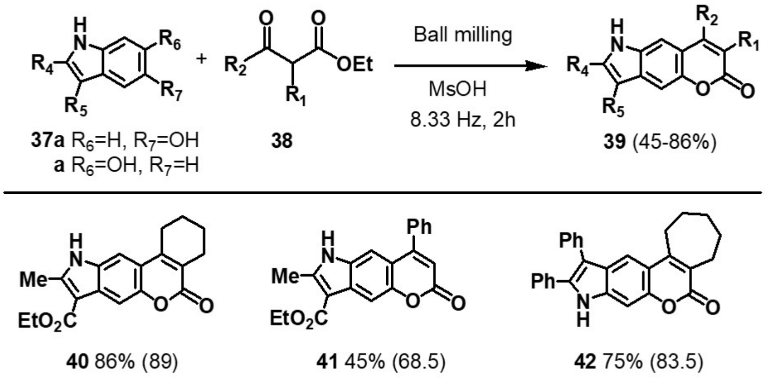
Scheme 5. Synthesis of diaryl thioureas

4. Green parameters and metrics

Different green parameters and metrics were devised in the literature and applied to organic reactions[30] as well as to mechanochemical synthesis to assess greenes. For instance, Ranu has applied the EcoScale index and E-factor in study of the mechanochemical Pechmann condensation of coumarins (Scheme 6) and pyranoindoles (Scheme 7).[31] Applied ball milling conditions for the reaction of 5-hydroxyindole **37** with β-ketoesters provided linear pyranoindole isomers, whereas in the classical conditions in previously published reports angular products were obtained. This exemplifies the change of the reactivity (and regioselectivity) in solid state reactions. The mechanochemical method has provided an increase in reaction yield for product **34** to 86%, whereas 81% yield was obtained by simple stirring when perchloric acid was used as a solvent.



Scheme 6. Pechmann condensation of coumarins

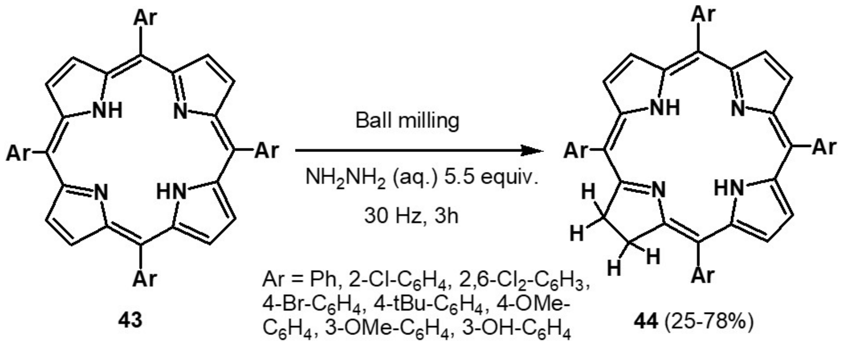


Scheme 7. Pechmann condensation of pyranoindoles

The E-factor quantitatively assesses the efficacy of organic reaction taking into acount the waste generated in the process. On the other hand, the EcoScale score reveals the simplicity and generality of a method, and takes into account yields, cost of materials, energy, safety, technical setup and purification issues. For most of the products in Schemes 6 and 7 the EcoScale values (indicated in parentheses) are above 80 and 70, respectively. For product **34** comparison of mechanochemical conditions was made with literature solvent-free method under conventional stirring and estimated to be 87.5, whereas for the mechanochemical process the value is higher 89.5, which indicates that mechanochemical method is environmentally less harmful. Similar indication on the advantageous use of mechanochemical method was obtained by the calculated E-factor for synthesis of product **34**. The E-factor score (0.67) is better than previous conventional stirring method (0.76 kg waste/kg product).

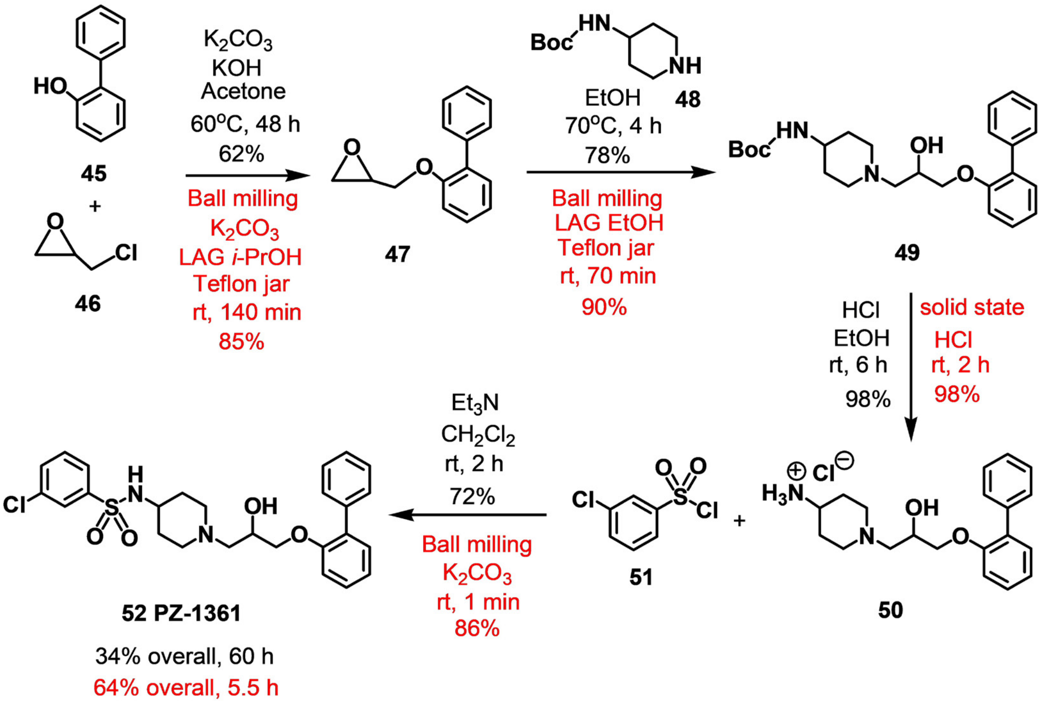
Similarly, Leahy et al. reported that the EcoScale rating for Wittig reaction[32] has been improved by carrying synthesis in mechanochemical conditions (toluene/reflux, NaOH/CH_2Cl_2 vs. milling, Cs_2CO_3, LAG-EtOH): EcoScale in solution is 35, whereas mechanochemical is 77.

Hydrogenation of porphyrins **43** into chlorins **44** employing hydrazine hydrate proceeds with high efficiency (Scheme 8).[33] Here, hydrazine hydrate is a precursor for hydrogen production in CO_2-free manner, producing gasses as the only reaction waste. This process proceeds with 100% of carbon efficiency with a very high atom economy (97%). The E-factor is decreased to an almost ideal value (0.96) by removal of solvent and consequent reduction of the mass of produced waste. For this diimide mechanical generation method, an EcoScale value of 63 was estimated, the highest of the known methods, whereas for diimide generation with base in solution, EcoScale value is 25, and for diimide thermal generation is 54.4. The obtained EcoScale value of 63 is comparable to the EcoScale value of 62 for an alternative mechanochemical generation of hydrogen from ammonium formate, Pd/C and silica gel.[34]



Scheme 8. Hydrogenation of porphyrins

Green chemistry metrics for multistep mechanochemical reactions are even more illustrative on the reduction of the impact on the environment.[35] Compound **52** (**PZ-1361**), a 5-HT7 receptor antagonist was synthesized in four reaction steps using classical and mechanochemical procedures (Scheme 9). Synthesis consists of four reaction steps, and starts with the base catalyzed *O*-alkylation of 2-phenylphenol with chlorohydrin to obtain the ether **47**. This synthetic intermediate was used in *N*-alkylation of 4-Boc-*N*-aminopiperidine, providing product **49**. Boc-deprotection of amine with gaseous hydrochloric acid quantitatively produce amino salt **50**. Synthesis is completed by mechanochemical sulfonamidation of amine to sulfonamide **52** employing base catalysis.



Scheme 9. Synthesis of **PZ-1361** in solution and solid-state conditions

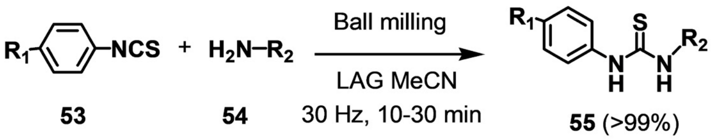
Scheme 9 illustrates clearly the advantageous application of ball milling in this synthesis. Two obvious and significant differences are in the efficacy of mechanochemistry, with the improvement in yields in all three reaction steps which were carried out mechanochemically. Solution synthesis was carried out in 34% overall yield, which was doubled (to 64%) in solid state conditions. The other improvement is a significant reduction in reaction time, from 60 h to only 5.5 h. Solid state reactions also feature limited use of alkylation reagent, minimal use of organic solvent and no chromatography. All these factors contribute to the improved green chemistry metrics E-factor and EcoScale for synthesis of **52** (Table 1). The cumulative E-factor for solution synthesis is reduced to one-third by solid state conditions (1932/715), whereas average EcoScale metrics is raised from 55 to 75.

Table 1. Green chemistry metrics for synthesis of **50**[a]

	Step 1		Step 2		Step 3		Step 4		Total	
	E-fact	EcoS	E-fact	EcoS	E-fact	EcoS	E-fact	EcoS	E-fact	$EcoS_{av}$
Solution	509	44	554	58	46	70	804	49	1932	55
Solid state	548	71	181	71	2	81	230	78	715	75

[a]E-fact = E-factor; EcoS = EcoScale; $EcoS_{av}$ = average EcoScale

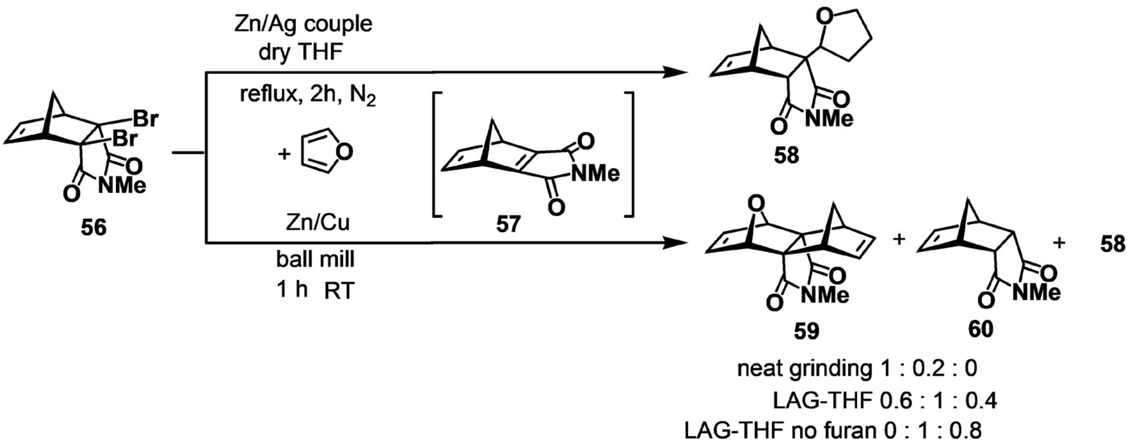
From an environmental point of view, it would be optimal to avoid the use of all organic solvents altogether, in the synthetic step, but also in manipulation, purification and structural characterization of products. This goal was achieved in mechanochemical synthesis of diaryl thioureas **55** which were prepared by ball milling of stoichiometric mixture of isothiocyanate and amines (LAG acetonitrile) in quantitative yields (>99%) (Scheme 10).[36] Excellent yields were obtained regardless of the electronic nature of substituents as well as in the case of the sterically hindered anilines. The workup procedure was simple, avoiding the use of any solvent, just scraping off the solid thiourea products from the walls of the grinding jar. Structural determination of prepared thioureas was also carried out without any solvent, by using powder X-ray diffraction (PXRD) technique. EcoScale factor for this synthetic method could be calculated as very high 77.5.



	Solvent use
Synthesis LAG	40 μL
Workup	No
Structural determination	No

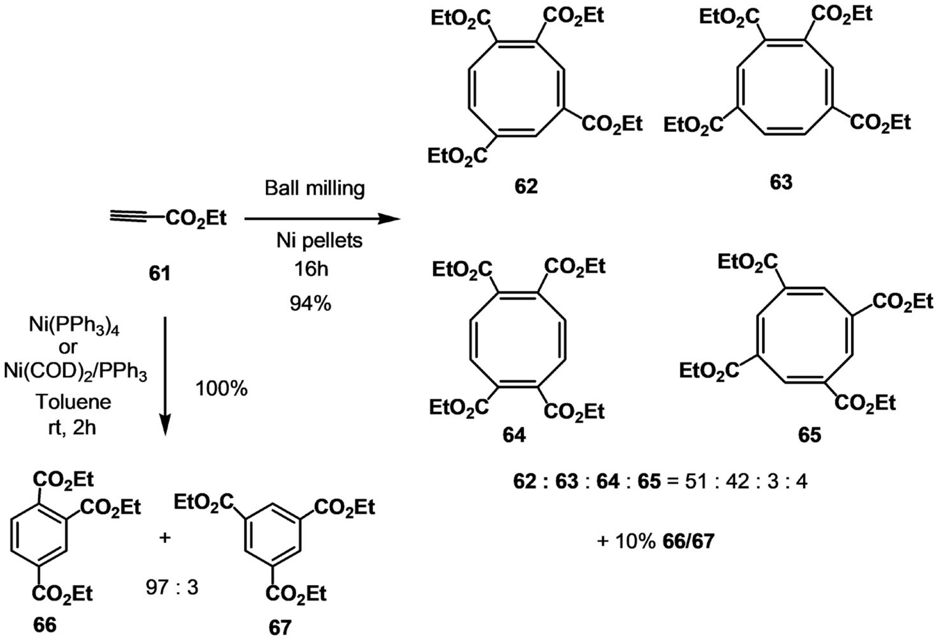
Scheme 10. Synthesis of thioureas

The replacement of metal catalyst with the one having lower carbon footprint[37] is another way to contribute to the development of greener organic synthesis. In the following account, silver metal was replaced by copper, for which carbon footprint (kg per CO^2e)[38] is reduced from 196 to 2.8. The debromination of norborneneimides in solution is usually affected by Zn/Ag couple, and this process has several operational disadvantages, such as the application of dry solvents, moisture precautions and tedious preparation of active metal couple. In addition, in the case of substrate **56**, cycloaddition step after debromination is suppressed by the reaction of very reactive alkene intermediate **57** with THF solvent leading to product **58** instead being involved in cycloaddition reaction (Scheme 11).[39] This reaction was successfully transferred to mechanochemical conditions, where the activation of metal couple was simplified by in situ preparation of metal couple from zinc and silver dusts. In addition to the removal of solvent, further greening improvement of the method was the replacement of silver with copper, which has a much lower carbon footprint. Solid state ball milling of dibromide **56** with Zn/Cu couple generated in situ from metal dusts succeeded in synthesis of the desired cycloadduct with furan, along side-product **60**. The change from neat grinding to LAG with THF alters the reaction outcome to a mixture of products in which THF-adduct **58** is also formed. Finally, when LAG grinding was carried out without the furan as diene trap, the amount of side-product **58** became significant.



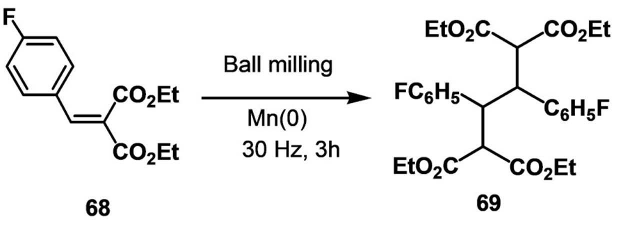
Scheme 11. Mechanochemical 1,2-debromination

The simple replacement of expensive metal catalyst by base metal could be also beneficial for decreasing the environmental impact of the chemical reactions. For example, an oxygen-sensitive catalyst Ni(COD)$_2$ was replaced by simple nickel metal pellets for mechanochemical synthesis of cyclooctatetraenes (Scheme 12).[40] Catalytic cyclotetramerization of ethyl propiolate in ball mill, with nickel pellets proceeds in high conversion via [2 + 2 + 2 + 2] cycloaddition to obtain cyclooctatetraenes **63-65**. In addition, about 10% of side-products 1,2,4- and 1,3,5-trisubstituted benzenes **66** and **67** were obtained. These two benzenes are the only products in the reaction which was carried out in the solution using Ni(COD)$_2$ catalyst, highlighting the change of reactivity going from solution to solid state conditions and allowing the access to previously unknown molecules. An additional benefit of the reaction is an easy way for nickel catalyst recovery by the use of a neodymium magnet.



Scheme 12. Nickel catalyzed cyclotetramerization of ethyl propiolate

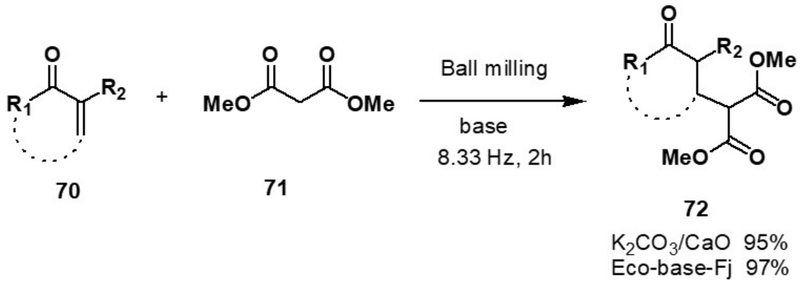
Reductive dimerization of arylidene malonates in solid state was achieved by the unprecedented reactivity of manganese metal used for catalysis (Scheme 13).[41] Previously, this transformation was carried out with the aid of SmI$_2$ catalyst prepared *in situ* or by photoredox reaction with Ir(ppy)$_3$/Sc(OTf)$_3$ whereas here simple milling with Mn(0) metal was employed. Solvent was not required, and these solid state conditions compared with reactions carried out in solution feature much higher reaction yields of product **69**. However, to activate manganese catalyzed reaction in THF solution, pre-milling for 3–5 min of the catalyst is required.



	Mn pieces (%)	Mn powder
30 Hz, 3h	80	78
THF rt, 24h	0	trace
THF reflux 24h	trace	11
30 Hz, 2 min then THF rt, 24h	69	65
30 Hz, 5 min then THF rt, 24h	86	78
mortar&pestle then THF rt, 24h	3	2

Scheme 13. Manganese mediation of reductive dimerization of arylidene malonates

Even better approach could be to substitute catalyst by material from bio-resources. Bio-sourced bases (Eco-bases) were prepared from plants with a high content of $K_2Ca(CO_3)_2$. When weak inorganic base was replaced by eco-base in Michael addition reaction of cyclopentenones, high efficiency was observed in ball milling conditions (Scheme 14).[42] Very high yields of Michael adducts **72** were obtained for all eco-bases studied, especially for and Eco-base-Fj retrieved from *Fallopia japonica* and mechanochemical reactions proceed in shorter time than in solution. Eco-bases were recycled and reused four times with the same performances which reduces the environmental impact of the method. Similarly, chitosan was employed by Gupta as a biodegradable catalyst for synthesis of pyrazol-5-oles and pyrazolopyranopyrimidines.[43]



Scheme 14. Catalytic efficiency of bio-sourced base

5. Conclusions

In summary, environmental benefits of mechanochemical reactions are multiple and can be visualized in Figure 2. The avoidance of organic solvents, reduction of time, temperature and energy consumption, with an increase of reaction efficiency and concomitant reduction of produced waste material, coupled with the simplicity of the execution of reactions are the major advantages.

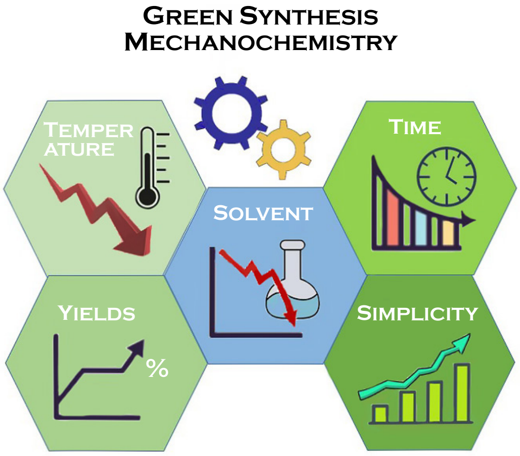


Figure 2. Green advantages of mechanochemical organic synthesis

Acknowledgments

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Conflict of interest

We declare that in this review there is no conflict of interest.

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