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Conference paper

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Recent applications of mechanochemistry in synthetic organic chemistry

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Abstract: The promotion of chemical reactions by an unconventional energy source, mechanical energy (mechanochemistry) has increasing number of applications in organic synthesis. The advantages of mechanochemistry are versatile, from reduction of solvent use, increase of reaction efficiency to better environmental sustainability. This paper gives a short review on the recent developments in the fast growing field of organic mechanochemistry which are illustrated by selected examples.

Keywords: Mechanochemistry; organic synthesis; solid-state reactions; sustainable chemistry; VCCA-2022.

Introduction

The move towards more sustainable manufacture is an important goal for worldwide producers of chemicals [1, 2]. Different approaches and strategies are explored which implement, for instance the use of less harmful starting materials and solvents, reduction in their usage, more efficient synthetic procedures, generation of less waste and energy saving [3]. Mechanochemistry is one of the synthetic approaches which is recognized recently by The International Union of Pure and Applied Chemistry (IUPAC) as the one of the important emerging technologies in chemistry with the potential to improve sustainability of chemical processes. Mechanochemical reactions employ an unconventional source of energy and chemical transformations are induced by the direct absorption of mechanical energy. The conventional organic synthesis usually involves solvent, heating and prolongued reaction time, whereas mechanochemical methods typically are carried out at room temperature, without solvent, in short time and with increased efficiency and product purity [4]. In addition, reactions do not depend on solvent solubility and are operationally simple [5]. These features are recognized by organic chemists and mechanosynthesis is nowadays accepted as an alternative synthetic method and has been applied to large number of chemical transformations [6]. The symbol of three circles for mechanochemical reaction as proposed by Hanusa and Rightmire [7] was used on all schemes. Besides the chemical transformations, mechanochemical technology was also applied to plant extraction of active organic substances such as quercetin, catechin, isoofloxacin and hypericin [8]. Cellulose, a raw material available from renewable sources has been subjected to mechanochemical transformation into useful chemicals and products [9, 10]. Nowadays, mechanochemistry is applied in various fields, as illustrated in Fig. 1.

In recent times, a variety of milling machines has become available for mechanosynthesis. The equipment for mechanochemical synthesis [11] is mainly user friendly and setting-up of ball-milling reaction is simple addition of reactants and milling balls in the reaction jars, followed by shaking at high speed in the milling machine. After the completion of reaction, the products are isolated and analysed.

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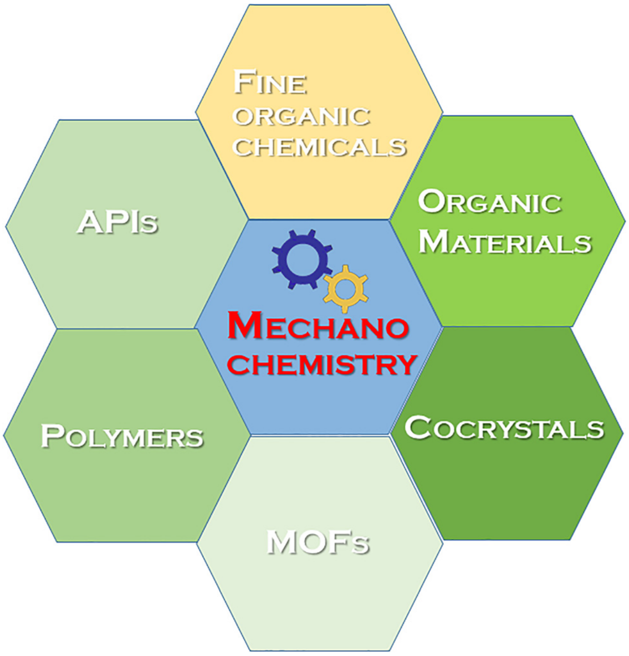
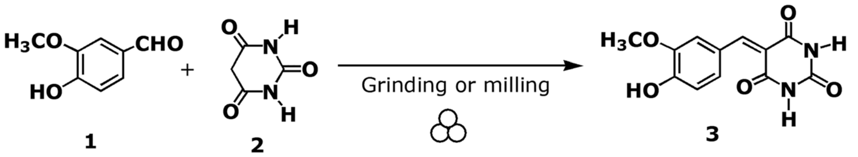


Fig. 1: Various applications of mechanochemistry.

The advantages of application of ball-mills on the efficacy of organic synthetic reactions could be illustrated by a comparative study performed by Stolle *et al.* (Fig. 2) [12]. As shown by the authors, the type of mill machine has an important effect on the outcome of the Knoevenagel condensation of barbituric acid **2** and substituted benzaldehyde **1**. In addition to difficulties to apply manual grinding for 60 min in a reproducible manner, the manually obtained reaction yield was remarkably low (11 %) in comparison with automated machines. A simple keeping of mixture of the reactants for 7 days at room temperature (aging) afforded product **3** in almost identical low yield. Thermally assisted grinding in rotary evaporator (TAG) with glass milling balls at 75 °C afforded product in high yield (75 %). The application of automated mortar mill (MM) triples the reaction yields obtained by manual grinding to 33 %, whereas mixer ball mill (MBM) increases yield to 80 %. Further raise in yield was obtained by grinding of reactants with the assistance of microwaves at 75 °C (MAG, microwave-assisted grinding) which required the addition of water and glass balls. Finally, the application of planetary ball mills (PMB), stirred media mill (SMM) and MM400 MBM afforded quantitative yields of 5-(4-hydroxy-3-methoxybenzylidene)-barbituric acid **3** within short reaction time (30–40 min).



	t/min	yield/%
mortar/pestle	60	11
aging	7 d	10
MM	120	33
TAG	60	75
MBM P23	60	80
MAG	10	90
PBM P7	10	>97
PBM P6	6	>97
PBM P5	30	>97
MBM MM400	35	>97
SMM P7	40	>97

Fig. 2: Comparison of reaction efficacy of various milling techniques for Knoevenagel condensation of barbituric acid and substituted benzaldehyde.

Important discoveries are made on mechanistic details of the processes of solid-state ball-mill reactions in recent years. For instance, Sanders has found that kinetics of chemical reactions could be affected by change in grinding frequency as well as by liquid assisted grinding (LAG) leading to changes in crystal forms of products [13], whereas Ito has reported that the addition of olefin additives causes significant acceleration of kinetics of the Suzuki-Miyaura Pd-catalyzed coupling of aryls [14]. New avenues of research are opened by development of methodologies and building up specialized equipment for real-time, *in situ* monitoring of physico-chemical processes during mechanochemical reactions [15]. In particular, Raman spectroscopy and synchrotron powder X-ray diffraction and more recently, nuclear magnetic resonance (NMR) spectroscopy and extended X-ray fine structure (EXAFS) technique are applied in mechanochemical studies. These techniques enabled important insights on reaction kinetics in solid state, molecular and atomic dynamics, the influence of solvent and additives, existence and nature of reactive intermediates [16].

Thermally controlled mechanochemical reactor with the possibility of *in situ* temperature monitoring was developed by Užarević *et al.* and its utility was tested by several reactions: Knoevenagel condensation, Schiff base formation, synthesis of metal-organic frameworks and amide/urea formation by the Curtius rearrangement [17]. The study of temperature development during ball-milling was also carried out by the construction of different technical setting, where the temperature recording at the surface of the milling jar was carried out by an infrared (IR) camera with simultaneous *in situ* Raman spectroscopy [18]. Investigation of cocrystal formation revealed that temperature increase proposed for the magma plasma and hot spot theory is not supported for soft matter milling syntheses. Sub-ambient temperatures (down to −5 °C) required for diastereoselective reduction of 4-*tert*-butylcyclohexanone with $NaBH_4$ in ball-mill were achieved by Mack by passing the chilling liquid through the tubing that wraps around the reactor jar [19]. The same setting could be also used for heating and the external jar temperature measurement was carried out by iButton temperature sensor or thermocouple attached on the jar.

The selection of reactor materials available for mechanosynthesis is continuously expanding. Materials for manufacturing of milling jars and balls nowadays vary from the most common stainless steel, ZrO_2, tungsten carbide to polytetrafluoroethylene (Teflon) and transparent poly-(methyl)methacrylate (PMMA) and new material such as Ertalyte® (polyethylene terephthalate, PET-P) is introduced by Colacino which is suitable for metal-free organic reactions [20].

Important advances have been also made in efforts of coupling of mechanochemistry with photochemistry, by the development of the photochemical reactor for mechanochemically assisted solid-state photocatalysis (MASSPC) and its utility was demonstrated by Štrukil in model reaction of photocatalytic oxidation of diphenylacetylene [21]. In different technical setup, blue LEDs (light-emitting diodes) light in the form of LED strips coiled around the milling vessel was applied by Hernandez for borylation of aryldiazonium salts [22].

Gaseous reagents were also used in ball milling reactions, which further widens the scope of application of mechanochemistry in organic synthesis [23]. Two technical approaches were used: the batch process, where the gaseous reagent was generated within the milling jar. This is simple procedure which does not require any specialized equipment, since the common milling jars are used. The other technical approach employs specially constructed milling jars which are equipped with gas inlet/outlet valves.

The first approach could be illustrated by an account from Cravotto's group where nitro and azido functionalities were reduced by hydrogen gas generated *in situ* from hydrazine (Fig. 3) [24]. This procedure is similar to catalytic transfer hydrogenation process employing ammonium formate and Pd/C which was independently discovered by Štrukil *et al.* [25]. When hydrazine was employed as a hydrogen source for ball milling reactions, nitrobenzene **4** was reduced to aniline quantitatively. In this reaction, KOH base and basic Al_2O_3 as grinding auxiliary were added to obtain good results. The employment of ammonium formate as a safer and less toxic source of hydrogen to reduce nitrobenzene derivatives **6** to anilines was highly effective. Full conversion and very high yields were obtained for most of the substrates. For instance, 3-nitrobenzonitrile was reduced by ball-milling within 90 min in 95 % yield, whereas conventional solution reaction in methanol after 2 h at room temperature proceeded in lower, 70 % yield. Furthermore, Cravotto has shown that planetary ball mill reduction of aryl azides **8** with *in situ* generated hydrogen from sodium formate is accelerated by the presence of KOH and the corresponding anilines **9** were obtained in high yields within 1.5 h. For this transformation, hydrazine was also used as the source of hydrogen instead of the formate salts and benzyl and alkyl azides **10** were reduced to amines in high or quantitative yields.

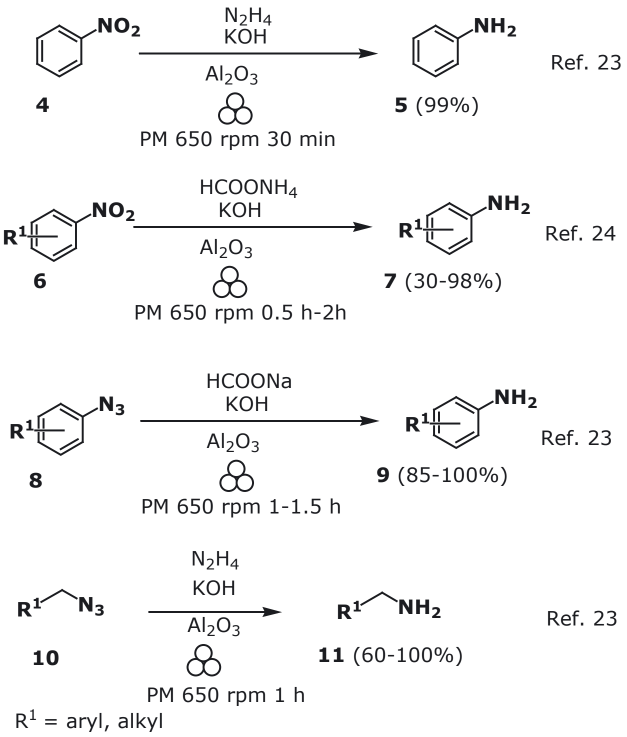


Fig. 3: *In situ* generation of hydrogen in ball mill for reduction of nitro and azide functionalities.

Specialized milling jar equipped with gas inlet/outlet was used by Bolm for the epoxide ring opening reaction in multi-step mechanochemical synthesis (Fig. 4) [26]. The substrate required for this transformation was prepared mechanochemically from oxiranylmethanol **12** and silyl ether **13** employing imidazole as base. This *tert*-butyldimethylsilyl (TBDMS) protected epoxide was subjected to selective ring opening with stearic acid employing Jacobsen cobalt(II)-salen catalyst **16**. It was established that catalyst is stable in mechanochemical conditions, and it could be even prepared by milling. The activity of catalyst in this key reaction step relies on the activation by oxygen and the reaction was performed in milling jar without the precaution from air. In such conditions, 1,3-protected monoacylglycerol **15** was obtained in 59 % yield after 3 h of milling. The efficacy of the reaction was significantly increased when a positive pressure of oxygen was introduced through gas inlet on the reaction vessel. The 1,3-protected monoacylglycerol **15** was afforded in 84 % crude yield, whereas upon chromatography **15** was isolated in 42 % yield. Further structural elaboration by the esterification of **15** with fatty acids, such as stearic acid using DCC/DMAP reagents provided almost quantitatively diacylglycerol **16** after 2 h of milling. After TBDMS deprotection, alcohol **18** was subjected to another mechanochemical reaction with 4-nitrophenyl chloroformate where two isomeric anhydrides **20** and **21** were obtained. Their treatment with 7-hydroxycoumarin **22** in ball mill afforded the mixture of coumarin-diacylglycerol conjugates **23** and **24** (72:28).

The introduction of small amount of solvent during the ball-milling (LAG) is beneficial in certain reactions. In addition to the positive effects on the reaction yields, LAG method could also assist in the increase of enantioselectivity of the reaction and influence the chemoselectivity. Browne has published study on the significant effects of added solvent as LAG on the reaction outcome (Fig. 5) [27]. When difluoro diketone **25** was ball-milled in the presence of Cs_2CO_3 and phenyl disulfide, a tetrafluorohydroxyketone **27** was obtained in high yield and product **30** was obtained in small amount as a side-product. On the other hand, product **29** was obtained in 83 % yield using same reagents in DMSO solution for 12 h at 40 °C, whereas in conventional conditions at 80 °C after 12 h thiol **30** was obtained. The addition of solvent had in some instances a profound effect on the composition of the product mixtures. Systematic variation of solvent used for LAG, with the gradual increase of their dielectric constants (ε) has led to the formation of two new products **28** and **29** which have not been obtained previously in LAG conditions. Whereas in the case of LAG with solvents with small dielectric constant such as hexane the reaction composition did not vary much from neat grinding, the application of very polar solvents such as water

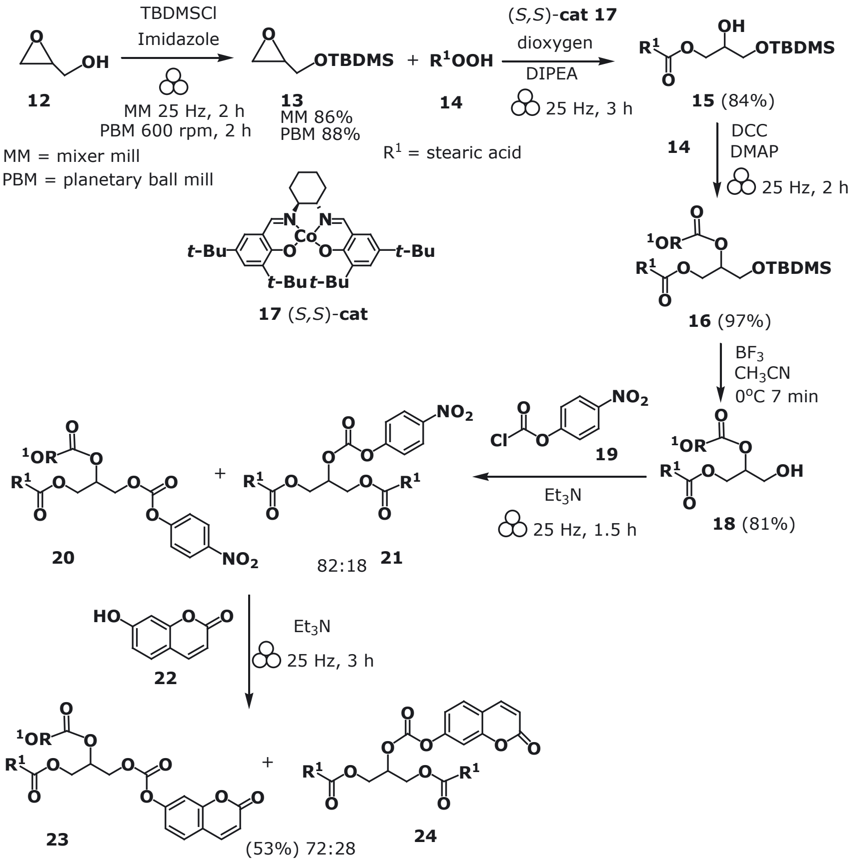
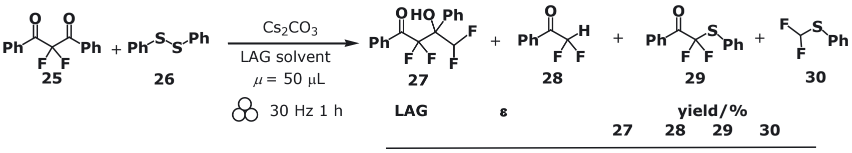


Fig. 4: Application of oxygen as gaseous reagent in ball milling synthesis of coumarin-diacylglycerol conjugates.

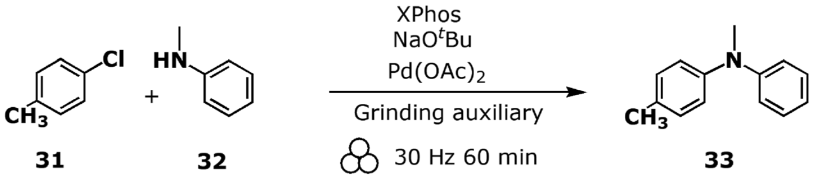
completely changed the reaction outcome and product **30** became dominant. Remarkably, LAG was used to switching chemoselectivity kinetics and to access alternative reactions and products, such as product **28** when DMF was used or thiol **29** in the case of the addition of DMSO.

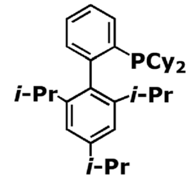
Besides the addition of some solvent in ball-milling reactions, various solid additives (grinding auxiliaries) could help in better performance of mechanochemical process. Some of them are neutral solids which aid to better mixing, energy or mass transfer, whereas others could also act as reagents and improve reaction kinetics. Thorough screening of grinding auxiliaries was carried out by Su *et al.* during the optimization of palladium catalyzed Buchwald-Hartwig aryl-amination of *p*-chlorotoluene **31** and *N*-methylaniline **32** (Fig. 6) [28]. The efficacy of grinding auxiliary depends on its chemical nature, as well as on the amount added to the milling vial, which is expressed by mass of added grinding auxiliary per gram of reagents. Whereas some of added solids were detrimental for reaction, Na_2SO_4 was found to be highly beneficial. The optimal mass ratio of grinding auxiliary



LAG	ε	yield/% 27	28	29	30
-	-	88	0	0	10
hexane	1.88	86	1	0	4
EtOAc	6.02	76	1	4	5
CH_2Cl_2	8.93	60	3	0	4
^{i}PrOH	17.9	74	1	1	3
DMF	36.7	23	27	0	4
DMSO	46.7	0	62	12	5
H_2O	80.1	28	0	0	35

Fig. 5: Influence of LAG on reaction outcome of solid state reaction of difluoro diketone and phenyl disulfide.





XPhos

	m/g	yield/%
Silica gel	0.3	n.d.
γ-Al_2O_3	0.5	21
NaCl	2.0	n.d.
K_2SO_4	2.0	75
Na_2SO_4	2.0	92
Na_2SO_4	1.5	72
Na_2SO_4	1.0	57
Na_2SO_4	2.5	85

Fig. 6: The effect of grinding auxiliary on Buchwald-Hartwig aryl-amination of *p*-chlorotoluene.

and reactants for this reaction was established to be 2:1. Addition of Na_2SO_4 in conventional solvent-heated reaction did not accelerate or improve reaction.

Multistep syntheses could be also carried out mechanochemically. For instance, Mack *et al.* have developed synthesis of polyaromatic hydrocarbon molecules in seven reaction steps, entirely mechanochemically (Fig. 7) [29]. After every ball-milling reaction step, reaction mixture was processed and product isolated. The first reaction step is Wittig reaction of 1,2-phthalic dicarboxaldehyde **34** with *in situ* generated phosphorous ylide (from bromo ethylacetate and triphenylphosphine) with subsequent closure into naphthalene **35**. Literature solution reaction conditions for the initial reaction step involved toxic and flammable triethyl phosphine in dichloromethane and then DBU base with 75 % yield of the corresponding ylide. Reduction of diester **35** was achieved by ball-milling with sodium borohydride in the presence of LiCl, and this protocol effectively and safely replaced the reduction with DIBAL-H in toluene. In the next synthetic step, diol oxidation to naphthalene 2,3-dialdehyde **37** was effected by 2-iodoxybenzoic acid (IBX) in high yield, which replaced Swern oxidation with oxalyl chloride at low temperature. For further ring annulation, synthesis of anthracene and tetracene esters **38** and **41**, the same mechanochemical conditions were applied. Due to slow down of the Wittig reaction step with the increased ring annulation, silica gel was added as milling auxiliary for anthracene **40**, which greatly improved the yield of the reaction. The sustainability of this mechanochemical procedure was assessed by the Ecoscale metrics and each synthetic step show better sustainability metrics in comparison to classical solution reaction conditions. Operational simplicity of procedures, where dry solvent and conditions preventing moisture were avoided is an additional advantage of this mechanochemical conditions.

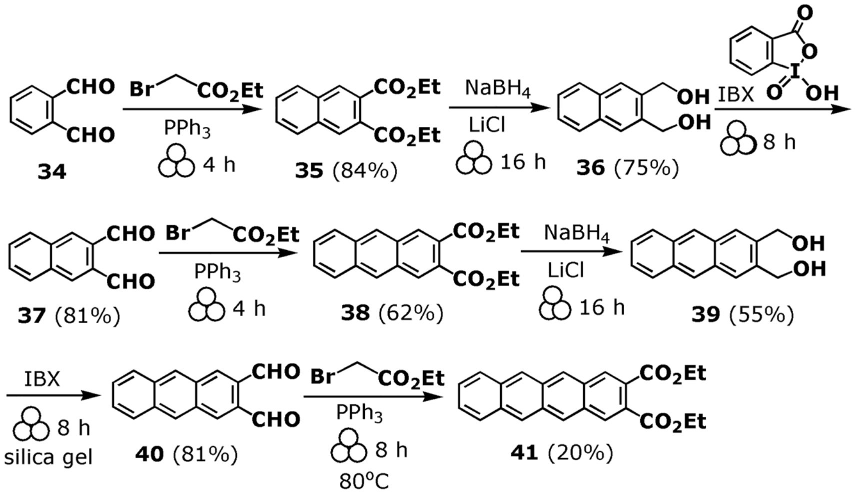


Fig. 7: Multistep mechanochemical synthesis of polyaromatic hydrocarbon molecules.

Multistep reaction, carried out in one-pot, without the isolation or purification of intermediate represents even more simplified synthetic procedure. For instance, Chu *et al.* developed two-step, one-pot synthesis of arylsulfonyl 4H-pyrans **45** (Fig. 8) [30]. The grinding of aryl aldehyde with phenylsulphonyl acetonitrile **43** catalyzed by L-proline was carried out firstly, providing condensation product, an iminium salt of proline, which after proline elimination forms intermediate (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile. Then, dimedone **44** was added to the reaction jar and milling was continued to initially afford condensation of proline with dimedone to an enamine, followed by the condensation with acrylonitrile intermediate formed in the first reaction and then the final product was obtained by intramolecular cyclization and tautomerization. Corresponding arylsulfonyl 4H-pyrans **45** were obtained in high yields. For comparison, the conventional solution-based protocol in EtOH provided after 14 h at RT product **45** (R = H) in less than 10 % yield.

Catalytic reactions with metal dust or particles could be carried in solid state conditions without the need of solvent in a homogeneous system. Preparation steps of catalyst could be reduced, by the *in situ* alloying of two metals which form an active catalyst such as milling of copper and zinc dusts employed in Cu/Zn couple 1,2-debromination reaction [31].

Further development in the simplification of organic chemical reactions carried out mechanochemically is the use of metal from the milling jar or milling balls which reduces the number of reagents employed in the synthetic process [32]. As an example, direct mechanochemical Glaser coupling was achieved by Borchardt and co-workers via ball milling of tolane **46** in the presence of base in the milling jar which was made out of bronze, a catalytically active metal which was combined with milling balls made out of an inert metal (ZrO_2) (Fig. 9) [33]. The yields of the direct mechanocatalytic Glaser coupling are lower than the values obtained in solution based syntheses at room temperature (93 and 99 % in DMF (4 h) and MeCN (2 h), respectively). *In situ* Raman measurements revealed important details of the reaction mechanism, which involves the formation of the intermediate complex on the metal surface acting as the active site.

Non-covalent interactions are operating in solid state ball-milling conditions in similar manner to supramolecular interactions in solution. For instance, the templating effect of the different size anions (chloride, perchlorate) was used by Friščić and Aav to pre-organize (*R,R*)-hexahydro-2-benzimidazolinone **49** monomers in reaction with paraformaldehyde and the corresponding acids (Fig. 10) [34]. After self-organization in ball mill, supramolecular complexes **50** and **51** were allowed to aging at 60 °C to afford final 6- or 8-membered cyclohexanohemicucurbituril macrocycles cycHC[6] **52** and cycHC[8] **53** in high yields. The size of the applied anion has defined the size of the macrocycle product.

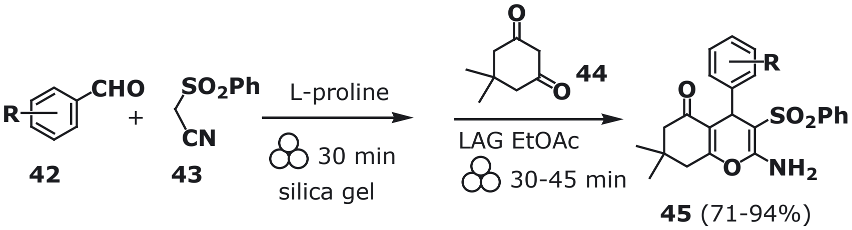


Fig. 8: Two-step, one-pot mechanochemical synthesis of arylsulfonyl 4H-pyrans.

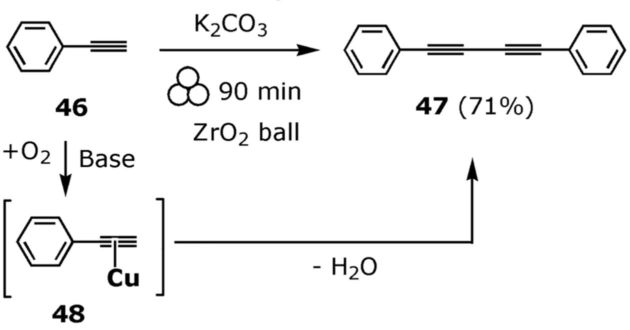


Fig. 9: Direct metal catalysis of Glaser reaction of tolane.

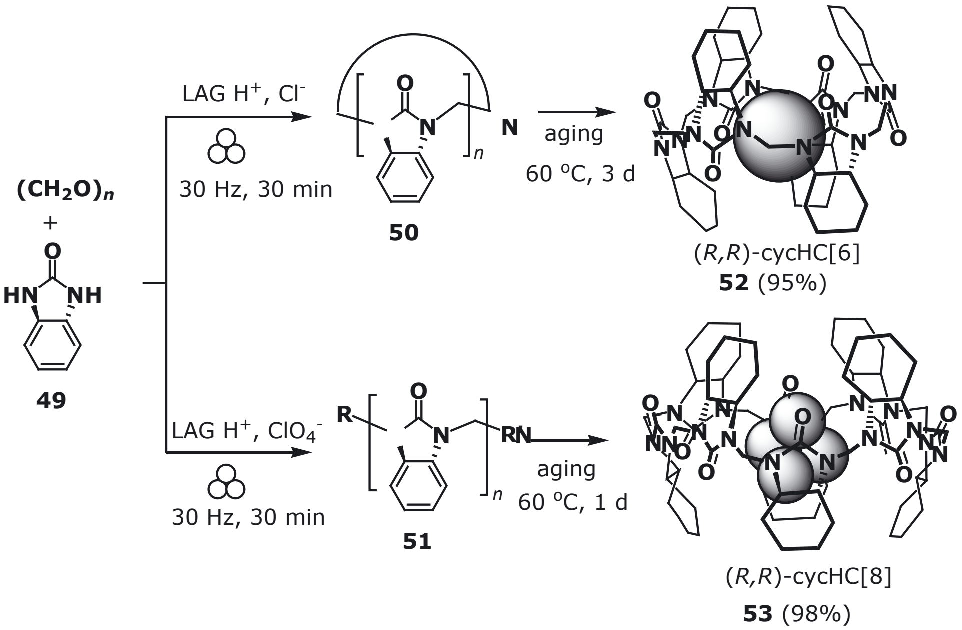
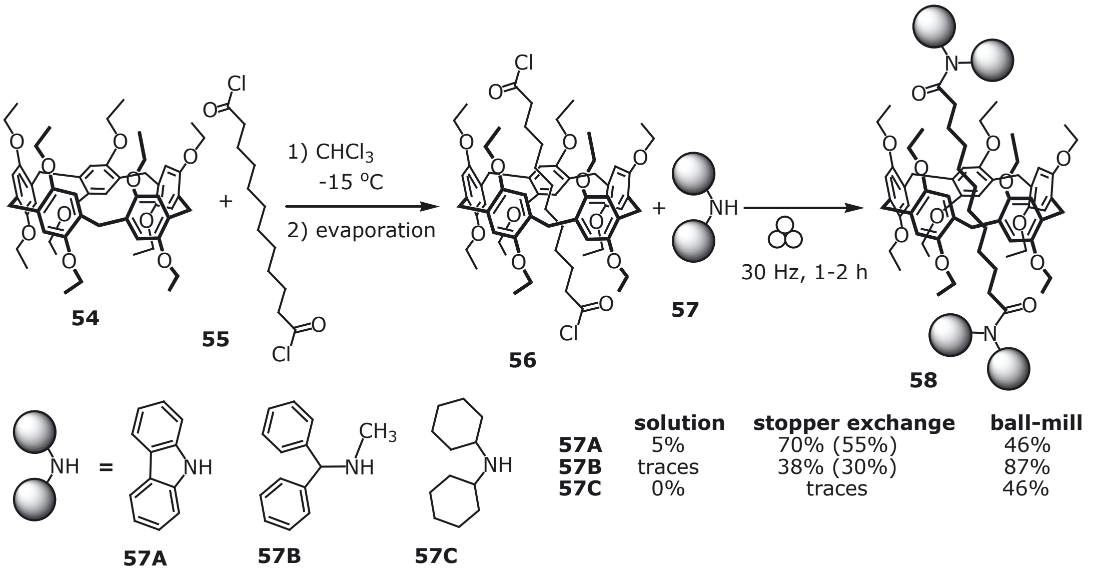


Fig. 10: Templating effects in ball-mill in synthesis of cyclohexanohemicucurbituril macrocycles.

Supramolecular systems such as rotaxanes were also prepared mechanochemically by formation of covalent bonds by Nierengarten (Fig. 11) [35]. The initial inclusion complex (pseudorotaxane) **56** was prepared in solution from pillar[5]arene macrocycle **54** and dodecanedioyl dichloride **55**. In the next step, amines were introduced as amide stoppers. Mechanochemical synthesis of diamide pillar[5]arene-containing [2]rotaxanes **58** proceeded in short reaction time and moderate to high yields (46–87 %), depending on the reactivity of used bulky secondary amines **57**. Advantageous application of solid state mechanochemical conditions over conventional solution synthesis is illustrated by several examples of the rotaxanes **58** which could not be prepared in solution (chloroform), and were also prepared in low yields by stopper exchange method. In solid state, only small amounts of unthreaded bis-amide were obtained, which shows the stability of the supramolecular complex **56** in ball-milling conditions.

Remarkable is the finding that the enzymatic activity remains during grinding in stainless steel vials as shown by Hailes *et al.* for transamination reactions of aldehydes and ketones (Fig. 12) [36]. Mechanochemical transamination reactions of aldehydes and ketones **59** were carried out by using the transaminase from *Chromobacterium violaceum* (*Cv*-TAm) as lyophilised whole cell with isopropylamine hydrochloride (IPA) as amine donor, pyridoxal 5-phosphate (PLP) **61** as the cofactor and potassium phosphate buffer. Ball milling at 25 Hz frequency for 2 cycles of 30 min milling followed by 30 min of aging (total reaction time 2 h) led to the formation of amines **60** in very high yields. It was found that all products of mechanochemical reactions are the single (*S*)-enantiomers. This mechanoenzymatic system, which can lyse cells and release active enzymes during the milling procedure is advantageous, as the whole cell biocatalysts were used directly in reactions. As such, the procedure is simplified in comparison to conventional conditions, eliminating the need for enzyme lysate preparation or purification procedure.

Organic chemical transformations could be carried out enantioselectively by ball-milling, which was applied to various reactions such as aldol reaction, Michael addition, Morita-Baylis-Hillman reaction [37] or epimerization [38]. These reactions could be illustrated by the Mannich reaction of ketimine isatine **62** with pyrazolone **63** followed by fluorination (Fig. 13) [39]. Mechanochemical enantioselective Mannich reaction was carried out by Šebesta with quinine-derived squaramide catalyst **66**, which showed the highest activity in the catalyst screening. It was found that dichloromethane used as LAG solvent is the most beneficial. Fluorination of substrate was achieved in the second step, employing *N*-fluorobenzenesulfonimide (NFSI) as the fluorination reagent. In these



	solution	stopper exchange	ball-mill
57A	5%	70% (55%)	46%
57B	traces	38% (30%)	87%
57C	0%	traces	46%

Fig. 11: Synthesis of supramolecular rotaxanes by stoppering of pseudorotaxane by ball milling.

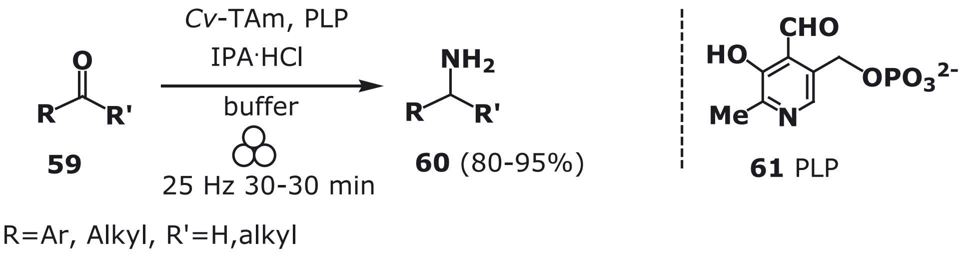


Fig. 12: Enzymatic transamination mechanochemical reaction of aldehydes and ketones with transaminase.

conditions, catalyst **66** performed the best, and product **65** was obtained in 94 % yield and enantiomeric purity of 99:1 e.r. For comparison, in solution conditions (dichloromethane), reaction requires longer time for each reaction step (22 h) and product was obtained with lower enantiopurity. Thirteen ketimine derivatives were transformed by the Mannich reaction – fluorination procedure into corresponding products in short time, high yields and good enantiopurity (20–25 min, 66–98 % yield, 95:5-99:1 e.r.). Modified reaction conditions were also applied to the reaction of isatin ketimine **62** with isoxazolone **67**, albeit obtained reaction yield and e.r. of the product **69** are significantly lower. Sustainability of the process is assessed by mass intensity parameter, which is 4.1 mg/mg for ball milling, and 42.2 mg/mg for solution reaction, and this higher efficiency of mechanochemical process is mainly coming from reduced use of solvent.

Juaristi has observed that solid state ball milling influences the change of diastereoselectivity in comparison to solution reaction conditions in synthesis of tricyclic systems pyrrolo[2,1-a]isoindolone and tetrahydropyrido [2,1-a]isoindolone (Fig. 14) [40]. When **rac-70** substrate was allowed to react with ethyl acrylate in ball mill in the presence of cesium carbonate, a pyrrolo[2,1-a]isoindolone **rac-72** product was obtained, in conjunction with reaction intermediate **rac-73**. This result is in contrast to solution reaction, where intermediate product could not be detected. Reaction mechanism leading to the formation of tricyclic products involves several steps, a cascade reaction starting with Michael addition onto α.β-unsaturated esters which is followed by an aldol-like cyclization reaction. Mechanochemical treatment of **rac-70** with acrylonitrile in ball mill provided three diastereoisomeric products **rac-75**, **rac-76** and **rac-77**, whereas solution conditions favored **rac-75** as the major product. The first reaction step in synthesis of tetrahydropyrido[2,1-a]isoindolone products was *N*-alkylation of phthalimide with

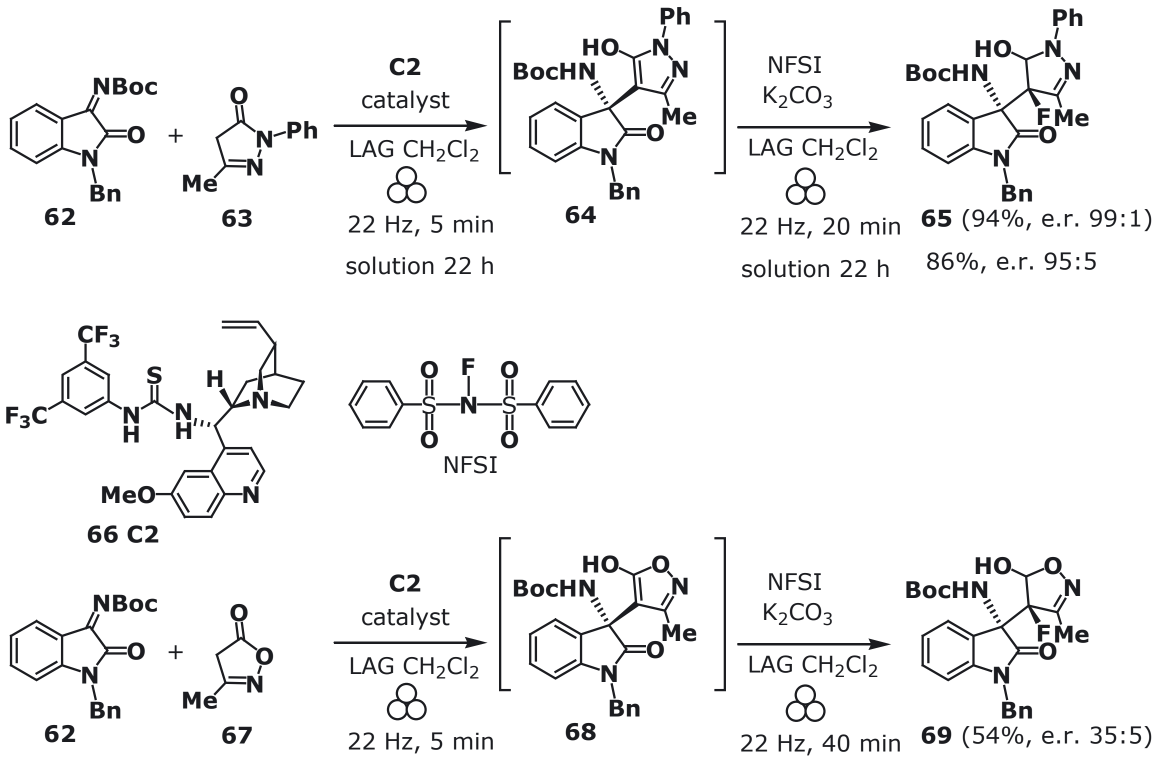


Fig. 13: Enantioselective Mannich mechanochemical reactions of ketimine isatine with pyrazolone and isoxazolone.

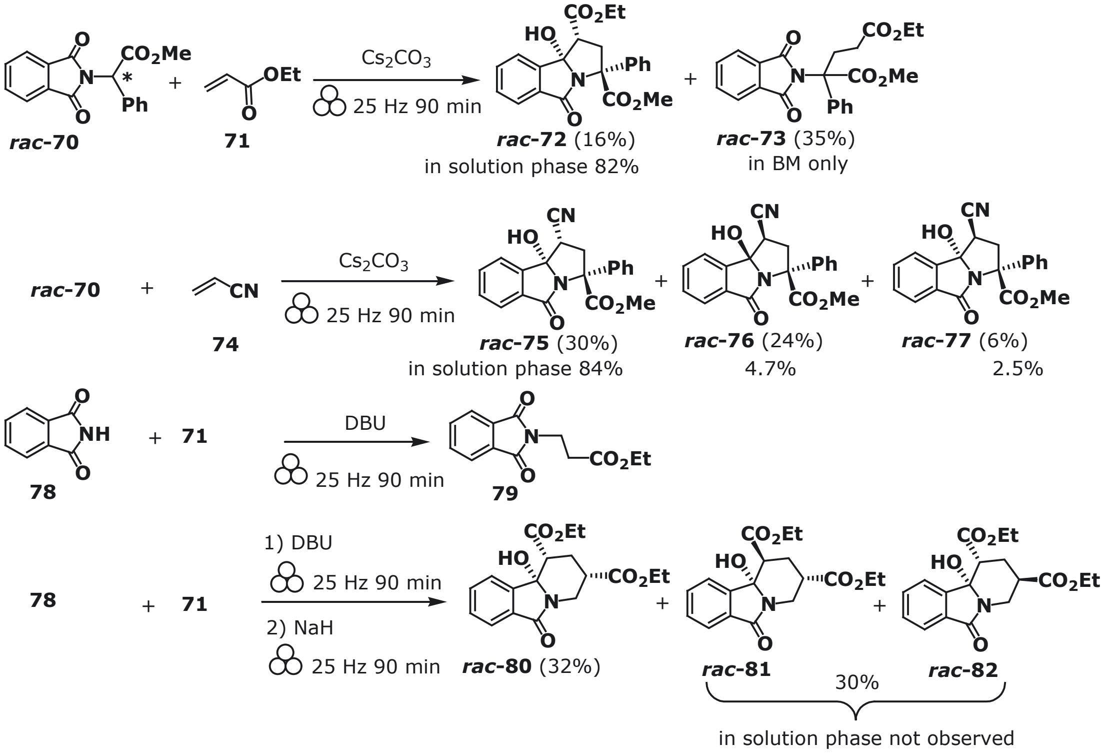
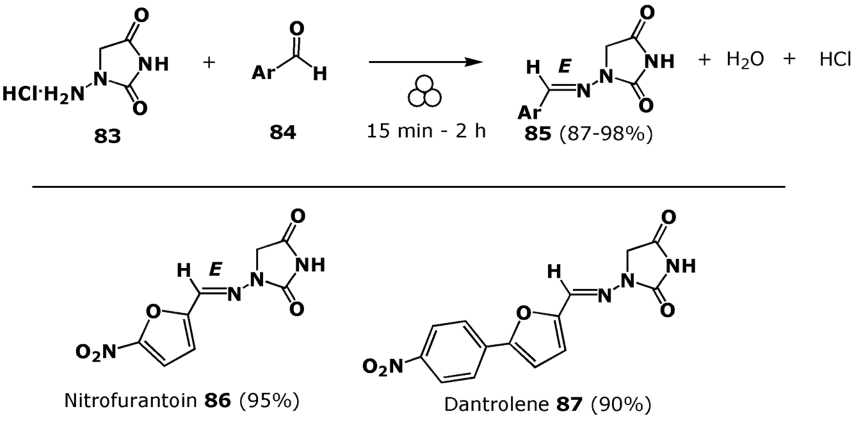


Fig. 14: Diastereoselective mechanochemical Michael addition/aldol-like cyclization reactions.

ethyl acrylate in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) base. Ball milling afforded product **79** in 70 % yield within 90 min. Then one-pot sequential mechanochemical reaction was carried out by initial milling of **78** with ethyl acrylate and DBU, which was followed by the addition of NaH and continued milling for another 90 min. This procedure afforded tetrahydropyrido-isoindolone **rac-80** in 32 % yield. In the same reaction, products **rac-81** and **rac-82** were also isolated (not observed in solution phase experiments in THF at −78 °C, 3 h + 2 h rt). Therefore, reactivity in solid state and solution phase conditions differs and allows the preparation and isolation of novel tricyclic products which are not observed in solution reactions. The diastereomeric distribution of products depends largely on reaction conditions applied.

Sustainability aspects of mechanochemical synthesis

The assessment of sustainability of mechanochemical reactions by the aid of green metrics could be illustrated by the reaction described by Colacino *et al.* Ball-milling reaction of 1-aminohydantoin hydrochloride **83** and aromatic aldehydes **84** was used for an effective synthesis of arylhydrazones **85** in short time and high yields (Fig. 15) [41]. This is almost zero-waste process where only water and hydrochloric acid are generated and due to quantitative conversion, during the workup only simple treatment with water and filtration were carried out. Amongst the prepared arylhydrazones, nitrofurantoin **86** and dantrolene **87** are the compounds of high interest as active pharmaceutical ingredients (APIs). Nitrofurantoin is usually obtained in solution (DMF) in 83–92 % yields, whereas dantrolene yields are within 41–96 % range. Important advantages of the novel process in comparison to solution reactions are the avoidance of solvents, the avoidance of use of bases and acids catalysts, reduction of the number of synthetic steps, energy cost reduction, shortening of reaction times, reduction of the environmental footprint positive effect on the cost reduction for synthesis of product. Several green metrics were applied to synthesis of nitrofurantoin **86** and dantrolene **87** to assess the advantage of the mechanochemical process in comparison to reaction carried out in solution: environmental factor (E-factor), the process mass intensity (PMI) and the atom economy (AE). Different metrics calculated clearly indicate green advantages of mechanochemical synthesis.



Green metrics solution/BM

	yields/%	t/h	E-factor	PMI	AE
86	95/95	8/0.25	16/0.29	17/1.29	81
87	95/90	1/2	239/0.30	240/1-30	85

Fig. 15: Mechanochemical synthesis of arylhydrazones from 1-aminohydantoin and aldehyde and reaction green metrics.

Future prospects

There is already a long list of organic transformations translated from solution phase to solid-state mechanochemical conditions. This trend will continue in the future as the mechanochemistry is getting more widely accepted by the organic chemical community. Further expansion of organic reactions which could be carried out in ball-milling conditions will be simultaneous with the simplifications and improvements of already developed mechanochemical procedures. The application of *in situ* spectroscopic methods and development of novel techniques will aid to better understanding of the underlying mechanistic processes during the promotion of chemical reactions by mechanical force.

There is a challenging task ahead in translation of a solid-state synthetic reactions carried in batch mode to continuous mechanochemical process. This step forward is of great importance for the applications of milling reactions in large scale industrial production [42]. Important advances were made in the development of continuous mechanochemical reactions by the use of continuous twin screw extruder technique, which could be exemplified by continuous fluorination of dibenzoylmethane in twin screw extruder carried out by James and Browne [43] and the reactive extrusion solvent-less peptide coupling reactions published by Métro *et al.* [44].

Abbreviations

AE	atom aconomy
API	active pharmaceutical ingredient
Cv-Tam	Chromobacterium violaceum transaminase
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-Dicyclohexylcarbodiimide
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E-factor	environmental factor
e.r.	enantiomeric ratio
Et_3N	triethylamine
EXAFS	extended X-ray fine structure
IBX	2-iodoxybenzoic acid
IPA	isopropylamine
IR	infrared
LED	light-emitting diode
LAG	liquid assisted grinding
MAG	microwave-assisted grinding
MASSPC	mechanochemically assisted solid-state photocatalysis
MBM	mixer ball mill
MM	mortar mill
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
PLP	pyridoxal 5-phosphate
PMB	planetary ball mills
PMMA	poly-(methyl)methacrylate
PMI	process mass intensity
SMMS	stirred media mill
TBDMS	*tert*-Butyldimethylsilyl
TAG	Thermally assisted grinding

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