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Recent Advances in Mechanochemical Organic Synthesis

Davor Margetić and Vjekoslav Štrukil

Abstract

In this review, the recent advances in mechanochemical organic synthesis are presented. These include variety of chemical reactions, organic functional group transformations, organic catalytic processes, and photochemical reactions which were not carried in mechanochemical conditions before.

Keywords: mechanochemistry, organic synthesis, green chemistry, ball milling, methodology and technique developments

1. Introduction

The use of mechanical energy to promote chemical reactions has become a fast-growing area of green chemistry research in the last decade. With the realization of its practical potentials by chemists and researchers in academia and industry, in recent years, the number of published accounts on mechanosynthesis in various research fields is increasing, ranging from inorganic, metal-organic to organic reactions. Mechanochemistry also become widely exploited for synthesis of drug solid forms [1]. The topic of mechanochemistry was the subject of several review articles [2–9] and books [10, 11]. In this review, the most recent accounts on the mechanochemical organic synthesis are covered.

2. Synthesis

Multi-step synthesis is applicable to ball milling solid-state conditions, which is documented by the increasing number of one-pot, multi-step reactions. In the initial milling process, compatible second reagents were added, and milling was continued. Among them are one-pot two-step Negishi C–C cross-coupling which applies different physical forms of zinc to generate organozinc reagent which was coupled with aryl halide and palladium catalyst in the second milling step. This reaction was also carried out as one-pot one-step reaction [12]. Further examples are one-pot two-step synthesis of thioureas from amines employing thiocarbamoyl benzotriazoles [13], one-pot two-step synthesis of pyrazolones [14], two-step synthesis of paracetamol and procainamide [15], and three-step, two-pot Gabriel synthesis of amines [16]. For illustration, reductive cyclization of fullerene was carried out by three consecutive ball milling reactions (**Figure 1**) [17]. This

solvent-free Michael reaction of fullerene anion to enones (chalkones) was carried out in a two-step, one-pot procedure, starting by zinc reduction of fullerene to carbanion, with water additive used to protonate generated carbanions. The mechanochemical conditions led to the formation of C₆₀-substituted cyclopentanol **3** and hydrofullerene derivative **4**. This mixture was transformed to **3** by short milling with Et₃N. Dehydration to C₆₀-fused cyclopentenenes **5** was achieved by milling of **3** with trifluoromethanesulfonic acid.

One-pot, three-step synthesis of pyrroles from amines, alkyne esters, and chalkones saves time and increases the practicality of synthesis (**Figure 2**) [18]. The first step is reaction of amines with alkyne esters which affords β-enaminoesters **7**. Without separation, chalkone, I₂, and Phi(OAc)₂ were added to vessel for subsequent milling, which produced dihydropyrroles **9** via Michael reaction. Dehydrogenative oxidation with DDQ led to formation of substituted pyrroles **10**.

Some novel variants and reagents were recently applied for reactions which were previously carried out in ball mill such as the formation of peptide bond and imines; Michael, Mannich, and Wittig reactions; porphyrin metalation; halogenations; and various multicomponent reactions. For instance, amide bond formation by one-pot two-step procedure, followed by polymerization in mill [19], application of Phi(OAc)₂ cross dehydrogenative coupling for the amidation of aldehydes via C—H activation [20], formation of phosphinecarboxamides [21], Rh catalyzed amidation [22] or via Ritter reaction [23] and amination to prepare sulfonamides employing Ir catalyst [24] were reported. In addition, a mechanistic study for amide bond formation is published [25].

Some of the traditional transition metal catalysts used in solution reactions can be replaced with elementary metals as catalysts under mechanochemical conditions. For this purpose, different materials for balls and milling vessels were used by Mack, including silver, copper [26], and nickel, even aluminum jars and balls for amorphization [27] and silicon nitride for Scholl reaction [28]. An exemplary reaction is cyclopropanation of alkynes with diazoacetates carried out in ball mill using various materials for vial and balls. Silver foil was found to be a recyclable metal catalyst which does not loose activity and diastereoselectivity after several reaction cycles [29]. The optimal results of [2+1] cycloadditions for internal alkynes were achieved with stainless steel vials and balls, with the addition of silver foil (**Figure 3**), whereas copper foil showed much better performance in cyclopropanations of terminal alkynes [30]. Silver foil in conjunction with PdCl₂(PPh₃)₂ catalyst

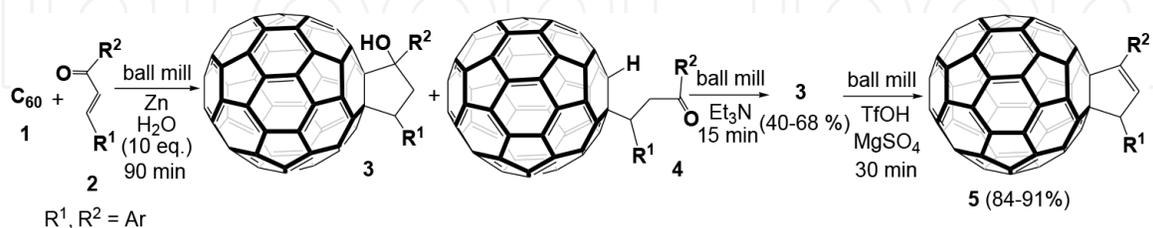


Figure 1.
Reductive cyclization of C₆₀ with enones by three-step milling.

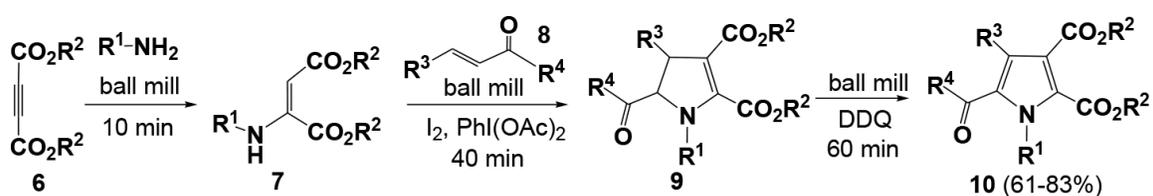


Figure 2.
Three-step synthesis of substituted pyrroles.

was also employed as the effective co-catalyst for mechanochemical Sonogashira coupling of aliphatic alkynes with aryl iodides.

On the other hand, catalysis of [2+2+2] cycloaddition of alkynes to cyclooctatetraenes (**Figure 4**) with Nickel foil was ineffective (SS vial/ball) and with Tungsten carbide balls was moderate, whereas with nickel powder (SS vial/ball), it was moderately active, and pellets were used to obtain high conversion. Nickel vial in combination with nickel balls provided low conversion [31]. Nickel powder generated in situ is responsible for the catalytic activity and, by using the neodymium magnet to separate nickel pellets from crude reaction mixture, makes the catalyst recyclable.

Metal catalyst additives such as Pd foil, Cr, and Ni powder showed the activity in alkyne hydrogenation using water as hydrogen source. Efficient mechanochemical hydrogenation method employs SUS304 stainless steel which contains zero-valent Cr and Ni constituents for balls and vial [32]. Alkene and alkyne bonds and nitro, azido, and keto groups were reduced in 62–100% yield by in situ hydrogen generation (**Figure 5**). Furthermore with SUS304 steel vials as catalyst, alkanes and Et₂O were used as hydrogen sources for hydrogenation of aromatic compounds, alkenes, alkynes, and ketones [33].

Novel mechanochemical C—C bond forming reactions include Friedel-Crafts acylation [34] and alkylation which was also employed in polymer synthesis [35]. Porphyrin synthesis in which mechanochemical procedure was reported earlier was extended to bulkier aromatics [36] and the solventless metalation of porphyrins [37, 38].

Mack has shown that different products could be obtained in enolate addition reactions, when solution procedure was replaced by solvent-free conditions (**Figure 6**) [39]. Whereas in solution 3-hydroxy-1,3-diphenylbutan-1-one and dypnone were formed by base-catalyzed aldol condensation of acetophenone, in ball mill

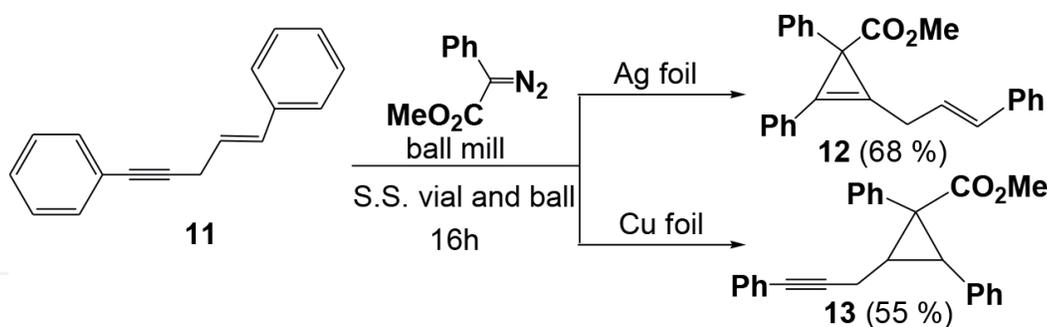


Figure 3.
 Cyclopropenation of alkenes and alkynes with diazoacetates.

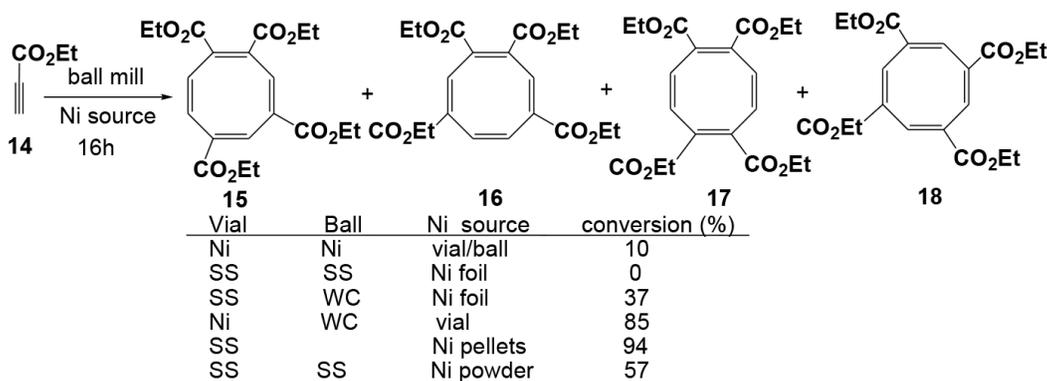


Figure 4.
 Nickel-catalyzed [2+2+2] cycloaddition of alkynes.

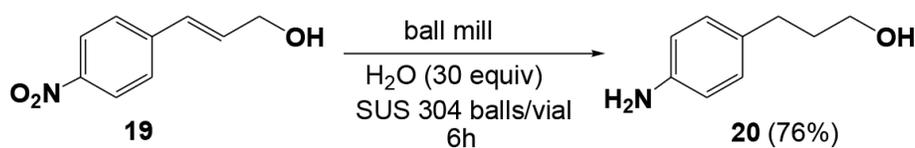


Figure 5.
Nickel-catalyzed hydrogenation reactions.

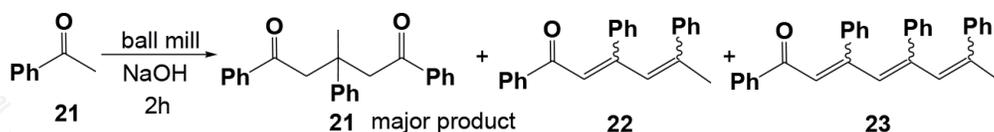


Figure 6.
Aldol condensation of acetophenone.

1,5-pentadione **21** was obtained as the major product. This product was formed by an initial aldol reaction followed by the Michael addition. In addition, products **22** and **23** arising from the 1,2-addition of the enolate with initial Michael adducts were obtained.

Dehydrogenative C—H/C—H arylation of oximes and anilides as directing groups was carried out by Xu (**Figure 7**) [40]. The mechanochemical process is fast (1 h, 6 × (10 min + 1 min break)) and mild, with less amount of arenes, and highly para-selective. A variety of functional groups could be tolerated in LAG (DMF) conditions with TfOH as an additive in conjunction with Pd catalyst and oxidant. Optimal reaction conditions were also applied to olefinic C—H arylation with simple arenes. Kinetic isotope effects of experiments using deuterated substrates showed KIE data which are consistent with those reported in the similar transformation using arenes as solvents. Slightly different mechanochemical conditions were employed by Su in oxidative C—H dehydrogenative homocoupling of *N*-arylcarbamates (**24**, R¹ = NHCO₂R): Pd(OAc)₂ catalyst in conjunction with Cu(OTf)₂ as an oxidant and HFIP additive and silica gel as grinding auxiliary [41].

The synthesis of benzo[*b*]furans by electrophilic cyclization of 2-alkynylanisoles **27** was accomplished by milling with equimolar amount of iodine (**Figure 8**) [42]. The formation of C—O bond is achieved in moderate to high yields (30–83%). This is an example of reaction where the optimization of conditions indicated that lower milling speed (15 Hz) and shorter milling time provided better yields. The increase of milling frequency, extension of the reaction time, or use of an iodine excess caused the formation of side products, diiodinated *E*-alkenes.

C—N bond forming reactions were paid larger attention to. Mechanochemical nitration reactions of aromatics are extended to various reagents: NaNO₃ in conjunction with MoO₃ as an additive [43], BiNO₃ with MgSO₄ [44], as well as BiNO₃ alone was applied for nitration of fullerene C₆₀ [45]. Amine guanylation with *N,N'*-Di-Boc-1H-pyrazole-1-carboxamide [46] and facile Boc deprotection was achieved with TsOH [47]. Another mechanochemical nitrogen deprotection (*N*-demethylation) by modified Polonovski reaction of various alkaloid *N*-oxide hydrochlorides (of biologically interesting molecules, dextromethorphan, atropine, noscapine, and benzoyltropine) was carried out using iron dust and LAG (**Figure 9**) [48]. Toxic and expensive reagents are replaced by iron dust.

Strecker reaction of benzaldehyde with benzylamine and KCN in simple reaction conditions using unusual material (stones as ball bearings) provided a mixture of α-aminonitrile **34** and imine **35** (**Figure 10**) [49]. A favorable formation of **34** was achieved by silica gel additive with its ability to adsorb moisture (instead of the common Brønsted and Lewis acid catalysts), and α-aminonitrile **34** was produced almost exclusively. The replacement of ZrO₂/stone material with agate

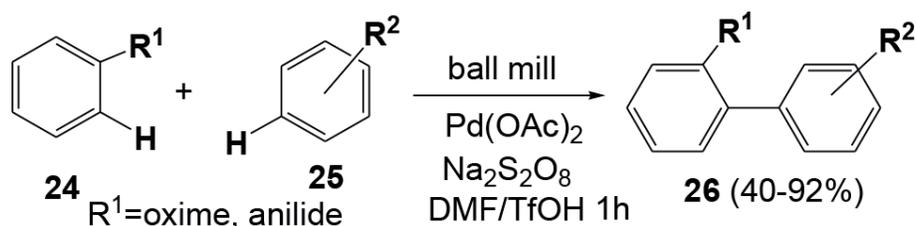


Figure 7.
 Dehydrogenative C—H/C—H arylation.

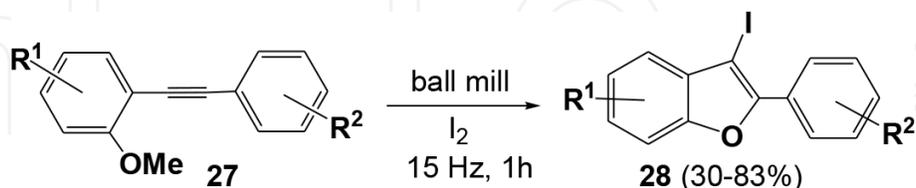


Figure 8.
 Synthesis of benzo[*b*]furans by electrophilic cyclization.

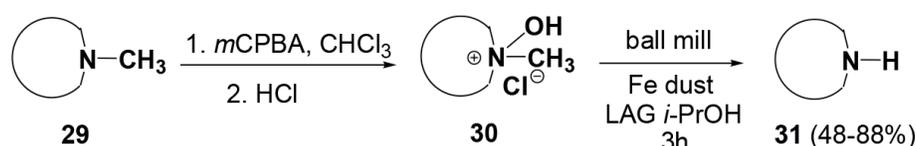


Figure 9.
 Demethylation of alkaloid N-oxide hydrochlorides.

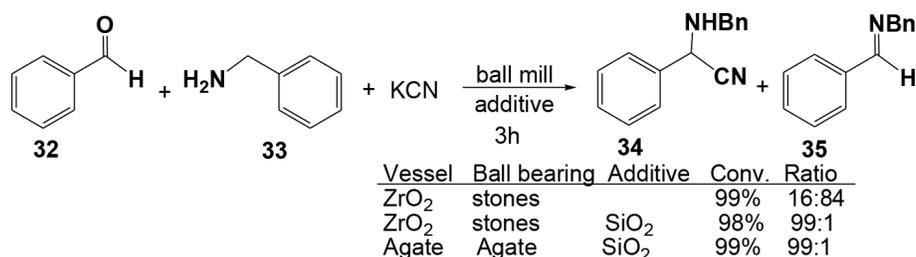


Figure 10.
 Strecker reaction.

worked equally well, and a variety of α -aminonitrile products was synthesized in high yields. Lignin additives as Brønsted acid also provided high yields, with α -aminonitrile/imine ratio less specific. The formation of gaseous HCN in Strecker reactions using $\text{K}_3[\text{Fe}(\text{CN})_6]$ was detected by trapping in modified milling jar with gas outlet [50].

Palladium-catalyzed Buchwald-Hartwig amination of aryl chlorides in ball mill has provided moderate to high yields of diarylamine products **38** (Figure 11) [51]. A sodium sulfate grinding auxiliary was necessary to improve mixing. Noteworthy, these reactions did not require inert gas protection. Under air, Browne used KO^tBu and Pd-PEPPSI-*i*PENT catalyst for Buchwald-Hartwig amination [52]. Ito has found that olefin additives can act as efficient molecular dispersants for catalysts in a solid-state Buchwald-Hartwig amination reaction (where aggregation is suppressed through olefin coordination with Pd catalyst). For instance, 1,4-cyclooctadiene facilitates the reaction of aryl halides **39** with diarylamines **40** to obtain triaryl-amines **41** in high yield [53].

Efficient spiroimidazoline synthesis by the reaction of 2-substituted 1H-indene-1,3-(2H)-diones **42** and barbituric acid-derived alkenes **45** with amidines promoted by *N*-iodosuccinimide (NIS) was reported by Wang (Figure 12) [54]. The

formation of two new C-N bonds in the process was achieved in a very short time by the reaction which started with aza-Michael addition to alkenes.

Another user and environmentally friendly protocol than isocyanide synthesis via Ugi reaction was the development of solid-state Hofmann reaction (synthesis of isocyanides from amines) (**Figure 13**) [55]. The implementation of the reaction in mechanochemical conditions significantly reduces the amounts of chloroform, from bulk solvent to 2.1 equivalents. Milling in two 15-minute steps, where chloroform was added each time, afforded better yields than one 30-min milling with all chloroform added at once. The addition of NBu_3 was beneficial for sterically more hindered substrates.

Enzymes can tolerate ball milling conditions, and enzymatic reactions were successfully carried out for several transformations: esterification of primary alcohols [56], peptide bond formation [57], ester hydrolysis [58], and cleavage of cellulose [59]. An enzymatic kinetic resolution of racemic secondary alcohols *rac*-**50** was performed by acylation with isopropenyl acetate catalyzed by lipase B from *Candida antarctica* lipase B (CALB) (**Figure 14**) [60]. Milling of *rac*-**50** in ZrO_2 vessel showed that biocatalyst is stable in reaction conditions and a partial highly enantioselective hydrolysis provided acetates (*R*)-**52** and the remaining alcohols (*S*)-**50**. High enantioselectivity was also obtained with immobilized lipase PS-IM. Acylative kinetic resolution could be coupled with ketone reduction in one-pot sequential process starting from acetophenone **49**.

Similar methodology was applied by Juaristi for the mechanoenzymatic resolution of racemic chiral amines. CALB was applied in the combination of isopropyl acetate as acylating agent and dioxane additive (in agate jars), and amide products were obtained with excellent enantiopurity (ee 66–>99%). Enantiopure chiral amines were used in the synthesis of (*R*)- and (*S*)-Rasagiline [61].

Besides hydrogenation reaction facilitated in SUS304 ss and Strecker reaction, gaseous reagents were also in situ generated in transfer hydrogenation of carbonyls with polymethylhydrosiloxane as hydrogen source [62], reduction of NO_2 group by catalytic transfer hydrogenation employing Pd and ammonium formate [15], and synthesis of thioureas by generation of ammonia from NH_4Cl and Na_2CO_3 [13].

Among the reactions for the formation of other types of bonds which were not previously carried in ball milling conditions are C—P bond by phosphonylation with MnOAc [63], O—P phosphate nucleoside bond using CDI [64], S—P bond via Arbuzov reaction [65], C—B bond by borylation using Ir catalyst [66], and P—S and P—Se bond formation by milling of phosphines with S and Se [67].

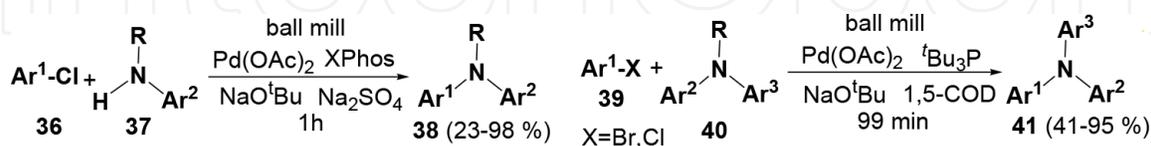


Figure 11.
Buchwald-Hartwig amination.

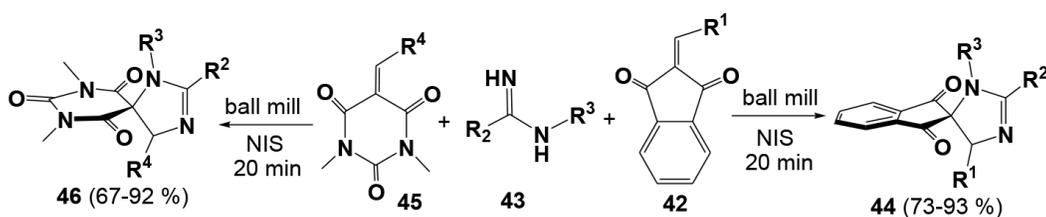


Figure 12.
Synthesis of spiroimidazolines.

A recent example of mechanochemical enantioselective reactions is the fluorination of aliphatic cyclic and acyclic β -keto esters using *N*-fluorobenzenesulfonimide with the aid of chiral oxazoline copper catalysts (**Figure 15**) [68]. Fluorinated keto esters **56** were obtained in moderate to high yields and ees.

The epimerization of (3*R*,6'*R*,3'*R*)-lutein to 3'-epilutein was successfully carried out in a stainless steel jar MET-A (composition 84.5% Fe, 13% Cr) in conjunction with acidic cation-exchange resin [69]. This transformation was accompanied with the formation of anhydrolutein, and the best *dr* ratio after optimization was 37:63.

Some cycloaddition reactions were carried out in ball mill for the first time. A mechanistic study of Diels-Alder reactions of selected anthracenes by Arrhenius kinetics was reported by Andersen and Mack [70]. The array of 1,3-dipolar cycloaddition reactions is recently extended with nitrones [71] and nitrile oxides [72].

Among the recent examples of oxidation/reduction reactions are Cannizzaro disproportionation of furfural [73] and benzylic oxidation of lignin by oxone and TEMPO [74]. Nitro group was reduced by $\text{Ni}_2\text{B-NaBH}_4$ system [75] and by AuNPs-catalyzed reaction with cyclodextrins as additives [76].

Ionic liquids as novel promoter/additive which could be regenerated were employed for the synthesis of imines [77] and in multicomponent synthesis of 4*H*-pyrans which started with Knoevenagel reaction [78].

Solvent-free mechanochemical conditions were also used in synthesis of reactive species. Synthesis of naphthalenediimide radical ions was achieved by milling of naphthalenediimides with trialkyl and triarylphosphines and Et_3N base [79]. The ArS_N reaction provides bistralkyl(aryl)phosphonium naphthalenediimide radical anions which were isolated, and automated ball milling procedure was superior to manual grinding and sonication conditions. The formation of free radicals was also obtained from glucose-based polysaccharides [80].

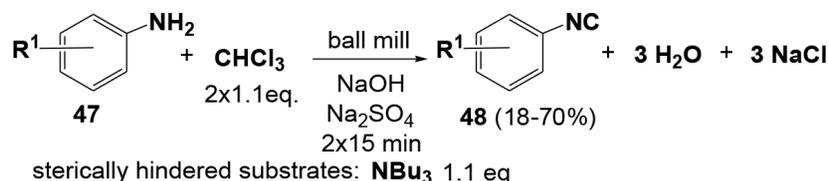


Figure 13.
 Hofmann reaction of amines with chloroform.

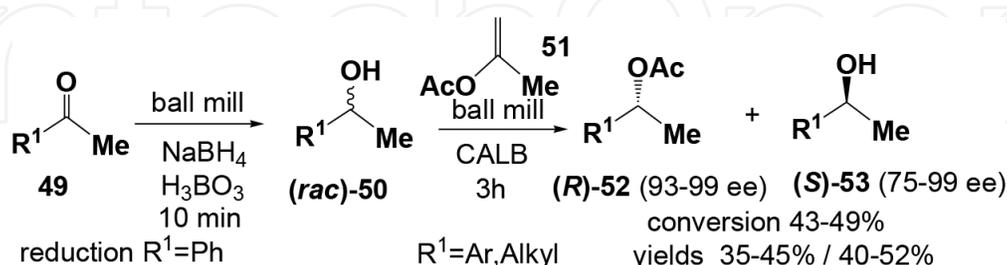


Figure 14.
 Acylative kinetic resolution of secondary alcohols.

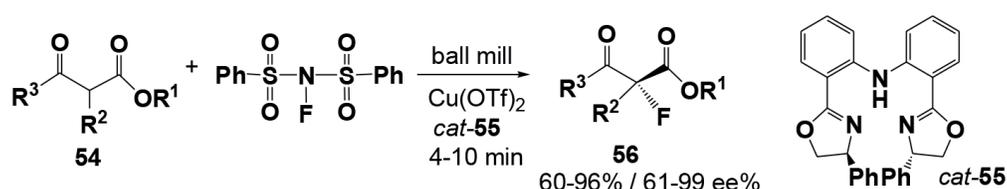


Figure 15.
 Enantioselective fluorination of β -keto esters.

Several examples of advantageous application of mechanochemistry in supramolecular chemistry are given in recent literature. The encapsulation of fullerene C₆₀ in mechanochemical conditions was extended from γ -cyclodextrin, cucurbit [15], uril and sulfocalix [16], arene hosts to molecular cages [81]. Other molecular guests were encapsulated by ball milling in calixarene (fluorene) [82], cyclodextrins (steroids) [83], as well as daidzein and genistein [84]. Synthesis of metal-organic framework in the presence of guest was used for the entrapment of boron dipyrromethene dyes in MOF. This complex could not be obtained by direct milling of MOF with BODIPY dyes [85]. Furthermore, the size of mechanochemically prepared hemicucurbituril macrocycles was effectively controlled by anion templating [86]. Pseudorotaxanes which were prepared in solution were transformed into diamide rotaxanes [2] by solvent-free reaction of amine and acyl chloride terminus forming amide stoppers [87]. On the other hand, for the synthesis of rotaxanes [2], a one-pot, two-step mechanochemical protocol was used. It involves the preparation of pseudorotaxane and stoppering by 1,3-dipolar alkyne-azide cycloaddition in the second step.

3. Methodology and technique developments

3.1 Mechanochemistry meets photochemistry

While the photochemical activation of molecules in solution is a well-known phenomenon, its integration with milling mechanochemistry has largely remained unexplored. The first step in this direction was made by MacGillivray who described the photochemical [2+2] dimerization of 4,4'-di(pyridyl)ethylene molecules, pre-assembled in a cocrystal by template-directed solid-state cocrystallization, into a cyclobutane product [88]. The milling, achieved by shaking a glass vial in a vortex machine, was required for the cocrystallization step, while the broadband UV lamp from a laboratory photoreactor was used to affect the dimerization in the solid state. This approach, named “vortex grinding,” requires the vortex shaker to be placed inside the photoreactor chamber and is not compatible with standard milling equipment. Recently, visible light photoredox catalysis has grown into an exciting and very productive research field, but the challenge of combining it with solid-state milling remained. Further investigations by König showed that solvent-free visible light-induced photocatalytic reactions could be realized in thin liquid films by means of a rod mill, consisting of a test tube containing the reaction mixture and a glass rod attached to a stirrer [89] or by a “rotating film reactor” where a glass vial is rotated at 1200 rpm to form a film exposed to blue light [90]. In this way, alcohol oxidations using riboflavin tetraacetate photocatalyst and coupling of aryl halides with pyrroles and phosphites in the presence of rhodamine 6G were accomplished (**Figure 16a**).

In 2017, our group reported on the first successful implementation of mechanochemical ball milling in a commercial shaker mill with visible light photocatalysis, named the “mechanochemically-assisted solid-state photocatalysis” or “MASSPC” [91]. The major obstacle in employing photochemical activation in mechanochemical reactions is the nontransparency of milling jars typically made of stainless steel, tungsten carbide, or Teflon. To overcome this issue, custom-made Duran glass jars completely translucent to visible light were designed. Plastic jars made of polymethylmethacrylate (PMMA), extensively used in real-time in situ monitoring of mechanochemical reactions [92], were found to be inadequate for this purpose due to the insufficient transparency caused by the wear of the plastic material during milling. In parallel, a photochemical reactor that would enable simultaneous

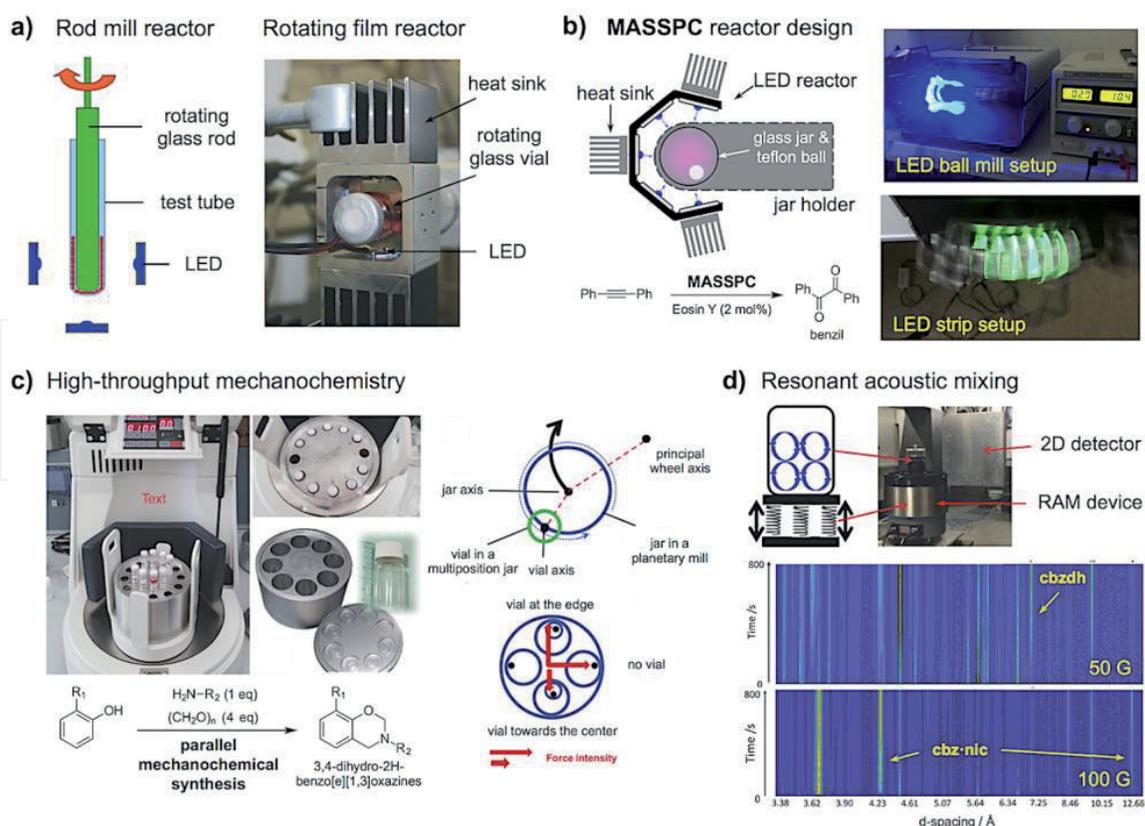


Figure 16. (a) Rod mill and rotating film reactors for solvent-free photocatalysis. (b) MASSPC reactor for simultaneous ball milling and LED irradiation. (c) A multiposition jar adapter for planetary ball milling and the lunar motion of vials in the adapter. (d) Resonant acoustic mixing device and the effect of acceleration on the cocrystallization of carbamazepine and nicotinamide.

high-speed vibrational milling and irradiation of the milled sample was constructed. While the initial experiments with LED strips wrapped around the glass jars showed promise as the simplest solution, prolonged exposure to high-frequency vibrations led to breakage of the strip, and this approach was eventually abandoned. Instead, an LED reactor that would fit around the oscillating glass jar was devised and successfully used in the aerobic thiophenol-promoted photocatalytic oxidation of diphenylacetylene to a diketone benzil (**Figure 16b**).

The obtained results suggested that singlet oxygen ($^1\text{O}_2$) was involved in the transformation of an alkyne into the diketone product, while the gas chromatographic analysis allowed reaction quantification and the detection of intermediate isomeric vinyl sulfides as the photoactive species that react with singlet oxygen. The formation of $^1\text{O}_2$ under these conditions was also demonstrated by the MASSPC approach by synthesizing anthracene-9,10-*endo*-peroxide from anthracene in the presence of eosin Y photocatalyst. The plastic PMMA jars and LED strips were next reported in the photochemical borylation of aromatic diazonium salts using eosin Y as the photocatalyst under milling conditions and green light irradiation [93]. All these results demonstrate the promising potential of merging mechanochemistry with photochemistry into a novel research area of solvent-free organic synthesis.

3.2 High-throughput mechanochemistry

One practical limitation of using conventional ball mills for synthetic purposes is their low throughput, i.e., the inability to process more than a few samples simultaneously. To address this problem, Cravotto and Colacino resorted to modification of a standard jar for planetary ball milling by transforming it to a multiposition jar

adapter capable of processing up to 12 samples at the same time [94]. The adapter can be made in different sizes to accommodate 4 vials of 100 mL, 8 vials of 20 mL, or 12 vials of 2 mL volume. In the case of a planetary ball mill equipped with four milling stations, this technical modification enables fast screening and optimization for up to 48 different reaction conditions. Besides high-throughput operation mode and time- and cost-effectiveness, “mechanochemical parallel synthesis” (1) avoids cleaning and cross contamination as the reaction mixtures can be stored or analyzed directly in the vial, (2) it allows reactions on a milligram scale (ca. 10 mg), (3) aluminum adapters serve as heat sinks and prevent reaction mixtures from overheating, and (4) the vials can be periodically loaded/unloaded to enable processing a large number of samples. Vials loaded into a multiposition adapter/jar experience the so-called *lunar motion* due to the existence of a separate rotation axis in addition to the adapter/jar axis and the principal “sun” wheel axis characteristic for planetary ball milling. This results in a motion different in conventional planetary ball mills with a nonconstant force exerted on the vials and their content. When the vials are closer to the principal axis, this force becomes less intense, while in the opposite position on the outer rim of the adapter, the force is as strong as in conventional milling (**Figure 16c**).

The development of mechanochemical parallel synthesis was successfully employed in the synthesis of a library of 3,4-dihydro-2H-benzo[e][1,3]oxazines by a one-pot three-component reaction between a phenol, a paraformaldehyde, and a primary amine. More than 60 experiments per week were performed, as opposed to expected 6–8 weeks required for the same output using conventional milling. A typical experiment in a 2 mL vial was done on 0.53 mmol scale using 60 stainless steel balls (1 mm diameter), while 20 mL vials were charged with 3.19 mmol of a phenol/amine along with 60 glass beads (3 mm diameter). The reaction mixtures were milled at 550 rpm for 4 h affording yields comparable to solution synthesis.

3.3 Ball-free milling: resonant acoustic mixing

The traditional paradigm of mechanochemistry is the use of milling balls to introduce mechanical and thermal energy into a system through mechanisms such as impact, shear, or their combination, depending on the milling mode. The number, mass, size, or material the balls are made of, as well as their relation to the volume of a milling jar, are all important variables in determining the outcome of a mechanochemical ball milling reaction. However, in a technique called the “resonant acoustic mixing” or RAM, solid-state reactions can be performed in the absence of milling bodies [95]. Unlike conventional ball milling, where the introduced energy causes physical damage to particles, generates defects, and often leads to aggregation of particulates, compaction, the so-called “snow balling,” or even complete amorphization, RAM is a much softer technique for mixing solids with minimal damage to particles. It is therefore particularly convenient in cases where mixing of impact-sensitive materials such as explosives and propellants is required. In a resonant acoustic mixer device, effective mixing is accomplished by transferring the mechanical energy of a vibrating plate connected to a bed of springs to a sample container placed on top of the plate. The plate and the container are set into an oscillating motion at a fixed resonance frequency, resulting in local zones of intense mixing (**Figure 16d**). Since the frequency of plate vibration is fixed (ca. 61 Hz), the intensity of mixing is simply adjusted by changing the amplitude of the oscillation; hence the acceleration or the “G-force” exerted on a powder sample in the container can be controlled.

In 2018, Michalchuk and Boldyreva reported the first in situ study of a RAM-induced cocrystallization of nicotinamide (NIC) and carbamazepine (CBZ) in

the presence of a catalytic amount of water, using synchrotron powder X-ray diffraction (PXRD). Two acceleration settings of 50 G and 100 G were employed to investigate the effect of mixing intensity on the course of the cocrystallization reaction to form the known 1:1 cocrystal **CBZ·NIC**. Although solvent-free (neat) conditions gave no reaction, the addition of ca. 20 μL of water facilitated the formation of carbamazepine dihydrate (**CBZDH**) at a continuous rate as the kinetically controlled product at 50 G acceleration. The Rietveld refinement revealed around 40% conversion to the dihydrate form **CBZDH**, while only a 10% ca. of **CBZ·NIC** cocrystal was observed. Since water was present in excess, the 40% conversion plateau to **CBZDH** suggests the hydration of **CBZ** particle surfaces as the primary process during mixing, which prevents the complete hydration to take place in deeper layers. On the other hand, RAM at 100 G acceleration provided a completely different reaction profile. Most of the reactants were consumed within the first 30 seconds, and after Rietveld refinement, ca. 70% of **CBZ·NIC** cocrystal, as the thermodynamically favored phase, was detected, alongside 15–20% of the dihydrate **CBZDH** (**Figure 16d**). Throughout the first 9 minutes, the Bragg reflections corresponding to reactants stochastically appeared and disappeared, suggesting an inhomogeneous mixing and distribution of powder inside the reaction zone. Additionally, the presence of **CBZDH** in the mixture was probably due to the hydration of aggregated **CBZ** in the corners of the container, where mixing was not effective enough as the vessel was designed primarily for in situ PXRD measurements. The observed differences in solid-state reaction rates were attributed to more intimate mixing of reacting powders by particle comminution and dissociation of aggregates, disruption of intermediate product-coated reactant particles, and generation of more fresh reactive surfaces under higher RAM accelerations. This study also demonstrated that solid-state RAM mechanochemical reactions can be carried out gently in the absence of milling balls where the mechanical energy is transferred by means other than impact or shear.

3.4 Real-time in situ reaction monitoring

Since the introduction of real-time in situ techniques for monitoring mechanochemical reactions [92], based on synchrotron PXRD, Raman spectroscopy, and their combination, mechanistic details for a number of organic transformations, metal-organic framework (MOF) systems, and solid-state cocrystallizations have been studied and revealed [96]. These in situ studies also allow for kinetic considerations of solid-state milling reactions under LAG conditions [97], as well as investigations of the effect of milling parameters such as frequency [98], number of milling balls [99], or the ball to reactant ratio on the course of mechanochemical reactions [100]. On a technical side, such investigations go hand in hand with the development of equipment necessary to conduct them. In this respect, accessories such as milling jars for in situ studies deserve special attention. Filinchuk et al. have employed a 3D printer as a low-cost and rapid way to fabricate several types of plastic jars made of PMMA or polylactic acid (PLA) transparent to X-rays and showed how different geometries and material of the jars can reduce background (due to scattering) and minimize absorption, as well as improve the angular resolution during PXRD measurements [101]. In comparison with standard jars used in most experiments (type 0 and its modification type 1), jars with thinner walls (type 2) and added grooves (type 3) or physically separated X-ray probing area in the “two-chamber” jar (type 4) displayed significantly lower background and absorption (**Figure 17a**). In designs 3 and 4, the size of the groove or the opening between the two chambers is smaller than the ball size, which eliminates the problem of X-ray scattering on milling balls and detection of the corresponding diffraction peaks. The sampling efficiency of 3D-printed jars

was tested on the solvent-free mechanochemical PbO polymorph interconversion from β -PbO to α -PbO phase, as a suitable model system. The results showed that the jar design generally affects the rate of β -PbO to α -PbO conversion, with the lowest rate expectedly recorded in the type 4 “two-chamber” jar where the analyzed sample resides in the bottom chamber, while ball milling and intensive mixing take place in the upper chamber. The authors also noted that types 3 and 4 jars are not compatible with liquid-assisted grinding since wet powder materials would probably stick and aggregate in the groove or in the chamber corners.

Besides improving the design of milling jars, the development of instrumentation for mechanistic studies is essential, as exemplified by Casati's design of a new type of in situ ball mill intended for real-time probing of reactions in solids [102]. The new setup, characterized by a dual motion during milling in the form of vertical shaking (up to 50–80 Hz) and continuous slow rotation of the jar, is capable of collecting PXRD data with significantly reduced background and sharper Bragg reflections, which becomes important if high-resolution measurements are desired. Such a design also prevented the aggregation of powder material in the grooves, often encountered in devices where the only motion is shaking insufficient to push the powder out of the groove. In combination with the new design of a two-part milling chamber surrounded by a continuous probing ring where the milling balls cannot enter, it provides opportunities for collecting better resolved PXRD data, reaction monitoring, phase quantification, and line profile analysis (**Figure 17b**).

An interesting recent contribution to real-time in situ monitoring of organic transformations is the detection of a cocrystal between barbituric acid and vanillin that precedes the formation of C=C bond in the final Knoevenagel product [103]. The reactant molecules in the cocrystal are positioned to allow nucleophilic attack of the methylene group in barbituric acid to the carbonyl group in vanillin. LAG using ethanol accelerated the reaction, while acetonitrile or nitromethane prolonged the life span of the cocrystal, the structure of which was elucidated from the laboratory PXRD data. Using *N,N*-diisopropylethylamine as the grinding liquid led to the Knoevenagel product directly, without the formation of intermediate cocrystal.

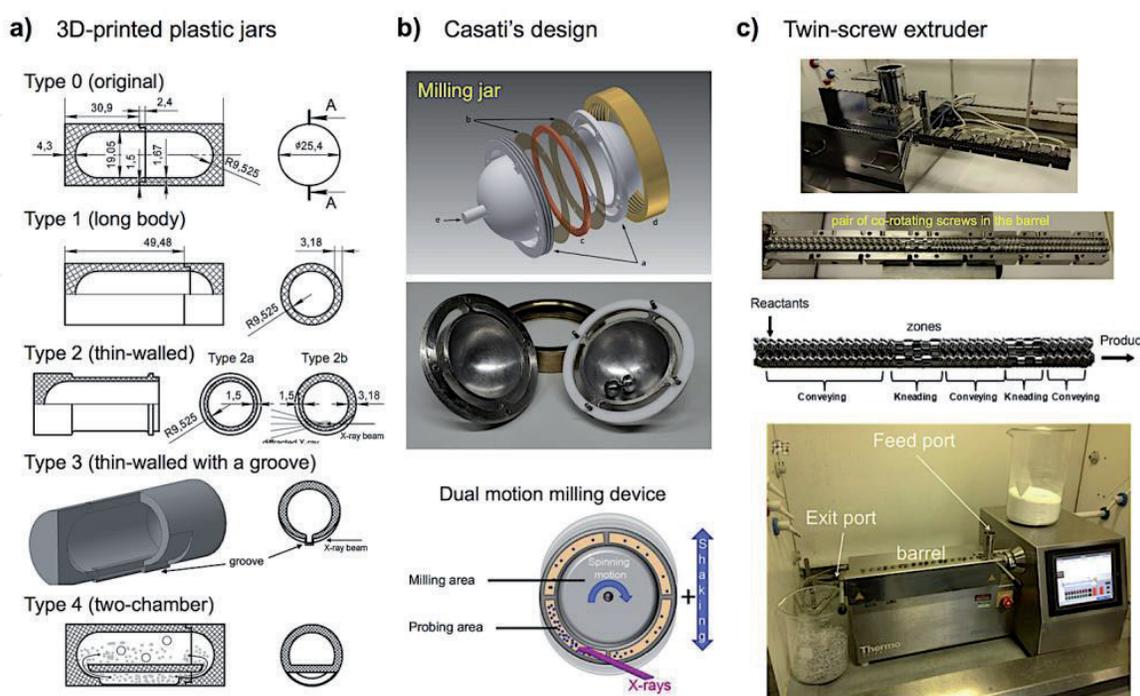


Figure 17.

(a) Different types of 3D-printed plastic jars. (b) Casati's design of a probing jar and a dual motion ball mill. (c) Twin-screw extruder and its components.

Since mechanochemical synthesis in ball mills is inherently associated with thermal effects accompanying the mechanical activation through impact or shear, a complete understanding of milling processes on a microscopic level must also take into consideration the corresponding evolution of heat. The Emmerling group described a combined in situ study of the Knoevenagel reaction between *p*-nitrobenzaldehyde and malononitrile by coupling PXRD, Raman spectroscopy, and temperature measurements using an IR thermal camera [104]. By employing custom-made PMMA milling jars equipped with an embedded aluminum plug that was in direct contact with the jar content, Užarević et al. demonstrated that the temperature profiles of milling reactions are mainly determined by the energy dissipated through friction between the moving balls, jar, and the sample contained within, whereas the reaction enthalpy contribution was relatively insignificant. Since frictional properties of the milled material change during the mechanochemical reaction, the dissipated energy will be more or less efficiently absorbed throughout milling [105].

3.5 Twin-screw extrusion: mechanochemistry grows in scale

One of the main drawbacks of mechanochemical synthesis is the lack of ability to perform milling reactions on large scales and in a continuous fashion. Industrial ball mills, which are typically used on these scales, can process tons of materials, whereas for laboratory use, planetary ball mills can deliver products up to several hundred grams. Currently, the most efficient way to increase the product output of mechanochemical reactions is the twin-screw extrusion (TSE), which has been successfully demonstrated in the large-scale solvent-free production of MOFs, cocrystals, and deep eutectic solvents, in space time yields ($\text{kg m}^{-3} \text{ day}^{-1}$) three to four times greater than the corresponding solution methods. In a typical TSE design, powdered reactants are fed into the instrument at a certain rate and conveyed by a pair of co- or counter-rotating screws encased in the extruder barrel. As the material moves along the barrel, mixing and kneading elements incorporated into the TSE design exert shearing and compression forces on the reactants, resulting in the product phase which is collected at the exit port (**Figure 17c**). Besides the screw speed and feed rate, the extruder barrel temperature is another processing parameter that can be modified [106].

James et al. have shown that organic molecules can be synthesized continuously on a large scale using TSE technique under solvent-free conditions. Four condensation reactions (the Knoevenagel reaction, the imine formation, the aldol reaction, and the Michael addition) were optimized by changing the screw speed, feed rate, and temperature, to provide a quantitative conversion to desired products. High-space time yields of $>250,000 \text{ kg m}^{-3} \text{ day}^{-1}$ for the vanillin-barbituric acid reaction, $14,900 \text{ kg m}^{-3} \text{ day}^{-1}$ for the imine product, $35,000 \text{ kg m}^{-3} \text{ day}^{-1}$ for the Michael product, and $32,000 \text{ kg m}^{-3} \text{ day}^{-1}$ in the case of the aldol product were achieved [106]. TSE was also applied in the large-scale synthesis of 2,2-difluoro-1,3-diphenylpropane-1,3-dione in the presence of Selectfluor as the fluorine source, with the space time yield of $3395 \text{ m}^{-3} \text{ day}^{-1}$ vs. only $29 \text{ m}^{-3} \text{ day}^{-1}$ obtained in the mixer mill [107]. The three-component solvent-free Biginelli reaction was successfully carried out using TSE, to afford 3,4-dihydropyrimidin-2-(1H)-ones/thiones in optimized yields of 85–91% [108].

4. Conclusions

A short review of recent literature dealing with organic mechanochemical synthesis is presented.

Acknowledgements

The authors acknowledge funding by the Croatian Science Foundation grant No. IP-2018-01-3298, cycloaddition strategies towards polycyclic guanidines (CycloGu).

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