

# Mechanochemical organic synthesis

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Recently, mechanical milling using a mixer mill or planetary mill has been fruitfully utilized in organic synthesis under solvent-free conditions. This review article provides a comprehensive overview of various solvent-free mechanochemical organic reactions, including metal-mediated or -catalyzed reactions, condensation reactions, nucleophilic additions, cascade reactions, Diels–Alder reactions, oxidations, reductions, halogenation/aminohalogenation, etc. The ball milling technique has also been applied to the synthesis of calixarenes, rotaxanes and cage compounds, asymmetric synthesis as well as the transformation of biologically active compounds.

## 1. Introduction

Mechanochemistry has attracted increasing attention from chemists.<sup>1–15</sup> Mechanochemistry is mainly promoted by either hand grinding or mechanical milling. Hand grinding, occasionally referred to as manual grinding, is usually performed in a mortar and pestle, while mechanical milling is generally conducted in a mixer/shaker mill or a planetary mill at a frequency of 5–60 Hz. Mechanical milling provides much higher energy and is more reliable and sophisticated than hand grinding because the latter may afford varying experimental results, which depend on the grinding strength and speed. In the literature, mechanical milling

is sometimes called grinding and may cause confusion. To differentiate these two mechanochemical techniques, it is strongly recommended that grinding is defined as the process in a mortar and pestle and the like, such as a Retsch RM100 mortar grinder, whereas milling should only refer to that in a mixer/shaker mill or a planetary mill.<sup>14</sup> A mixer or planetary mill can be a home-made high-speed vibration mill (HSVM) or a commercially available Retsch mixer mill, Spex CertiPrep mixer/mill, Fritsch “Pulverisette” planetary mill, AGO-2 planetary centrifugal mill and so on. Because mechanical milling in a mixer or planetary mill is always performed with the aid of milling ball(s), it is often called ball milling. Amongst technical variables such as milling frequency, milling time, size and number of milling balls, and the material of milling balls and beakers, the first two have been shown to be the most important parameters.<sup>14</sup> The operating devices and working mechanisms for mixer mills and planetary mills are different and would affect the efficiency of chemical reactions. Therefore, in this review article the mixer mill and planetary mill apparatuses will be denoted as MM and PM, respectively, in the reaction schemes together with the milling frequency, milling time and milling temperature whenever possible in order to provide the readers with more information on the employed mechanical milling conditions.

A mechanochemical process may involve carbon–carbon and carbon–heteroatom covalent bonds, metal–ligand coordination bonds, non-covalent interactions such as hydrogen bonds, halogen bonds or  $\pi \cdots \pi$  arene stacking interactions. The mechanochemical studies on metal complexes, including metal–organic frameworks (MOFs), cocrystallization, inorganic materials, pharmaceutical aspects, supramolecular aspects and industrial aspects, have already been covered in several excellent reviews.<sup>1–6</sup> The study of solvent-free organic reactions by hand grinding has been pioneered and reviewed by Tanaka and Toda,<sup>7</sup> and will not be included in the present review. The mechanochemistry of fullerenes, a family of unique cage-shaped all-carbon

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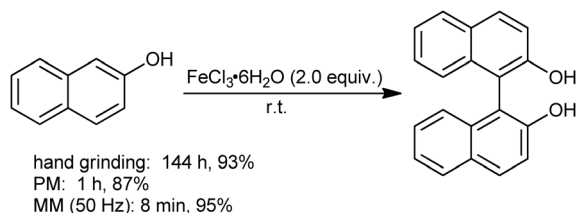
Fund for Distinguished Young Scholars (2001). His current research interests include fullerene chemistry, mechanochemistry and C–H activation reactions.

molecules, and related materials has been described in a few reviews.<sup>8–10</sup> Although organic reactions of non-fullerene organic molecules under mechanical milling conditions have been previously reviewed,<sup>3,5,6,11–14</sup> they are not comprehensive, either partially or not up to date. This review will extensively cover solvent-free organic reactions involving the formation of C–C, C–N, C–O, C–S, C–X (X = Cl, Br) and other covalent bonds of the main group elements using the ball milling technique. Metal-promoted and metal-catalyzed reactions have been widely employed in contemporary organic synthesis, and their mechanochemical reactions are reviewed first. Subsequently, various condensation and nucleophilic reactions as well as the derived cascade reactions in a ball mill are described. The commonly encountered Diels–Alder, oxidation, reduction and halogenation/aminohalogenation reactions under the ball milling conditions are then presented, followed by mechanochemical construction of macromolecules such as calixarenes, rotaxanes and cage compounds. Finally, the application of the ball milling technique to asymmetric synthesis and functionalization of biologically active compounds is demonstrated.

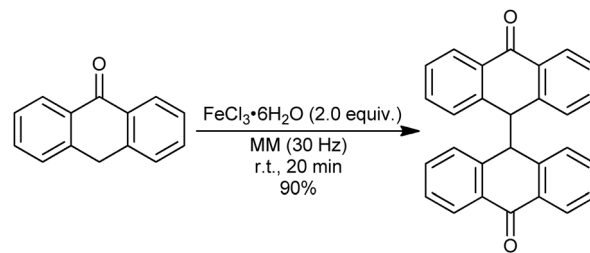
## 2. Metal-mediated mechanochemical reactions

### 2.1 FeCl<sub>3</sub>-promoted oxidative homocoupling of phenols

The optically pure 1,1'-bi-2-naphthol has been widely employed as a chiral auxiliary or catalyst in asymmetric synthesis. The oxidative homocoupling of 2-naphthol to give racemic 1,1'-bi-2-naphthol has been realized under solvent-free conditions.<sup>15–18</sup> Toda and coworkers reported the hand-grinding solvent-free synthesis of 1,1'-bi-2-naphthol from a mixture of 2-naphthol and 2 equiv. of FeCl<sub>3</sub>·6H<sub>2</sub>O by using an agate mortar and pestle. The reaction at room temperature required 144 h to obtain 1,1'-bi-2-naphthol in 93% yield (Scheme 1). The reaction time was too long to be practical. Raising the reaction temperature to 50 °C could reduce the reaction time to 2 h and afforded the product in 95% yield.<sup>15</sup> The same reaction promoted by ball milling in a Fritsch Planetary Micro Mill Pulverisette 7 (main disc speed: 100–800 rpm) at ambient temperature for 1 h generated 1,1'-bi-naphthol in 87% yield.<sup>16</sup> Solid sodium chloride was used as an additive to improve the mechanical properties of the reaction mixture. When a more efficient high-speed vibration mill (HSVM) at a speed of 3000 rpm (50 Hz) was used, the reaction could be completed within 8 min and provided the binaphthol in 95% yield.<sup>17</sup> As in other mechanochemical reactions (*vide infra*), the reaction proceeded faster at higher vibration frequencies.<sup>18</sup>



Scheme 1



Scheme 2

It is obvious that the reaction under mechanical milling conditions is much more efficient than that by hand grinding.

This solvent-free mechanochemical protocol could be extended to other phenols such as 2,3-dihydroxy-1,4-naphthalene and anthrone, and the corresponding dehydrogenative homocoupling products were obtained in 94% and 90% yields, respectively, at a frequency of 30 Hz within 20 min (Scheme 2).<sup>18</sup>

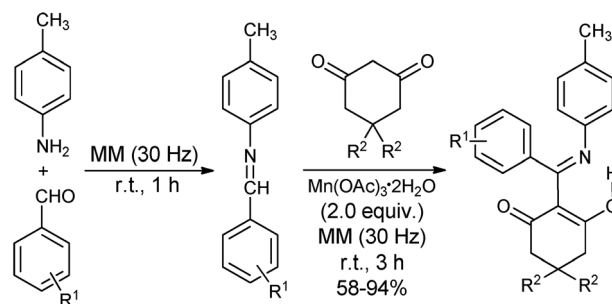
### 2.2 Mn(OAc)<sub>3</sub>-mediated mechanochemical reactions

Manganese(III) acetate (Mn(OAc)<sub>3</sub>) is most commonly used as a single-electron-transfer reagent to generate carbon-centered radicals from various carbonyl compounds, and has been applied in oxidative radical reactions with alkenes<sup>19–21</sup> as well as fullerenes in the liquid phase.<sup>22,23</sup>

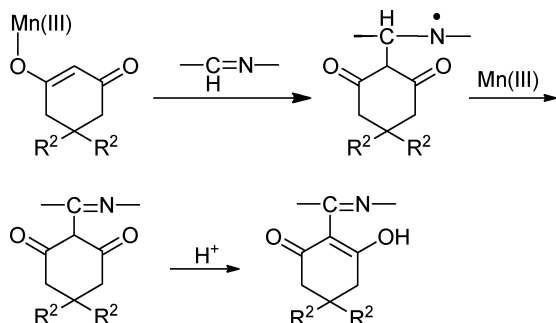
The solvent-free mechanochemical Mn(OAc)<sub>3</sub>-mediated reaction of [60]fullerene with β-dicarbonyl compounds has been reported in the literature<sup>24</sup> and described in the accompanying review article.<sup>10</sup> In this section, only the Mn(OAc)<sub>3</sub>-mediated reactions of non-fullerene molecules under mechanical milling conditions are included.

**2.2.1 Mn(OAc)<sub>3</sub>-mediated reaction of 1,3-cyclohexanediones with imines.** The first Mn(OAc)<sub>3</sub>-mediated mechanochemical reaction was reported by Wang and coworkers.<sup>25</sup> They found that the solvent-free reaction of 1,3-cyclohexanediones with *in situ* generated imines unexpectedly afforded the non-reductive radical addition products (Scheme 3).

The first-step in the reaction was the *in situ* quantitative formation of imines, which was realized by ball milling of equimolar amounts of 4-methylaniline and aromatic aldehydes at a frequency of 1800 rpm (30 Hz) at room temperature for 1 h. To the *in situ* formed imines were added Mn(OAc)<sub>3</sub> and 1,3-cyclohexanediones for the subsequent radical reactions. Mechanical



Scheme 3



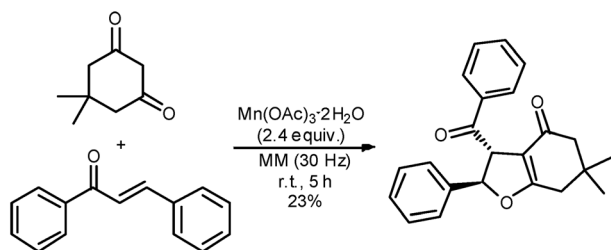
Scheme 4

milling of the reaction mixtures of imine, 1,3-cyclohexanedione and  $\text{Mn}(\text{OAc})_3$  in a molar ratio of 1:1:2 for 3 h afforded products in 58–94% yields. Experimental results indicated that the solvent-free mechanochemical reaction exhibited advantages over the corresponding liquid-phase reaction in terms of product yield, selectivity and reaction time.

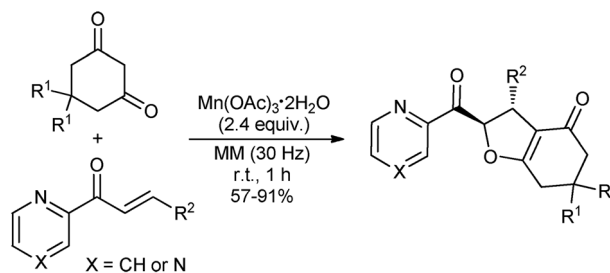
A tentatively proposed reaction mechanism is shown in Scheme 4. For 1,3-cyclohexanediones, enolization occurred readily. The homolytic addition of the  $\text{Mn}(\text{III})$  enolates to the *in situ* formed imines gave the nitrogen-centered radicals. Subsequent oxidation with a second molecule of  $\text{Mn}(\text{OAc})_3$  followed by enolization afforded the non-reductive addition products.

**2.2.2  $\text{Mn}(\text{OAc})_3$ -mediated reaction of 1,3-cyclohexanediones with 1-(pyridin-2-yl)-enones.** The intriguing addition mode of 1,3-cyclohexanediones to the  $\text{C}=\text{N}$  bond of imines<sup>25</sup> prompted the Wang group to investigate their additions to  $\text{C}=\text{C}$  bonds. The  $\text{Mn}(\text{OAc})_3$ -promoted reaction of dimedone with (*E*)-1,3-diphenylprop-2-en-1-one under the ball-milling conditions was first examined. However, the desired product was obtained in only 23% yield by milling the reaction mixture of dimedone, chalcone and  $\text{Mn}(\text{OAc})_3$  in a molar ratio of 1.2 : 1 : 2.4 at a rate of 30 Hz at room temperature for 5 h (Scheme 5).<sup>26</sup>

Interestingly, the  $\text{Mn}(\text{OAc})_3$ -mediated cycloadditions of 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione to various 1-(pyridin-2-yl)-enones proceeded efficiently under solvent-free ball-milling conditions to afford *trans*-2-acyl-3-aryl/alkyl-2,3,6,7-tetrahydro-4(*5H*)-benzofuranone derivatives. The cyclization reactions exhibited good to excellent yields (57–91%), as well as extremely high diastereoselectivity and reversed regioselectivity (Scheme 6).

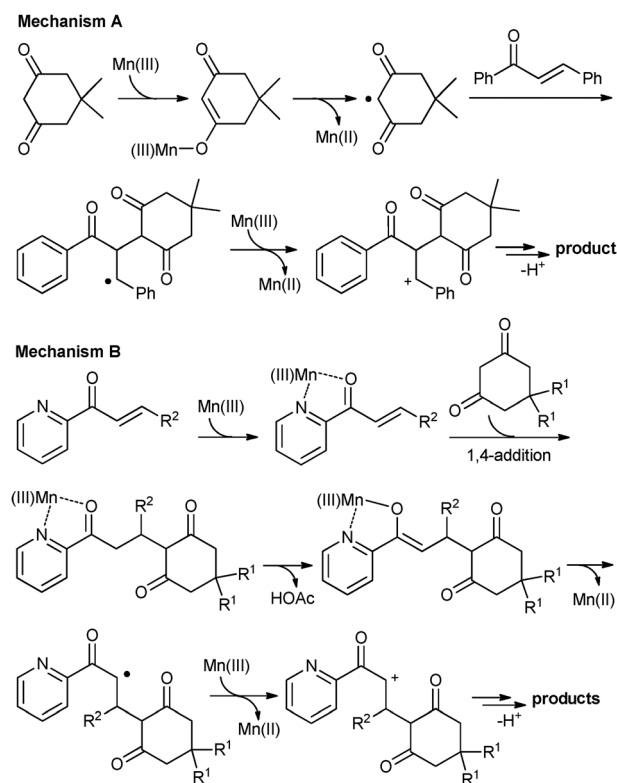


Scheme 5

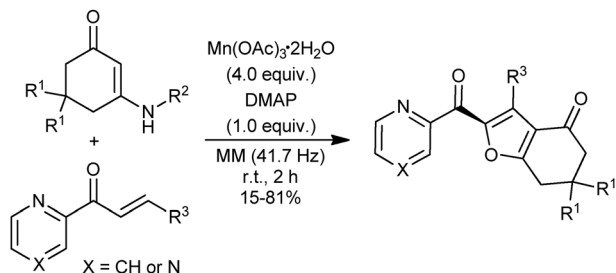


Scheme 6

The proposed plausible reaction mechanisms are shown in Scheme 7. The product from chalcone should be formed *via* Mechanism A: addition of the radical generated from the  $\text{Mn}(\text{III})$ -enolate complex of dimedone to chalcone, followed by oxidation and cyclization. The reversed regioselectivities of 1-(pyridin-2-yl)-enones and chalcones towards the additions of 1,3-cyclohexanediones in the presence of  $\text{Mn}(\text{OAc})_3$  must be attributed to the role played by the nitrogen atom of the pyridine ring. The plausible reaction pathway is shown as Mechanism B in Scheme 7. The concerted chelation of the pyridinyl and carbonyl moieties of 1-(pyridin-2-yl)-enones to  $\text{Mn}(\text{III})$  increased the electron deficiency of the  $\text{C}=\text{C}$  bond, thus facilitating the conjugate addition of 1,3-cyclohexanediones to produce  $\text{Mn}(\text{III})$ -complexed intermediates. Subsequent enolization, elimination of  $\text{Mn}(\text{II})$  species, oxidation and cyclization provided the final products. Thus,  $\text{Mn}(\text{OAc})_3$  behaves as a Lewis acid as well as a radical initiator, and alters the regioselectivity.



Scheme 7



Scheme 8

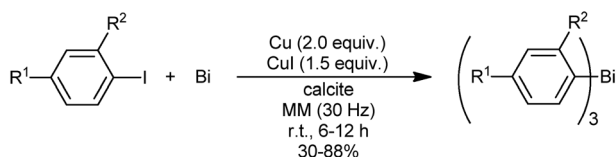
**2.2.3 Mn(OAc)<sub>3</sub>-mediated reaction of  $\beta$ -enamino carbonyl compounds with 1-(pyridin-2-yl)-enones.** In 2006, the Wang group successfully realized the Mn(OAc)<sub>3</sub>-promoted reaction of C<sub>60</sub> with  $\beta$ -enamino carbonyl compounds to generate C<sub>60</sub>-fused pyrroline derivatives.<sup>27</sup> Recently, they found that in the Mn(OAc)<sub>3</sub>-mediated reaction with 1-(pyridin-2-yl)-enones, replacement of 1,3-cyclohexanediones with their  $\beta$ -enamino carbonyl compounds afforded dihydrobenzofuran derivatives, instead of the expected 2-acyl-3-aryl-indole derivatives (Scheme 8).<sup>28</sup>

The addition of a base such as *N,N*-dimethylaminopyridine (DMAP) improved the product yields, and *N*-unsubstituted  $\beta$ -enamino carbonyl compounds performed better than their *N*-substituted counterparts. The products under optimized conditions were obtained in 15–81% yields after treatment in a Spex 5100 mixer mill at a speed of 2500 rpm (41.7 Hz) for 2 h. The amino group in the  $\beta$ -enamino carbonyl compounds must play a crucial role, as the products were different from those for 1,3-cyclohexanediones.

### 2.3 Copper-mediated synthesis of triarylbismuthanes

Triarylbismuthanes are usually prepared by the reaction of an aryl Grignard or aryllithium reagent with anhydrous bismuth(III) halides. However, direct treatment of functionalized organometallic reagents with BiCl<sub>3</sub> leads to an intractable tarry substance in most cases. To overcome this limitation, Suzuki and coworkers developed the solvent-free mechanochemical synthesis of *ortho*-functionalized triarylbismuthanes from aryl iodides bearing an electron-withdrawing group at the *ortho* position (Scheme 9).<sup>29</sup> The reaction was conducted in a ball mill at 30 Hz for 6–12 h together with bismuth shots and calcite grains in the presence of Cu powder and CuI, giving *ortho*-functionalized triarylbismuthanes in 30–88% yields.

A combination of Bi and Cu or CuI was indispensable for the present reaction, and the combined use of Cu powder and CuI gave better results than the separate use of either one of them. Without copper species, no triarylbismuthanes were formed.



Scheme 9

The reaction was supposed to proceed by the initial formation of an arylcopper species, which would undergo transmetalation with a bismuth atom on the new metal surface, eventually leading to triarylbismuthanes *via* either stepwise arylation of bismuth or disproportionation of some arylbismuth species.

## 3. Metal-catalyzed mechanochemical reactions

### 3.1 Pd-catalyzed reactions

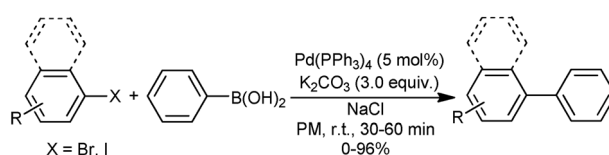
Palladium has been widely used to catalyze organic reactions, and has been demonstrated in numerous applications in cross-coupling reactions, particularly of aryl halides with alkenes and organoboron compounds.<sup>30</sup>

**3.1.1 Suzuki reaction.** The first Pd-catalyzed coupling reaction under ball-milling conditions was reported by Peters and coworkers.<sup>31</sup> One problem encountered in a ball-milled reaction is the degree of stickiness of the reaction mixture. It is difficult to mill very soft or waxy substances in a productive way because they stick to the walls of the milling chambers and milling balls. In this Suzuki reaction, inert sodium chloride was added to the reaction mixture to make it sufficiently powdery. Among the examined bases, K<sub>2</sub>CO<sub>3</sub> gave the best yield. Milling the mixtures of aryl halide (1 equiv.), phenylboronic acid (2 equiv.), K<sub>2</sub>CO<sub>3</sub> (3 equiv.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) in a Fritsch Planetary Micro Mill Pulverisette for 30–60 min afforded the desired cross-coupling products in up to 96% yield (Scheme 10).

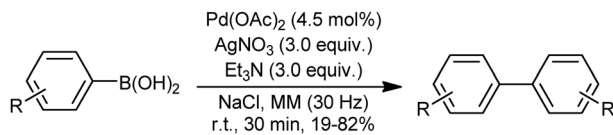
This Suzuki reaction was often accompanied by the homocoupling of phenylboronic acid. Therefore, an excess (2 equiv.) of boronic acid was used to prevent the homocoupling being a limiting factor. No attempts were made to remove air from the reaction mixture. Replacing the Pd(0) catalyst with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> resulted in the homocoupling of phenylboronic acid as the main pathway.

Klingensmith and Leadbeater then developed the ligand-free Pd(II)-catalyzed coupling of aryl halides with phenylboronic acid in a ball mill.<sup>32</sup> By using Pd(OAc)<sub>2</sub> as the catalyst, Et<sub>3</sub>N as a base and NaCl as an additive to make a paste before milling, the mechanochemical reaction of phenylboronic acid with aryl bromides or aryl iodides at a vibration frequency of 30 Hz for 10–30 min provided cross-coupling products in 20–97% yields. The reactions were performed without the need to use dry reagents or anaerobic conditions. Compared to the previous work,<sup>31</sup> the protocol reduced the stoichiometric ratio of aryl halide to boronic acid from 1:2 to 1:1 and widened the substrate scope of aryl bromides and iodides.

It was also found that AgNO<sub>3</sub> significantly facilitated the homocoupling of phenylboronic acid in the Suzuki reaction.



Scheme 10



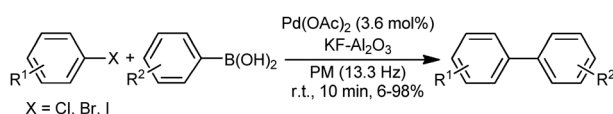
Scheme 11

This opened up the possibility of preparing symmetrical biaryls from boronic acids, and the desired homocoupling products were obtained in moderate to good yields (Scheme 11). Deactivated boronic acids could be coupled using this methodology, but only in low yields.<sup>32</sup>

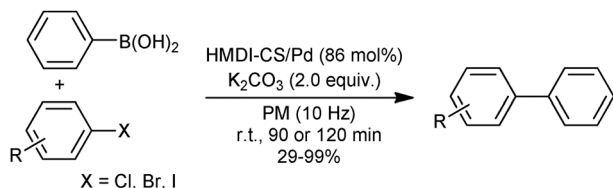
Schneider and Ondruschka reported that the Pd(II)-catalyzed coupling of aryl halides with phenylboronic acids in the presence of KF-Al<sub>2</sub>O<sub>3</sub> in a planetary ball mill at a speed of 800 rpm (13.3 Hz) for 10 min afforded the cross-coupling products in 6–98% yields (Scheme 12).<sup>33</sup> KF-Al<sub>2</sub>O<sub>3</sub> was used as the base and milling auxiliary. The *in situ* generation of KOH from KF-Al<sub>2</sub>O<sub>3</sub> required water, and thus the water content in the system had a strong influence on the product yield. Bernhardt *et al.* revealed a strong dependency of the product yield on the water content in self-prepared and commercially available KF-Al<sub>2</sub>O<sub>3</sub>.<sup>34</sup> KF-Al<sub>2</sub>O<sub>3</sub> with a KF content of 30–40 wt% was sufficient for good results. Although the reaction had been extended to *para*-substituted arylboronic acids, aryl halides were still mainly limited to aryl bromides and iodides.<sup>33</sup>

More recently, Cravotto *et al.* developed the synthesis of a new cross-linked chitosan/Pd(II) catalyst and applied it to the mechanochemical Suzuki coupling of phenylboronic acid with (hetero)aryl halides with K<sub>2</sub>CO<sub>3</sub> as the base (Scheme 13).<sup>35</sup>

The ultrasound-assisted cross-linking of chitosan with hexamethylene diisocyanate with the simultaneous incorporation of Pd(OAc)<sub>2</sub> resulted in the HMDI-CS/Pd catalyst. The solvent-free Suzuki reactions were carried out in a planetary ball mill at 600 rpm (10 Hz) for either 90 or 120 min. Both aryl iodides and bromides could be employed to give the cross-coupling products in 72–90% yields along with homocoupling products. The amount of homocoupling products (15–22%) was considerably higher for the present CS-based catalyst system than for other Suzuki cross-coupling procedures in ball mills using Pd(PPh<sub>3</sub>)<sub>4</sub>.<sup>31</sup>



Scheme 12



Scheme 13

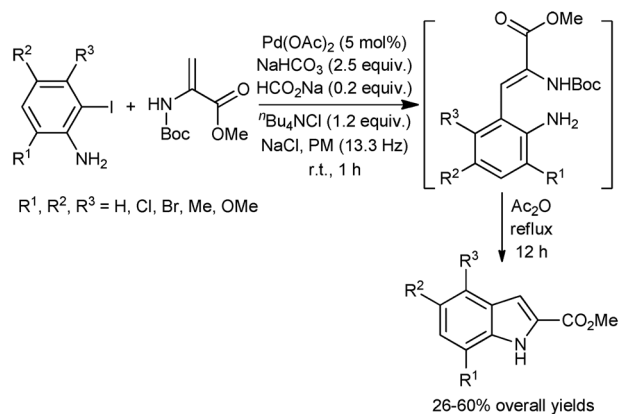
or Pd(OAc)<sub>2</sub>.<sup>32,33</sup> In spite of this shortcoming, the poorly reactive (hetero)aryl chlorides could be used with the cross-linked CS/Pd catalyst and afforded the cross-coupling products in 29–99% yields, much better than the previous systems (<10%).<sup>32,33</sup> However, it should be pointed out that the Pd catalyst loading (86 mol%) was quite high relative to the previous procedures.<sup>31–33</sup>

In all of the above mechanochemical Suzuki reactions,<sup>31–33,35</sup> aryl bromides showed higher reactivity and selectivity than aryl iodides. The observed order of reactivity for aryl halides (Br > I ≥ Cl) was uncommon for the Suzuki reaction.

Using the cross-coupling of phenylboronic acid and 4-bromoacetophenone as a model Suzuki reaction, Ondruschka and coworkers further investigated the influence of technical variables in a planetary ball mill, such as revolutions per minute (rpm), milling time, size and number of milling balls, or the material of milling balls and beakers, on the product yield.<sup>36</sup> All investigated variables showed influences on the product yield. The observed order regarding their positive influence on the product yield is: rpm > milling time > size of milling balls > number of milling balls > grinding material. When carrying out the Suzuki reaction with a high rpm with an adequate reaction time and grinding material one can obtain quantitative yields. The Ondruschka group also described the energetic assessment of the Suzuki reaction. They explored the influence of different activation techniques, *i.e.*, ball milling and microwave irradiation, on the Suzuki reaction of phenylboronic acid with five different aryl bromides.<sup>37</sup> Under the applied reaction and boundary conditions for the solvent-free Suzuki reaction, ball milling using a planetary ball mill or mixer mill has been proven to be a more effective tool for energy entry than microwave irradiation and provides higher yields.

**3.1.2 Heck reaction.** Frejd and coworkers were the first to apply the ball milling technique to the Heck reaction.<sup>38,39</sup> The Pd-catalyzed Heck–Jeffery reaction of *N*-substituted amino acrylates with aryl halides was conducted in a planetary ball mill at a speed of 800 rpm (13.3 Hz) for 1 h, giving the cross-coupling products in 13–88% yields.

The composition of the reaction mixture was essentially adopted from the Heck reaction in molten tetrabutylammonium bromide using conventional laboratory glassware,<sup>40</sup> and included aryl halide, protected amino acrylate, Pd(OAc)<sub>2</sub>, NaCl, NaHCO<sub>3</sub>, HCO<sub>2</sub>Na and <sup>n</sup>Bu<sub>4</sub>NCl. It was claimed that tetrabutylammonium halides have a stabilizing effect on the catalytic species Pd(0), and the addition of sodium formate as a reductant for Pd(II) improved the yields. Excess sodium chloride had been used as a grinding aid in previous ball-milling Suzuki reactions.<sup>31,32</sup> In comparison, the present Heck reaction performed best when no NaCl or a relatively small amount of NaCl was added; 5 mg mg<sup>-1</sup> aryl halide seemed to be a good proportion. Both aryl iodides and aryl bromides could undergo coupling with protected amino acrylate to provide unsaturated unnatural amino acids as the *Z*-isomers, whereas aryl chlorides were unreactive. The coupling of electron-deficient aryl or heteroaryl halides was not successful in the ball-milling Heck reaction, providing a reactivity pattern different from traditional procedures. Similar behaviour was also noticed in the mechanochemical



Scheme 14

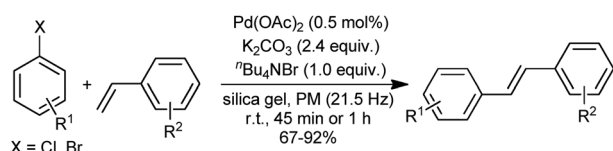
Suzuki reaction.<sup>31</sup> The product yields of the ball-milling Heck reactions were found to be higher than those of the corresponding microwave-irradiated ones. Again, the same phenomenon was observed for the Suzuki reaction.<sup>37</sup>

By using the same mechanochemical protocol, the Frejd group further synthesized various amino- and hydroxy-substituted dehydrophenylalanine derivatives under solvent- and phosphine-free conditions.<sup>39</sup> The influences of electron-withdrawing groups and of the location of the heteroatom substituent relative to the halide were investigated. It was found that suitably substituted *ortho*-amino dehydrophenylalanine derivatives underwent cyclization–elimination reaction to the corresponding 2-substituted indoles, particularly under acidic conditions (Scheme 14).

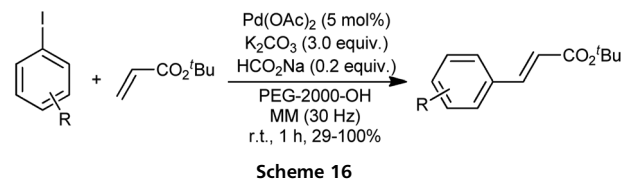
Su and coworkers reported the solvent-free mechanochemical synthesis of (*E*)-stilbene derivatives by the Heck reaction of styrenes with aryl bromides or aryl chlorides (Scheme 15).<sup>41</sup>

The synthesis of (*E*)-stilbene derivatives was performed by milling a mixture of aryl halide, olefin, <sup>n</sup>Bu<sub>4</sub>NBr, K<sub>2</sub>CO<sub>3</sub> and Pd(OAc)<sub>2</sub> with silica gel as the milling auxiliary in a planetary centrifugal mill AGO-2 at a rotational speed of 1290 rpm (21.5 Hz) for 45 min or 1 h. It is noteworthy that the catalyst loading could be reduced to 0.5 mol%, and there was no significant increase in yields when the catalyst loading was between 0.5 mol% and 3 mol%. The coupling of aryl bromides with styrene derivatives gave good to excellent yields (69–91%) in 45 min. There was no striking difference in product yields between the electron-deficient and electron-rich aryl bromides. Interestingly, this reaction could be extended to electron-deficient aryl chlorides and afforded the stilbene derivatives in 67–92% yields. Experimental results showed that the reaction by simple thermal heating or hand grinding performed much worse than the ball milling technique.

Polyethylene glycol (PEG) has already been shown to reduce Pd(OAc)<sub>2</sub> to Pd(0). The solvent-free Pd-catalyzed Mizoroki–Heck



Scheme 15



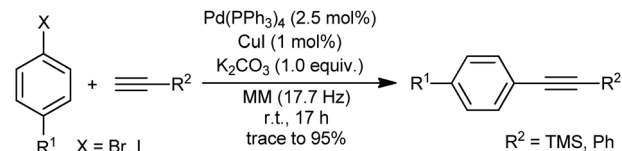
Scheme 16

reaction of aryl iodides with *tert*-butyl acrylate by ball milling in solid PEG was developed very recently by Lamaty and coworkers (Scheme 16).<sup>42</sup>

As found earlier,<sup>38,39</sup> HCO<sub>2</sub>Na as a reducing agent was required to activate Pd(OAc)<sub>2</sub> under the ball-milling conditions. Due to the stabilizing effect of oxygen atoms in PEG, no phosphine ligand was necessary for the catalysis. Attempts to improve the product yields by changing K<sub>2</sub>CO<sub>3</sub> to other bases failed. Switching to Na<sub>2</sub>CO<sub>3</sub> resulted in a lower conversion, most probably because the PEG–K<sup>+</sup> interaction was stronger than the corresponding PEG–Na<sup>+</sup> interaction and thus enhanced the base activity. Several PEGs were tested, and PEG-2000-OH gave the best results. Both electron-donating and -withdrawing groups on the aryl iodides were well tolerated, and quantitative yields were obtained in some cases using the appropriate polymer PEG-2000-OH. A Mizoroki–Heck reaction generally requires elevated temperature, unfriendly solvent and an inert atmosphere. In this study, the use of PEG in a vibratory ball mill at a speed of 30 Hz allowed the reaction to proceed in air under mild conditions. However, the present protocol indeed encountered some limitations. For example, aryl bromides and aryl chlorides were unreactive even when sodium iodide was added to the reaction mixtures. The reaction was efficient only with *tert*-butyl acrylate. Either no reaction or a very poor yield was obtained with acrylonitrile, acrylamide, methyl methacrylate or styrene.

**3.1.3 Sonogashira reaction.** Mack and coworkers described the first mechanochemical Sonogashira reaction.<sup>43</sup> The Pd-catalyzed coupling of aryl halides with trimethylsilylacetylene or phenylacetylene in the presence of CuI and K<sub>2</sub>CO<sub>3</sub> was conducted in a Spex CertiPrep 8000 M mixer mill at a clamp speed of 1060 rpm (17.7 Hz) for 17 h under aerobic conditions (Scheme 17).

Tetrakis(triphenylphosphine) palladium, a Pd(0) species, was used as the catalyst, and could be replaced by *trans*-dichlorobis(triphenylphosphine) palladium with similar catalytic activity. It is known that the activated palladium(0) catalyst can be formed *in situ* from palladium catalysts such as palladium chloride and palladium acetate and free ligand. However, when palladium acetate and triphenylphosphine were used, the reaction did not give the coupling product even after extended milling time.



Scheme 17

A variety of aryl iodides and aryl bromides with different functionalities could be used to couple with trimethylsilyl acetylene and phenylacetylene. Consistent with the reaction in solution, aryl iodides were more reactive than aryl bromides. As usual, aryl chlorides and aryl fluorides were inert coupling partners. It was found that although the copper-free Sonogashira could be realized under the ball-milling conditions, the yields were much lower than those when CuI was used. Interestingly, if the reaction was conducted with a copper ball in a copper vial in lieu of CuI, the yields were generally comparable to those with CuI as the co-catalyst. This is the first example demonstrating the use of the vial and ball material as a catalyst in a ball-milled chemical reaction.

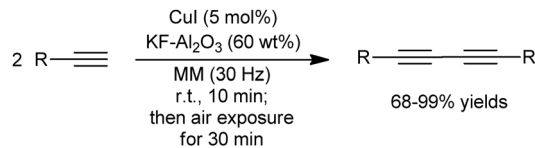
1,4-Diazabicyclo[2.2.2]octane (DABCO) has been found to be an excellent base for the Sonogashira reaction,<sup>44</sup> and it is a solid that is suitable for implementation in a reaction in a ball mill. Stolle and coworkers recently developed a rapid mechanochemical Sonogashira reaction of aryl halides with aryl- and alkylacetylenes in the presence of DABCO without the use of copper.<sup>45,46</sup> The employment of Pd(OAc)<sub>2</sub> in combination with fused quartz sand (SiO<sub>2</sub>) as a milling auxiliary allowed the solvent-free reaction of different aryl iodides with aryl- and alkylacetylenes to proceed well in a planetary ball mill at 800 rpm (13.3 Hz) within 20 min, affording the cross-coupling products in 45–98% yields (Scheme 18).

An interesting result was obtained when the Sonogashira reaction was performed in the presence of 5 mol% CuI in addition to Pd(OAc)<sub>2</sub>. The conversion of aryl iodide decreased accompanied by the increasing formation of the homocoupling product. Obviously, CuI had no positive influence on the Sonogashira coupling itself under the mechanochemical conditions.

Further screening of milling auxiliaries and materials of the milling ball and beaker indicated that Al<sub>2</sub>O<sub>3</sub> and zirconia performed much better than silica gel and agate, respectively. By using more active catalyst Pd(PPh<sub>3</sub>)<sub>4</sub>, basic α-Al<sub>2</sub>O<sub>3</sub> and zirconia as a milling auxiliary and as beaker/ball, six aryl bromides could also couple with arylacetylenes resulting in 51–97% yields.<sup>45</sup> The present protocol has advantages over that by Mack and coworkers<sup>43</sup> because the reaction time was much shorter, no additional copper was required, and milling balls or containers made of copper were not needed.

### 3.2 Cu-catalyzed mechanochemical reactions

**3.2.1 Homocoupling of terminal alkynes.** During the investigation of the mechanochemical Sonogashira reaction, the addition of CuI to the reaction mixture caused the formation of alkyne homocoupling product. This result prompted Stolle and coworkers to explore the Glaser reaction of the Cu-catalyzed



Scheme 19

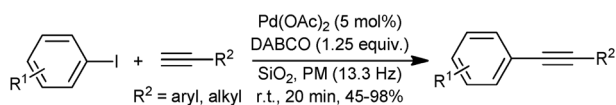
homocoupling of terminal alkynes by the ball milling technique.<sup>46,47</sup> Aryl- and alkyl-substituted terminal alkynes underwent homocoupling in 68–99% yields with the use of KF–Al<sub>2</sub>O<sub>3</sub> and CuI as the milling auxiliary and catalyst, respectively, in a vibration ball mill at 30 Hz for 10 min and subsequent exposure to air for 30 min (Scheme 19). Furthermore, the addition of DABCO (1.25 equiv.) could lower the KF loading from 60 wt% to 32 wt%. Silica and alumina, which showed high activity in the Sonogashira reaction in the presence of DABCO, failed.

The commonly accepted reaction mechanism for the catalytic cycle of the Glaser reaction involves oxidative regeneration of the Cu catalyst after reductive elimination of the 1,3-diyne products. Generally, the reactions are carried out in air either under active mass transport of the oxidant into the solution (solvent saturation) or by passive exposure to air. Thus, an oxidant deficiency is normally present and will prevent the reaction from proceeding to completion under standard mechanical milling conditions. Opening of the reactor after milling for 30 min exposed the reaction mixture to air and incorporated oxygen into the reaction mixture. This fast post-milling process probably accounted for the high yields.

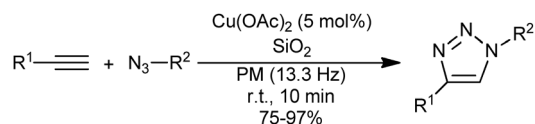
**3.2.2 Click reaction.** Stolle and coworkers reported a ligand- and solvent-free 1,3-dipolar cycloaddition of alkynes with azides catalyzed by Cu(OAc)<sub>2</sub> using a planetary ball mill at 800 rpm (13.3 Hz) for 10 min (Scheme 20).<sup>48</sup> Besides various alkynes and azides, a propargyl functionalized polystyrene could react with decyl azide by mill clicking. Moreover, the click polymerization of 1,12-diazidododecane and bis-ethynyl compounds proceeded well in the ball mill. Other copper salts such as cuprous iodide and cupric sulfate showed similar results.

**3.2.3 Cu-catalyzed CDC reaction.** The study of the cross-dehydrogenative coupling (CDC) reaction has been pioneered by Li.<sup>49</sup> Copper has shown high activity in oxidative CDC reactions, and 2,3-dichloro-5,6-dicyanoquinone (DDQ) has been investigated as a powerful oxidation agent for oxidative carbon–carbon coupling reactions. Su *et al.* recently reported the mechanochemical CDC reaction of tetrahydroisoquinolines with alkynes and indoles catalyzed by recoverable copper balls (Scheme 21).<sup>50</sup>

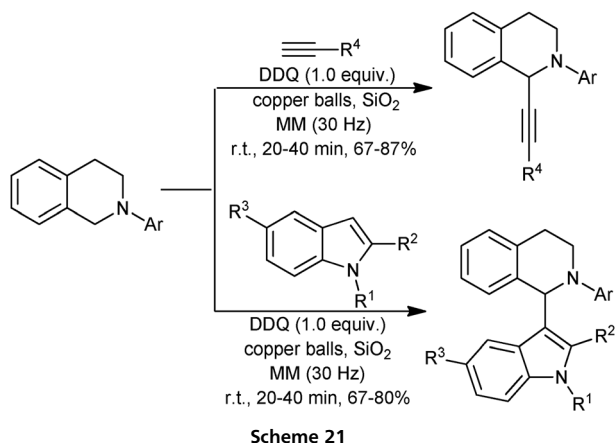
Silica gel was found to be the most effective among the milling auxiliaries, and might act as both the grinding-aid



Scheme 18



Scheme 20



agent and absorbent in the reaction. The solvent-free reaction of tetrahydroisoquinolines with either alkynes or indoles in the presence of DDQ gave unsatisfactory results in a ball mill at 30 Hz. However, the addition of a catalytic amount (5 mol%) of CuBr, Cu(OAc)<sub>2</sub>, Cu(OTf)<sub>2</sub> and copper powder could significantly improve the product yields. Intriguingly, the authors chose to use copper balls instead of stainless steel balls without additional catalysts to promote the CDC reaction with good yields in no more than 40 min. The copper balls were used both as the reacting catalyst and milling balls, and the recovery of the catalyst would be as simple as removing the copper balls from the reaction medium.<sup>43</sup>

## 4. Mechanochemical condensation reactions

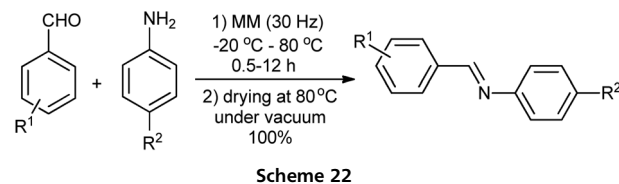
### 4.1 Condensations of amines

**4.1.1 Imine formation.** Kaupp and coworkers found that imines could be quantitatively obtained in less than 30 min when stoichiometric mixtures of the starting materials were ball milled (Scheme 22).<sup>51,52††</sup> Most of the reactions were cooled to 0 °C or even to -20 °C (below the eutectic temperatures) to secure the reaction mixtures in the solid state, followed by drying at 80 °C under vacuum. However, some unusual combinations for imine formation required heating. For example, the condensations of 4-nitroaniline with 4-hydroxybenzaldehyde and 4-nitrobenzaldehyde had to run at 60 °C and 80 °C, respectively.

The formation of imines from the condensation of 4-methylaniline with various aromatic aldehydes in a mixer mill at a frequency of 30 Hz has been reported by the Wang group as precursors for the Mn(OAc)<sub>3</sub>-mediated radical reaction with 1,3-cyclohexanediones<sup>25</sup> as well as the reduction by Hantzsch 1,4-dihydropyridine.<sup>53</sup> In addition, imine formation was proposed

† Known from personal communication with Prof. Gerd Kaupp; a Retsch MM2000 mixer mill with a double walled beaker at a standard frequency of 30 Hz was used for reactions performed in his group.

†† The phrase "100% yield" was often used for the so-called quantitative reactions in the literature, and is reproduced in this review in order to be consistent with the original papers. Because the obtained practical yield will never be 100%, the use of ">99% yield" would be more appropriate.



as one of the reaction pathways in the oxidative amidation of aldehydes with anilines.<sup>54</sup>

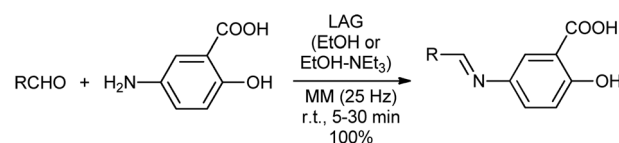
The mechanochemical reaction could be scaled up. 200 g batches were run in the exploratory investigation. Stoichiometric reaction of solid *p*-hydroxybenzaldehyde with solid *p*-aminobenzoic acid in a horizontal ball mill (Simoloyer<sup>®</sup>) for 15 min with a rotor frequency of 900 rpm afforded the pure imine derivative in a quantitative yield without waste-producing work-up procedures.<sup>55</sup>

The effect of ambient humidity and vapour environment on the reactivity of aromatic amines and aldehydes in the solid state has scarcely been explored. Very recently, Cincić *et al.* found that the presence of water or organic solvent vapour could accelerate the solid-state condensation of solid aromatic amines and aromatic aldehydes into Schiff bases.<sup>56</sup> Liquid-assisted grinding (LAG)<sup>57</sup> has shown great potential as an efficient mechanochemical method for supramolecular and covalent synthesis.<sup>5</sup> LAG of 5-aminosalicylic acid and vanillin, *o*-vanillin or 2-hydroxy-1-naphthaldehyde in a ball mill for 5–30 min in the presence of a small amount of EtOH or EtOH-TEA afforded the Schiff bases in quantitative yields (Scheme 23).

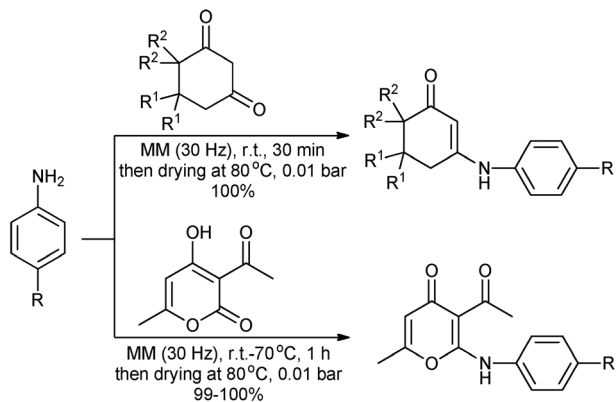
**4.1.2 Enamine formation.** The Kaupp group found that cyclic 1,3-dicarbonyl compounds such as 1,3-cyclohexanedione, dimedone and dehydracetic acid could react with aniline derivatives without any catalyst to provide enamino ketones quantitatively by ball milling within 1 h, followed by drying at 0.01 bar at 80 °C (Scheme 24).<sup>58</sup>

The mechanochemical reaction of aliphatic primary amines with acyclic 1,3-dicarbonyl compounds (1,3-pentadione and ethyl acetoacetate) in the absence of catalyst and solvent was reported recently by Li and coworkers (Scheme 25).<sup>59</sup> A series of enamino ketones and esters could be obtained in 61–97% yields by ball milling the mixtures of amines and 1,3-dicarbonyl compounds in a ratio of 1 : 1 in a mixer mill at 30 Hz for 0.5–2 h.

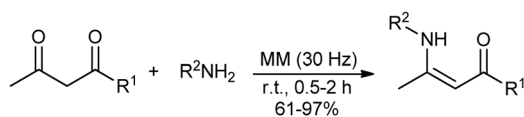
Thorwirth and Stolle described a solvent-free synthesis of enamines by the addition of amines to dialkylacetylenedicarboxylates or alkylpropiolates using a planetary ball mill at 800 rpm (13.3 Hz) (Scheme 26).<sup>60</sup> Reactions with several anilines and secondary alkyl amines in the absence of any catalyst or base were completed within 5 min and afforded high isolated yields (81–96%). Beside the *E*/*Z*-isomers, no side products such as imines were formed.



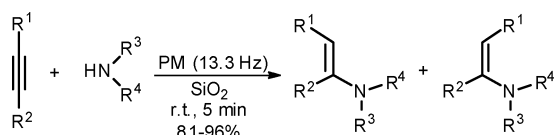




Scheme 24



Scheme 25

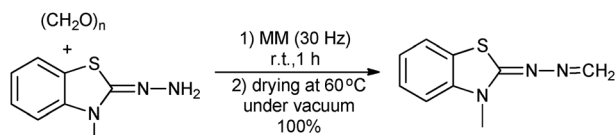


Scheme 26

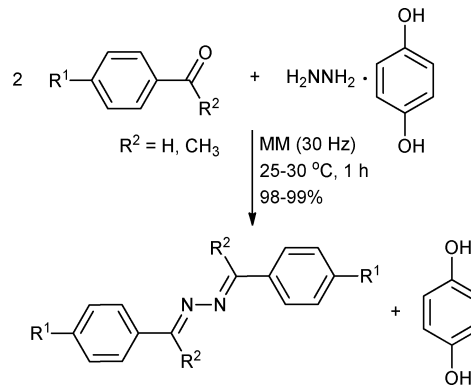
**4.1.3 Hydrazone formation.** Paraformaldehyde is a solid and can be most easily used as a source of formaldehyde in mechanochemical reactions. Methylene imines from anilines are labile. However, Kaupp and coworkers found that the methylene azine was quantitatively obtained from a solid hydrazone by ball milling for 1 h followed by drying at 0.01 bar at 60 °C (Scheme 27).<sup>58</sup>

The reaction of solid aldehydes or ketones with hydrazine–hydroquinone complex in a 2 : 1 ratio provided quantitatively solid mixtures of the azine products and hydroquinone when ball-milled at 25–30 °C for 1–3 h (Scheme 28).<sup>61</sup>

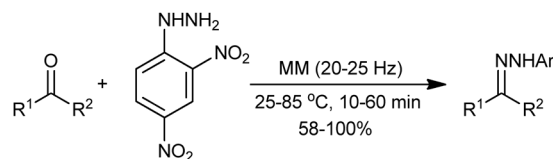
Naimi-Jamal, Kaupp and coworkers employed the so-called “kneading ball-milling” for partly liquid or sticky stoichiometric carbonyl derivatization reactions with the poorly mixing hydroxylamine hydrochloride and wetted 2,4-dinitrophenylhydrazine.<sup>62</sup> Owing to the potential explosiveness of dry 2,4-dinitrophenylhydrazine, 50 wt% H<sub>2</sub>O was added to wet the crystals. The stoichiometric reaction of 2,4-dinitrophenylhydrazine with aldehydes or ketones occurred rapidly in the kneading ball



Scheme 27



Scheme 28

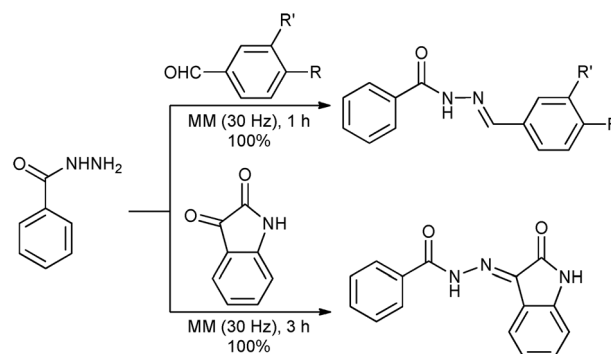


Scheme 29

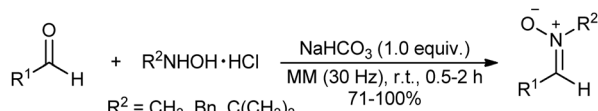
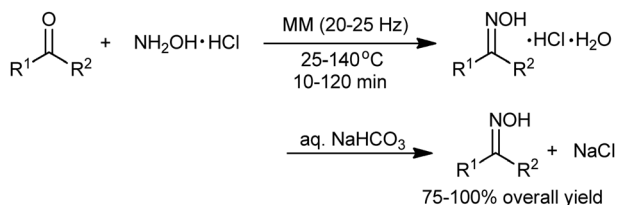
mill at 25–85 °C for 10–60 min, giving the desired hydrazones in 58–100% yields (Scheme 29).

When benzhydrazide and solid aldehydes in a molar ratio of 1 : 1 were ball-milled for 1 h at 25–30 °C, the corresponding benzoylhydrazones could be obtained in spectroscopically pure form. In comparison, the mechanochemical reaction of benzhydrazide with isatine required 3 h of ball milling for completion (Scheme 30).<sup>58</sup>

**4.1.4 Oxime formation.** Similarly, aldehydes and ketones were stoichiometrically ball-milled with hydroxylamine hydrochloride at 25–140 °C for 10–120 min to provide the hydrated oxime salts in sticky form, from which the free oximes could be obtained in 75–100% yields after treatment with base (Scheme 31).<sup>62</sup> The only waste produced was stoichiometric NaCl in water for the quantitative reactions. Aldehydes were found to be more reactive than ketones towards hydroxylamine. The different reactivities of aldehydes and ketones could be utilized as a versatile method for protecting aldehydes by oximation in the presence of a ketone functional group.



Scheme 30



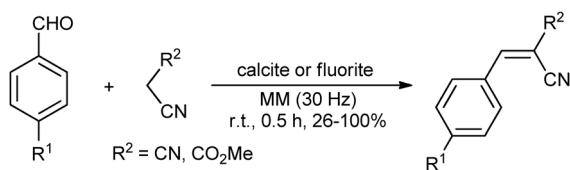
**4.1.5 Nitronium formation.** Lamaty and coworkers reported that various *C*-aryl and *C*-alkyl nitroniums were obtained in 71–100% yields by condensation of aldehydes with equimolar amounts of *N*-substituted hydroxylamines in a ball mill at a frequency of 30 Hz for 0.5–2 h (Scheme 32).<sup>63</sup> Reactions could be performed without the need to exclude air and moisture and provided the expected products with no need for further purification.

## 4.2 Knoevenagel condensation

The Knoevenagel condensation has been an important tool for synthesizing  $\alpha,\beta$ -unsaturated structure units from aldehydes/ketones and active methylene compounds. The reaction is usually carried out in the presence of a weak base. Alkaline earth carbonate and fluoride exist as limestone (calcite) and fluorite (fluorite) in nature. By using calcite ( $\text{CaCO}_3$ ) or fluorite ( $\text{CaF}_2$ ) as the catalyst, Wada and Suzuki reported the mechanochemical Knoevenagel condensations of malononitrile and methyl cyanoacetate with aromatic aldehydes (Scheme 33).<sup>64</sup>

The reaction mixtures were milled in a mixer mill at a speed of 30 Hz for 30 min to give arylidenemalononitriles and (*E*)- $\alpha$ -cyanocinnamic esters in 26–100% yields. It was noteworthy that the reagent-grade calcium carbonate and fluoride in the form of fine powders, however, proved to be unsatisfactory for Knoevenagel condensations under the milling conditions. It was believed that when the minerals were mechanically crushed, the newborn solid surface should be highly activated with the naked ionic species generated *in situ*.

During their work on the direct reductive benzylation of malononitrile, Wang and coworkers found that ball milling of aldehydes with malononitrile at a frequency of 30 Hz afforded quantitative yields of benzylidene malononitriles in the presence



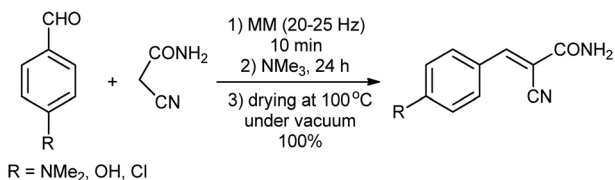
of a catalytic amount (5 mol%) of the Hantzsch ester 1,4-dihydropyridine (HEH).<sup>53</sup> Therefore, HEH employed here should act as a base to catalyze the Knoevenagel condensation step, similar to that catalyzed by piperidine.

Initial attempts to carry out solvent- and catalyst-free Knoevenagel condensations failed by the Kaupp group for the reaction of aldehydes with both malononitrile and methyl cyanoacetate milled in a swing mill at a frequency of 20–25 Hz at room temperature.<sup>65</sup> However, Ondruschka and coworkers later found that the Knoevenagel condensations without any catalysts or water-absorbing agents indeed proceeded to some extent in a vibration mill after milling for 1 h, yet a massive leakage of fluid out of the hand-tightened reaction vessel occurred during the reactions in some cases.<sup>66</sup> The observed leakage probably resulted from the heating of the reaction vessel to 70–90 °C, causing the thermally expanding cap of the vessel to lose its seal. Hence a planetary ball mill, in which the reaction vessel is closed by an external compression seal that prevents any leakage, was used to replace the vibration mill. The solvent-free Knoevenagel condensation by ball milling at a rotational speed of 800 rpm (13.3 Hz) for 1 h afforded 5–99% yields. As observed earlier, the pre-reacted reaction mixtures continued to convert into the desired products after completion of the milling process when left to stand at room temperature. The continued reaction of these reaction mixtures was ascribed to direct crystallization. Standing for 24 h under a  $\text{N}_2$  atmosphere<sup>66</sup> or dissolving in an organic solvent<sup>67</sup> after initial mechanochemical treatment allowed the improvement of the product yields for the slowly reacting aldehydes.

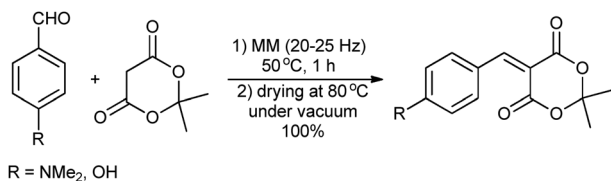
In Suzuki's work, it was believed that when the natural calcite and fluorite were mechanically crushed, the newborn solid surface should be highly activated with the naked ionic species generated *in situ*.<sup>64</sup> Because Ondruschka and coworkers realized the catalyst-free Knoevenagel condensation under the mechanical milling conditions, they argued that the added minerals in Suzuki's work did not act as a catalyst but merely served as additional grinding stones during milling of the reactants. When mineral powder was used instead, the reaction mixtures became effectively diluted and the grinding was less effective, explaining the unsuccessful conversions.

Although the mechanochemical reaction of aldehydes with cyanoacetamide was too slow at room temperature, the addition of gaseous trimethylamine, which could be easily removed together with the stoichiometric amount of the water of reaction, gave the condensation products quantitatively after milling for 10 min, subsequent treatment with the amine for 24 h and finally drying at 100 °C under vacuum (Scheme 34).<sup>65</sup>

After ball-milling a stoichiometric mixture of Meldrum's acid and 4-dimethylaminobenzaldehyde or 4-hydroxybenzaldehyde at 50 °C for 1 h followed by drying at 80 °C in a vacuum, a quantitative yield of the condensation products could be achieved (Scheme 35). However, the reaction at 50 °C gave an intermediate melt, from which the product crystallized quantitatively at the reaction temperature. Therefore, these Knoevenagel condensations must be termed as "melt-reactions with direct crystallization".<sup>65</sup>



Scheme 34



Scheme 35

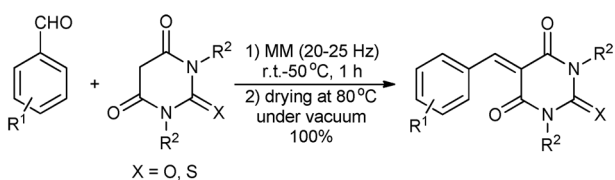
In contrast, aldehydes and barbituric acids did not melt upon ball-milling of stoichiometric mixtures for 1 h, but provided the solid condensation products quantitatively and in pure form (Scheme 36). No purifying work up was required in the absence of solid supports, microwave, catalyst or solvent. Therefore, these reactions were truly solvent-free.<sup>65</sup>

### 4.3 Aldol reaction

The aldol reaction as one of the sequential steps in cascade reactions will be included in Section 6, and asymmetric aldol reactions will be covered in Section 13. In this section, only non-asymmetric aldol reactions with aldol condensation products as the final isolated compounds will be discussed. Raston and Scott first reported the aldol reaction among veratraldehyde, 4-phenylcyclohexanone and 1-indanone in the presence of NaOH in a vibrating ball mill for a total of 2 min over a 10 min period (Fig. 1).<sup>68</sup> Single crossed aldol condensation products were produced in high yields even in reactions where a mixture of products was possible. These reactions were highly atom-economic and highly chemoselective.

Kaupp *et al.* reported that the solid-state reaction of ninhydrin with dimedone in a ball mill proceeded only as a one-step condensation to give the aldol product (Scheme 37).<sup>69</sup> No dehydration was observed in the solid state even with gaseous trimethylamine, hydrogen chloride or *p*-toluenesulfonic acid. Such reluctance for solid-state elimination of water is not typical for all condensation reactions of ninhydrin in the solid state.

Mitchell and coworkers showed a novel method for the aluminium-catalyzed self-aldol reaction of valeraldehyde. This mechanochemical method utilized high-energy ball milling to



Scheme 36

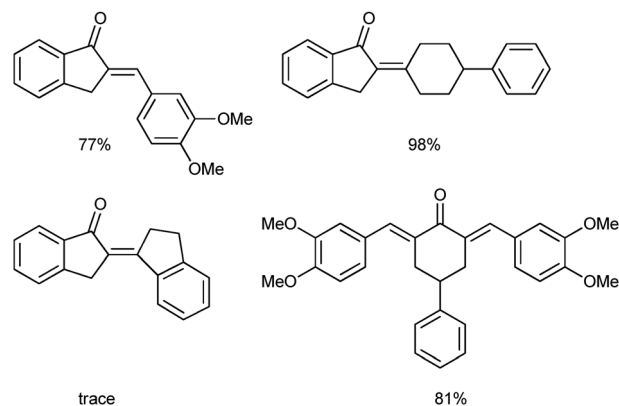
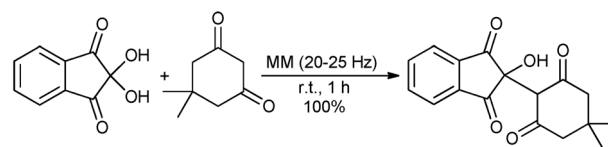


Fig. 1 Structures and yields of aldol products.



Scheme 37

produce fresh Al surface, which served to tautomerize the carbonyl to form the enol complex, and activated the carbonyl group of another molecule rendering it electrophilic. Nucleophilic attack of the enol on the activated carbonyl compound led to the formation of 2-propyl-3-hydroxy-heptanal in >67% yield after 24 h (Fig. 2).<sup>70</sup>

In an attempt to alkylate cyclohexanone with ethyl bromide in the presence of NaOH, Mack and coworkers observed that the aldol self-condensation product of cyclohexanone was the major product (Scheme 38).<sup>71</sup>

### 4.4 Michael addition

Michael addition of 1,3-dicarbonyl compounds to  $\alpha,\beta$ -unsaturated ketones has usually been performed in organic solvents and

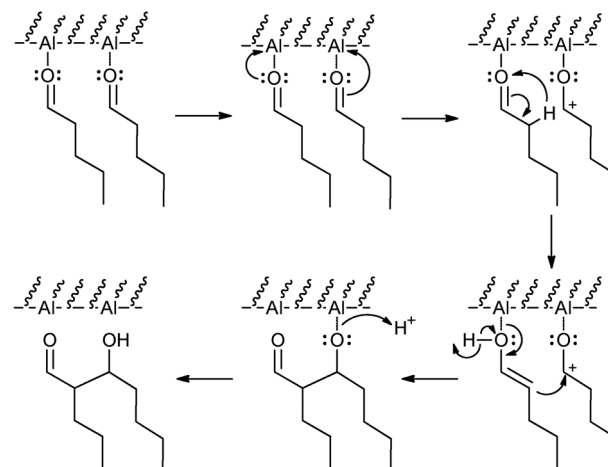
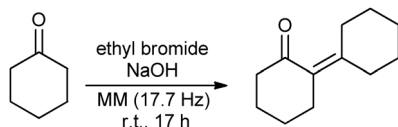


Fig. 2 Proposed pathway for the self-condensation of valeraldehyde.



Scheme 38

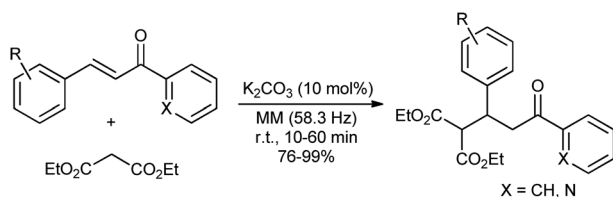
catalyzed by strong bases such as NaOH, KOH, Ba(OH)<sub>2</sub> and NaOEt. Wang and coworkers reported the first mechanochemical Michael reaction by exploring the addition of 1,3-dicarbonyl compounds to chalcones and azachalcones catalyzed by weak base K<sub>2</sub>CO<sub>3</sub>.<sup>72</sup> The solvent-free reaction of diethyl malonate with an equimolar amount of chalcone or azachalcone in the presence of 10 mol% K<sub>2</sub>CO<sub>3</sub> in a home-made high-speed vibration mill (HSVM) at a rate of 3500 rpm (58.3 Hz) for 10–60 min gave the Michael adducts in 76–99% yields (Scheme 39).

This reaction had a wide substrate scope; chalcones and azachalcones with both electron-withdrawing and electron-donating groups could be employed. Most of the mechanochemical reactions were quantitative and provided essentially pure products after washing the reaction mixtures with water to remove the inorganic catalyst.

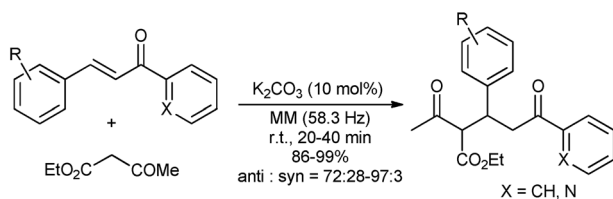
Similarly, replacement of the malonate ester with ethyl acetoacetate resulted in Michael products in very high yields after milling for 20–40 min (Scheme 40).<sup>73</sup>

It was found that the use of weak base K<sub>2</sub>CO<sub>3</sub> was very important to achieve high yield and selectivity. Stronger bases such as NaOH and KF/Al<sub>2</sub>O<sub>3</sub> caused further intramolecular aldol condensation and subsequent dehydration (Fig. 3).

A catalyst was required to obtain a satisfactory yield. For example, the solvent-free reaction of ethyl acetoacetate with 4-chlorochalcone in the absence of any catalyst at 3500 rpm for 40 min gave the Michael adduct in only 28% yield. The influence of vibration frequency was also investigated at the early stage of the mechanochemical organic synthesis, and was found to have a significant effect on the reaction. The same mechanochemical reaction at 3500 rpm and 1200 rpm provided 99% and 19% yields, respectively.<sup>72</sup>



Scheme 39



Scheme 40

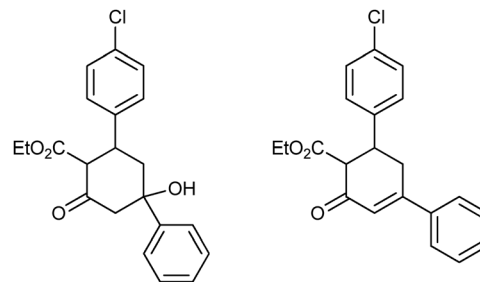


Fig. 3 Structures of intramolecular aldol condensation products.

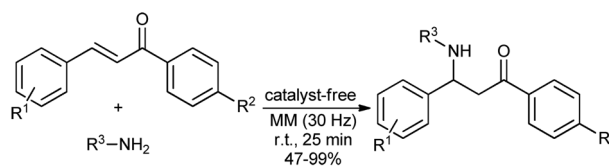
Recently, Li *et al.* reported the solvent- and catalyst-free azo-Michael addition of chalcones with amines (Scheme 41).<sup>74</sup> The mechanochemical reaction conducted in a mixer mill at 1800 rpm (30 Hz) for 25 min afforded the azo-Michael products in 47–99% yields. Both aliphatic and aromatic amines were used, and enones could be either electron-rich or electron-poor chalcones.

#### 4.5 Morita–Baylis–Hillman reaction

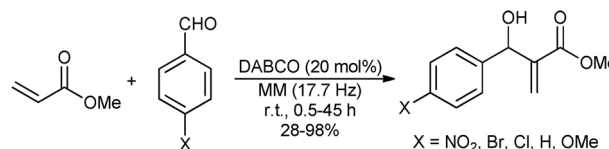
The Morita–Baylis–Hillman reaction (MBH), also known as the Morita–Baylis reaction, employs an electron-deficient olefin, a tertiary amine catalyst and an electrophile such as an aldehyde to produce a multifunctional product. However, the MBH reaction is rather slow, typically taking days to weeks to produce adequate product yields. Mack *et al.* found a significant rate enhancement of the MBH reaction by ball milling.<sup>75</sup> The reaction of methyl acrylate with different *p*-substituted aryl aldehydes in the presence of 20% 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyst in a Spex CertiPrep 8000 M mixer/mill for 0.5–45 h afforded the MBH products in 28–98% yields (Scheme 42).

#### 4.6 Formation of boronic esters and amides

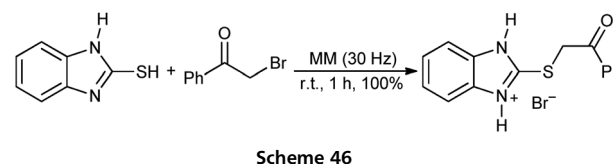
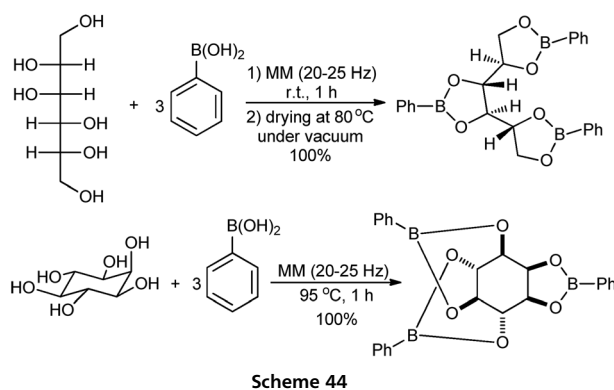
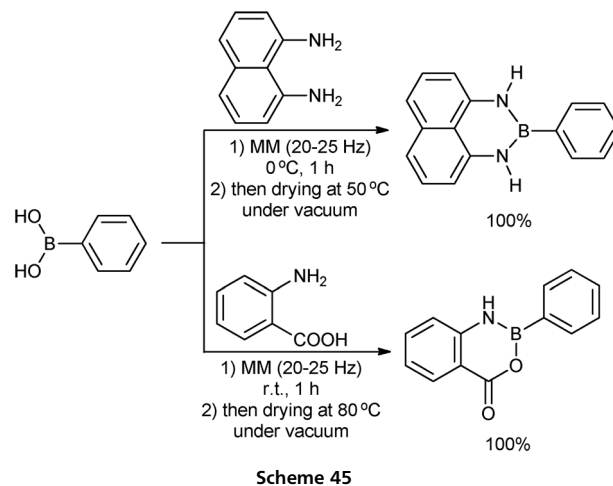
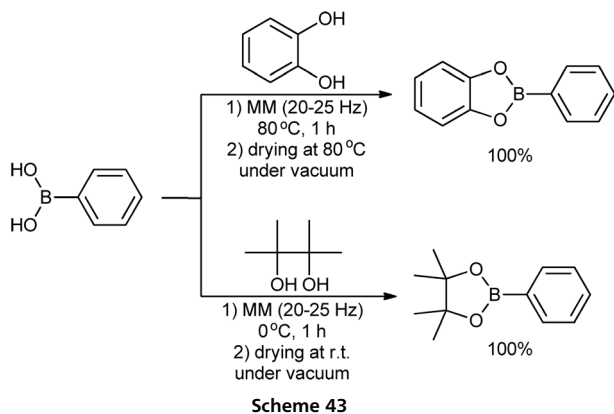
Protection and deprotection of hydroxy and amino groups are frequently encountered in organic synthesis. If the two functional groups are present in 1,2- or 1,3-positions, cyclic esters or amides may be formed. Kaupp *et al.* reported the mechanochemical synthesis of boronic esters of phenylboronic acid with both aromatic and aliphatic diols in quantitative yields (Scheme 43).<sup>76</sup>



Scheme 41



Scheme 42



Schnürch *et al.* later extended phenylboronic acid to other aryl, heteroaryl and alkyl boronic acids.<sup>77</sup>

Interestingly, the solvent-free protection of 1,2- and 1,3-diols could be applied to sugar alcohols and cyclic polyalcohols. D-Mannitol and *myo*-inositol reacted quantitatively with three molecules of phenylboronic acid in a ball mill at 20–25 Hz for 1 h to give tris-boronic esters (Scheme 44).<sup>76</sup> The reaction with *myo*-inositol required 95 °C, and the formation of five-membered and six-membered rings was dependent on the relative positions of the –OH groups in the initial chair conformation.

Boronic amides could also be formed by the same procedure. Equimolar mixtures of 1,8-diaminonaphthalene or anthranilic acid and phenylboronic acid were ball milled in the solid state for 1 h followed by heating in a vacuum to provide the six-membered diazaborinine and *O,B,N* six-membered heteroborinone in quantitative yields (Scheme 45).<sup>76</sup> Both the primary amino and carboxylic acid groups were protected.

## 5. Mechanochemical nucleophilic reactions

### 5.1 Nucleophilic addition reactions

**5.1.1 Addition reactions of S-, O-, N- and halo nucleophiles.** The thiuronium salt from solid 2-mercaptobenzimidazole and phenacyl bromide could be quantitatively obtained after ball milling for 1 h (Scheme 46).<sup>58</sup>

Similar mechanochemical reaction of phenacyl bromide with pyrazolone derivatives in a swing mill at 20–25 Hz for

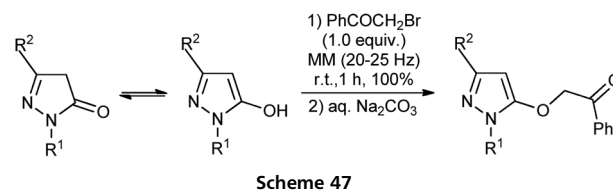
1 h quantitatively afforded pyrazolyl ethers after washing with sodium carbonate solution and drying at 0.01 bar at 80 °C in a vacuum (Scheme 47).<sup>78</sup>

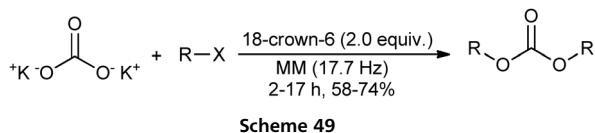
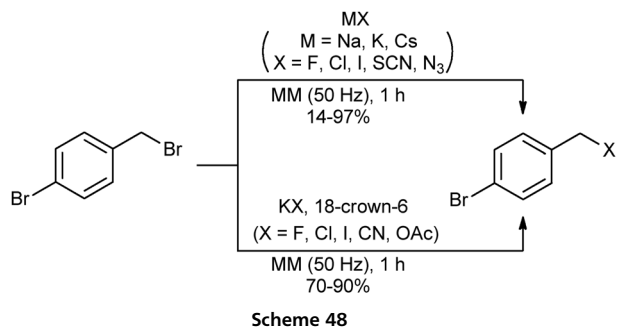
Mack and coworkers described the heterogeneous nucleophilic additions of alkali salts of thiocyanate, azide, acetate and halides to 4-bromobenzyl bromide with/without 18-crown-6 by ball milling in a Spex CertiPrep mixer/mill 5000 M (Scheme 48).<sup>79</sup>

It was found that thiocyanate and azide provided excellent yields of the expected nucleophilic addition products, whereas the potassium and sodium salts of fluoride, chloride, acetate and cyanide did not give high yields of nucleophilic addition products. 18-Crown-6 can complex  $K^+$  cation to increase the basicity and nucleophilicity of the employed nucleophiles, and was first used in ball-milling synthesis by the Wang group in 2008.<sup>80</sup> As desired, the addition of 18-crown-6 led to an increase in yield and conversion for all of the potassium salt nucleophiles including fluoride, acetate and cyanide, which were previously unsuccessful.<sup>79</sup>

Recently, the Mack group reported the mechanochemical synthesis of dialkyl carbonates of various metal carbonates with the assistance of metal complexing reagents (Scheme 49).<sup>81</sup>

The reaction of various metal carbonates including  $Li_2CO_3$ ,  $Na_2CO_3$ ,  $K_2CO_3$  and  $Cs_2CO_3$  with 4-bromobenzyl bromide gave very poor results (0–18% yields). The authors found that the



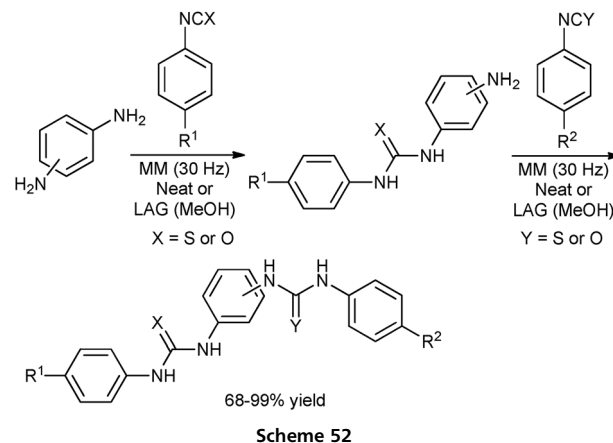
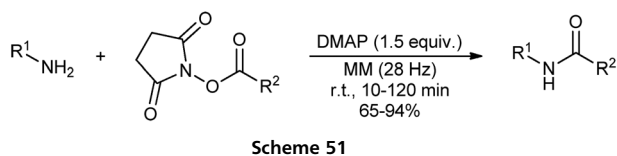
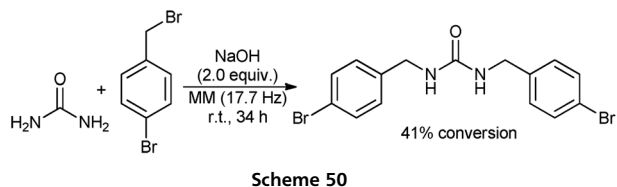


addition of 2 equiv. of 18-crown-6 could complex the potassium salt and improved the yield from 2% to 74%. The same product was obtained as the major product in the reaction of cyclohexanone with *p*-bromobenzyl bromide using  $K_2CO_3$  as the base in the presence of 18-crown-6.<sup>82</sup> Under the optimal conditions, other aliphatic halides such as benzyl bromide, (2-bromoethyl)benzene and benzyl chloride could be employed and provided dialkyl carbonates in 58–67% yields.<sup>81</sup> Replacing 18-crown-6 with 5 mol% of Tween<sup>®</sup> 80 resulted in a lower yield due to by-product formation.

Urea is very unreactive toward alkylation. However, under mechanical milling conditions and in the presence of NaOH, the reaction of urea with 4-bromobenzyl bromide for a total milling time of 34 h gave the di(4-bromobenzyl)urea in a conversion of 41% (Scheme 50).<sup>81</sup>

The chemoselective acylation of primary aliphatic amines with *N*-hydroxysuccinimidyl (NHS) esters in the presence of DMAP was achieved in less than 10 min (and for aromatic amines in less than 120 min) using the vibration ball-milling technique (Scheme 51).<sup>83</sup>

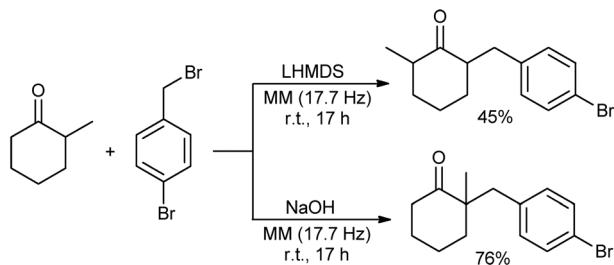
The importance of thioureas as organocatalysts is growing. Consequently, an efficient procedure for the synthesis of thioureas is demanded from both the economic and environmental points of view. Kaupp *et al.* reported the formation of



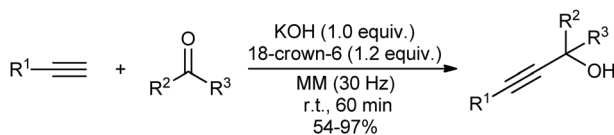
*N,N'*-diaryl thioureas as unstable intermediates by milling *o*-phenylene diisothiocyanate with three substituted anilines (*vide infra*).<sup>84</sup> Recently, Štrukil *et al.* reported the quantitative formation of a series of mono- and bis(thio)ureas or mixed thiourea-ureas by the neat ball milling and/or LAG method.<sup>85–87</sup> They first described the quantitative synthesis of mono- and bis(thiourea)s by the reaction of aromatic and aliphatic (di)amines with aromatic isothiocyanates by neat ball milling and/or LAG using methanol as a grinding liquid at a frequency of 30 Hz.<sup>85</sup> The formed chiral bis(thiourea)s could be used as organocatalysts or anion sensors. Then they conducted the quantitative synthesis of 49 different *N,N'*-disubstituted symmetrical and non-symmetrical monothioureas based on variously substituted aromatic, aliphatic, heterocyclic, primary, as well as secondary amine building blocks.<sup>86</sup> Very recently, they reported that *ortho*- and *para*-phenylenediamines were desymmetrized and transformed into mono- and bis(thio)ureas or mixed thiourea-ureas by neat ball milling or LAG methods (Scheme 52).<sup>87</sup>

**5.1.2 Addition reactions of C-nucleophiles.** Mack and coworkers investigated the mechanochemical reaction of *p*-bromobenzyl bromide with cyclohexanone and 2-methylcyclohexanone in the presence of a base.<sup>82</sup> The reaction of cyclohexanone with *p*-bromobenzyl bromide and KOH using a Spex CertiPrep Mixer/Mill 8000 M for 17 h provided the mono- and dibenzylated products in 29% and 9% yields, respectively. Replacing KOH with a stronger base, lithium hexamethyldisilazide (LiHMDS), resulted in a much higher yield (64%) of monoaddition product along with 15% of dibenzylated product after milling for 17 h. For the mechanochemical reaction of 2-methylcyclohexanone with *p*-bromobenzyl bromide, the use of NaOH (NaH or  $NaNH_2$ ) or LiHMDS as the base led to the thermodynamic product (2-methyl-2-*p*-bromobenzyl cyclohexanone) and kinetic product (2-methyl-6-*p*-bromobenzyl cyclohexanone) as the major product, respectively (Scheme 53).

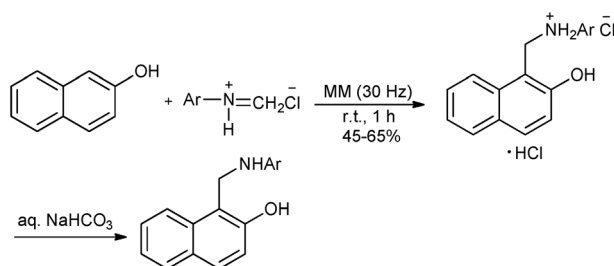
Because the reaction vials were sealed under the mechanochemical conditions, the only water and oxygen that were present in the reactions were the small amounts that were in the reactants or in the air before the vial was sealed. As a result, only a small amount of reagent was needed to be sacrificed in order to have completely moisture- and oxygen-free reaction



Scheme 53



Scheme 54



Scheme 55

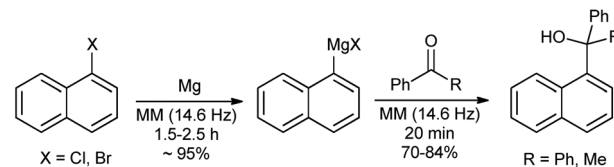
conditions. It was believed that the levels of water and oxygen were already at the ppm level under the mechanochemical conditions. Accordingly, it was found that this moisture sensitive nucleophilic reaction in a sealed dry box and in an open atmosphere gave essentially the same results. The reaction of *p*-bromobenzyl bromide with cyclohexanone and 2-methylcyclohexanone and  $\text{NaNH}_2$  after milling for 10 min in an open atmosphere afforded the corresponding products in 89% and 55% yields, respectively.<sup>71</sup>

Wang and coworkers reported the nucleophilic addition reactions of various terminal alkynes to ketones in the presence of KOH and 18-crown-6 under solvent-free ball-milling conditions (Scheme 54).<sup>80</sup> The addition of 18-crown-6 was found to improve the yields significantly. A series of propargylic alcohols could be obtained in 54–97% yields after milling the reaction mixtures at a rate of 1800 rpm (30 Hz) for 1 h.

Solid-state arylaminomethylation of  $\beta$ -naphthol with methylene iminium cations was realized in a ball mill (Scheme 55).<sup>58</sup> The yields were low in these cases due to intermediate melting to viscous oils. The final products were obtained by neutralization with aqueous  $\text{NaHCO}_3$ .

## 5.2 Nucleophilic addition of organometallics

Aromatic Grignard reagents were prepared *in situ* from halonaphthalenes and magnesium, and then reacted with aromatic ketones using the ball milling technique (Scheme 56).<sup>88</sup>



Scheme 56



Scheme 57

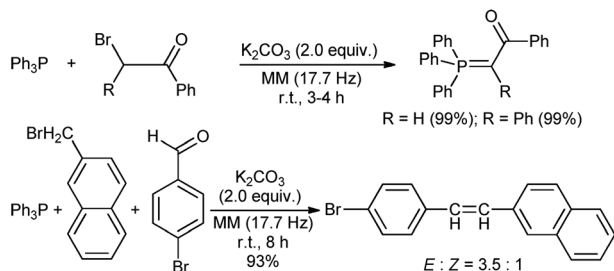
The solvent-free reactions were conducted in a Spex 8000 vibrational ball mill at a clamp speed of 875 rpm (14.6 Hz) under an inert atmosphere, and the tertiary alcohols were obtained in 70–84% yields.

The Mack group succeeded in the Grignard reaction under sealed mechanochemical conditions with no precautions taken to avoid moisture in the air.<sup>71</sup> The reaction of a solution of methyl Grignard in ether with 4-bromobenzophenone after milling for 1 h afforded a 42% conversion to 1-bromo-4-(1-phenylethenyl)benzene and a 58% conversion to 1-(4-bromophenyl)-1-phenylethanol. Pre-evaporation of the ether from the methyl Grignard reagent and milling for 17 h provided the 1-bromo-4-(1-phenylethenyl)benzene as the major product.

The bismuth-mediated Barbier-type allylation of aromatic aldehydes and ketones under mechanical milling conditions was explored by Suzuki and coworkers.<sup>89</sup> When the mixtures of aromatic aldehydes, allyl halides and bismuth were milled in a mixer mill at 30 Hz for 0.5–1.5 h, the corresponding homoallylic alcohols were obtained in 34–95% yields (Scheme 57). In contrast to the failure of the reaction in solution, aromatic ketones also underwent Barbier-type allylations to give the expected tertiary homoallylic alcohols in 20–70% yields.

## 5.3 Wittig reaction

Balema *et al.* reported the solvent-free mechanochemical synthesis of phosphonium salts.<sup>90</sup> They also showed that stabilized, semistabilized and nonstabilized phosphorus ylides could be generated mechanochemically in the presence of weak base  $\text{K}_2\text{CO}_3$  in the solid state.<sup>91</sup> Stabilized ylides generated from (phenacyl)triphenylphosphonium bromide and (carbomethoxy)methyltriphenylphosphonium bromide were isolated in pure form. In contrast, semistabilized and nonstabilized phosphoranes formed from (benzyl)triphenylphosphonium bromide or (methyl)triphenylphosphonium bromide could be trapped by a solid organic carbonyl compound and transformed into alkenes and triphenylphosphine oxide in a solvent-free mechanochemical Wittig reaction. Furthermore, the mechanochemical preparation of stabilized phosphorus ylides and the solvent-free Wittig reaction could be successfully carried out as a “one-pot” process starting with triphenylphosphine, an organic halide and an aldehyde or ketone in the presence of  $\text{K}_2\text{CO}_3$  (Scheme 58).<sup>91</sup>



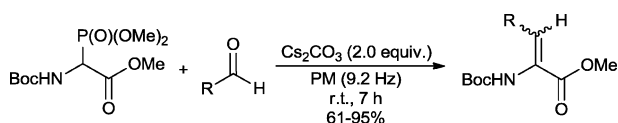
Scheme 58

The Horner–Wadsworth–Emmons (HWE) version of the Wittig reaction utilizes more stabilized phosphonate ylides. The phosphonate stabilized carbanion is nucleophilic enough to react with an aldehyde or ketone under mild conditions to yield an alkene. Lamaty and coworkers developed a HWE reaction in a ball mill as a valuable route for the synthesis of unsaturated amino esters.<sup>92</sup> Starting from a phosphonate-substituted glycine and an aldehyde in the presence of a mild carbonate base ( $\text{Cs}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$ ), this mechanochemical method gave access to Boc-protected unsaturated amino esters in 61–95% yields (Scheme 59). The obtained alkenes were either exclusively or dominantly *Z*-isomers. However, ketones were ineffective under the present conditions.

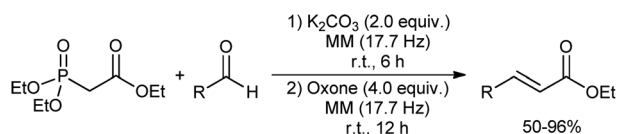
Soon afterwards, Mack and coworkers reported the solvent-free mechanochemical synthesis of  $\alpha,\beta$ -unsaturated esters from the HWE reaction of triethyl phosphonoacetate with various aryl and alkyl aldehydes in the presence of  $\text{K}_2\text{CO}_3$ .<sup>93</sup> In order to avoid the use of solvents for purification, they used excess (2.0 equiv.) aldehyde to achieve quantitative conversion. After completion of the HWE reaction, the excess aldehyde was oxidized with Oxone to the corresponding carboxylic acid, which could easily be removed by an aqueous wash, thus eliminating the common chromatographic separation. By this procedure, a series of  $\alpha,\beta$ -unsaturated esters could be obtained predominantly as the *E*-isomers in 50–96% yields (Scheme 60).

#### 5.4 Nucleophilic aromatic substitution

A novel solid-state mechanochemical method was developed for the synthesis of fluoroaromatic compounds from appropriate chloroaromatic derivatives in a planetary-centrifugal mill AGO-2.<sup>94</sup>



Scheme 59



Scheme 60

Alkaline and earth metal fluorides were used as fluorinating agents. Hexachlorobenzene (HCB), pentachloropyridine (PCP) and octachloronaphthalene (OCN) were the starting polychloroaromatic compounds. The depth of fluorination was dependent on both the fluorinating agent used and the reaction duration.

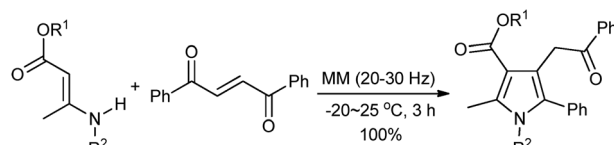
## 6. Mechanochemical cascade reactions

Cascade reactions are very important for the construction of complex molecules. One of the sequential steps in a cascade reaction often involves a nucleophilic reaction or a condensation reaction as described in Sections 4 and 5. The Kaupp group was the first to systematically investigate cascade reactions by the mechanical milling technique. They reported the reaction of *trans*-1,2-dibenzoyl ethene with primary or secondary enamine esters or enamine ketones in a ball mill to give the pyrrole or indole products in quantitative yields (Scheme 61).<sup>95</sup> The reactions took place through four sequential steps: an initial Michael addition of the enamine nitrogen, cyclizing addition of the enamine double bond, rearrangement to the enamine and elimination of water.

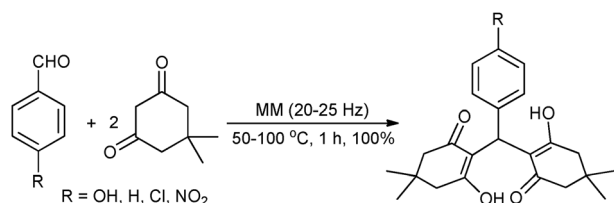
Dimedone is not only a Knoevenagel reagent, but also adds easily to electron-poor alkenes in Michael additions. When investigating the reaction of aldehydes with dimedone, Kaupp *et al.* found that a cascade reaction *via* addition, elimination and addition occurred to give the 2 : 1 adducts (Scheme 62). The intermediate Knoevenagel products could not be isolated even in 1 : 1 experiments under the mechanical milling conditions.<sup>65</sup>

Surprisingly, Wang *et al.* found that the mechanochemical reaction of aldehydes with dimedone promoted by molecular iodine and DMAP afforded spiro dihydrofuran derivatives in a mixer mill at a rate of 30 Hz for 1 h.<sup>96</sup> This reaction had a wide substrate scope: aryl aldehydes with either electron-withdrawing or electron-donating groups, heteroaryl and alkyl aldehydes could be employed to give the spiro products in 77–92% yields. Intriguingly, replacing dimedone with 1,3-indandione led to the formation of spiro cyclopropane derivatives in 60–89% yields (Scheme 63).

Control experiments showed that when the 2 : 1 adducts were employed as the starting materials instead of the combination of

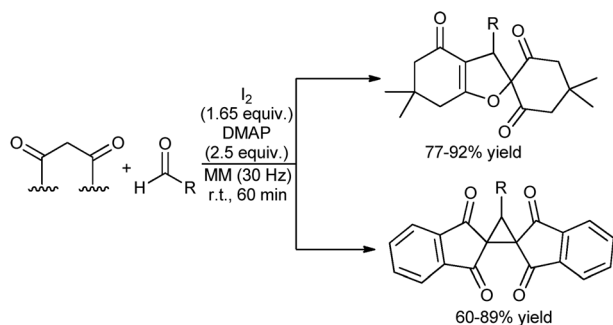


Scheme 61



Scheme 62



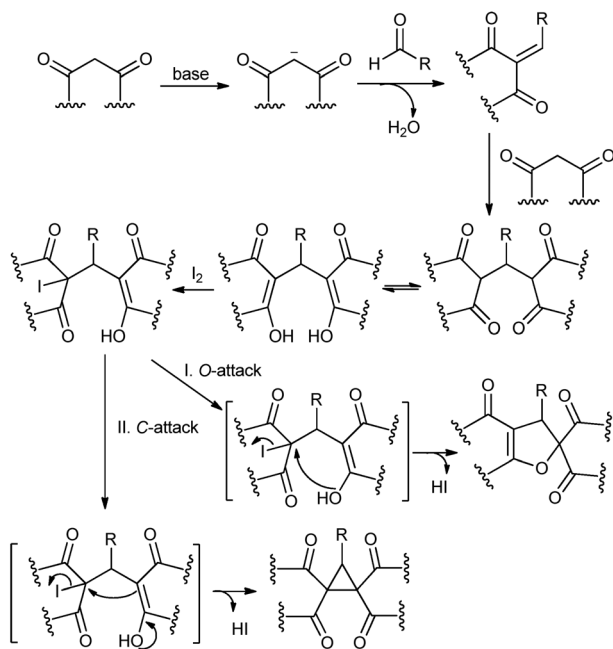


Scheme 63

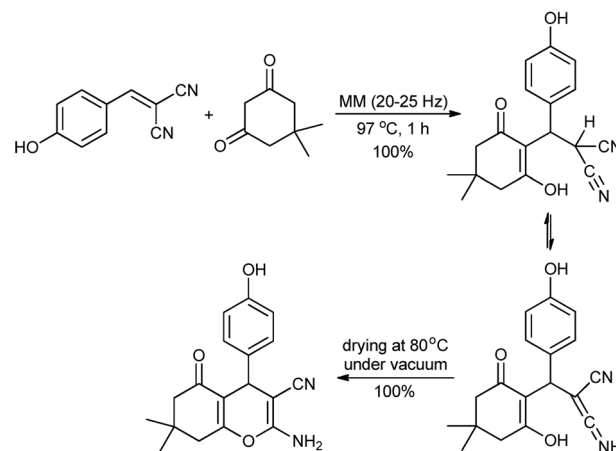
the 1,3-dicarbonyl compounds and aldehydes, the desired products were also obtained in similar yields. Although the exact mechanism for the formation of the spiro products was not clear, the proposed reaction mechanism is shown in Scheme 64. The Knoevenagel condensation followed by Michael addition led to 2:1 adducts, which reacted with iodine to give the  $\alpha$ -iodonated products. From these intermediates two pathways could proceed. For dimedone, an intramolecular nucleophilic O-attack with an elimination of HI afforded dihydrofurans. While for 1,3-indandione, nucleophilic C-attack with the loss of HI gave cyclopropanes.

When a stoichiometric mixture of 4-hydroxybenzylidene malonitrile and dimedone was ball milled for 1 h, the dihydropyran derivative was obtained in 100% yield after drying at 80 °C in a vacuum. The reaction should proceed *via* a Michael addition, rearrangement and cyclization sequence (Scheme 65).<sup>65</sup>

Mashkouri and Naimi-Jamal later reported a one-pot synthesis of pyran[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in 94–99% yields by simply ball-milling a stoichiometric mixture of an aldehyde,



Scheme 64

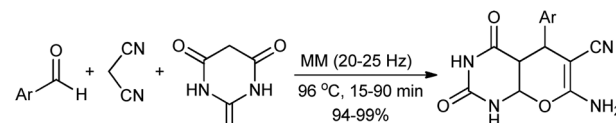


Scheme 65

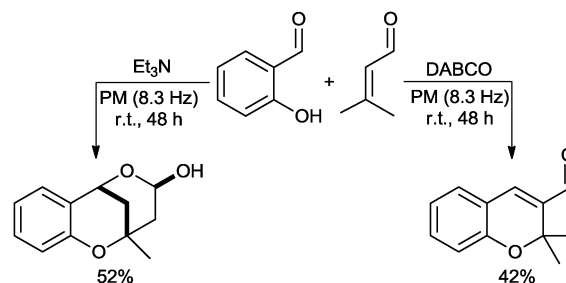
malonitrile and barbituric acid without any catalyst or solvent at 96 °C and 20–25 Hz for 15–90 min (Scheme 66).<sup>97</sup>

Recently, Bräse and coworkers reported domino oxo-Michael-aldol reactions giving tetrahydroxanthenones by the ball milling technique.<sup>98</sup> A systematic investigation of parameters such as rotation frequency, milling time, ball mass, reagent molar ratio and base was carried out for the reaction of salicylaldehyde with cyclohexenone. A highest yield of 62% for tetrahydroxanthenone could be obtained under the optimized conditions. For the base-catalyzed condensation of salicylaldehyde with prenal, an  $\alpha,\beta$ -unsaturated aldehyde, both dihydrobenzopyran and xanthenone derivatives could be obtained *via* either the oxo-Michael-aldol reaction or vinylogous aldol reaction followed by oxo-Michael addition, respectively, with different bases (Scheme 67).

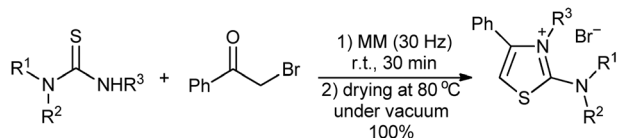
Kaupp *et al.* found that the mechanical milling of thioureas and phenacyl bromide in a ratio of 1:1 for no more than 1 h and subsequent drying at 0.01 bar at 80 °C gave biologically active 2-amino-4-phenylthiazole hydrobromides in 100% yield (Scheme 68). The reaction should proceed *via* nucleophilic



Scheme 66



Scheme 67



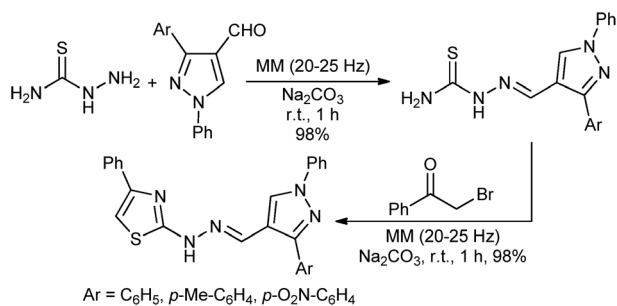
Scheme 68

substitution to generate thiuronium salts, which cyclize with the more nucleophilic amino groups to afford 2-aminothiazoles.<sup>58</sup>

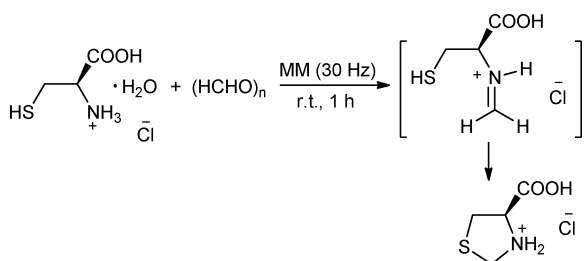
Similarly, Abdel-Latif, Bondock and coworkers reported that the solvent-free reaction of  $\alpha$ -haloketones with arylidene-thiosemicarbazone derivatives, ethyl 3-thiosemicarbazidobutanoate and its derived arylhydrazonopyrazolones in a Retsch MM 2000 swing mill at 20–25 Hz afforded the corresponding thiazole derivatives in quantitative yields after neutralization with  $\text{Na}_2\text{CO}_3$  and drying in a vacuum.<sup>78,99</sup> The mechanochemical treatment of thiosemicarbazide with a series of 4-formylpyrazoles gave pyrazolylthiosemicarbazones, which then reacted with phenacyl bromide to afford the corresponding 2-(arylidenehydrazino)-4-phenylthiazoles in 98% yield (Scheme 69).

Even methylene iminium salts could be formed from the ammonium salts and  $(\text{HCHO})_n$  in a ball mill. Albeit extremely labile, they could be efficiently trapped by adjacent thiol group. Kaupp *et al.* showed that milling of stoichiometric quantities of (*L*)-cysteine (or its hydrochloride) and solid paraformaldehyde  $(\text{HCHO})_n$  gave a quantitative yield of the (*L*)-thiazolidine (or its hydrochloride) within 1 h (Scheme 70). The crystal water was removed at 80 °C in a vacuum. Both  $\text{NH}_2$  and  $\text{SH}$  reacted in this cyclization.<sup>58,84</sup>

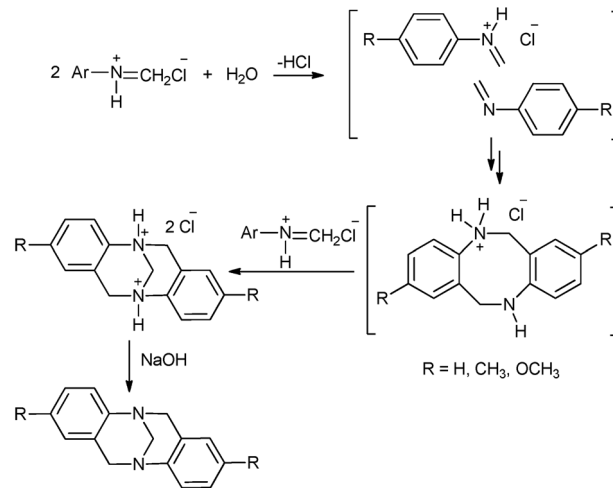
Interestingly, *N*-arylmethylene iminium salts could be transformed to Tröger's bases after milling for 5–10 min in the presence of water vapour or  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ . The products were



Scheme 69



Scheme 70

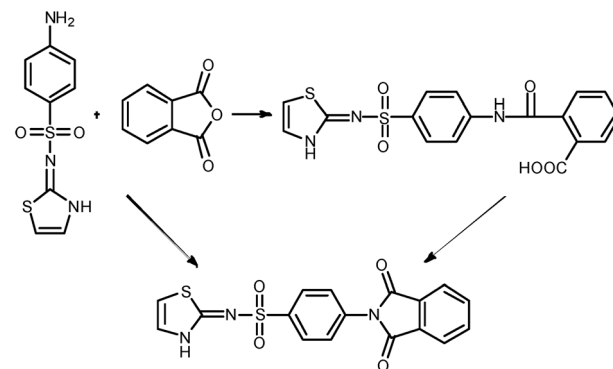


Scheme 71

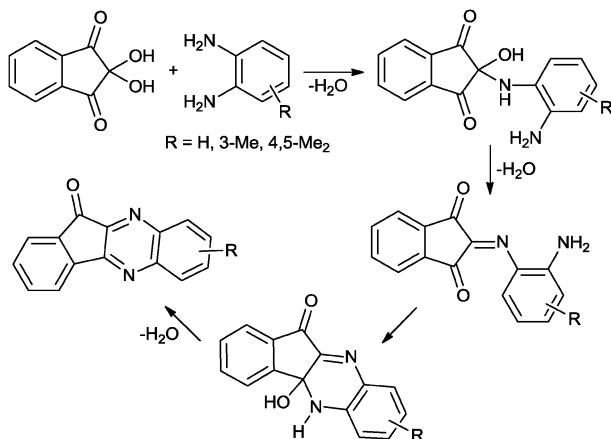
formed *via* a 3-cascade: double arylaminomethylation and methylenation of the tetrahydro-1,5-diazocine intermediate. The  $\text{H}_2\text{O}$  molecules behaved as a weak base to deprotonate the iminium salts (Scheme 71).<sup>58</sup>

Imides could be mechanochemically synthesized *via* nucleophilic addition of amines followed by intramolecular cyclization under solvent-free conditions. *N*-(4-Tolyl)-phthalimide<sup>84</sup> and phthalylsulphathiazole<sup>100</sup> could be obtained by reaction of phthalic anhydride with 4-methylaniline and sulfathiazole, respectively (Scheme 72). The reaction was accelerated in the presence of benzoic acid.<sup>100</sup>

The Kaupp group also reported the solid-state cascade reactions of ninhydrin with *L*-proline, three *o*-phenylenediamines, *o*-mercaptoaniline, two ureas, three thioureas and methyl 3-aminocrotonate in a mixer mill at 20–25 Hz:<sup>69</sup> *L*-proline reacted quantitatively with ninhydrin in a 3-cascade (substitution, elimination and decarboxylation) to produce the versatile azomethine ylides; *o*-phenylenediamines reacted quantitatively with ninhydrin in a 4-cascade (substitution, elimination, cyclization and elimination) to give the indenoquinoline ketones (Scheme 73); stoichiometric reaction of *o*-mercaptoaniline hydrochloride with ninhydrin gave quantitatively the hydroxyindeno[2,1-*b*]benz[1,4]thiazin-11(10*aH*)-one HCl salt in a 3-cascade (substitution, cyclization



Scheme 72

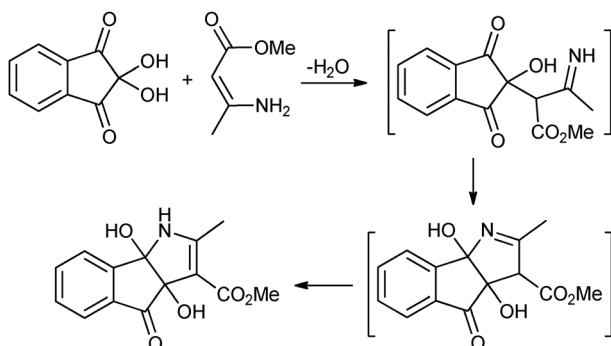


Scheme 73

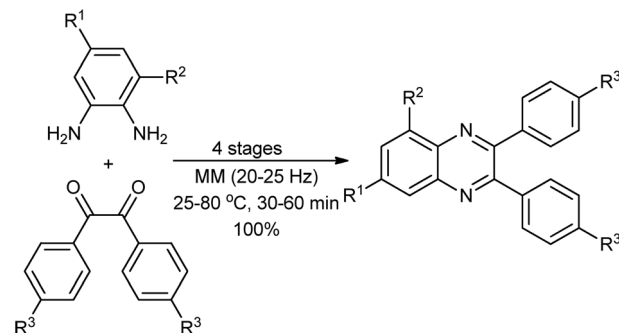
and elimination); an enamoester reacted quantitatively with ninhydrin to give the heterocyclic building block with  $\alpha$ -hydroxyketone and *N/O*-semiaminal functionality *via* a 3-cascade (vinylogous substitution, cyclization and 1,3-hydrogen shift) (Scheme 74); the reaction of ureas/thioureas with ninhydrin quantitatively afforded heterocyclic bis-*N/O*-semiacetals in a 2-cascade (substitution and addition). The presumed elimination of water from the *N/O*-semiaminal and *N/O*-semiacetals could not be achieved in the solid state.

Soon afterwards, Kaupp *et al.* described the mechanochemical cascade condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds to afford quantitative yields of heterocycles in a swing mill at 20–25 Hz frequency:<sup>101</sup> condensation of *o*-phenylenediamines with benzils or 2-hydroxy-1,4-naphthoquinone gave substituted quinoxalines in a 4-cascade (addition twice and elimination twice) (Scheme 75); condensation between *o*-phenylenediamine and 2-oxoglutaric acid after milling for 10 min gave 3-oxodihydroquinoxaline in 90% yield *via* condensation, salt formation and cyclization; condensation of *o*-phenylenediamines with alloxane hydrate provided 3-oxodihydroquinoxaline-2-carbonylureas in a 4-cascade consisting of substitution, elimination, cyclization and ring-opening (Scheme 76).

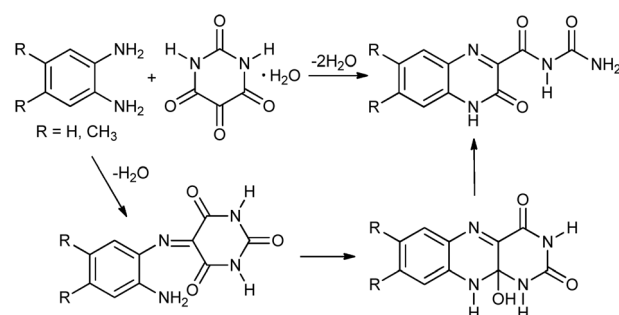
Kaupp *et al.* also found that the reaction of solid *o*-phenylene diisothiocyanate with solid anilines in a ball mill at room temperature gave substituted (anilino-thiocarbonyl)-



Scheme 74



Scheme 75



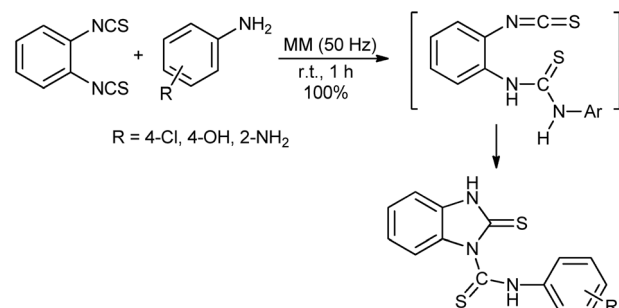
Scheme 76

benzimidazolidine-2-thiones in 100% yield, presumably *via* a mono thiourea intermediate (Scheme 77).<sup>84</sup>

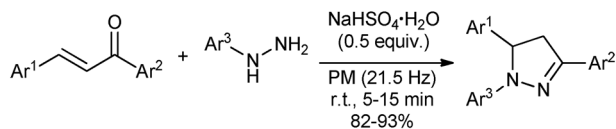
Su and coworkers described the solvent-free synthesis of 1,3,5-triaryl-2-pyrazolines in 82–93% yields from chalcones and phenylhydrazines catalyzed by  $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$  using an AGO-2 planetary centrifugal mill with a rotational speed of 1290 rpm (21.5 Hz) (Scheme 78).<sup>102</sup> Thiosemicarbazides and aliphatic enones could replace phenylhydrazines and chalcones, respectively, to give the corresponding 2-pyrazolines.

Pinhas and coworkers reported the solvent- and catalyst-free conversion of an unactivated 2-alkyl or 2-aryl aziridine to an oxazolidinone with good regioselectivity using only dry ice (carbon dioxide) at room temperature (Scheme 79).<sup>103</sup>

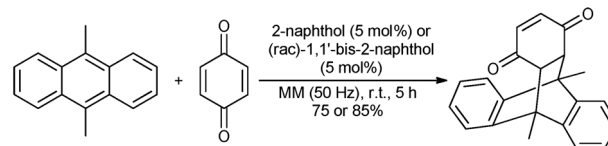
After shaking in a Spex 8000 M mixer mill for 17 h, the reaction mixtures gave oxazolidinones in nearly quantitative yields. Based on the obtained stereochemistry, the authors



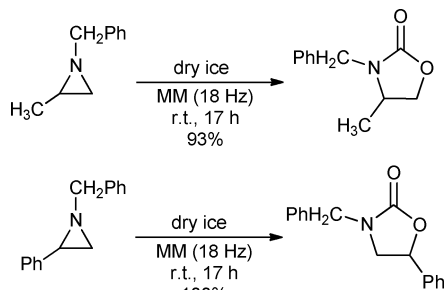
Scheme 77



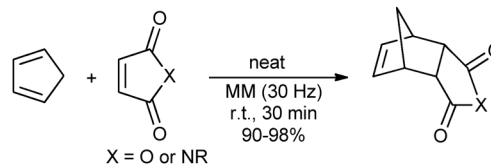
Scheme 78



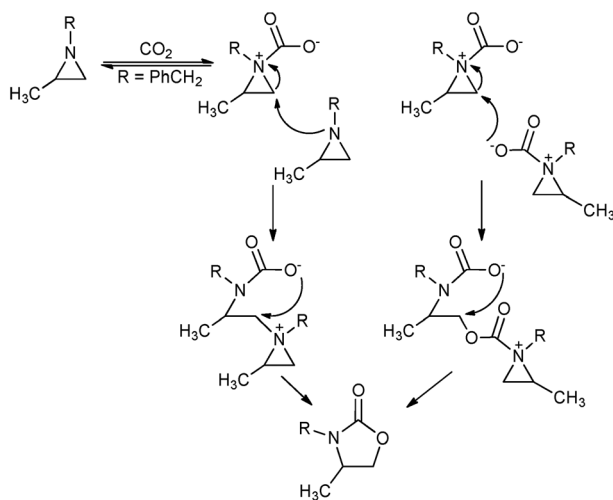
Scheme 82



Scheme 79



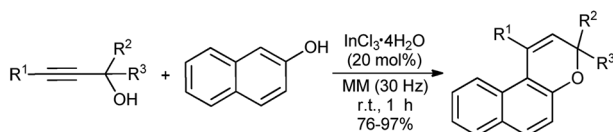
Scheme 83



Scheme 80

proposed two mechanisms for this transformation. The initial step of each is the nucleophilic attack of the aziridine on  $\text{CO}_2$  giving a zwitterionic intermediate, followed by nucleophilic attack with either a second molecule of the aziridine or the carboxylate anion of the intermediate, and final cyclization to afford the oxazolidinones (Scheme 80).

Wang and coworkers disclosed the solvent-free synthesis of naphthopyrans in 76–97% yields from propargylic alcohols with 2-naphthol catalyzed by indium trichloride tetrahydrate using a mixer mill at a rate of 1800 rpm (30 Hz) for 1 h (Scheme 81).<sup>80</sup>



Scheme 81

## 7. Mechanochemical Diels–Alder reactions

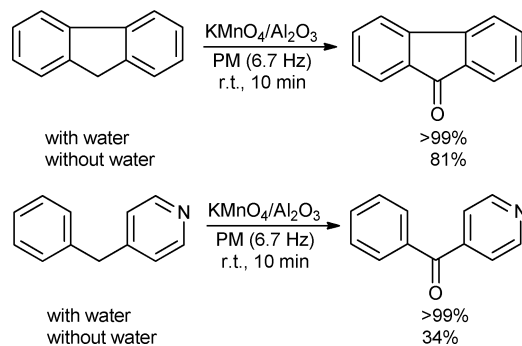
Watanabe and Senna reported the first mechanochemical Diels–Alder reactions between anthracene (AN) derivatives and *p*-benzoquinone (BQ) in the solid state.<sup>104</sup> They found that only anthracene derivatives with electron-donating groups such as 9,10-dimethylantracene could react with BQ after milling at 298 K for 5 h, yet a yield of only 26% was obtained. Intriguingly, the addition of a stoichiometric amount of 2-naphthol (NP) or (*rac*)-1,10-bis-2-naphthol (BN) increased the yield above 99%. Even the addition of 5 mol% of NP or BN could increase the yield from 26% to 75% or 85%, respectively (Scheme 82). The catalytic effect was ascribed to the formation of the charge transfer complex (CTC) with strong hydrogen bonds.

Zhang *et al.* reported the solvent- and catalyst-free Diels–Alder reactions of cyclopentadiene with maleic anhydride and maleimide derivatives promoted by the mechanical milling technique (Scheme 83).<sup>105</sup> The neat reaction in a mixer mill at 30 Hz at room temperature for 30 min afforded various endo-norbornene derivatives in 90–98% yields.

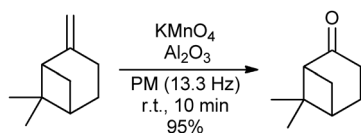
## 8. Oxidation reactions

Nüchter *et al.* reported the oxidation of several types of organic compounds by potassium permanganate supported on inorganic carriers in a Pulverisette 7 mill at 400 rpm (6.7 Hz) for 10 min. The presence of water enhances the yields of almost all products. Olefins were oxidized to carboxylic acids. The conversion of benzyl-type arenes was selective, providing ketones with good yields (Scheme 84).<sup>106</sup>

Recently, Stolle and coworkers described the oxidative cleavage of  $\beta$ -pinene yielding nopinone with potassium permanganate as an oxidant under solvent-free conditions (Scheme 85).<sup>107</sup> The reaction was performed in a planetary ball mill with the use of a milling auxiliary. Different chemical parameters such as oxidants, milling auxiliaries and quantities as well as technical variables including milling time, rotation frequency and number of milling balls were explored concerning their influences on yield and selectivity. Nopinone could be obtained in 95% yield within 10 min under optimized conditions.



Scheme 84

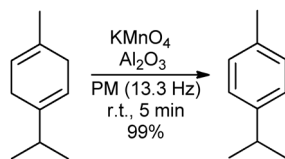


Scheme 85

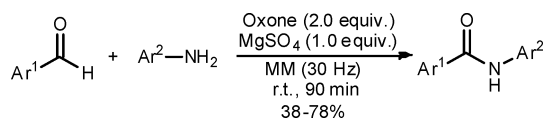
Stolle and coworkers also reported the solvent-free dehydrogenation of  $\gamma$ -terpinene in a planetary ball mill affording *p*-cymene as the predominant reaction product (Scheme 86).<sup>108</sup> The influences of various reaction parameters and technical variables on the dehydrogenation reaction were also assessed. The transformation could be fine-tuned by variation of the oxidant-to-substrate ratio, the rotation frequency, the number of milling balls or the type of employed grinding auxiliary. A quantitative yield was obtained after milling for 5 min at 13.3 Hz and with  $\text{KMnO}_4$  as the oxidant in the presence of alumina.

Gao and Wang found that Oxone was an effective oxidant for the oxidative amidation of aldehydes with anilines to afford amides in a one-pot process under mechanical milling conditions (Scheme 87).<sup>109</sup> The solvent-free reaction was conducted in a mixer mill at 30 Hz for 90 min, and amides were obtained in 38–78% yields.

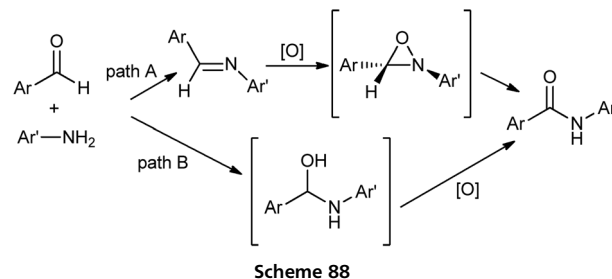
This oxidative amidation reaction may proceed by two pathways (Scheme 88): (1) imines are formed from aldehydes and anilines rapidly, which are oxidized by Oxone to generate oxaziridines. Subsequent rearrangement of oxaziridines *via* the initial cleavage of the N–O bond followed by migration of



Scheme 86



Scheme 87

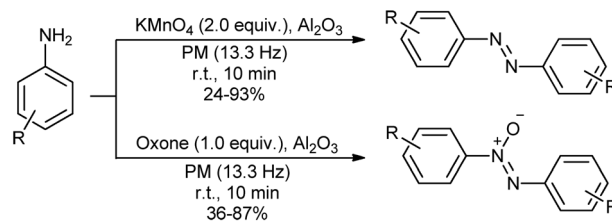


Scheme 88

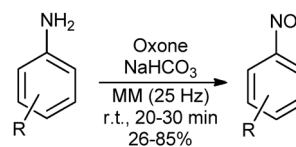
the substituent (hydrogen) *trans* to the nitrogen lone pair results in the formation of amides. (2) Carbinolamine intermediates are generated after the nucleophilic addition of anilines to aldehydes, followed by oxidation with Oxone to form the amide products. Even though control experiments showed that imines could be employed as the starting materials to perform the amidation reaction directly, the exact mechanism was thought to remain obscure and both pathways could be operating.

Stolle and coworkers developed a solvent-free method for the direct oxidation of anilines to the corresponding azo and azoxy homocoupling products by using a planetary ball mill (Scheme 89).<sup>110</sup> Various oxidants and milling auxiliaries were tested with a variety of substituted anilines. It was possible to generate chemoselectively either azo, azoxy, or nitro compounds from the reaction of aromatic anilines. The selectivity of the solvent-free reaction could be switched by applying different combinations of oxidant and milling auxiliary: the oxidations with  $\text{KMnO}_4$  and Oxone furnished the azo and azoxy compounds, respectively.

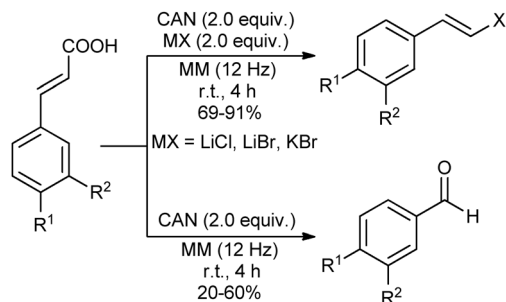
More recently, Halasz and coworkers showed that nitrosobenzene intermediates could be obtained in 26–85% yields from the mechanochemical Oxone oxidation of selected *para*-substituted anilines in the presence of  $\text{NaHCO}_3$  at a frequency of 25 Hz for 20–30 min (Scheme 90).<sup>111</sup> The addition of  $\text{NaHCO}_3$  to neutralize potassium hydrogen sulfate and other acidic species was very important to facilitate the formation of nitrosobenzenes. Besides avoiding bulk solvents and shortening reaction times, the authors exploited the high vapour pressure



Scheme 89



Scheme 90



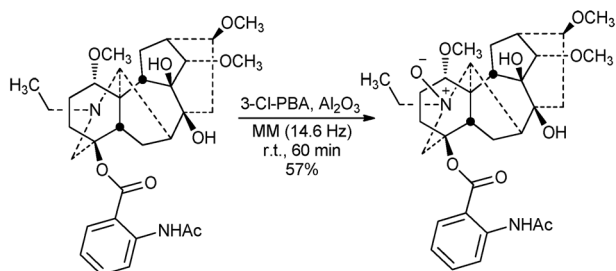
Scheme 91

of nitrosobenzenes for the solvent-free separation of the products by sublimation, demonstrating an entirely solvent-free route to chemical synthesis and product isolation.

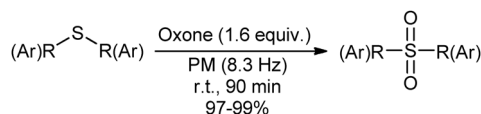
The solid-state oxidation of cinnamic, 4-methoxy- and 3,4-dimethoxycinnamic acids with  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  (CAN)–MX systems in a vibratory mill at a frequency of 12 Hz for 4 h led to  $\beta$ -halostyrenes in 69–91% yields. A similar procedure in the absence of a metal halide resulted in the cleavage of the C=C bond to afford the corresponding benzaldehydes in 20–60% yields (Scheme 91).<sup>112</sup>

A tertiary amine could also be oxidized under ball-milling conditions. Pankrushina *et al.* found that the nitroxide derivative was formed from the mechanochemical oxidation of lappaconitine with 3-chloroperbenzoic acid in a SPEX-8000 vibratory mill (Scheme 92).<sup>113</sup>

Cravotto *et al.* reported that organosulfur compounds could be easily and selectively oxidized to sulfones using a small excess of Oxone (1.6 equiv.) under solventless mechanical milling conditions (Scheme 93).<sup>114</sup> Substrates such as 3,6-dithiaoctane-1,8-diol (Lindlar catalyst poison), 4-(methylthio)benzaldehyde as well as a series of *S*-heterocycles including thiophene, benzothiophene, dibenzothiophene and substituted derivatives were examined. All substrates exclusively afforded the sulfones as the oxidation products in 97–99% yields after milling for 90 min in a planetary mill. No traces of sulfoxides were detected, reflecting the high chemoselectivity of the mechanochemical oxidation with Oxone.



Scheme 92



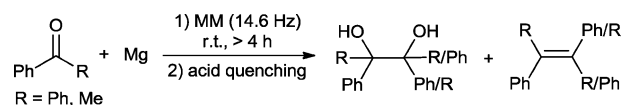
Scheme 93

## 9. Reduction

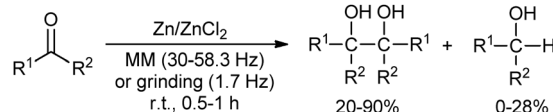
When direct mechanochemical reactions of benzophenone and acetophenone with 4 equiv. of Mg were investigated, the products included those of coupling to give pinacol, alkene and alkane species, as well as simple reduced species. After acid quenching, benzophenone provided 1,1,2,2-tetraphenylethanol, tetraphenylethene and 1,1,2,2-tetraphenylethane as major products, along with small quantities of diphenylmethanol and diphenylmethane. Acetophenone afforded principally *cis*- and *trans*-2,3-diphenylbut-2-ene plus *meso*- and *rac*-2,3-diphenylbutane-2,3-diol, as well as some 1-phenylethanol (Scheme 94).<sup>88</sup> Replacement of Mg with other metals (Al, Fe, Ti and Zn) led to much slower reactions, and only McMurry coupling products with Ti and Zn were readily detected.

Wang *et al.* reported the solvent-free reduction of aromatic ketones and aldehydes by Zn–ZnCl<sub>2</sub> with the aid of a high-speed vibration mill, Retsch MM200 mixer mill and Retsch RM100 mortar grinder to give pinacol coupling and reduction products in varying yields (Scheme 95).<sup>115</sup> However, the pinacol coupling products were formed predominantly or exclusively in all cases.

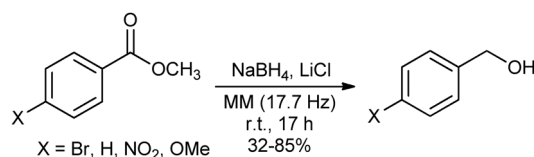
The mechanochemical reduction of aldehydes, ketones and esters with NaBH<sub>4</sub> was reported by Mack *et al.*<sup>116</sup> Using 1 equiv. of NaBH<sub>4</sub>, both aldehydes and ketones were successfully reduced in 65–73% yields after milling in a Spex CertiPrep mixer/mill 8000 M within 6 h. The reduction was also realized with 1/4 equiv. of NaBH<sub>4</sub>, although much longer reaction times were required to achieve comparable yields. Esters are not typically reduced with NaBH<sub>4</sub>, and demand more powerful and hazardous reducing agents such as LiAlH<sub>4</sub>. It was found that the mechanochemical reduction of esters could be achieved with a combination of NaBH<sub>4</sub> and LiCl, which presumably generated the more reactive LiBH<sub>4</sub>. The alcohols could be obtained in 32–85% yields after milling for 17 h (Scheme 96).



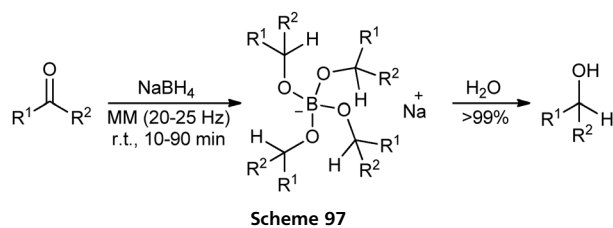
Scheme 94



Scheme 95



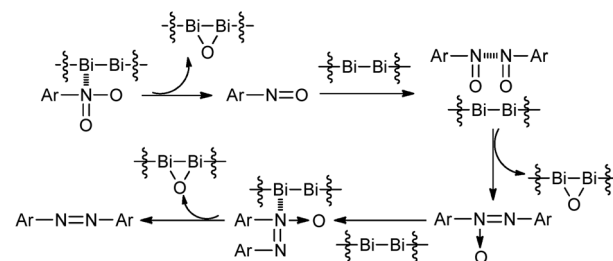
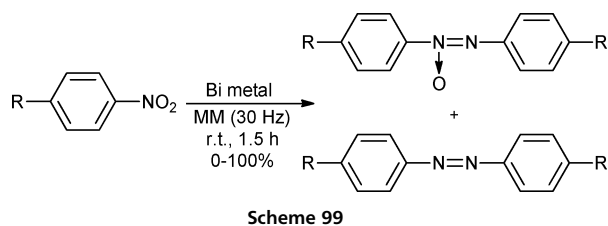
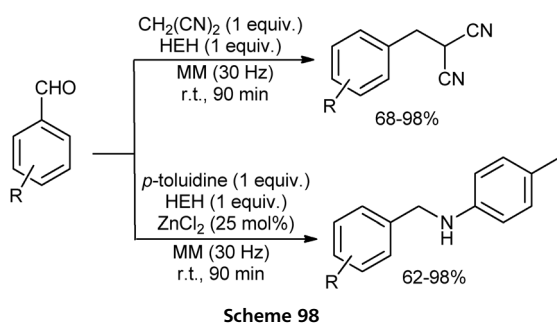
Scheme 96



Naimi-Jamal *et al.*<sup>117</sup> recently showed that sodium tetraalkoxyborates from the reduction of aldehydes and ketones with  $\text{NaBH}_4$  could be isolated as the thermally stable intermediates in quantitative yields. Nevertheless, the easily isolated solids were extremely sensitive towards hydrolysis, and led to the corresponding alcohols (Scheme 97).

The  $\text{C}=\text{C}$  and  $\text{C}=\text{N}$  bonds in benzyldenemalononitriles and imines are known to be reduced with metal hydrides and occasionally with organoreductants. Wang and coworkers described the solvent-free mechanochemical and one-pot reductive benzylizations of malononitrile and 4-methylaniline using Hantzsch 1,4-dihydropyridine (HEH) as the reductant (Scheme 98).<sup>53</sup> The *in situ* formed benzyldenemalononitriles and imines could be efficiently reduced to give benzylated malononitriles and anilines in 62–98% yields after milling at 30 Hz within 90 min. The organoreductant HEH demonstrated complete selectivity, as there was no reduction of labile functional groups such as aldehyde, nitro and cyano groups.

Suzuki and coworkers reported the bismuth-mediated solvent-free one-step reduction of nitroarenes to azoxy- and azoarenes by the ball milling technique (Scheme 99).<sup>118</sup> Although the reaction with Bi shot gave azoxyarenes as the major products under aerobic conditions, azoarenes were formed predominantly under the protection of nitrogen. Interestingly, the addition of a drop of an inert organic solvent such as hexane or benzene to the nitroarene-bismuth mixture prior to milling led to the complete formation



**Fig. 4** Proposed pathway for the deoxygenative dimerization of nitroarenes.

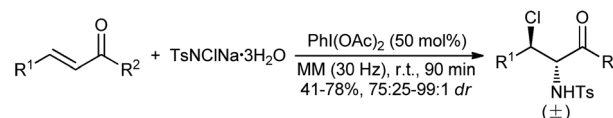
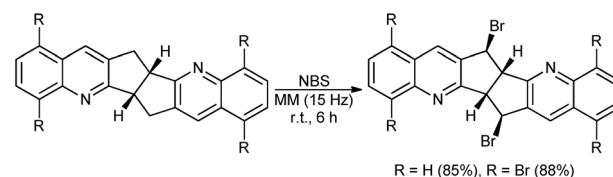
of azoxyarenes. Replacement of Bi with Pb selectively provided azoarenes instead.

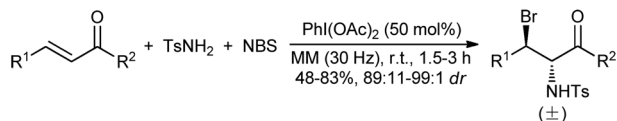
The proposed pathway for the deoxygenative dimerization of nitroarenes on the activated bismuth surface is shown in Fig. 4. Nitroarenes were adsorbed and deoxygenated on the newborn bismuth surface to form nitrosoarenes as the initial products, which underwent dimerization to afford azoxyarenes. In the presence of oxygen or some additive, part of the active metal surface would be destroyed or occupied by these molecular species and further reduction would be suppressed. Otherwise, the reaction proceeded further to produce azoarenes.

## 10. Halogenation and aminohalogenation

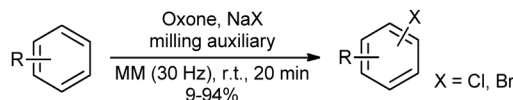
The solvent-free benzylic bromination of diquinoline derivatives by *N*-bromosuccinimide (NBS) in a regio- and stereoselective manner was reported by Rahman *et al.* (Scheme 100).<sup>119</sup> The dibromide products could be obtained in 85–88% yields after milling the diquinoline derivatives and NBS in a mixer mill at 15 Hz for 6 h.

Wang and Wu demonstrated the solvent-free mechanochemical aminochlorination of electron-deficient olefins promoted by (diacetoxyiodo)benzene [ $\text{PhI}(\text{OAc})_2$ ] using commercially available and cheap chloramine-T as a nitrogen and chlorine source (Scheme 101).<sup>120</sup> The aminochlorination of electron-deficient olefins including various  $\alpha,\beta$ -unsaturated enones, a representative cinnamate and cinnamide was conducted in a mixer mill at a speed of 30 Hz for 90 min to provide the chloramine products predominantly or exclusively as the *anti* isomers in 41–78%

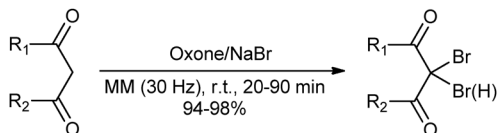




Scheme 102



Scheme 106



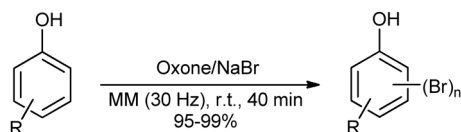
Scheme 103

yields. The vicinal chloramine derivatives were obtained in high regio- and stereoselectivity.  $\text{PhI}(\text{OAc})_2$  was found to be superior to metal salts for the aminochlorination of electron-deficient olefins.

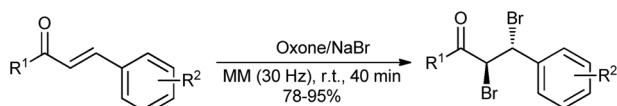
The Wang group later showed that the mechanochemical aminobromination of electron-deficient olefins and styrenes with good yields and excellent diastereoselectivities could be realized by replacing chloramine-T with  $\text{TsNH}_2$  and NBS (Scheme 102).<sup>121</sup>

Recently, Wang and Gao reported the solvent-free brominations of 1,3-dicarbonyl compounds, phenols and various alkenes including chalcones, azachalcones, 4-phenylbut-3-en-2-one, methyl cinnamate, styrene and 1,3-cyclohexadiene by employing sodium bromide and Oxone under mechanical milling conditions.<sup>122</sup> It was found that cyclic 1,3-dicarbonyl compounds afforded  $\alpha,\alpha$ -dibromo derivatives in 94–96% yields. In contrast, acyclic 1,3-dicarbonyl compounds selectively gave  $\alpha$ -monobromo derivatives in 96–98% yields (Scheme 103). Multibrominated phenols could be obtained exclusively from substituted phenols with extremely high efficiency (Scheme 104). The attempted monobromination using 1 equiv. of NaBr failed because the reaction tended to give a mixture of products. A wide range of chalcones and azachalcones with either electron-withdrawing groups or electron-donating groups were successfully transformed into the corresponding *anti*  $\alpha,\beta$ -dibromo derivatives in 78–95% yields (Scheme 105).

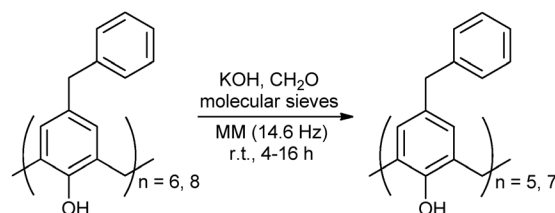
Nearly at the same time, Stolle and coworkers disclosed the mechanochemical halogenations of arenes by employing Oxone and NaX ( $\text{X} = \text{Cl}, \text{Br}$ ) as the oxidant and halogen source, respectively (Scheme 106).<sup>123</sup> It was found that bromination



Scheme 104



Scheme 105



Scheme 107

afforded higher product yields than chlorination. Investigation of the reaction parameters indicated that the oscillation frequency, milling time and the number of milling balls were the main influencing variables. Halogenation of styrene and phenylacetylene was also investigated.

## 11. Formation of calixarenes, rotaxanes and cage compounds

Raston and coworkers reported that *p*-benzylcalix[5]arene and *p*-benzylcalix[7]arene were generated from *p*-benzylcalix[6 or 8]arenes in the presence of KOH and molecular sieves (4 Å) using a Spex 8000 mixer mill for 4–16 h (Scheme 107).<sup>124</sup> *p*-Benzylcalix[5 and 7]arenes were separated in 10–15% and 5–10% yields, respectively. Calixarenes could be synthesized using the ball milling technique from paraformaldehyde, base, molecular sieves and *p*-benzylphenol, however only in trace amounts. These findings suggested that the products were not generated *via* a simple disproportionation mechanism.

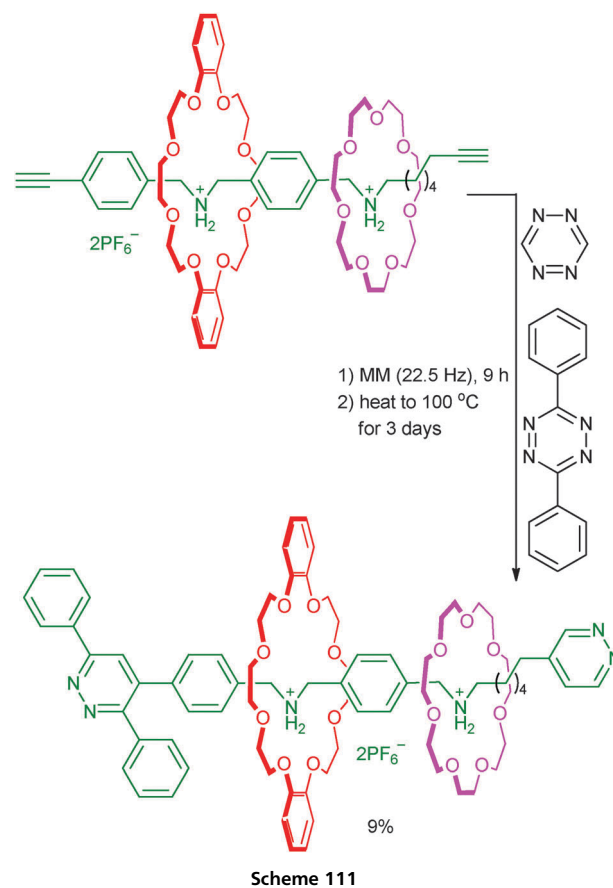
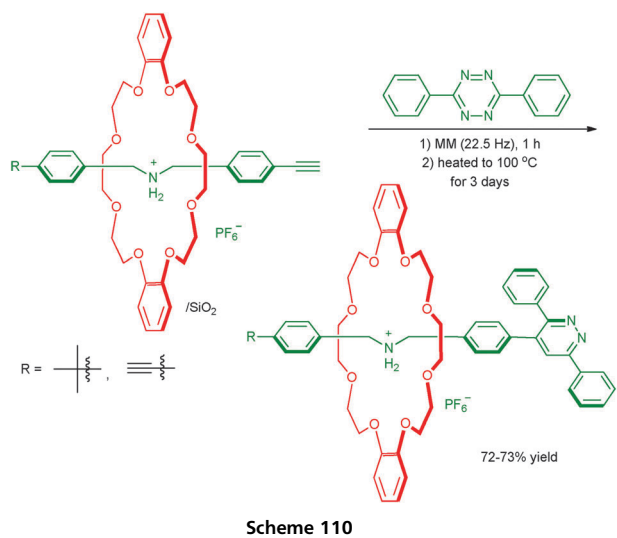
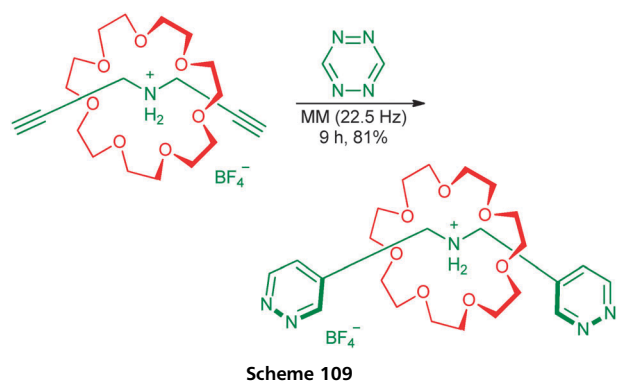
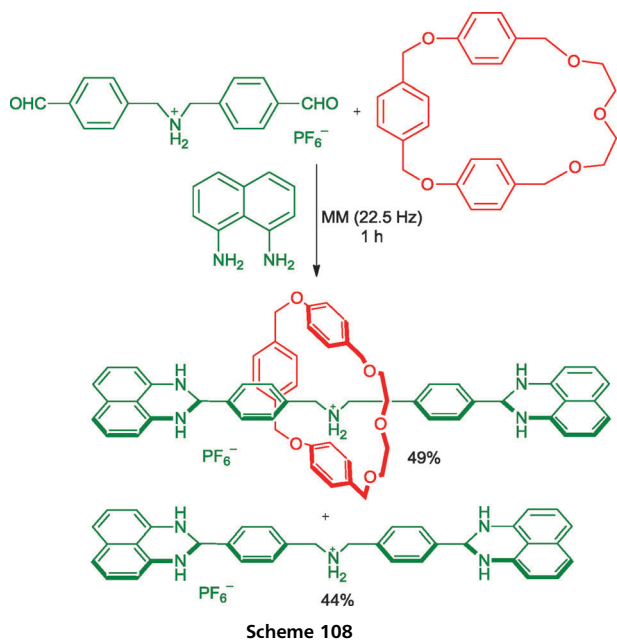
Chiu and coworkers reported a new solid-state mechanochemical reaction that produced both [2]- and [4]rotaxanes in high yields using a swing mill at a frequency of 22.5 Hz (Scheme 108).<sup>125</sup> The solid-state ball-milling condensation of 1,8-diaminonaphthalene and benzaldehyde derivatives was a convenient, waste-free and efficient reaction for preparing interlocked molecules such as [2]- and [4]rotaxanes due to the steric bulk and stability of the resulting dihydropyrimidine stopper units.

Soon afterwards, the Chiu group described the mechanochemical synthesis of the smallest rotaxane.<sup>126</sup> The authors utilized the Diels–Alder reaction of 1,2,4,5-tetrazine with the terminal alkyne units of a 21-crown-7 (21C7)-based [2]pseudorotaxane to produce pyridazine end groups as stoppers in a 21C7-containing [2]rotaxane in 81% yield (Scheme 109).

Chiu and coworkers later employed the same strategy to construct both non-symmetric and symmetric [2]rotaxanes incorporating either 24- or 25-membered-ring macrocycles (Scheme 110).<sup>127</sup>

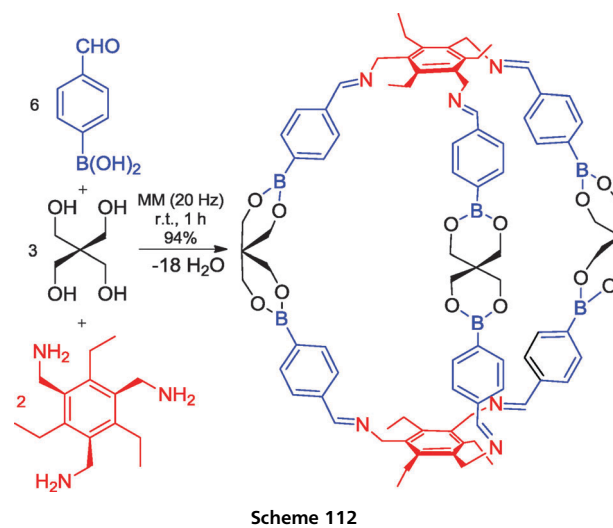
Recently, the Chiu group reported the one-pot synthesis of a hetero[3]rotaxane, assembled from five different molecular components under solvent-free conditions, through “self-sorting”





of the bead and stopper units during the threading and stoppering processes (Scheme 111).<sup>128</sup>

The mechanochemical synthesis of molecular nanostructures by multicomponent condensation reactions in a ball mill was demonstrated by Severin and coworkers.<sup>129</sup> When 4-formylphenylboronic acid was ball-milled with pentaerythritol and 1,3,5-trisaminomethyl-2,4,6-triethylbenzene for 1 h at 20 Hz, the cage compound was obtained in 94% yield after an additional heating step to remove the by-product water (Scheme 112).



## 12. Transformation of biologically active compounds

### 12.1 Nucleoside and sugar protection

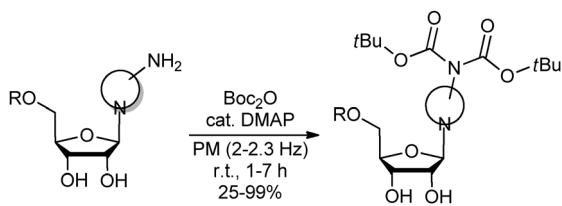
A solvent-free reaction employing a simple low-energy ball mill apparatus converts the amino groups of adenosine, 2-deoxyadenosine, cytidine, 2-deoxycytidine, guanosine and 2-deoxyguanosine as well as some of their ribosyl *O*-protected derivatives to the corresponding bis-*N*-Boc carbamates (Scheme 113).<sup>130</sup>

Vyle, James and coworkers showed the persilylation of nucleoside hydroxyls in quantitative yields under solvent-free conditions using a ball mill (Scheme 114).<sup>131</sup> Furthermore, one-pot persilylation and acylation of cytidine was performed as an exemplar reaction to demonstrate the utility of solvent-free approaches to nucleoside chemistry.

Patil and Kartha<sup>132</sup> successfully used a planetary ball mill for the regioselective 6-*O*-tritylation/silylation of various monosaccharides and their derivatives in the presence of DABCO or Na<sub>2</sub>CO<sub>3</sub> under solvent-free conditions by dry milling. Further wet milling of the reaction mixture with Ac<sub>2</sub>O in the presence of DMAP led to the fully protected hexosides in good to excellent yields. This one-pot two-step synthesis was efficient under solvent-free conditions (Scheme 115).

### 12.2 Functionalization of sugars

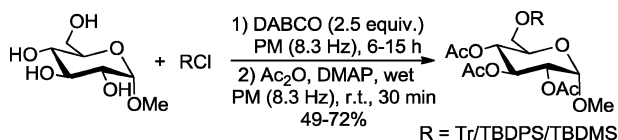
Mugunthan and Kartha reported the displacement of different glycosyl halides by sodium azide *via* a cyclic oxocarbenium ion intermediate in a planetary ball mill (Scheme 116).<sup>133</sup> After mechanochemical treatment of glycosyl halides with 10 equiv. of NaN<sub>3</sub> at 500/600 rpm for 8 h, 1,2-*trans*-linked glycosyl azides were obtained in 87–99% yields.



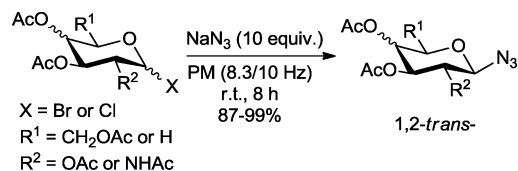
Scheme 113



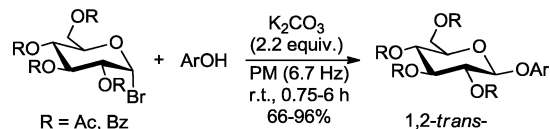
Scheme 114



Scheme 115



Scheme 116



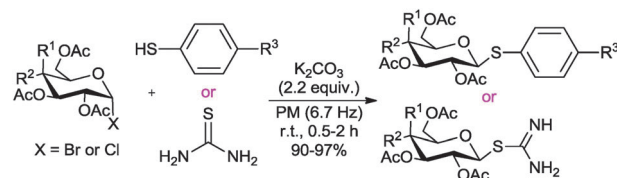
Scheme 117

Patil and Kartha reported that aryl glycosides were prepared from the solvent-free reaction of readily available glycosyl bromides with phenols in the presence of K<sub>2</sub>CO<sub>3</sub> by employing a planetary ball mill at 400 rpm in excellent yields (Scheme 117).<sup>134</sup>

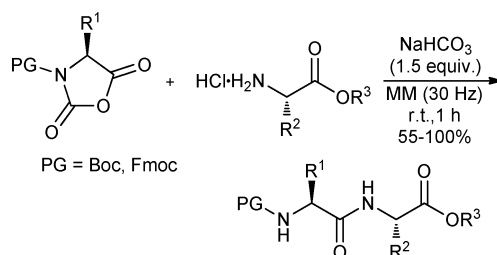
Patil and Kartha also disclosed the solvent-free mechanochemical synthesis of thioglycosides from glycosyl halides in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>135</sup> Various glycosyl bromides and chlorides could be used to react with thiophenols, thiourea or KSAC in a planetary ball mill at 400 rpm for 0.5–2 h, providing the thioglycosides in high yields (Scheme 118). Multi-step synthesis of alkyl, aryl and glycosyl thioglycosides *via* the glycosyl thiuronium salt intermediate could be achieved in one pot. The above procedures required neither chromatographic purification nor use of a phase-transfer catalyst.<sup>134,135</sup>

### 12.3 Peptide and nucleoside synthesis

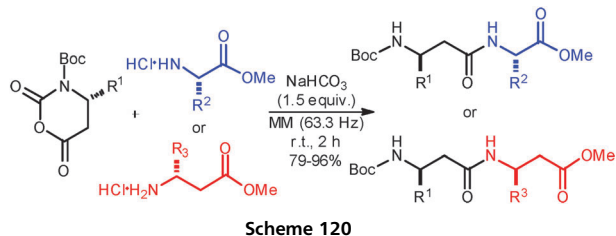
The field of peptide synthesis has seen significant progress over the past few decades. One of the major remaining challenges is to reduce the amounts of solvent used. Lamaty and coworkers studied the opening of urethane protected  $\alpha$ -amino acid *N*-carboxyanhydride (UNCA) derivatives with  $\alpha$ -amino acid



Scheme 118



Scheme 119



derivatives to afford the corresponding peptides including dipeptides and a tripeptide under solvent-free conditions using a ball milling method (Scheme 119).<sup>136</sup>

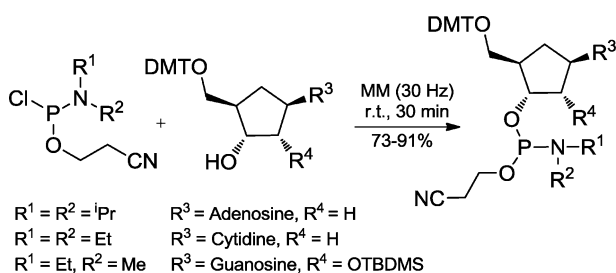
Similarly, Hernández and Juaristi reported the solvent-free reaction of  $\beta$ -UNCAs derived from  $\beta$ -alanine, (*S*)- $\beta^3$ -homophenylglycine and (*S*)- $\beta^3$ -carboxyhomoglycine with different  $\alpha$ - and  $\beta$ -amino ester hydrochlorides under ball-milling conditions. Good to excellent yields of several relevant  $\alpha,\beta$ - and  $\beta,\beta$ -dipeptides were obtained (Scheme 120).<sup>137</sup>

Hardacre *et al.* combined ionic liquids with ball milling to synthesize phosphitylate nucleosides and 2-deoxynucleosides with a range of chlorophosphoramidite reagents (Scheme 121).<sup>138</sup> The enhanced stability provided by the ionic liquid-mediated processes combined with efficient mass transfer induced by ball milling enabled excellent yields to be obtained even when using small dialkyl amino groups as well as the more commonly used diisopropylamino protection.

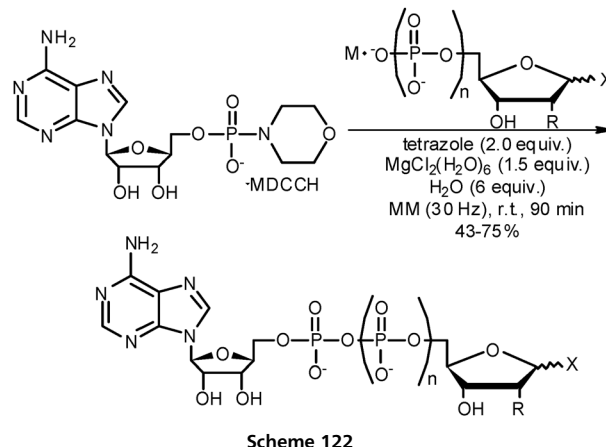
Migaud, Vyle and coworkers showed a rapid, atom-economic pyrophosphate bond formation between adenosine-5'-phosphoromorpholidate and sodium or barium salts of phosphorylated ribose derivatives in a ball mill (Scheme 122).<sup>139</sup>

### 13. Asymmetric synthesis

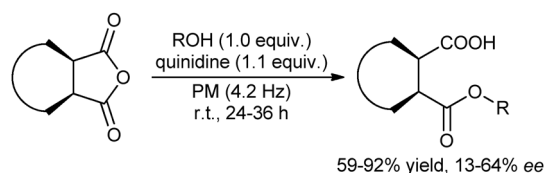
The Bolm group was the first to investigate asymmetric synthesis using the mechanical milling technique under solvent-free conditions. The alkaloid-mediated asymmetric opening of a cyclic *meso*-anhydride with *p*-methylbenzyl alcohol was explored as a proof-of-concept reaction in a ball mill. The solvent-free quinidine-mediated reaction was conducted in a planetary micro mill with a rotational speed of 250 rpm (4.2 Hz) for 24–36 h, and a hemiester was obtained in 91% yield with an enantioselective excess of 61%, comparable to the reaction performed in solution.<sup>140</sup> This desymmetrization reaction affording optically active dicarboxylic acid monoesters was later



**Scheme 121**



**Scheme 122**

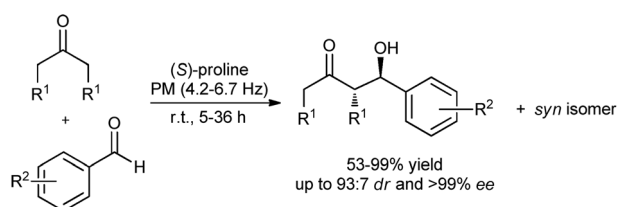


**Scheme 123**

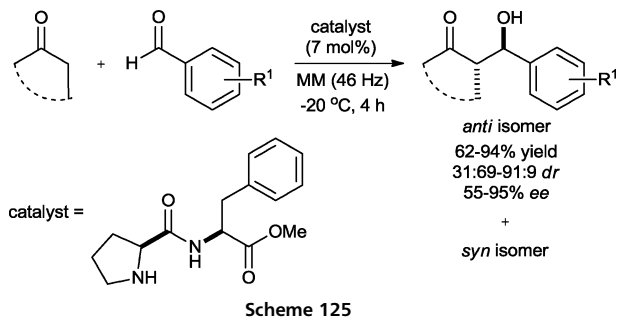
extended to various *meso*-anhydrides and alcohols, demonstrating the wide scope of this methodology (Scheme 123).<sup>141</sup>

With the initial success in the organocatalytic enantioselective reaction, Bolm and coworkers further studied the proline-catalyzed aldol reaction of ketones with aromatic aldehydes in a ball mill. The solvent-free enantioselective aldol reaction performed with a rotation speed of 250–400 rpm for 5–36 h led to the formation of *anti*-isomers as the major products with good stereoselectivities (up to 93:7 dr and >99% ee) (Scheme 124).<sup>140</sup>

The Bolm group then investigated the proline-catalyzed aldol reaction in detail by examining the effects of concentration, water, impurities in starting materials, milling frequency and by extending it to more substrates.<sup>142</sup> They found that neither dry conditions nor an inert atmosphere was required, and non-purified starting materials could be used directly. In addition, the same group employed ball milling to study the phase behaviour of the proline-catalyzed aldol reaction between solely solid substrates under solvent-free conditions.<sup>143</sup> A significant nonlinear relationship between the enantiomeric excess of the catalyst and that of the aldol product was observed.



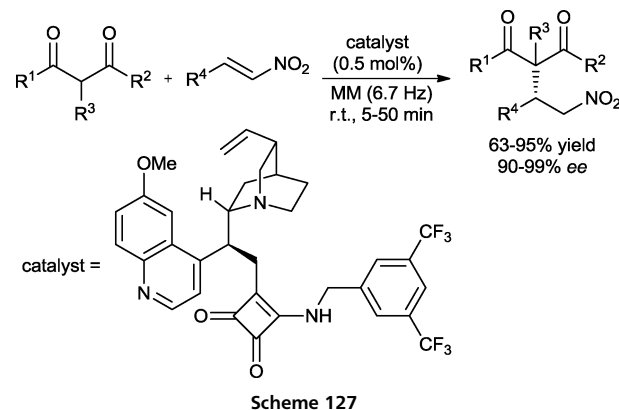
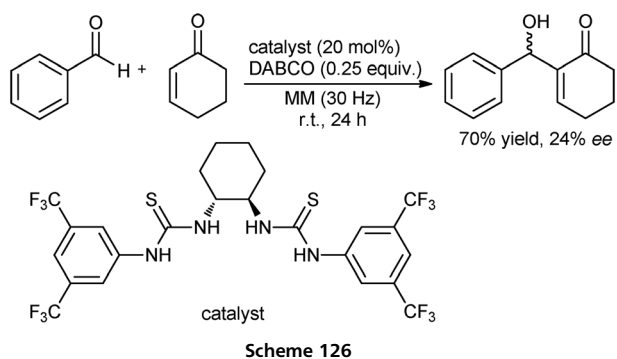
**Scheme 124**



Nájera and coworkers attempted the solvent-free enantioselective aldol reaction between cyclic ketones and 4-nitrobenzaldehyde catalyzed by a combination of (*S*)-binam-L-prolinamide (5–10 mol%) and benzoic acid (10–20 mol%) in a ball mill at a rotation speed of 300–400 rpm.<sup>144</sup> The *anti*-isomers were also obtained as the major aldol products. However, no obvious advantages were found for the ball-milling conditions compared to the solvent-free reaction conditions under simple and conventional magnetic stirring in terms of product yield, reaction time and stereoselectivity.

Hernández and Juaristi investigated the organocatalytic activity of the methyl ester of (*S*)-proline-(*S*)-phenylalanine in the asymmetric aldol reactions of cyclohexanone and acetone with various aromatic aldehydes under solvent-free conditions in a ball mill.<sup>145</sup> At a milling frequency of 2760 rpm (46 Hz) and -20 °C, the (*S*)-proline-containing dipeptide catalyzed the stereoselective formation of the expected aldol products in 62–94% yields, with up to 91:9 *anti*:*syn* *dr* and up to 95% *ee* (Scheme 125). They also found that when the catalyst was replaced with the methyl ester of (*S*)-proline-(*S*)-tryptophan and with the addition of water and benzoic acid, higher diastereo- and enantioselectivities (up to 98:2 *anti*/*syn* *dr* and up to 98% *ee*) were achieved.<sup>146</sup> Furthermore, (*S*)-proline-containing dipeptides and thiodipeptides could be employed for the mechanochemical asymmetric aldol reaction, and proved to be better organocatalysts relative to their analogous amides.<sup>147</sup>

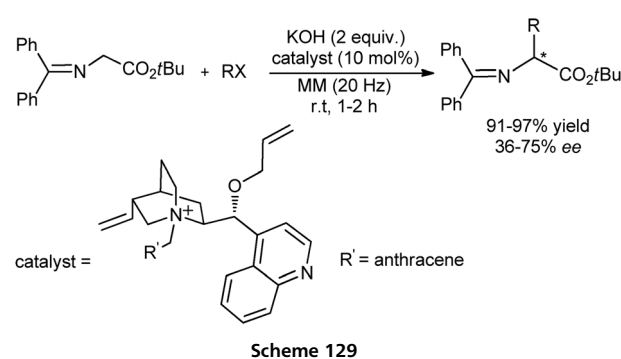
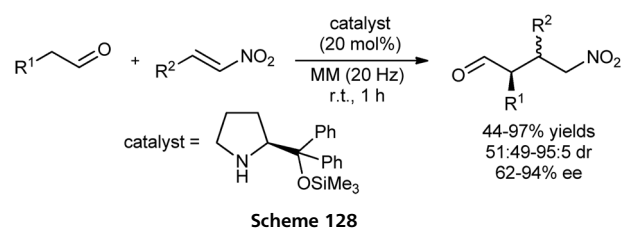
The chiral bis(thiourea) prepared quantitatively from 3,5-bis(trifluoromethyl)phenyl isothiocyanate and (1*R*,2*R*)-diaminocyclohexane was examined as an organocatalyst in the asymmetric Morita–Baylis–Hillman reaction of benzaldehyde with 2-cyclohexene-1-one; the product was obtained in 70% yield and 24% *ee* after milling for 24 h (Scheme 126).<sup>85</sup>



Xu and coworkers developed the asymmetric Michael addition reaction of 1,3-dicarbonyl compounds to nitroolefins catalyzed by chiral squaramide derivatives under solvent-free conditions using a planetary ball mill (Scheme 127).<sup>148</sup> Remarkably, a catalyst loading of 0.5 mol% was sufficient to complete most reactions at a rotational speed of 400 rpm (6.7 Hz) within 50 min, and the Michael adducts were obtained in 63–95% yields and 90–99% *ee*.

The enantioselective Michael addition of aldehydes to nitroalkenes was investigated under solvent-free ball-milling conditions (Scheme 128).<sup>149</sup> A range of pyrrolidine-derived organocatalysts were tested, and  $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether was found to be the best one. After ball milling at a frequency of 20 Hz for 1 h, the Michael adducts were obtained in 44–97% yields, 51:49–95:5 *anti*:*syn* *dr* and 62–94% *ee*.

Lamaty and coworkers performed the solvent-free asymmetric alkylation of Schiff bases under basic conditions in a ball mill.<sup>150</sup> The starting Schiff bases of glycine were nearly quantitatively prepared by milling a stoichiometric mixture of glycine acid methyl ester hydrochloride and benzophenone imine in a vibratory ball



mill at a frequency of 30 Hz for 3 h. Non-asymmetric alkylation was then conducted to optimize the applied base, and KOH turned out to be the best base. By adding a chiral ammonium salt derived from cinchonidine, the reaction proceeded asymmetrically under phase-transfer catalysis conditions in a ball mill at 20 Hz for 1–2 h, giving 91–97% yields with up to 75% ee (Scheme 129).

## 14. Miscellaneous mechanochemical reactions

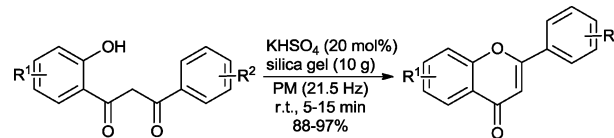
Makhaev *et al.* studied the formation of ferrocenes *via* the solid-state mechanochemical reaction of iron(II) chloride with cyclopentadienides of alkaline metals or thallium (CpK, CpTl, CH<sub>3</sub>C<sub>5</sub>H<sub>4</sub>Na).<sup>151</sup> The reaction was performed in a ball mill at a frequency of 12 Hz for 15–60 min to afford the ferrocenes in 84–90% yields (Scheme 130). Nickelocene could be similarly prepared in 90% yield by the reaction of NiCl<sub>2</sub> with CpTl.

When nitroalkanes were allowed to react with tetrahydroquinolines in the presence of DDQ, the CDC products could be obtained in 70–85% yields after milling at 30 Hz for 10–30 min (Scheme 131).<sup>50</sup> A metal catalyst was not required in this case.

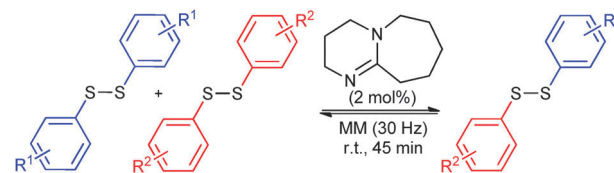
Waddell and Mack reported the solvent-free Tishchenko reaction of aryl aldehydes with NaH as the catalyst by ball milling (Scheme 132).<sup>152</sup> The esters were obtained in 69–98% yields by milling in a Spex CertiPrep mixer/mill 8000 M open to the atmosphere for 0.5–16 h. It was found that magnesium metal could replace NaH under the present mechanical conditions.

Su and coworkers described an efficient solid-state KHSO<sub>4</sub>-catalyzed synthesis of flavones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones (Scheme 133).<sup>153</sup> The cyclodehydration was performed in a planetary centrifugal mill AGO-2 with a rotational speed of 1290 rpm (21.5 Hz) for 5–15 min to give flavones in 88–97% yields.

Recently, Belenguer, Frišćić and coworkers demonstrated the reversibility and thermodynamic control in covalent



Scheme 133

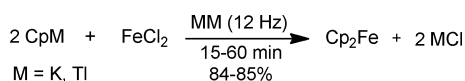


Scheme 134

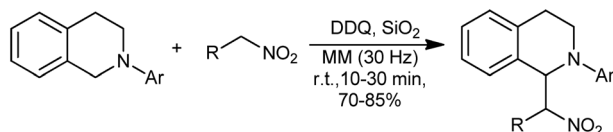
mechanosynthesis, by using the base-catalyzed metathesis of aromatic disulfides as a model reaction in a mixer mill at 30 Hz (Scheme 134).<sup>154</sup> The mechanochemical formation of thermodynamic equilibrium mixtures was observed for both neat milling and LAG methodologies. Different methodologies resulted in mutually different equilibrium compositions, which also differed from those obtained by solution equilibration.

## 15. Conclusions

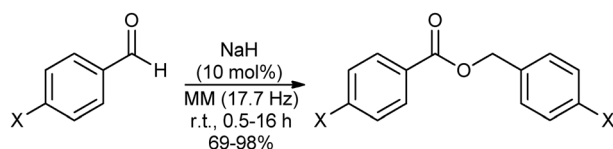
Most organic reactions have been performed in the liquid phase with an organic solvent as the reaction medium. Solvent-free organic synthesis in a mortar and pestle has been known for about two decades and reviewed in a number of journals and books. In comparison, the application of the more reliable and sophisticated mechanical milling technique using a vibration mill to organic synthesis began later and was first initiated in organic reactions of fullerenes in the mid-1990s.<sup>155</sup> Right now, organic synthesis utilizing a mixer mill or planetary mill is attracting intensive attention. In this review, mechanochemical organic synthesis limited to the use of the ball milling technique under solvent-free conditions has been covered. Fe-, Mn- and Cu-mediated reactions as well as Pd- and Cu-catalyzed reactions have been explored to show the suitability of dehydrogenative couplings, radical reactions, Suzuki reactions, Heck reactions, Sonogashira reactions, click reactions, *etc.* to the mechanical milling protocol. Various mechanochemical condensation reactions including those of amines and boronic acids, Knoevenagel, aldol, Michael and Morita–Baylis–Hillman reactions have been studied. Nucleophilic reactions including nucleophilic addition reactions, Wittig reactions/Horner–Wadsworth–Emmons reactions and nucleophilic aromatic substitutions in a ball mill have also been demonstrated. Diels–Alder, oxidation, reduction and halogenation/aminohalogenation reactions prove to be feasible under mechanical milling conditions. Mechanochemical cascade reactions involving nucleophilic reactions and condensation reactions have been shown to be very efficient. The ball milling technique has been successfully employed in the synthesis of calixarenes, rotaxanes and cage compounds. Interestingly, mechanochemical asymmetric synthesis shows great potential for desymmetrization,



Scheme 130



Scheme 131



Scheme 132

aldol, Michael and alkylation reactions. In addition, the solvent-free transformation of biologically active compounds by ball milling is attractive for practical applications. Although various solvent-free organic reactions under mechanical milling conditions have been investigated, recent work shows that more attention is paid to metal-mediated/catalyzed reactions, asymmetric synthesis and the synthesis of macromolecules.

As usual, performing a solvent-free mechanochemical reaction also requires optimization of the reaction conditions. Technical variables such as milling frequency/revolutions per minute, milling time, size and number of milling balls, and the material of milling balls and beakers have all exerted influences on a chemical reaction. A number of investigations have demonstrated that the milling frequency and milling time are the most important parameters. The discovery of the use of the vial and ball material as a catalyst in ball-milled chemical reactions is interesting. New Cu- or Fe-catalyzed reactions may be designed to exploit the vial and ball as the catalyst.

A solvent-free mechanochemical organic reaction exhibits many advantages over its liquid-phase counterpart in terms of higher product yield, better selectivity, shorter reaction time, simpler work-up procedure, elimination of harmful organic solvent, *etc.* It should be pointed out that although the efficiency for solvent-free mechanochemical reactions is generally very high compared to those of either reactions by hand grinding or their liquid-phase counterparts, it is hard to achieve a quantitative or 100% yield. Occasionally, a drying agent ( $\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$ ) is added or a drying process under high vacuum and heating conditions is often employed in the work-up treatment. Just like the solvent-free reactions by hand grinding, the drying process may drive the reactions for the milled samples to completion, particularly for condensation and cascade reactions generating water as the by-product. Nowadays, no difficulty exists in scaling-up mechanochemical syntheses up to 200 g batches,<sup>55,156</sup> and final large-scale industrial productions. The most attractive feature of the mechanochemical methodology may lie in the discovery of new chemical reactions, which are only available under the solvent-free conditions. It is expected that the continuous study of solvent-free mechanochemical organic synthesis will attract increasing attention, bring about the discovery of many new organic reactions and eventually lead to practical applications in the chemical industry, pharmaceutical science and life science.

## Acknowledgements

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