

Speed-up your synthesis lab: Planetary Ball Mills as a tool in organic synthesis

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Ball Mills are apparatus designed for the refinement of particles or desagglomeration of aggregated species. Thus, ball milling is a valuable technology for up- and down-stream processes with myriad of applications in chemical industry, food technology, pharmacy and further branches. Refinement of particles to a defined size is generally accompanied by an increase of the specific surface area which itself goes along with rising number of surface defects. Those are centers for reactivity. Thus, comminution of particles results in chemical activation of solids and as a final consequence reactions can occur between solids: *reactive milling*. For long time reactive milling using Ball Mills was restricted to the field of inorganic synthesis and materials science allowing the synthesis and design of advanced materials with unique properties; often difficult or even impossible to synthesize on classical routes. One type of Ball Mill which is often applied for such reactions are Planetary Ball Mills, whose operating principle is shown in Figure 1: Grinding balls are accelerated due to rotation of the grinding bowls which themselves are mounted on sun disc rotating in the opposite direction. The resulting trajectories of the grinding balls result in frictional forces and impact processes between the grinding balls and of course between the grinding balls and the grinding bowl wall. The kinetic energy is transformed and dissipated as thermal energy and allows the initiation of chemical reactions resulting in the above described phenomenon of *reactive milling* or *mechano-chemical reactions*.

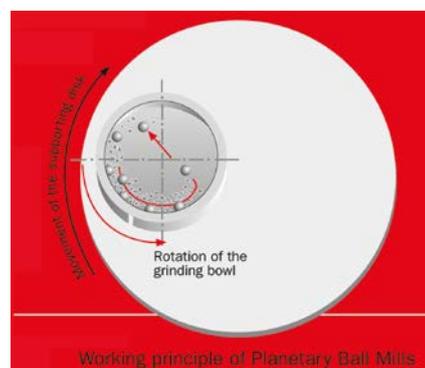


Figure 1. Planetary Ball Mill PULVERISETTE 7 *premium line* (Fritsch GmbH) and general operating principle of Planetary Ball Mills.

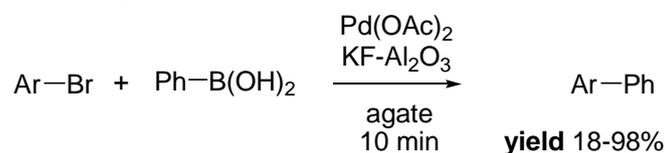
The concepts of Sustainable Chemistry and Process Intensification are the main driving forces leading to application of Ball Mills as reactors in organic synthesis also. Although, theoretical models predict extreme reaction conditions in the impact zones of grinding balls, several publications indicate that this type of synthesis is possible and often result in spectacular and unintended results regarding chemical reactivity or selectivity in comparison to classical solution-based synthesis [1,2]. The omission of solvents in the reaction step is for sure one of the many advantages of ball milling making this technology a tool with fast growing fields of application, beyond solely organic synthesis and particle refinement.

Cooperation of the author's institutions contributes to the development of new reaction protocols for the synthesis of organic molecules without solvent in Planetary Ball Mills. Thus, it was possible to widen the scope of reactions including advanced methodologies for the formation of carbon-carbon bonds *via* Pd-catalyzed cross-couplings as well as techniques allowing the construction of heterocycles from readily available building blocks like alkynes and azides. Scheme 1 provides a short overview regarding such metal-catalyzed reaction protocols. Cross-coupling of aryl bromides (Ar-Br) with phenylboronic acid in the solid state yielded the respective biphenyls in 18-98% yield depending on the substituents of the first coupling partner [3]. Reactions are catalyzed using plain Pd(OAc)₂ and the presence of KF-Al₂O₃ was necessary as basic reagent. Yields were able to be fine-tuned by variation of the molar ratio of KF and Al₂O₃ as well as the content of water being adsorbed on the reagents surface [4]. Application of the same catalyst for the Sonogashira cross-coupling of aryl iodides with terminal alkynes furnished alkynes with two different substituents at the carbon-carbon triple bond [5]. Similar to the above mentioned example the yield depends on the nature of the coupling partners. Furthermore, diazabicyclo[2.2.2]octane (DABCO) was applied as solid base and has been proven as most effective for this type of solid-state reaction in a Planetary Ball Mill. Surprisingly, the selectivity for the cross-coupling product is high (> 95%) regardless from the type of substituent and the fact that the reaction is carried out in the presence of air in heterogeneous phase. Side reactions often observed for such reaction conditions like homo-coupling, were not observed at all or the content of respective products was below the detection limit. Apart from Suzuki and Sonogashira cross-coupling solvent-free methodologies for the Heck reaction have been published also [6].

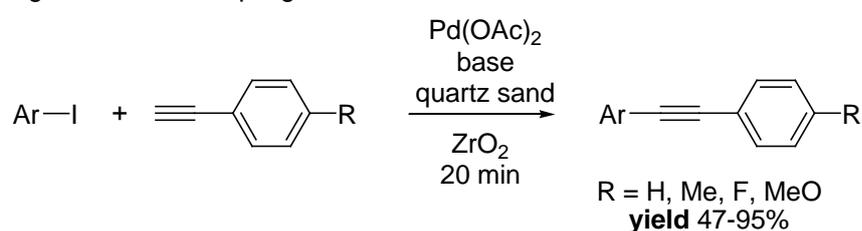
Beside Pd-catalyzed reactions Scheme 1 shows also an example for a Cu-catalyzed alkyne-azide cycloaddition (CuAAC), [7] a prototype for so-called *Click-reactions*, characterized by high yield, high selectivity, and easy accomplishment [8]. Performance of such reactions in Ball Mills afforded some precautions since azides are in general shock-sensitive materials. However, phlegmatization of the reaction mixture with quartz sand as milling auxiliary provides the respective 1,4-substituted 1,2,3-triazoles in yields ranging from 80 to 98% [7]. The reaction methodology was furthermore applied for the functionalization of an azido-sugar

and of a polystyrene which was modified with a terminal alkyne allowing the reaction with *n*-decyl azide. Since the last reaction proceeded without disintegration of the polymer chain, attempts to carry out polymerization in a Planetary Ball Mill have been undertaken with promising results for future applications.

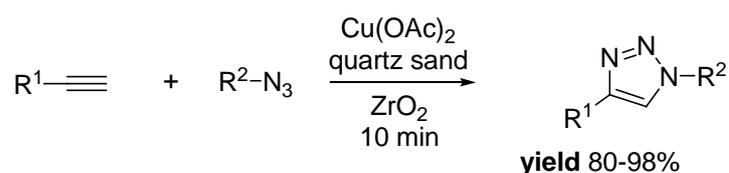
Suzuki cross-coupling



Sonogashira cross-coupling



azid-alkyne-cycloaddition



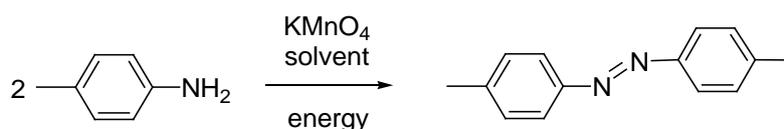
Scheme 1. Metal-catalyzed reactions carried out in Planetary Ball Mills at lab-scale.

Beside chemical aspects of reactions in Ball Mills, technological parameters influence the reactions considerably. Several model reactions from different fields of organic synthesis have been chosen to investigate the effects of those variables on the outcome of the reaction. Suzuki cross-coupling provide valuable information [9] as well as the dehydrogenation of γ -terpinene to *p*-cymene [10] and the oxidative cleavage of β -pinene affording nopinone [11]. Especially the last example proved to be a real alternative for ozonation at low temperatures. Assessment of the parameters indicate that the type of Ball Mill – Planetary Ball Mill or Mixer Ball Mill – is not relevant for the outcome of the reaction; variables like the milling material, the number and size of grinding balls, as well as the filling degree of the grinding bowls are much more important [9-12]. Contrarily to particle refinement the size of the grinding balls seemed not to be important, as long as the cumulative mass of the grinding balls is kept constant [10]. The choice of the milling material is not only important for the amount of transferrable kinetic energy, since the material density determines the transferred wear energy, but also chemical aspects should be considered [2,5,12], *i.e.* the chemical resistance and the mechanical stability of the material. The filling

degree of the grinding bowls is important with respect to the number of collisions and impacts during ball milling. Low filling degree results in deterioration of the grinding media, whereas grinding bowls completely filled with the feed material hamper the movement of the grinding balls. Although, technological parameters are important for several reasons, experiments in Ball Mills with respect to organic synthesis are significantly influenced by process parameters like operating frequency and reaction time [2,9-11]. Correlation of those variables to either the wear energy (frequency) or the reaction rate (time) displays the importance of those for successful accomplishment of reactions in a Ball Mill. Investigation of the effects for different model reactions draw a heterogeneous picture, not allowing to draw general conclusions, since the kinetic prerequisites are very different for the individual transformations.

Calculation of the energy intensity for the synthesis of one mole of a desired product allows the energetic assessment of reaction procedures or process technologies. With respect to this value synthesis in Ball Mills is comparable to ultrasound-assisted reactions and outperform syntheses in microwave ovens and classical heating baths as exemplified in Table 1 for the solid-state oxidative homo-coupling of *p*-toluidine to the azo dye in presence of KMnO_4 [12]. The efficiency of the energy transfer from the power socket into a desired product is proven for several examples. Comparison of different Ball Mills regarding their gross power input and the degree of efficiency to transform this energy into kinetic energy, prove that large-scale Planetary Ball Mills operate more efficiently. Although, the net power input is higher for those the efficiency is significantly increased, thus from a relative point of view, less energy is wasted for auxiliary components of the machine. Especially the last aspect is important for the scale-up of organic syntheses in Ball Mills.

Table 1. Comparison of different possibilities for energy entry regarding yield and energy intensity E_m for the model oxidation of *p*-toluidine to its azo-compound [12].



energy entry	device	condition	yield [%]	E_m [kWh mol ⁻¹]
mechanical	Planetary Ball Mill	solvent-free ^{a)}	97	18
	Mixer Ball Mill	solvent-free ^{a)}	94	5
	ultrasound (24 kHz, 200 W)	H ₂ O/acetonitrile ^{b)}	94	24
radiation-based	heating bath	H ₂ O/acetonitrile ^{c)}	86	37
	microwave (multimode)	H ₂ O/acetonitrile ^{d)}	85	118

^{a)} milling material: agate, 20 min, 800 min⁻¹ $\hat{=}$ 13.3 Hz.

^{b)} 20 min at 20 °C with maximal power input.

^{c)} 60 in at 80 °C.

^{d)} 30 min at 80 °C, maximal power input = 300 W.

Planetary Ball Mills have been proven their applicability as reactors for organic syntheses from different points of view. Performance of chemical reactions in the solid state without a solvent takes advantage of the high mixing efficiency of Ball Mills and the continuous particle refinement resulting in surfaces with high activity. Thus, often increased selectivity and reactivity have been found paving the ground for future developments and applications of Ball Mills in organic synthesis. The second most important advantage is the reaction time, which is often restricted to several minutes, which is in the same range of magnitude as microwave-assisted processes. Compared to transformations in solution high concentration of substances speed-up the reactions considerably. Although some tasks have to be solved in future (temperature regulation), the direct generation of thermal energy in the grinding bowls results in low energy intensities of reactions carried out in Ball Mills. Recent and many reactions published in literature for organic syntheses using Ball Mills refute Aristotle's citation *No coopora nisi fluida* and the method of ball milling enlarges the toolbox available for organic synthesis.

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