Electronic Supplementary Information (ESI)

Ball Milling in Organic Synthesis: Solutions and Challanges

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Getting started with ball milling: A Tutorial

The present *Tutorial* is addressed to those who wanted to explore their organic syntheses with ball mills. Some of suggestions summarized below are in agreement with references provided by the manufacturer of ball mills. However, this tutorial does not replace a manual and the operator is strongly asked to consider the respective data also. Since most ball mills are originally designed to perform particle refinement, some suggestions might not agree with the standard literature referring to this topic.

Type of reaction:

- The chemistry in ball mills is not restricted to a special type of chemical synthesis, if some requirements are fulfilled.
- At least one of the reactants and the product(s) should have melting points above 70 °C.
- No shock-sensitive materials should be exposed to mechanical stress.
- No gas-evolving reactions should be carried out under closed-vessel conditions, unless not special pressure-save milling beakers are applied.

Type of ball mill:

- There is no fundamental restriction to the type of ball mill used for organic synthesis (planetary ball mill, mixer ball mill, vibration ball mill, …).
- The scale of reaction determines the size and the type of ball mill.
- Vessels for laboratory vibration ball mills are normally restricted to a volume of 50 cm^3.

Milling material:

- The material density determines the energy entry and therefore, the choice of material influence the dissipative heat formation during ball milling. The higher the material density, the higher is the energy entry.
- Milling beakers and milling balls should be of the same material. At least, the material density of the milling beaker should be higher than that of the milling balls.
- The applied material should be chemically inert towards the reaction mixture. For most applications in organic synthesis, including catalysis, ceramic materials (e.g. ZrO_2) are the best choice. They are chemically inert and the material abrasion is comparably low.
- Some materials posses a high porosity (agate, steel) which could lead to memory effects.

Filling degree – Scale of synthesis:

- The scale of the chemical synthesis is related to the type of reaction, the available ball mill(s) and the size of the milling beakers. It is rather recommended to start the reaction at a small scale (≤ 10 mmol) and in case of success perform an up-scaling.
- The filling degree of the milling beakers is essential for the energy entry. Thus, a rule of thumb suggests that **one third** of the beaker volume should be taken up by the milling balls, **one third** of the total volume is for the reaction mixture and the remaining **third** is required for the movement of the milling balls.
- For reason of reproducibility, the procedure for loading of the milling beakers should be maintained throughout a series of experiments: At first the milling balls followed by the reaction mixture **or** the other way round.

Number and size of milling balls:

- The volume of the milling balls should relate to **one third** of the milling beaker volume.
- In contrast to particle refinement, for application in chemical synthesis the size of the milling balls seems not to be crucial. The operator is referred to suggestions provided by the manufacture or to similar examples published in literature.

- It is suggested to work with ≥ 2 milling balls. Otherwise the material abrasion becomes relevant.

Frequency and reaction time:

- In case of new reaction procedures, compare to related examples which have eventually been published.
- It is rather recommend changing reaction time than frequency.
- Start with 75-100% of the maximal operation frequency of the ball mill.
- The thermal stress for the reactants could be reduced by using cycled mode: mill for a specific amount of time – 5-10 min pause – start milling again and repeat the procedure for the required amount of time.