Mechanochemistry in Organic Synthesis

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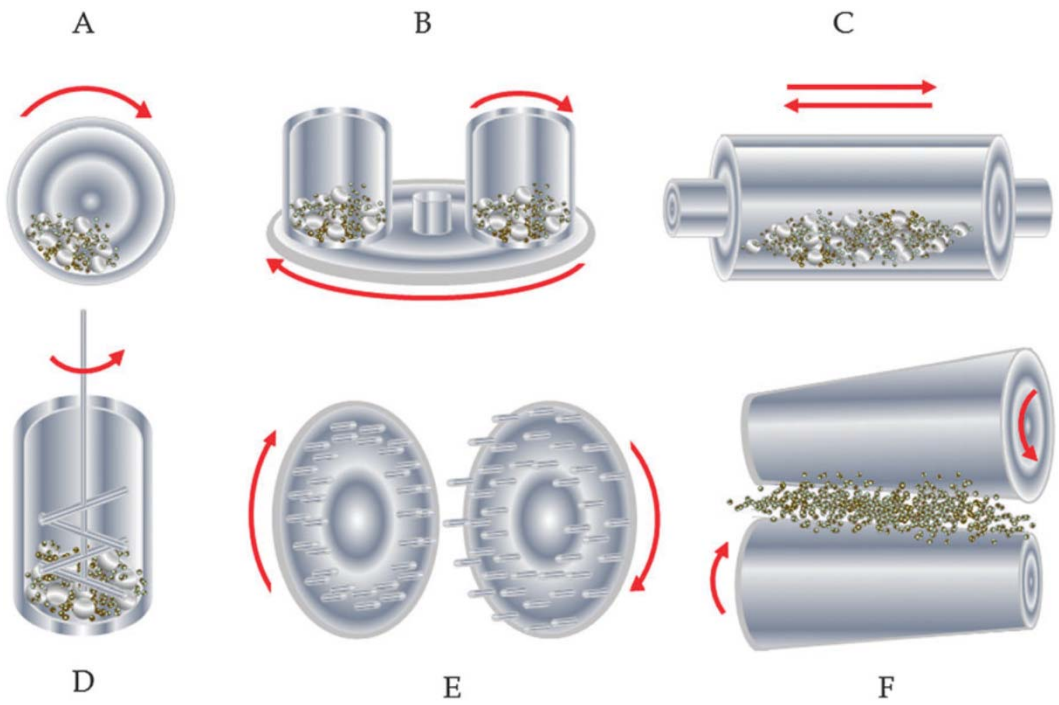
Ways to perform organic reactions:

- ❑ **Thermochemistry**
- ❑ **Photochemistry**
- ❑ **Electrochemistry**
- ❑ **Mechanochemistry**

Fernandez-Barton, J. F. Mechanochemistry: an overview. *Pure Appl. Chem.* **1999**, *71*, 581.



Types of mills for high-energy milling: A – ball mill, B – planetary mill, C – vibration mill, D – attritor (stirring ball mill), E – pin mill, F – rolling mill.

Balaź, P.; Achimovicˇ ovaˇ, M.; Balaź, M.; Billik, P.; Cherkezova- Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutkova, E.; Gaffet, E.; Gotor,́ F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Streletskii, A.; Wieczorek-Ciurowa, K. *Hallmarks of Mechanochemistry: from Nanoparticles to Technology. Chem. Soc. Rev.* **2013**, *42*, 7571.

The occurrence of the reactions in milling process

- Heat generated in the milling process
- Large area of contact between the solids

How?

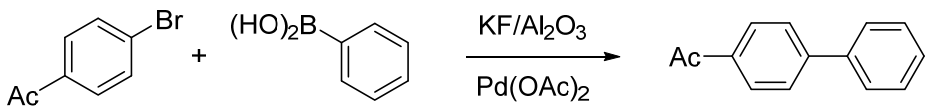
The grinding of two solid substances generates a complex series of transformations, the mechanical energy breaking the order of the crystalline structure, producing cracks, and new surfaces. At the point of collision of the edges the solids deform and even melt, forming hot points where the molecules can reach very high vibrational excitation leading to bond breaking. These stochastic processes occur in a period of 10^{-7} s.

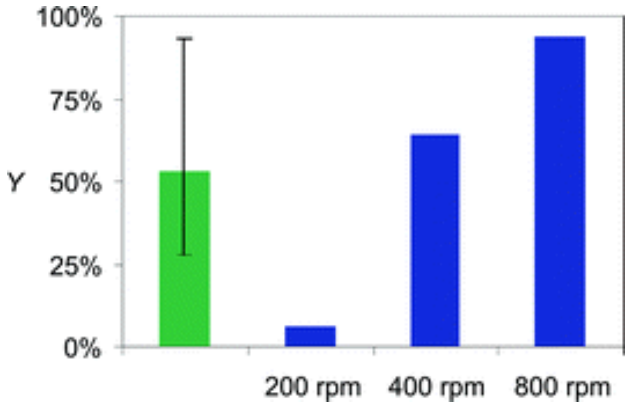
Mechanochemical processes are different from thermal processes?

For example, heating of AgCl and HgCl leads to melting and subliming of these solids, while milling them produces their decomposition into Cl_2 gas and metal.

(1) Heinicke, G. *Tribochemistry*; Akademie-Verlag: Berlin, 1984. (2) Tkacova. K. *Mechanical Activation of Minerals*. Elsevier, Amsterdam, 1989. (3) Boldyrev. V. V. *Solid State Ionics* **1993**, *63–65*, 537.

Comparison between hand grinding and ball milling



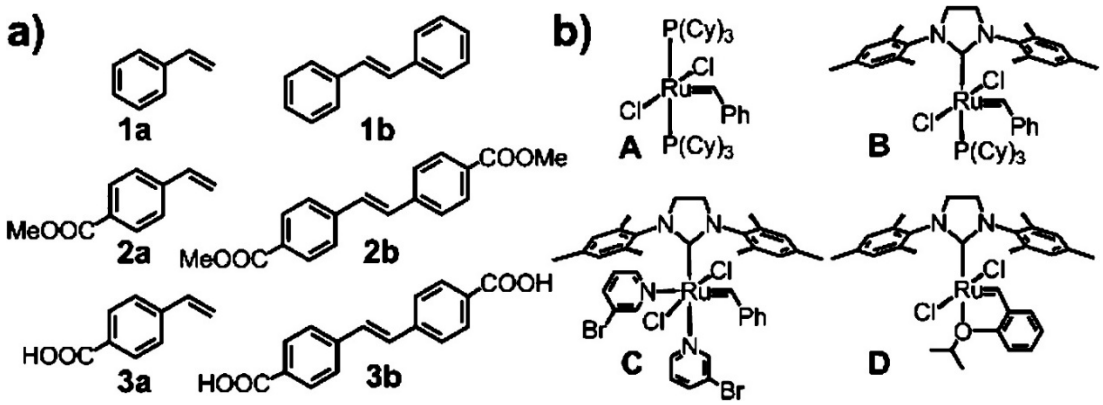


- Ball mills have a higher reproducibility than reactions performed using mortar and pestle.

(1)) Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. *Energetic assessment of the Suzuki–Miyaura reaction: a curtate life cycle assessment as an easily understandable and applicable tool for reaction optimization. Green Chem.* **2009**, *11*, 1894

Example of using ball mills in organic synthesis

Mechanochemical Ruthenium-Catalyzed Olefin Metathesis.



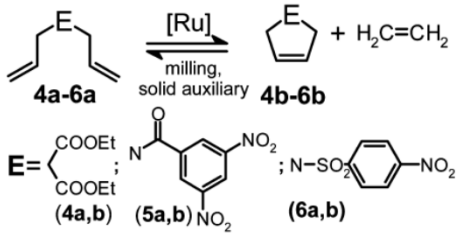
Mechanochemical cross-metathesis substrates/products (a) and Catalysts (b)

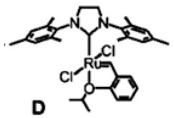
Reactions were conducted in a Retsch MM400 mill using 2 mmol (~300 mg) of olefin in a 14 mL Teflon milling jar milled at 30 Hz using one stainless steel ball (10 mm diameter, 4.0 g).
Conventional steel jars gave irreproducible results, most likely due to enhanced catalyst reduction by impact of steel media against the steel vessel.

Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščič , T. *J. Am. Chem. Soc.* **2015,** 137, 2476.

Mechanochemical Ruthenium-Catalyzed Olefin Metathesis.

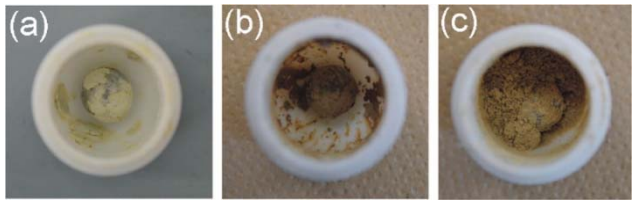
Olefin ring-closing metathesis using 0.5 mol % D[a]





entry	olefin	liquid[b]	solid auxiliary[c]	yield (%)
1	5a	–	–	–
2	5a	EtOAc	–	33
3	5a	EtOAc	NaCl	92[d]
4	5a	EtOAc	KCl	90
5	5a	EtOAc	K_2SO_4	91
6	6a	–	–	–
7	6a	EtOAc	–	39
8	6a	EtOAc	NaCl	94[d]
9	6a	EtOAc	KCl	91
10	6a	EtOAc	K_2SO_4	89

[a]Catalyst was added in 2–4 portions over 3 h using 1 mmol of reactant. [b]75 μL. [c]450 mg of salt (~150% of reactant weight). [d]Similar results were obtained with NaBr and NaI.

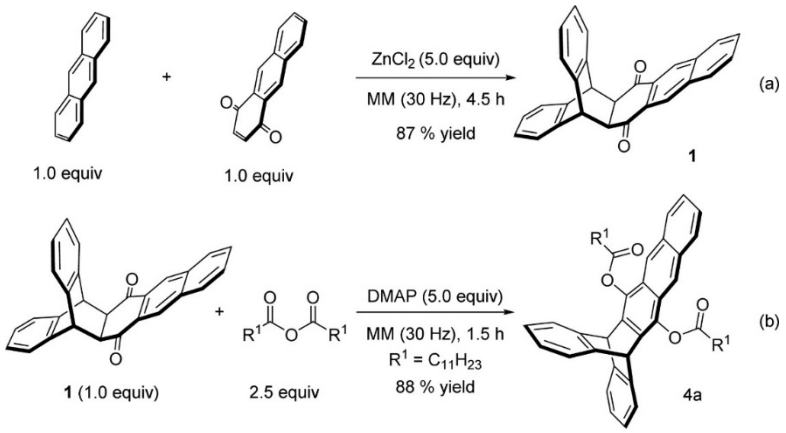


Reaction mixture (**3a**, 2 mol % D) after LAG with and without a solid auxiliary: aggregation on the milling ball (a) after 15 min, (b) after 5 h, and (c) after 2 h of milling with NaCl (34% yield).

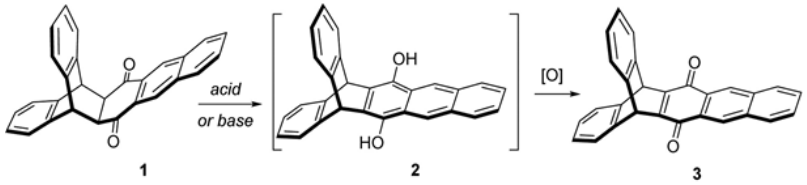
LAG reactions are characterized by ratios of added liquid volume to reactant weight (η) of 0.1–1 μL mg^{-1}.

(1) Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščič , T. *J. Am. Chem. Soc.* **2015,** 137, 2476. (2) Fris.c.ic., T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. *CrystEngComm*. **2009**, *11*, 418.

Mechanochemical Synthesis of Extended Iptycenes



*MM stands for mechanical milling



Benefits of ball milling

- ✓ Thermally activated Diels−Alder reactions often require long reaction times, which makes and this limitation cannot be solved using higher temperatures, because of retro-Diels−Alder reactions.
- ✓ The conversion is lower than 5% if the reaction was carried out in 1,2-dichloroethane in the presence of $ZnCl_2$ at 80 °C after 24 h.

- ✓ Strong Lewis acids catalysts, such as $AlCl_3$, are not compatible with many functional groups and also anthracene-1,4-diol (**2**) produced by the enolization of **1** undergoes rapid air oxidation to form anthracene-1,4-dione (**3**).
- ✓ Solvent-free conditions are compatible with sensitive intermediates that have greater persistence in the solid state.

Zhao, Y.; Rocha, S. V.; Swager, T. M. *J. Am. Chem. Soc.* **2016**, *138*, 13834.

Mixer Mill MM 400


Retsch
Mixer Mill
MM 400

An overview of characteristics of grinding set such as hardness, energy input, wear resistance and possible contamination through abrasion

Materials					
	Hardness	**Density**	**Energy input***	**Wear resistance***	**Possible contamination through abrasion**
Stainless steel	48 – 52 HRC (approx. 550 HV)	7.8 g/cm³	very high	good (to a limited extent)	Fe, Cr
Hardened steel	58 – 63 HRC (approx. 750 HV)	7.85 g/cm³	very high	good	Fe, Cr, C (less than stainless steel)
Steel for heavy-metal-free grinding	up to 62 HRC (Rockwell)	7.85 g/cm³	very high	good	Fe, Mn, C, Si
Manganese steel („Manganese investment casting")	up to 55 HRC (Rockwell)	7.2 g/cm³	very high	good	Fe, Mn, C, Cr
Tungsten carbide	approx. 1250 HV	14.8 g/cm³	extremely high	very good	WC, Co (extremely low)
Agate	hard and brittle 6.5 – 7 Mohs (approx. 1000 HV)	2.65 g/cm³	very low	good (to a limited extent)	SiO_2
Sintered aluminum oxide	hard and brittle 8 – 8.5 Mohs (approx. 1750 HV)	3.9 g/cm³	low	good	Al_2O_3, SiO_2 (low), no contamination with Fe, Cr, Ni or Co
Zirconium oxide	hard and brittle, tougher than agate 7.5 Mohs (approx. 1200 HV)	5.9 g/cm³	high	very good	ZrO_2 und Y_2O_3 (marginal), insignificant for analyses
Silicon nitride	approx. 1500 HV	3.2 g/cm³	low	excellent	Si_3N_4, Y_2O_3, Al_2O_3
PTFE	Elastic Shore hardness D 56	2.1 g/cm³	very low	poor	contamination with F, C

* e.g. ball mills

What we should look for

- Reactions that are not possible using thermal process or giving low yields.
- Mechanochemical products which are different from thermal processes.
- Enhanced or execptional selectivity: enantio-, regio- and chemoselectivity.
- Cheap process, great results.

Acknowledgement

- Thanks to Professor Schreiner for making this instrument available.

Thank You for Your Attention