Continuous Process Intensification

Practical Tips

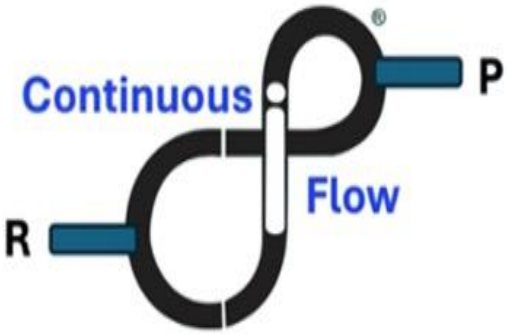
Anil Kumar

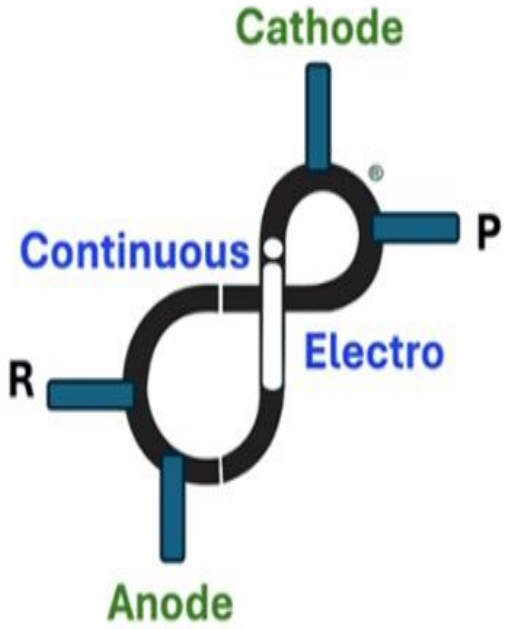
GenZ Materials
Continuous Process Intensification

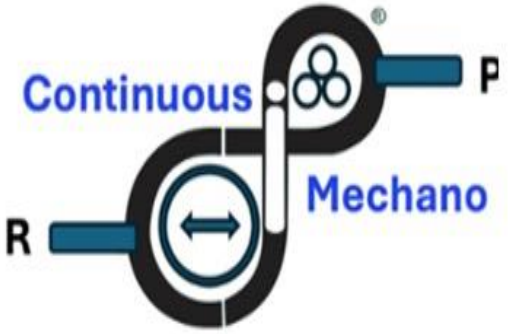
FCPI
Foundation for Continuous Process Intensification

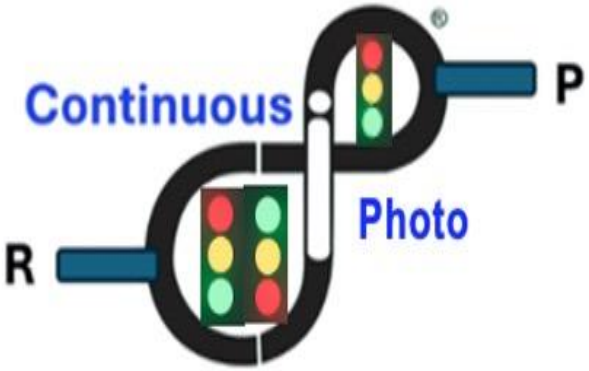
processintensification

Continuous Process Intensification



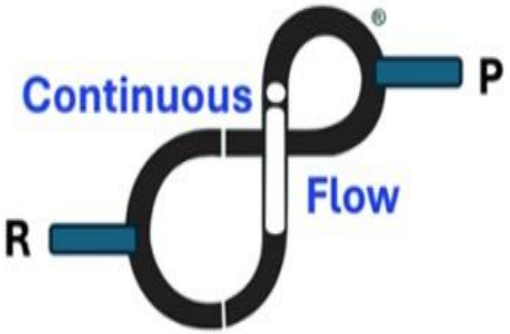


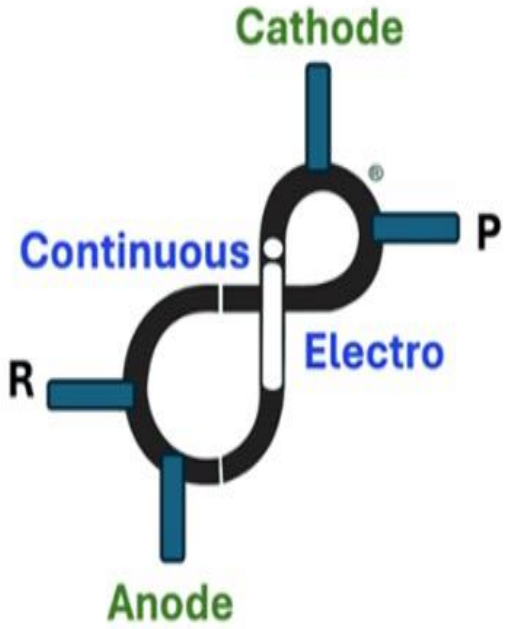


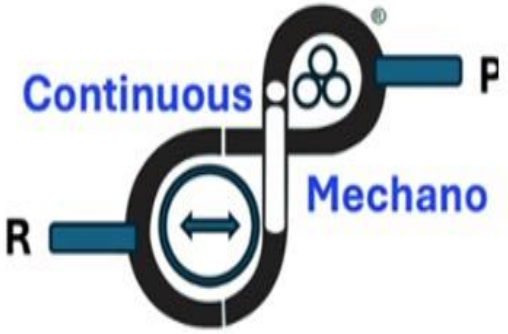


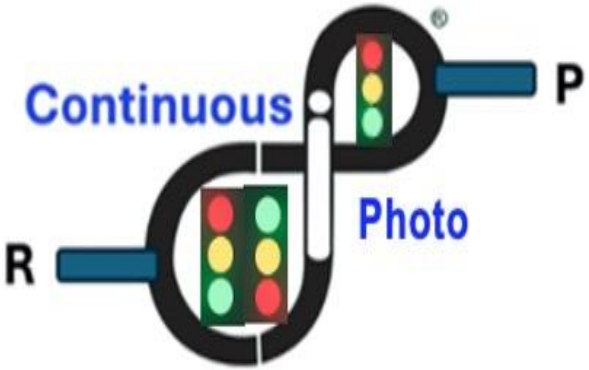
Flow **Electro** **Mechano** **Photo**

Continuous Process Intensification









Flow **Electro** **Mechano** **Photo**

Photo by default is Flow as of now

Continuous Process Intensification

Tools for the State-of-the Art lab Setup

Vapourtec R Series: Fully Automatic Lab in a Fumehood

Continuous Process Intensification

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Autichem: For Slurry Reactions, L-S-G/L-L

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Synthetron (SDR): For Exothermic and G-L reactions

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Khimod: For High Temperature and High Pressure and Fixed Bed

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Protrix SiC: If Corrosive Metal Incompatible Chemistry

Continuous Process Intensification

Reactions vs Process vs Tools

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Reactions vs Process vs Tools

Exothermic Reactions (Need Cooling in Batch Process)

Continuous Process Intensification

Reactions vs Process vs Tools

Exothermic Reactions (Need Cooling in Batch Process)

Continuous Flow Process

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Metal Compatible: SDR (S and G)

Continuous Process Intensification

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Continuous Flow Process

Metal Compatible: SDR (S and G)

Metal Compatible (not very exothermic): Autichem/AMT (S and G)

Continuous Process Intensification

Reactions vs Process vs Tools

Exothermic Reactions (Need Cooling in Batch Process)

Continuous Flow Process

Metal Compatible: SDR (S and G)

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Metal Incompatible: SiC Chemtrix (Solid formation, Gas)

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HT/HP and Chemistry in New Spcae: Khimod

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Continuous Electro (to save one reagent but not solvent)

Continuous Process Intensification

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Redox Reactions

Reduction, Oxidation, C-C, Decarboxylation, Halogenation…

Continuous Process Intensification

Reactions vs Process vs Tools

Non-Exothermic Reactions (Need Heating in Batch Process)

Continuous Electro and Mechano (Flow is also possible)

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All Reactions

Continuous Process Intensification

Reactions vs Process vs Tools

Non-Exothermic Reactions (Need Heating in Batch Process)

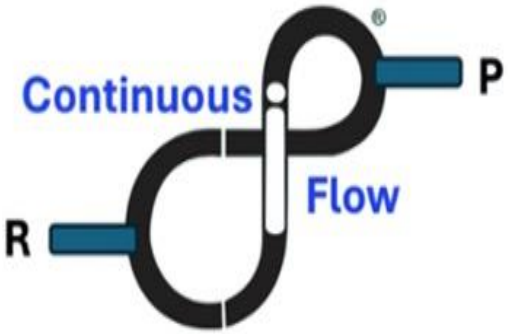
Continuous Electro and Mechano (Flow is also possible)

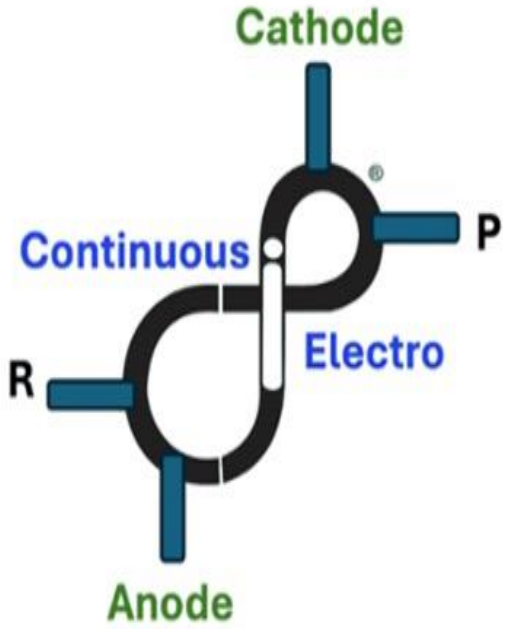
Continuous Mechano (to save Solvent but not Reagent)

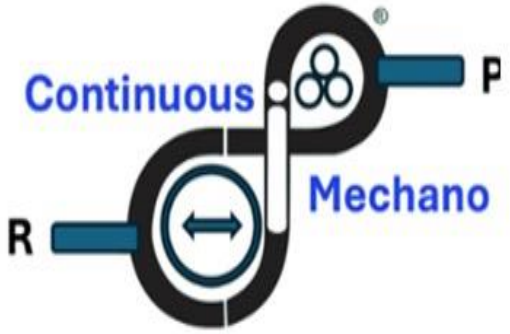
All Reactions

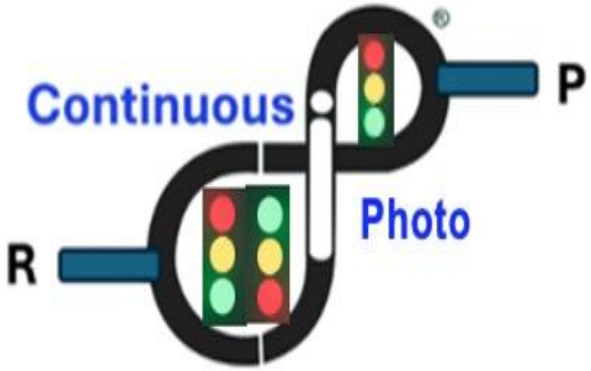
Practically no limitation other than Metal Compatibility

Continuous Process Intensification









Flow **Electro** **Mechano** **Photo**

Practical Tips

Continuous Flow Process Intensification

- **Prelim Investigation (Syringe pump and Tube)**
- **Lab Modules (prelim Optimization)**
- **Interface Modules (Final Process Optimization)**
- **Production Modules (Plant Scale Production)**

  - **If everything goes as per plan, one can have fully functional plant from the conceiving the idea in around 4-8 months**

Continuous Flow Process Intensification

Flow Chemistry
Planning, Execution and Scale-up

Step by Step Tutorial on how to go about doing

A reaction in flow for the first time and then

How to go about optimization and scaling up

Continuous Flow Process Intensification

Why Flow from Batch

- Poor control in batch process (very tight process conditions)
- Highly exothermic reaction
- Multistep reaction with unstable or hazardous intermediate
- Selectivity is an issue in batch
- Difficult to prevent side reactions
- Particle size need to be controlled
- To reduce effluent, improve safety, decrease capex and opex cost
- Chemistry in New Space (HTHP)
- Chemistry not possible in batch: Ultrafast reactions or intermediates

Continuous Flow Process Intensification

Almost, every type of chemistry

has already been developed via CFP

Please Refer to literature

before you start your flow reaction

Continuous Flow Process Intensification

IMPORTANT

Document everything from here in your notebook

Continuous Flow Process Intensification

- **Write the reaction scheme (Fully Balanced)**
- **Write down all the possible by-products**
- **Write down complete mechanism (Product and By-Products)**
- **Understand the role of each reagent or intermediate**
- **Understand if any of the product or by-product interact with any reagent or among themselves**
- **Check maximum solubility of each reagent in various solvents**
- **Decide which solvent to use (based on precedence or experience)**

Continuous Flow Process Intensification

- **Identify the limiting reagent and solubility (Balanced Equation)**
- **This will be the ultimate intensified state wrt solubility**
- **Prepare half ml of each reagent, at maximum concentration, based on limiting reagent**
- **Starting point will be trial Reaction using a drop of each reagent**

Continuous Flow Process Intensification

Prelim Tests

1. Place an empty vial in fume-hood

2. Add a drop of each reagent (one by one) and observe how the reaction is

↓

Very violent reaction

↓

Dilute the reagents by half
and
repeat until controlled reaction

Continuous Flow Process Intensification

No violent reaction

↓

Repeat the experiment
while holding the vial in hand

↓

Vials gets very hot (highly exothermic reaction)

Observe the physical state (ppt etc)

One can do develop a prelim TLC (analytical) method
of monitoring the reaction

Continuous Flow Process Intensification

If the vial gets very hot

↓

Dilute the reagents by half
And
Repeat the experiment

↓

Vial is still reasonably hot
Repeat by dilution till its just warm

↓

This is the starting point for flow process (room temp or higher)

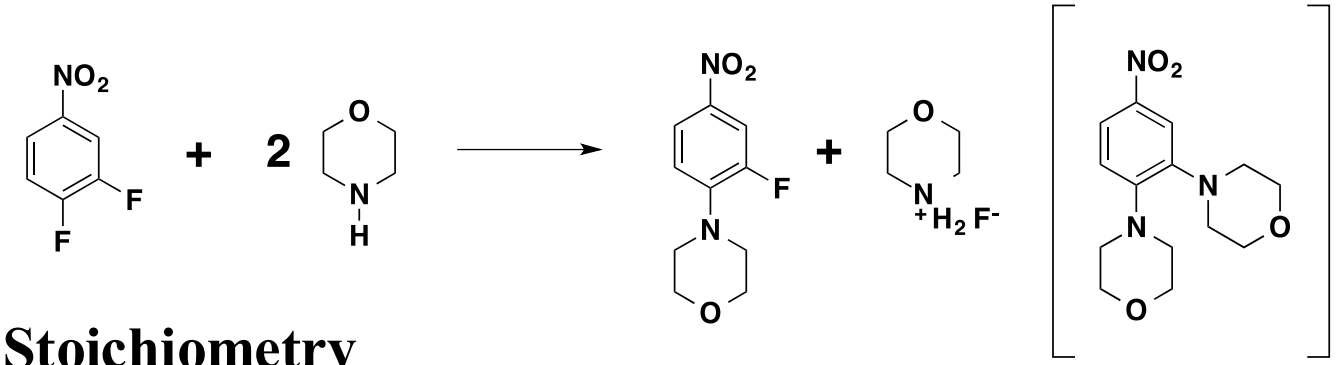
Continuous Flow Process Intensification

If the vial gets hot even at 100 mM,

starting point will be a low temperature reaction

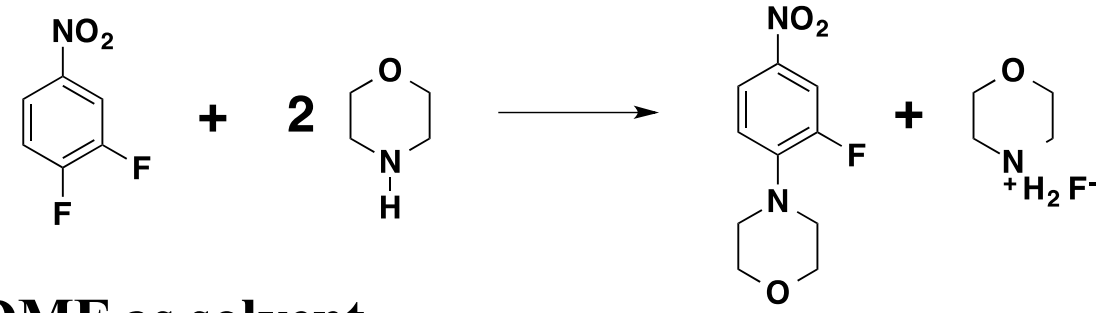
Continuous Flow Process Intensification

Tutorial



- 1:2 Stoichiometry
- Both the starting materials are liquid.
- Di-substitution is a possible side reaction at HT or high concentration
- Molarity of DFNB is 9M (density 1.44, mol wt 159)
- Molarity of Morpholine 11.5M (Density 1.0, mol wt 87)
- As per stoichiometry, one can use 1ml DFNB and 1.56 ml of morpholine
- Since salt is going to ppt out and the product is solid, we need a solvent.
- Another option could be to use morpholine as solvent (di-substitution)
- Best is to use DMF as solvent

Continuous Flow Process Intensification

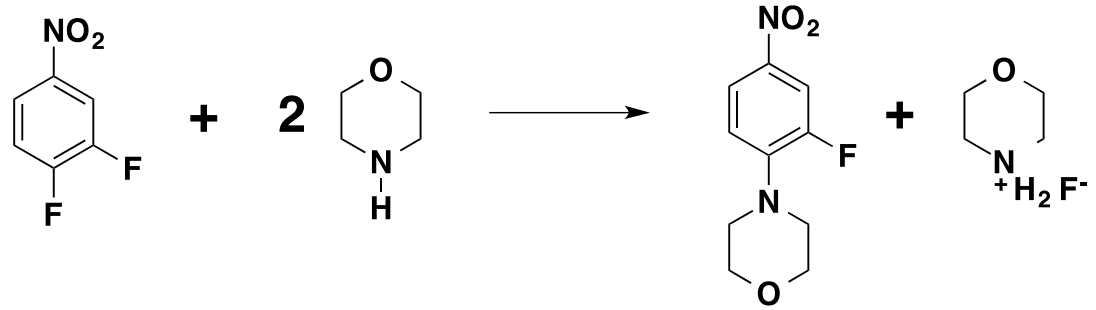


- Let us use DMF as solvent
- To use morpholine as pure, we need to make 5.75M DFNB in DMF
- This will allow us to keep the flow rate of DFNB solution and pure morpholine as equal
- So, our limiting intensification is 5.75M DNFB in DMF and pure morpholine
- Now start the drop test and find out the optimum starting point.

PLEASE DOCUMENT EVERYTHING

PREPARE THE FINAL TABLE SUMMARIZING ALL THE DROP TEST RESULTS

Continuous Flow Process Intensification

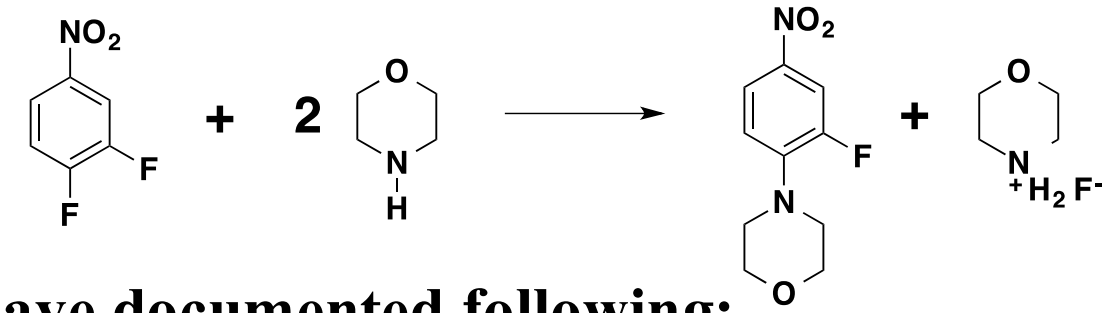


Solvent Selected: DMF

DFNB (M)	Morph (M)	Exothermicity	Observations
5.75 M	11.5 (Pure)		Ppted (thick), color etc
Up to 200 mM			

- Highlight where the exotherm was small
- Highlight where the preciptation (if any) observed or large exotherm

Continuous Flow Process Intensification



At this stage you will have documented following:

- **Starting concentration of reagents (~100-200 mM)**
- **Weather you are going to do reaction at High or Low Temp.**
- **What is the maximum intensification possible based on the information wherein precipitation happens.**

Goal is to intensify (highest concentration and lowest time, i.e. highest throughput) as close to this as possible based on the reactor and utility chosen.

Batch to Flow: General Idea

- Check and Confirm that it is a single step reaction
- Calculate Stoichiometry of each reagent
- Calculate the total volume of solvent used
- Now distribute the solvent among each reagent (equal, if possible)
- Prepare separate solution for each reagent
- Calculate molarity of each reagent
- Calculate the flow rate of each reagent for given stoichiometry
- This will be your total flow rate (X1)
- Now calculate the total flow rate (X2) for given reaction time (reactor volume/time)
- Calculate the ratio of X1 to X2
- Divide each reagent flow rate by this ratio to get the final flow rates for the reaction

Continuous Electro Process Intensification

Life is very Easy for a chemist here

Fastest Transition (half an hr) to Electro Organic

Exactly Same Process as Batch

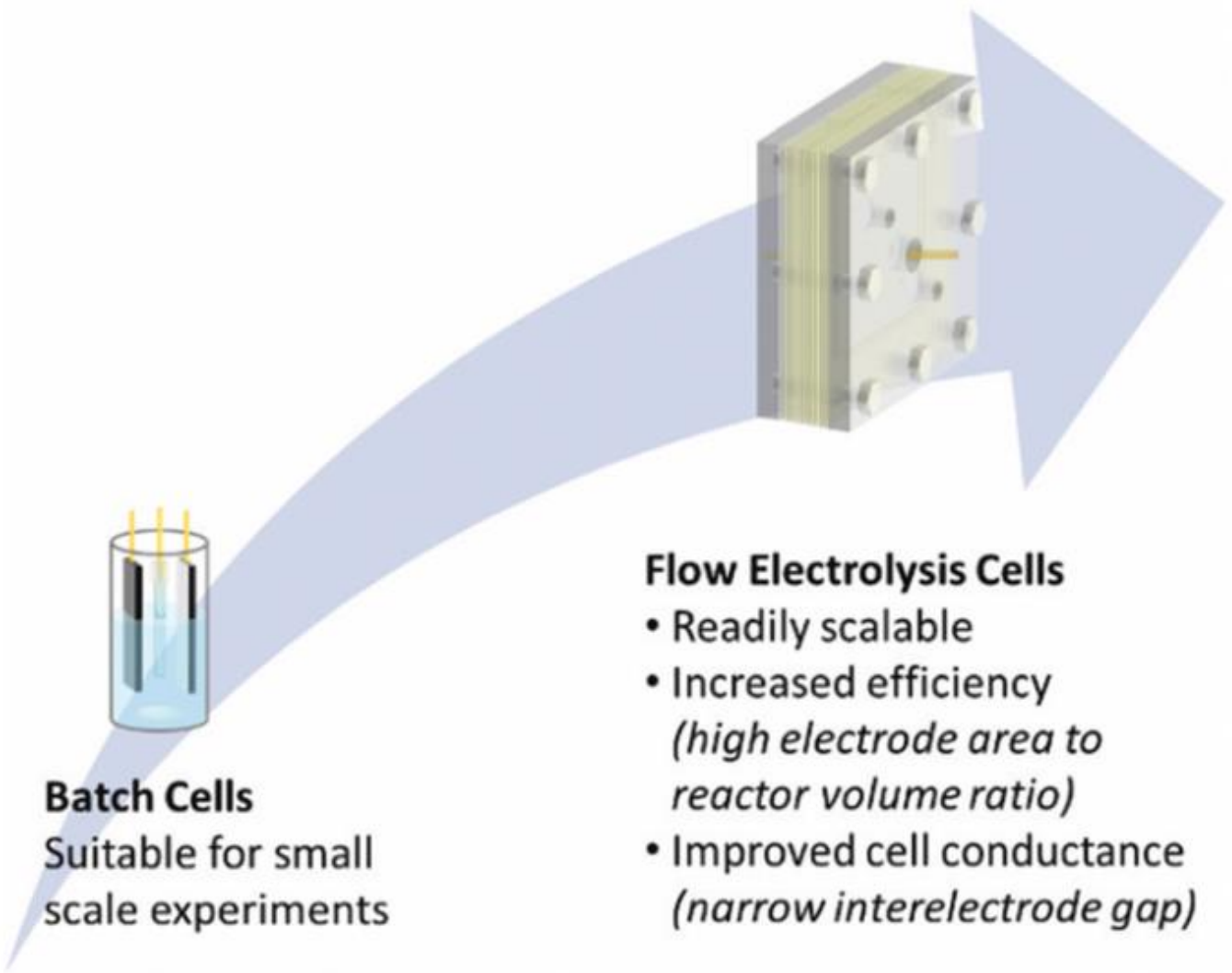
You save One Reagent but not Solvent

Continuous Electro Process Intensification

Chemical	vs	Electrochemical
Substrate		Substrate
Reagent		Electricity
Solvent		Solvent
Catalyst		(Mediator)
		Electrodes
		Electrolyte
		Constant I or V
Flask		(Un)Divided Cell

The number of experimental parameters that may be manipulated in electrosynthesis is large

Continuous Electro Process Intensification



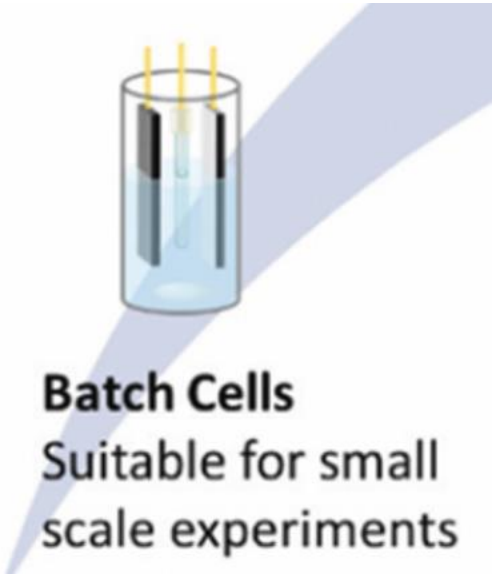
Batch Cells
Suitable for small scale experiments

Flow Electrolysis Cells
- Readily scalable
- Increased efficiency *(high electrode area to reactor volume ratio)*
- Improved cell conductance *(narrow interelectrode gap)*

Continuous Electro Process Intensification

The initial reaction setup should be kept as simple as possible.

The following conditions are usually used as a starting point:



Anode: Graphite or Pt

Cathode: Stainless steel or Pt

Substrate: 20 to 50 mM

Electrolyte: 100 mM ($TBABF_4$ for Organic, KF/KCl salts for Aqueous);

Constant Current Mode: 20-50 mA, 1–2 F mol–1

Monitoring of the reaction by TLC, GC, LCMS etc. over time

Continuous Electro Process Intensification

Electrodes

Anodes

Anode for Reduction

Anode for Oxidation

Sacrificial anode (Dissolve when used as anode)

Non sacrificial anode

Cathodes

Cathode for Reduction

Mg Al Fe Sn Pb Hg Carbon-based

Fe Au Ni Pt

Good for reduction of organic compounds

When HER Needed

Continuous Electro Process Intensification

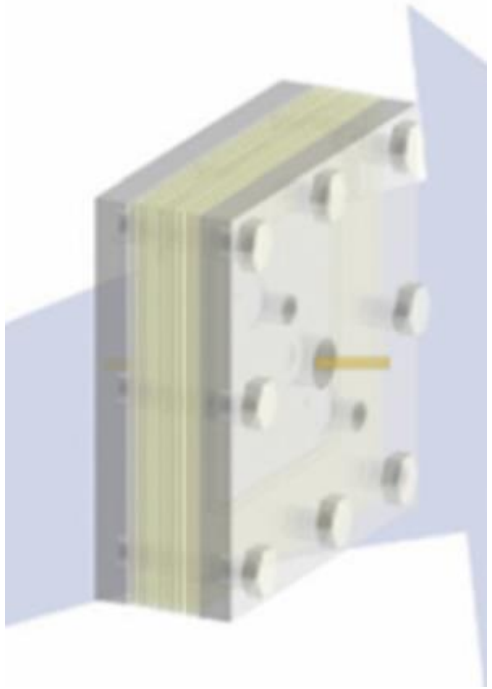
At this stage you will have following information (economy also):

Electrode Combinations vs Yield and Faradaic Efficiency

Economy: Which is the cheapest electrode combination for a given outcome

Now move to Continuous Flow Process for Intensification/Scale up

Continuous Electro Process Intensification



Optimization

- Max Yield
- High Selectivity
- Max Current Density
- High Faradaic Efficiency
- Cost of Electrode Material
- Cost of Solvent
- Cost of Electrolyte

Once Everything is in place, explore paired chemistry

Continuous Mechano Process Intensification

Continuous Mechano Process Intensification

Life is very Easy for a chemist here

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Fastest Transition (half an hr) to Mechano Organic Chemistry

Continuous Mechano Process Intensification

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You save Solvent but not Reagents

Continuous Mechano Process Intensification

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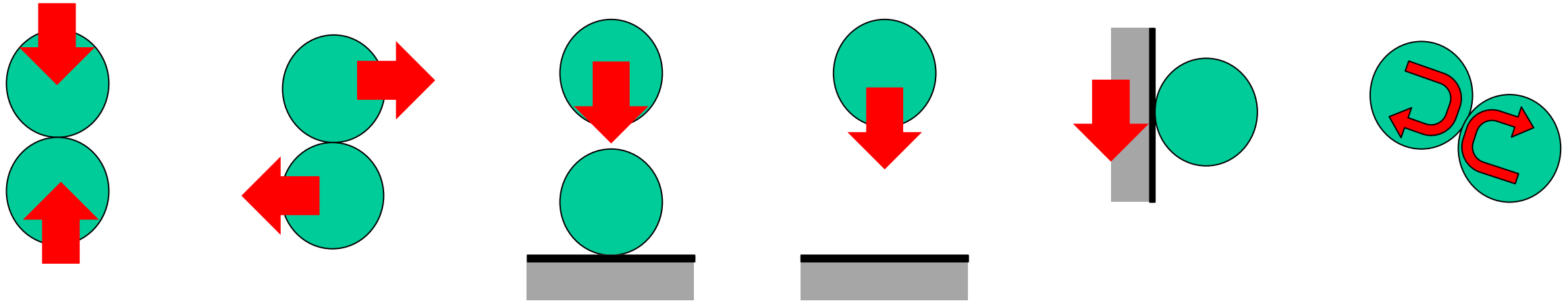
Fastest Transition (half an hr) to Mechano Organic Chemistry

You save Solvent but not Reagents

Just mix everything and you are ready to go

Mechanochemistry

A mechanochemical reaction is defined as "a chemical reaction that is induced by the direct absorption of mechanical energy" (IUPAC Compendium of Chemical Terminology 2009)



Pressure **Friction** **Shock** **Impact** **Shear** **Torsion**

https://www.wab-group.com/flow-chemistry/

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Continuous Mechano Process Intensification

Life is very Easy for a chemist here

Fastest Transition (half an hr) to Mechano Organic Chemistry

You save Solvent but not Reagents

Just mix everything and you are ready to go

There is no restriction on chemistry at and above RT

Except Shear/Shock/Stress/Friction Sensitive Chemistry

Continuous Mechano Process Intensification

Safety in Mechanochemistry – Lab Scale

Safety Considerations and Proposed Workflow for Laboratory-Scale Chemical Synthesis by Ball Milling

Ian Priestley,* Claudio Battilocchio, Andrei V. Iosub, Fabien Barreteau, Gavin W. Bluck, Kenneth B. Ling, Katharine Ingram, Maria Ciaccia, Jamie A. Leitch, and Duncan L. Browne*

Cite This: *Org. Process Res. Dev.* 2023, 27, 269–275

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ABSTRACT: Chemical reactions that take place in a ball mill and in the absence of a bulk reaction solvent present different safety profiles to stirred solution reactions. Herein, we present and describe steps that a researcher may take to better ensure that they have considered some of the hazards and measures that emerge and minimize the risk to themselves and their colleagues.

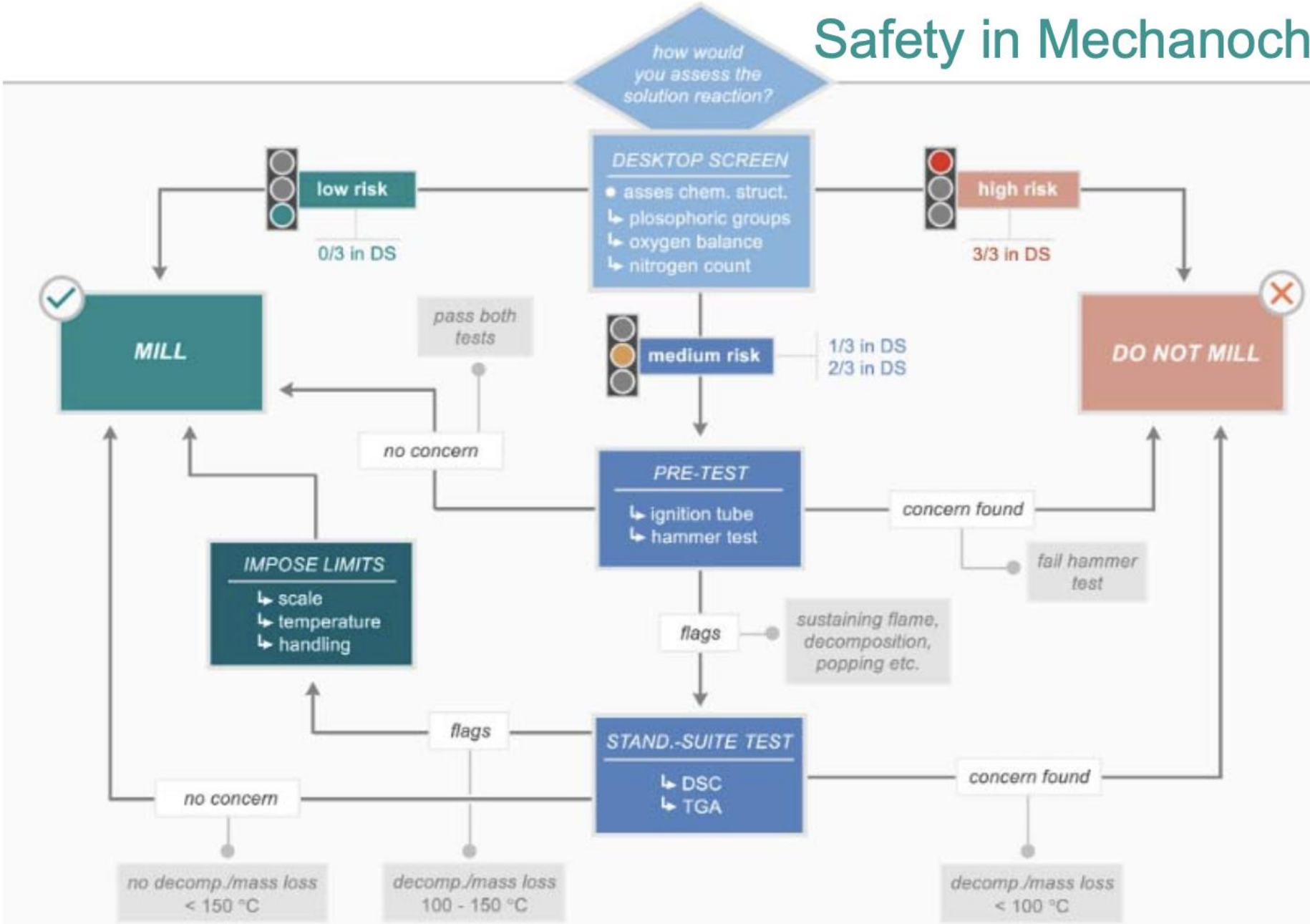
KEYWORDS: *ball milling, mechanochemistry, safety, laboratory scale*

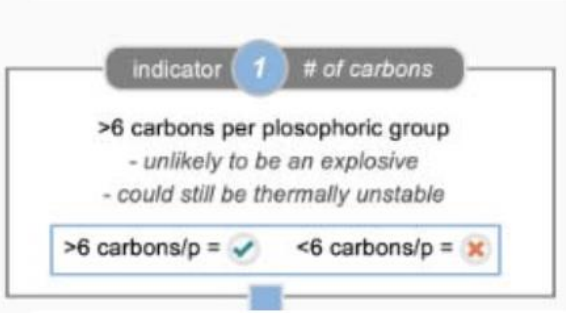
Priestley, I. et al. (Syngenta) *Org. Process Res. Dev.* **2023**, *27*, 269

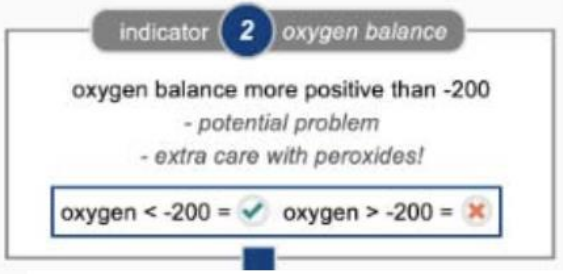
Slide: Prof. Kappe

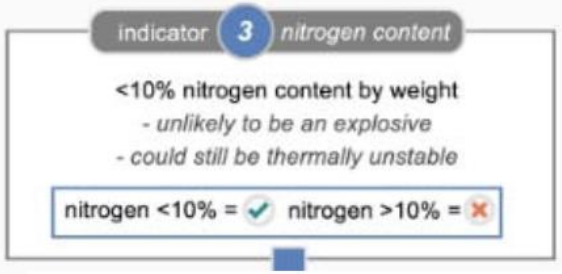
Continuous Mechano Process Intensification

Safety in Mechanochemistry – Lab Scale









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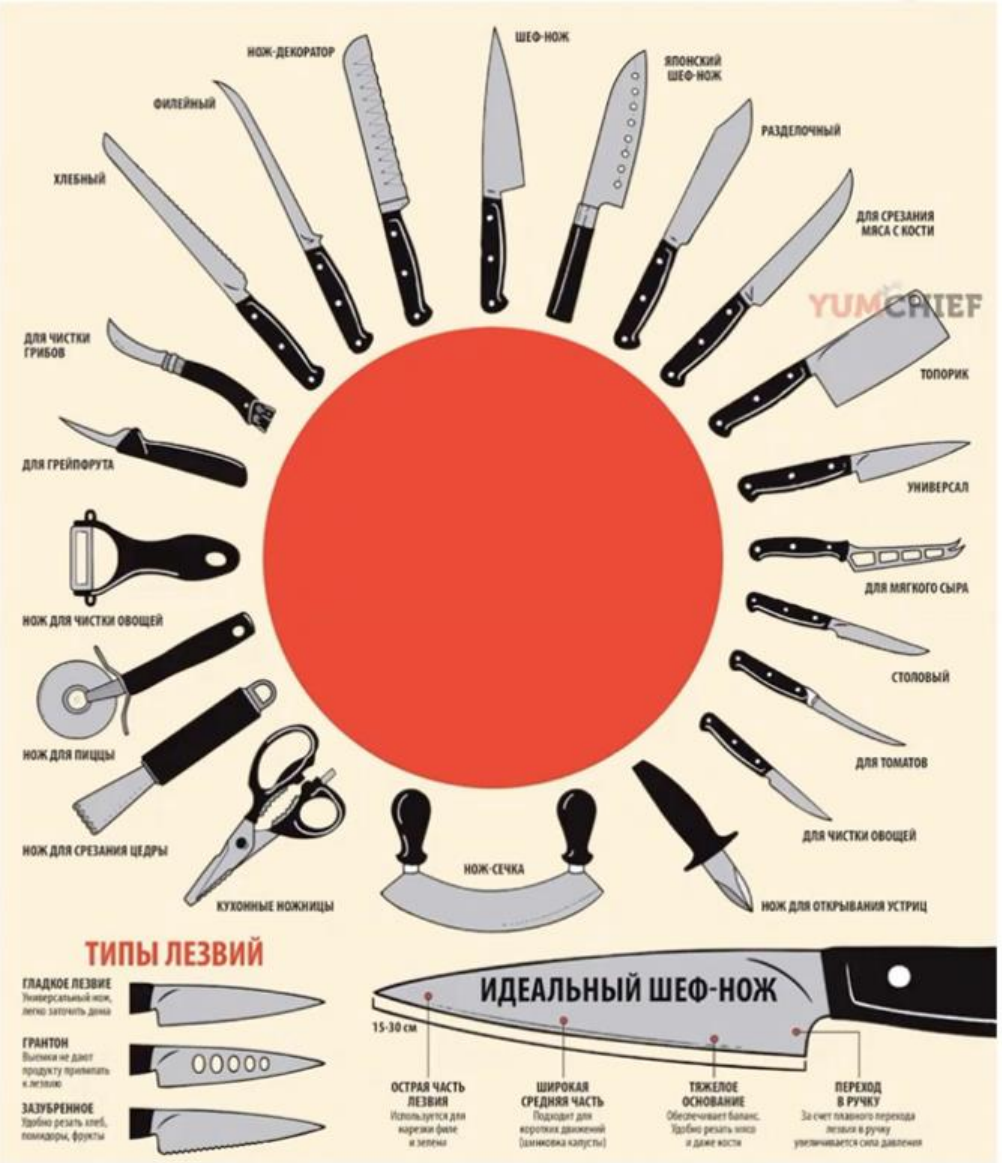
Continuous Mechano Process Intensification

Safety in Mechanochemistry – Pilot/Commercial Scale

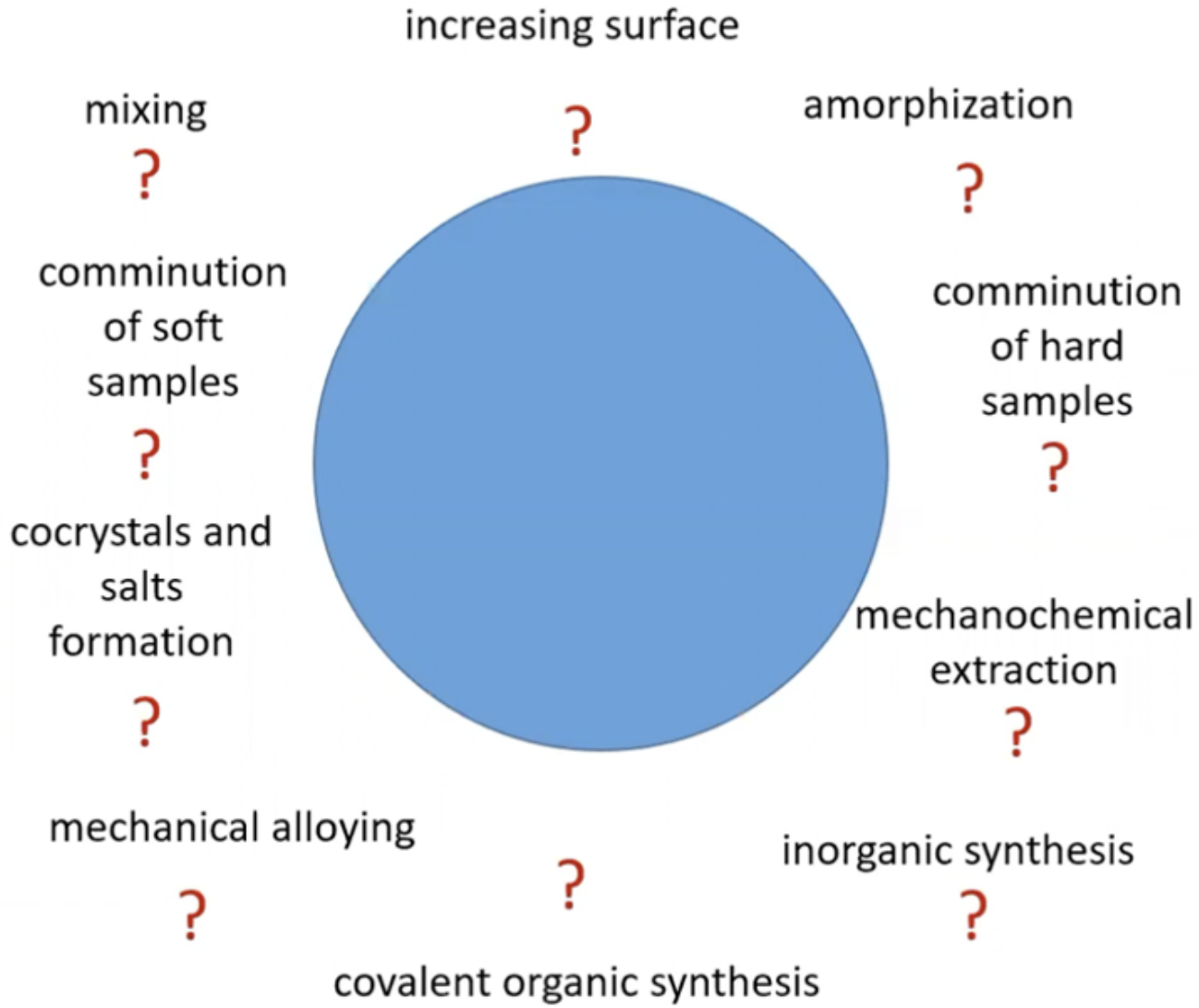
- Be aware of shock-sensitive or shear-sensitive reagents/substrates/products (see above)
- Accelerated reaction rates due to higher concentrations/absence of solvents and….
- …..milling effect increasing specific surface of reagent
- Solvent-free environments may lead to exothermic reactions and self-accelerating thermal decomposition (use of LAG agents increases safety as heat exchange capacity is higher)
- Heat duty must be estimated and appropriate temperature controls and external cooling in place
- Beware of pressure generation from low boiling byproducts/solvents (pressure relieve valves/rupture disks)
- Use of pressure and temperature transmitters will help avoid run-away conditions
- Energy input and power drawn by the mechanochemical system should be monitored (stable during steady state – increase indicates excessive friction)
- Rigorous risk assessments must be performed before experiment
- DSC, TGA, appropriate safety shields and emergency shut downs in place

Atapalkar, R. S.; Kulkarni, A. A. Batch and Continuous Flow Mechanochemical Synthesis of Organic Compounds Including APIs,Rea ct. Chem. Eng. 2024, 9, 10

Mechanochemistry



https://www.pinterest.ru/pin/675821487817105608/



https://www.youtube.com/watch?v=WPyzykk79K0&list=PLdesNkcRuf70shzcrbWS8dwixJdnSVYWD

Mechanochemistry

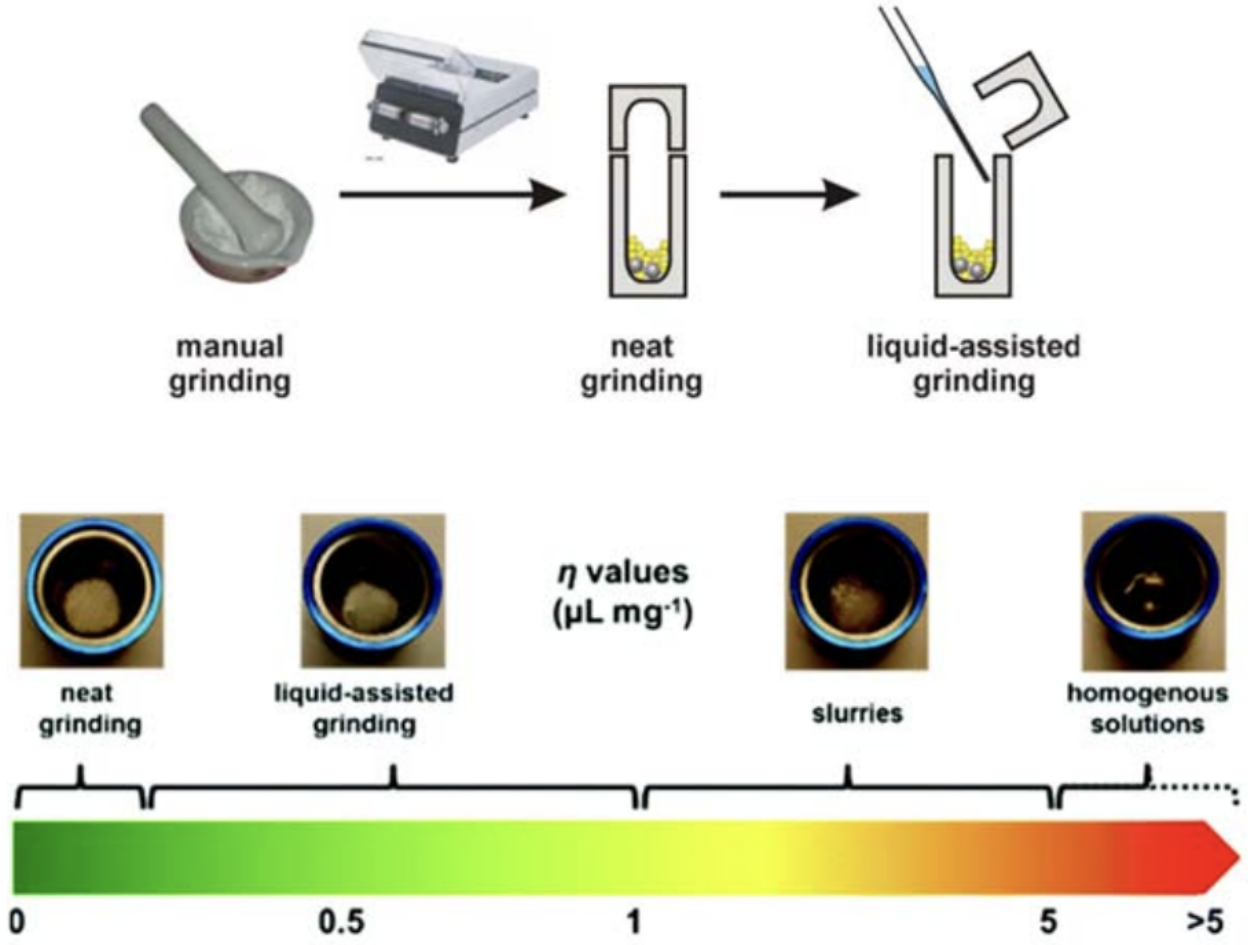
What happens **DURING** impacts?

- Vibrational and electronic excitation
- Generation of defects
- Heating
- Mixing
- Comminution (generation of surfaces, size decrease)
- **Reaction itself**

What happens **BETWEEN** impacts?

- Annealing or re-grouping of defects,
- Cooling (heating for exothermic reactions)
- Relaxation of stresses
- **Reaction itself**

Mechanochemistry – Liquid-Assisted Grinding (LAG)



LAG uses a small amount of a liquid to accelerate reactions, as well as to enable and direct transformations that do not take place by neat grinding.

A value of η = 0 corresponds to neat grinding, η > 10 μL/mg corresponds to a typical solution reaction, while ***LAG lies in the range of ≈0–1 μL/mg.*** *In that range, reactivity appears independent of reactant solubility, distinguishing LAG from slurry reactions (η > 1 μL/mg) in which low solubility does hinder reactivity.*

$$\eta = \frac{V\,(\text{LAG liquid, } \mu\text{L})}{m\,(\text{reagents, mg})}$$

Friščić,T.; Childs, S. L.; Rizvic, S. A. A.; Jones, W. *CrystEngComm* **2009**, *11*, 418
Friščić, T. et al. *ACS Cent. Sci.* **2017**, *3*, 13; Wenger, L. E.; Hanusa, T. P. *Chem. Commun*. **2023**, *59*, 14210
Breinsperger, J. et al. *Chem. Eur. J.* **2026**, *32,* e03536; Fang, Y. et al *Adv. Synth. Catal*. **2026**, *368*, e70372

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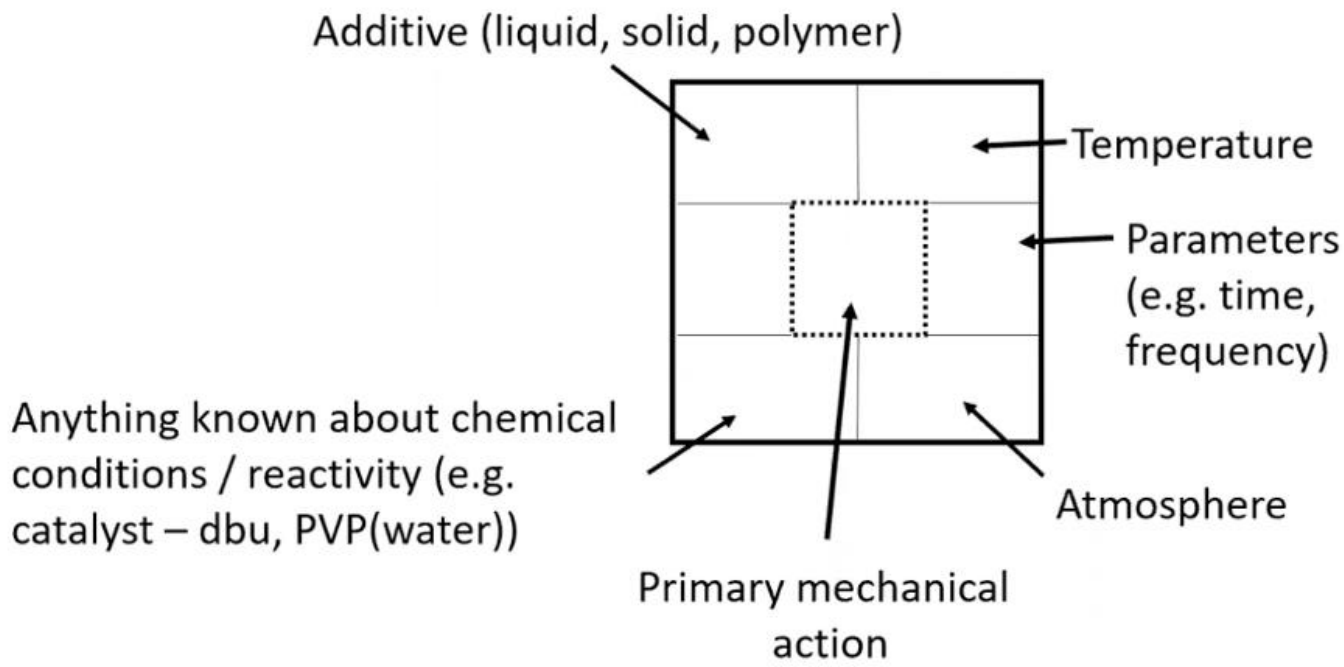
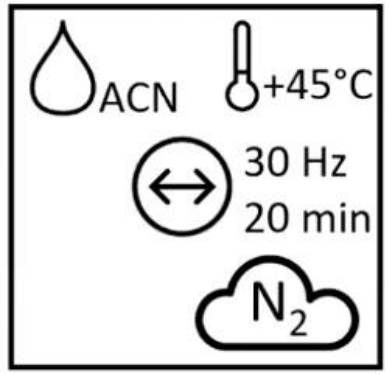
Mechanochemistry

Mechanochemical Notations





Michalchuk, A. A., Boldyreva, E. V., Belenguer, A. M., Emmerling, F., & Boldyrev, V. V. (2021). Tribochemistry, mechanical alloying, mechanochemistry: what is in a name?. Frontiers in Chemistry, 9, 359

Nicolas Fantozzi et al. Chem. Soc. Rev., 2023, 52, 6680

Mechanochemistry

Mechanochemistry – Scale-up

Mortar and pestle
(Operator dependent)

Scale: < 2.0 g
No temperature control
Cryomilling available

Vibratory Mills

Planetary Mills

Scale: < 1.0 Kg
No temperature control
Multi-station device available

Simoloyer

Scale: < 10 Kg
No temperature control
Large scale batch process

Eccentric Mill

SCALE UP

Extruder

Scale: grams to tonnes
- continuous
- Accurate temperature control

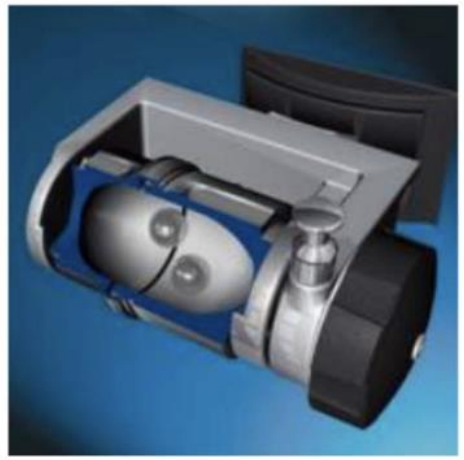
Slide: Prof. Kappe

Mechanochemistry

Mechanochemistry – Critical Operational Parameters (Milling)

General Parameters

- Type of mill (e.g. mixer of planetary)
- Material of mill and balls
- Grinding agents (liquids or solids)
- Temperature



Specific (Numerical) Milling Parameters

- Cavity or jar volume
- Ball diameter
- Number of balls
- Volume of reactants
- Volume ratio of balls : sample : free space
- Milling oscillating frequency (or rpm)
- Milling time

Howard, J. L.; Cao, Q.; Browne, D. L. *Chem. Sci.* **2018**, *9*, 3080

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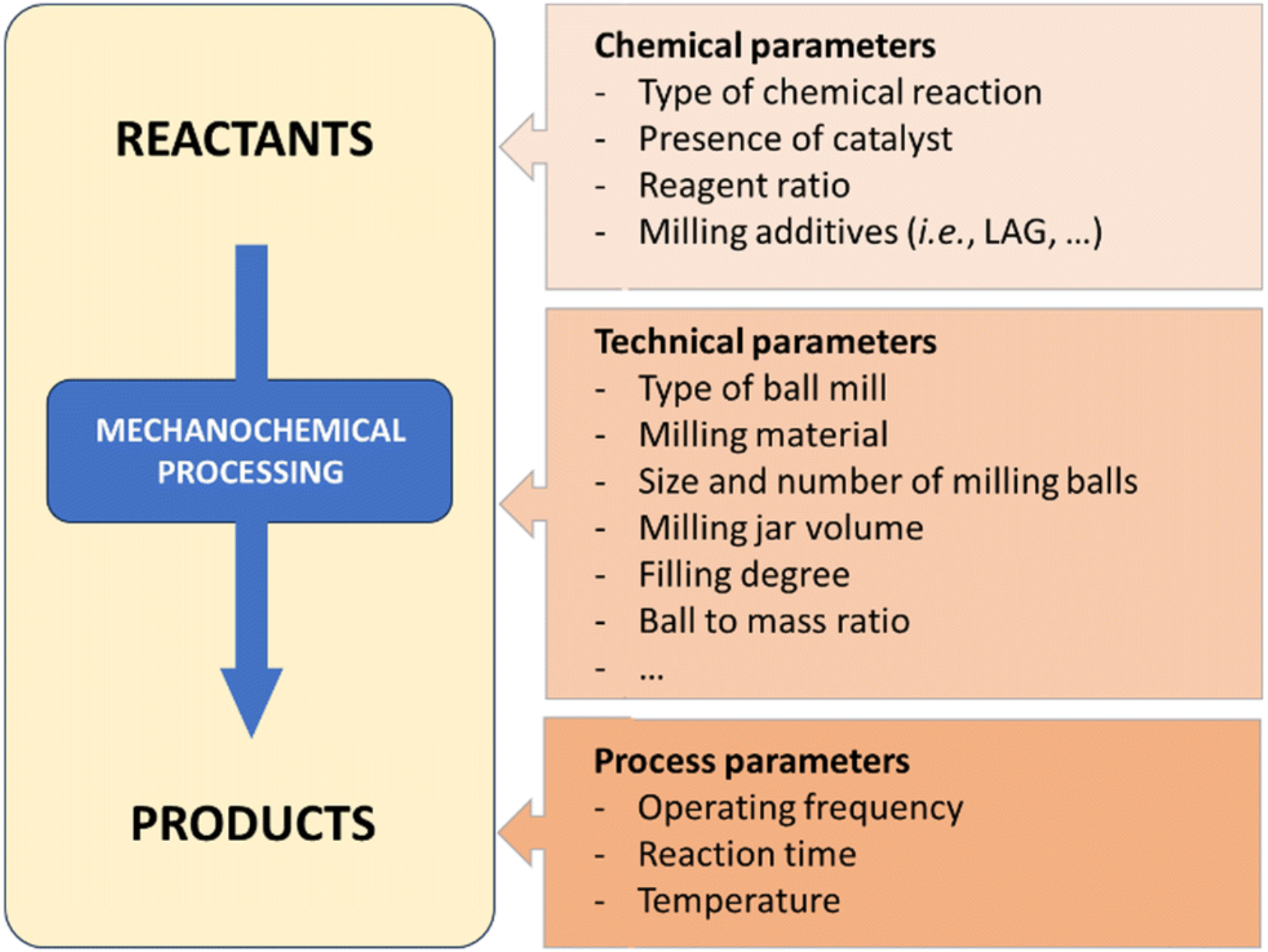
Mechanochemistry



Mechanochemistry

Reactive Extrusion - Fundamentals

Check for updates

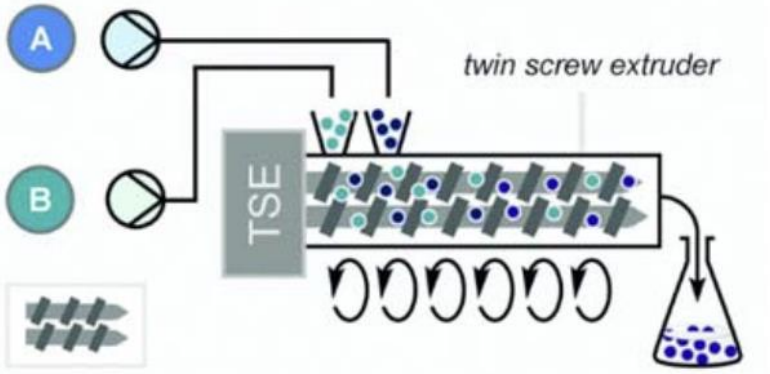
Cite this: *Chem. Soc. Rev.*, 2022, **51**, 4243

[covering 10 publications since 2017]

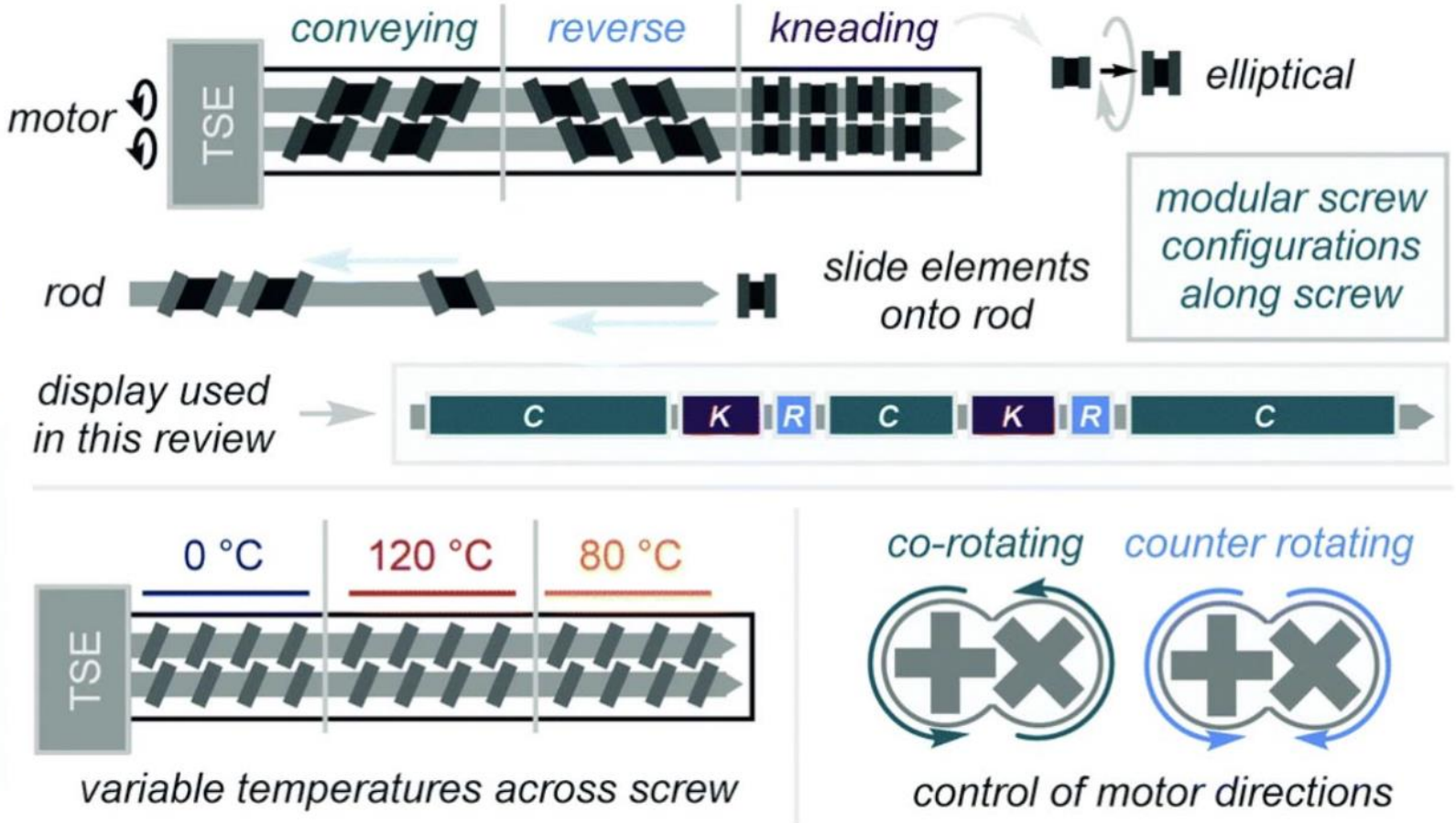
Received 11th October 2021

DOI: 10.1039/d1cs00657f

rsc.li/chem-soc-rev



Continuous flow mechanochemistry: reactive extrusion as an enabling technology in organic synthesis



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Mechanochemistry

Reactive Extrusion – Key Review Articles (~40 Publications)

[Browne, D. L. et al. *Chem. Soc. Rev.* **2022**, *51,* 4243, covering 11 publications since 2017]

Evolution of Solid Processing Methods in Continuous Flow Technology: Reactive Extrusion

CHIMIA **2023**, *77*, 339

Jamie A. Leitch[a], Paul Richardson[b], and Duncan L. Browne*[a]

ROYAL SOCIETY OF CHEMISTRY

Batch and continuous flow mechanochemical synthesis of organic compounds including APIs

React. Chem. Eng. **2024**, *9*, 10 (covering +4 publications]

Ranjit S. Atapalkar[ab] and Amol A. Kulkarni *[ab]

ROYAL SOCIETY OF CHEMISTRY

Flow-through mechanochemical synthesis by reactive extrusion

RSC Mechanochem. **2026**, *3*, 144 (covering + 8 publications)

Paolo Freisa, [a] Luciano Lattuada, [b] Alessandro Barge [a] and Giancarlo Cravotto *[a]

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Mechanochemistry

Commentary | 01 May 2026

A reflection on synthesis by extrusion ten years on: achievements, challenges and opportunities for solvent-free, sustainable, continuous chemical manufacturing

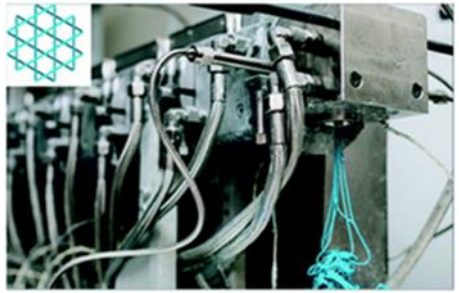
Deborah E. Crawford; Stuart L. James

10 years

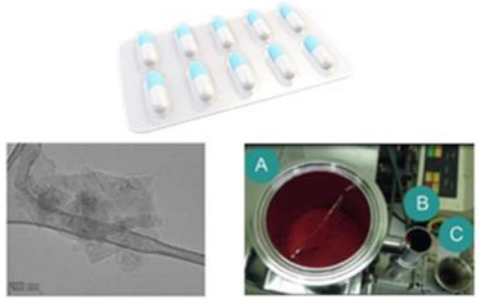
Scalability

Solvent-free

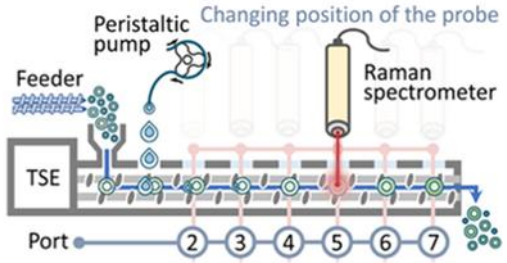
8-fold reduction in environmental impact and costs



Synthesis and Formulation



Synthesis of pharmaceuticals, graphene and dyes



Online analysis

Mechanochemistry

Bead Milling Technology – Fundamentals

Operates on the principle of impact and attrition: grinding media (Ø <1 mm beads) are agitated inside a vessel/ chamber by a rotating shaft with impellers, causing particles to break into smaller sizes due to collision and shear forces

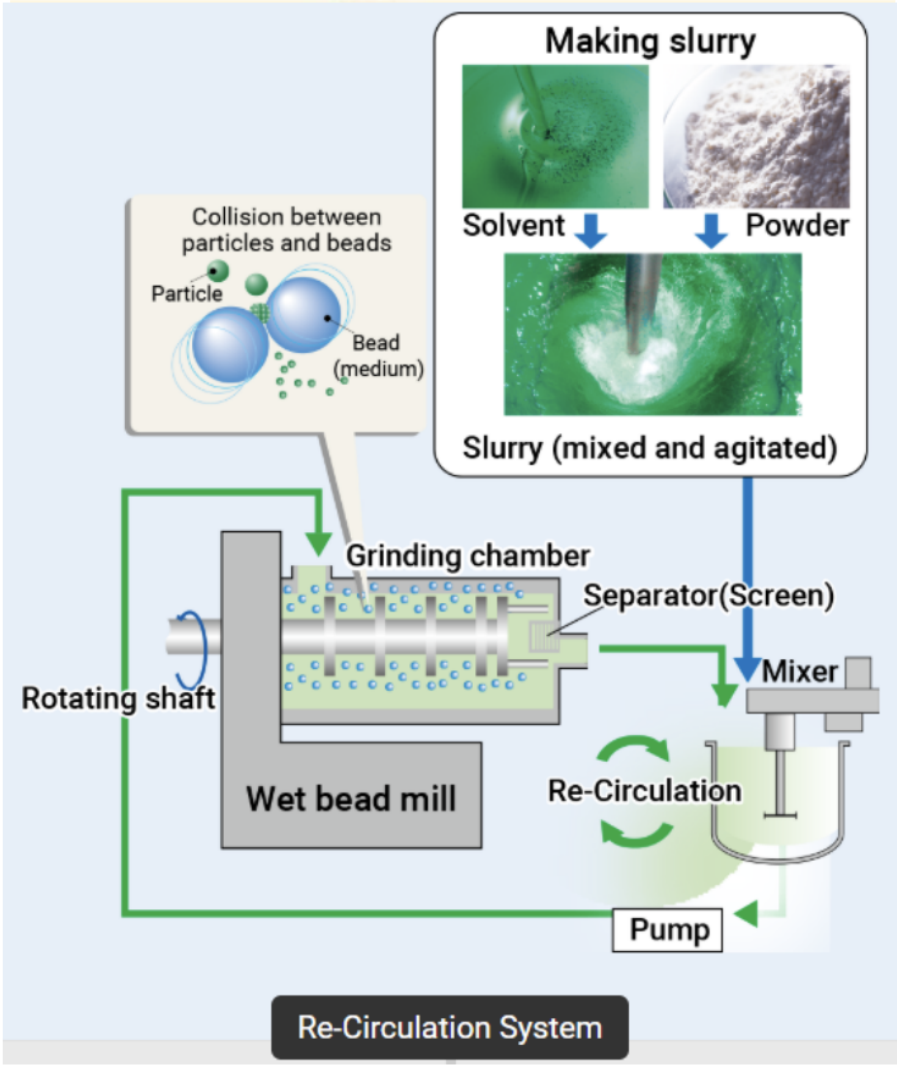
- Horizontal, vertical, and basket mills, which can be operated in batch or circulation mode
- Scalable from lab to production scale
- Primarily used for ultrafine grinding and dispersion of particles to nano and sub-micron levels
- Especially effective for materials that are difficult to grind, including pigments, nanoparticles, and pharmaceuticals

Rapid development of API nano-formulations from screening to production combining dual centrifugation and wet agitator bead milling

Martin Hagedorn[a,d,*], Lena Liebich[a], Ansgar Bögershausen[a], Ulrich Massing[d,e], Sven Hoffmann[b], Stefan Mende[c], Matthias Rischer[a]

Int. J. Pharm. **2019**, *565*, 187

https://www.ashizawa.com/en/technology/bead_mills.html



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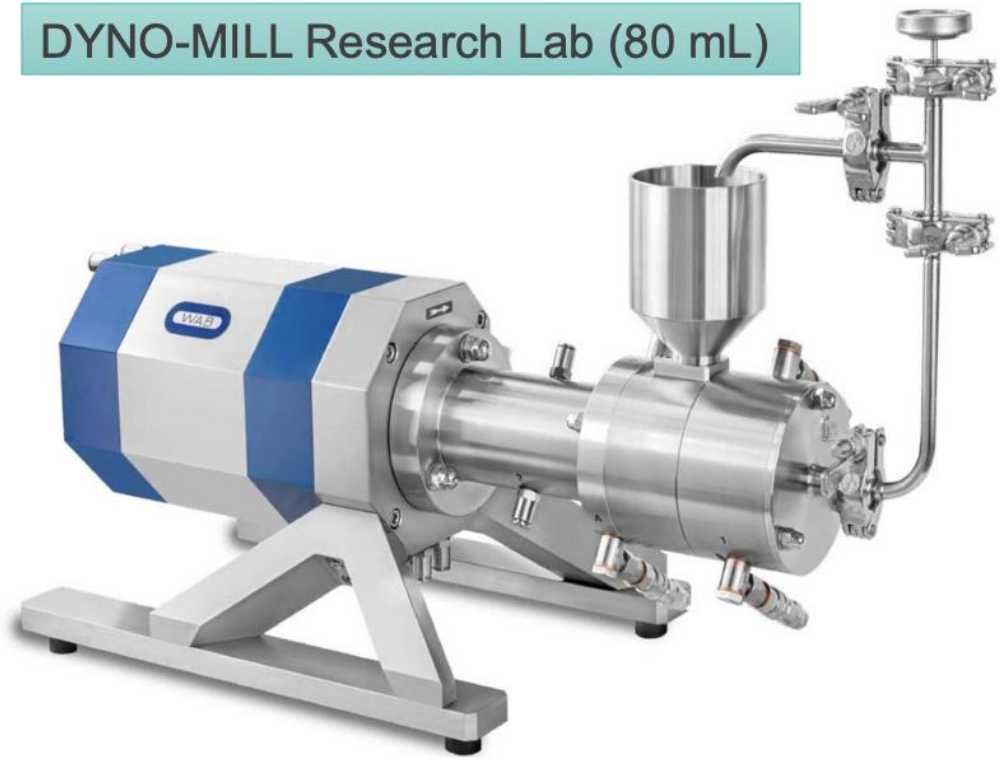
Mechanochemistry

Horizontal Agitator/Atrittor Bead Mill

DYNO-MILL Research Lab (80 mL)



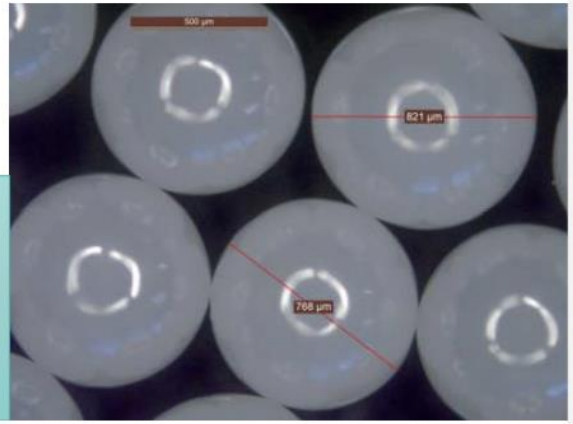
- Mechanochemical reactor with bead mill technology
- Different grinding chamber/reactor volumes (0.08 L)
- High-speed accelerator/rotor (1500-6000 rpm)
- Heating and cooling possible
- Parts in contact with product in metal or ceramic
- Different bead sizes/materials (beads < 1 mm)
- Processing of liquids, solids and powders
- Batch, continuous or recirculation mode

https://www.wab-group.com/flow-chemistry

Review:
Ötvös, S. B.; Kappe, C. O.
Chim. Oggi **2026**, *44(2)*, 8

Beads

ZrO_2/Y_2O_3
ø 0.8 mm
Mohs scale 9
600 beads/g



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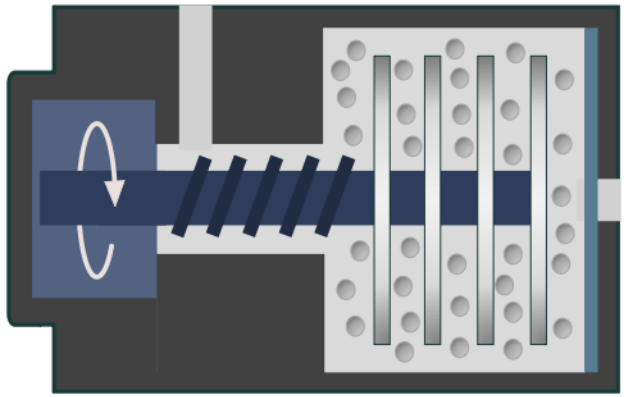
Mechanochemistry

Bead Milling with DYNO-MILLS – Critical Operational Parameters



General Parameters

- MOC grinding chamber (e.g. SS, ZrO_2, SiC)
- MOC accelerator/rotor (e.g. SS, ZrO_2, SSiC)
- MOC feed screw (PEEK)
- MOC beads (i.e. ZrO_2/Y_2O_3)
- Batch mode (cap) versus continuous or recirculation (sieve plate: sieve hole = 50% or 33% of bead diameter)

Specific (Numerical) Milling Parameters

- Bead diameter
- Number of beads (% filling volume/no beads)
- Volume of reactants
- Amount of LAG
- Volume ratio of beads : sample/LAG : free space
- Rotation/tip speed (rpm or m/s)
- Feed screw speed
- Temperature (control of exotherms)
- Feeding rate/residence time (flow)
- Reaction time (batch)

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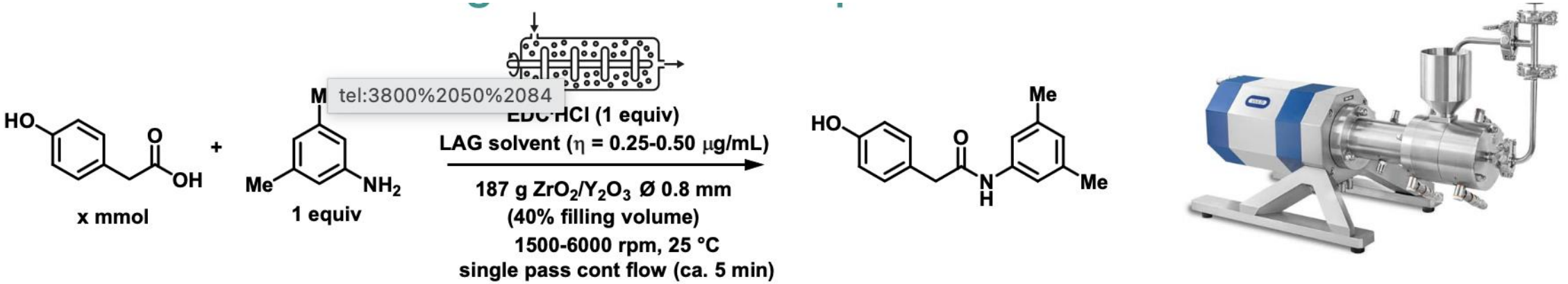
Mechanochemistry



#	LAG solvent	Rotor Speed [rpm]	Scale [mmol]	Yield[a] [%]
1	EtOAc (η=0.50)	3800	50	84
2	EtOAc (η=0.50)	3800	200	86
3	EtOAc (η=0.50)	6000	50	95
4	EtOAc (η=0.50)	1500	50	51
5	EtOAc (η=0.34)	3800	50	96
6	EtOAc (η=0.25)	3800	50	82
7	DMSO (η=0.34)	3800	50	29
8	2-MeTHF (η=0.34)	3800	50	97

[a] Determined by HPLC-UV at 215 nm

cf. couplings using HPMC/water: Anandhi Rajendran, S. H. et al. *ACS Sustain. Chem. Eng.* **2025**, *13*, 6432
cf. mechanochemistry coupling conditions without base: Nikonovich, T. et al. *RSC Mechanochem.* **2024**, *1*, 189

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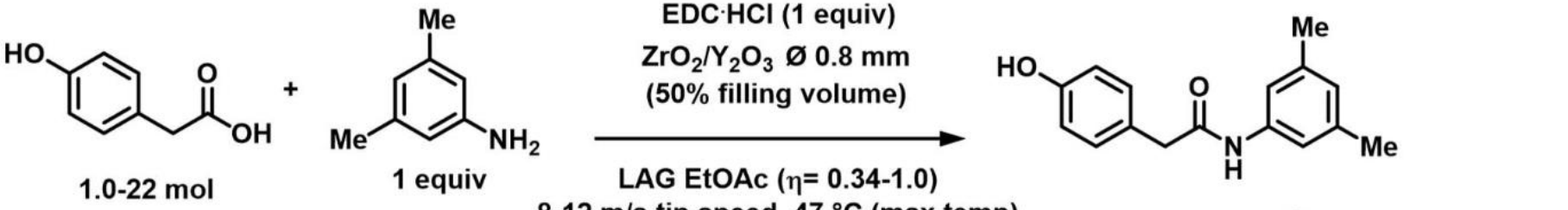
Mechanochemistry



DYNO-MILL Research Lab (80 mL)

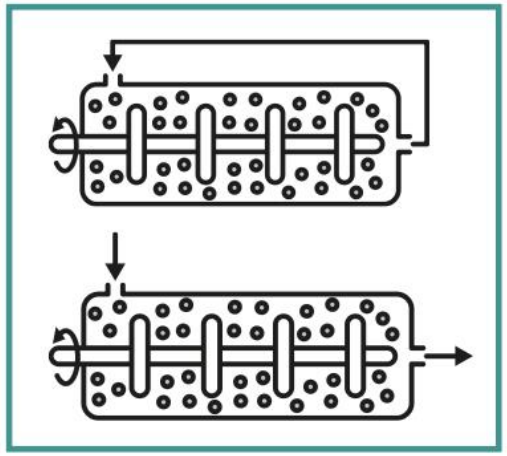
1.0 mol scale
η= 0.34, recirculation mode
yield: 94% (240 g)
productivity: 2.89 kg/h

DYNO-MILL UniLab (0.5 L)

5.7 mol scale
η= 1.0, continuous mode
or
η= 0.5, recirculation mode
HPLC yield (continuous): 94%
HPLC yield (recirculation): 99%

DYNO-MILL UBM5 (5 L)

22.2 mol scale
η= 0.5, recirculation mode
HPLC yield: 99%
productivity: ca 65 kg/h



WAB

Banderob, K.; Roth, P.; Caboni, P.; Kappe, C. O.; Ötvös, S. B., *submitted*

Caboni, P.; Porcheddu, A.; Ötvös, S. B.; Kappe, C. O. *Green. Chem.* **2026**, *28*, 2049

Ötvös, S. B.; Kappe, C. O. *Chim. Oggi* **2026**, *44(2)*, 8

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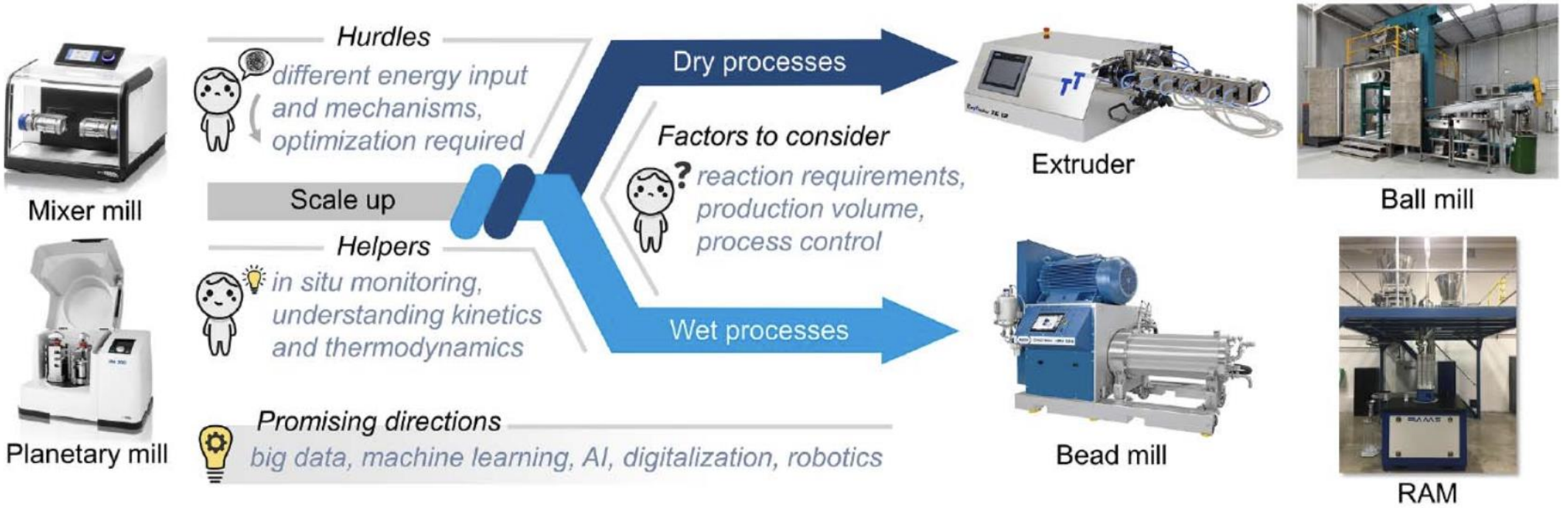
Mechanochemistrv

Mechanochemistry – Scale-up

"One of the primary obstacles in upscaling mechanochemical processes is the lack of standardization. Unlike solution-based chemistry [….], mechanochemical processes are still in their infancy when it comes to industrial implementation. This lack of standardization makes it difficult to directly translate laboratory-scale successes into industrial settings."



Stolar, T.; Emmerling, F. et al. Mechanochemistry: Looking Back and Ahead, *Chem* **2026**, *12*, 102880

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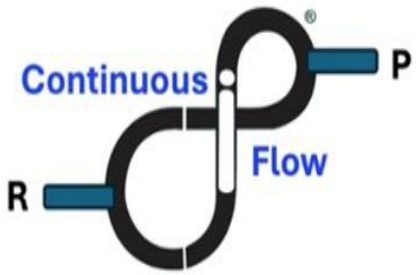
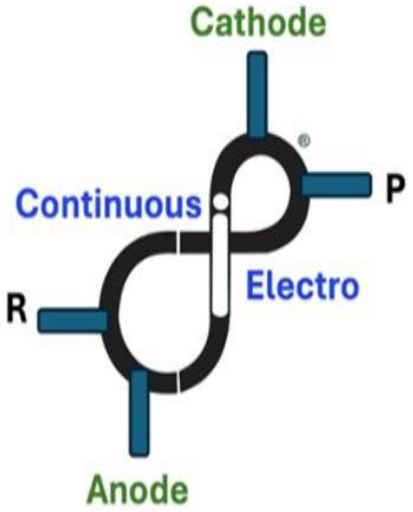
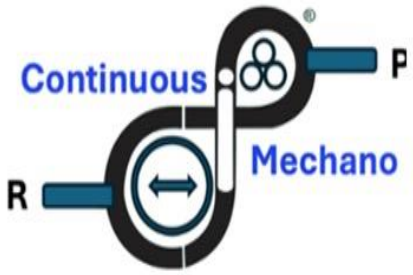
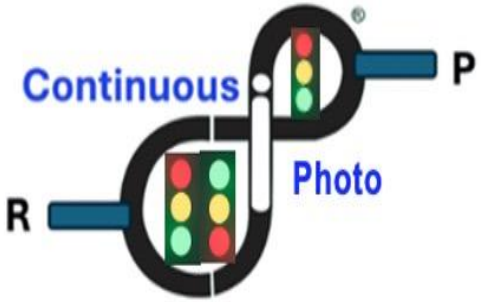
Continuous Process Intensification









Flow **Electro** **Mechano** **Photo**

GenZ Materials
Continuous Process Intensification

FCPI
Foundation for Continuous Process Intensification

processintensification