

An Introduction to Mechanochemistry: Underlying Theory and Applications in Organic Synthesis

Denmark Group Meeting

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Outline

What is Mechanochemistry?

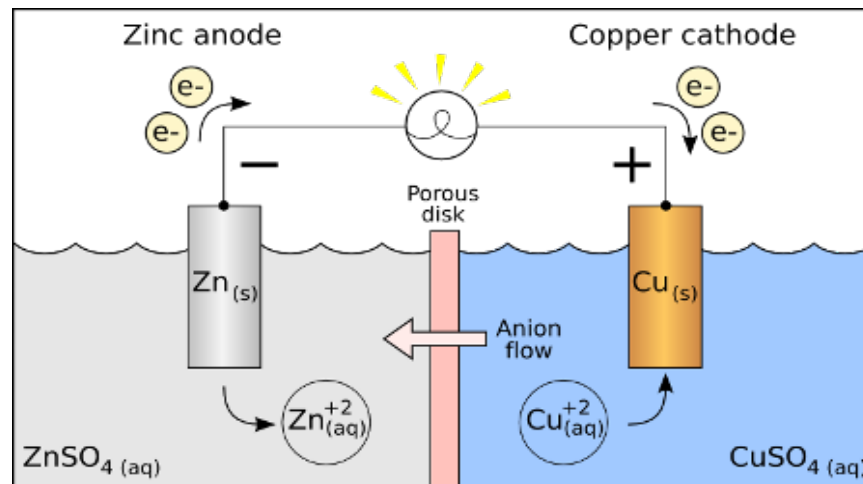
Methods of performing a mechanochemical reaction

Synthetic applications of mechanochemistry

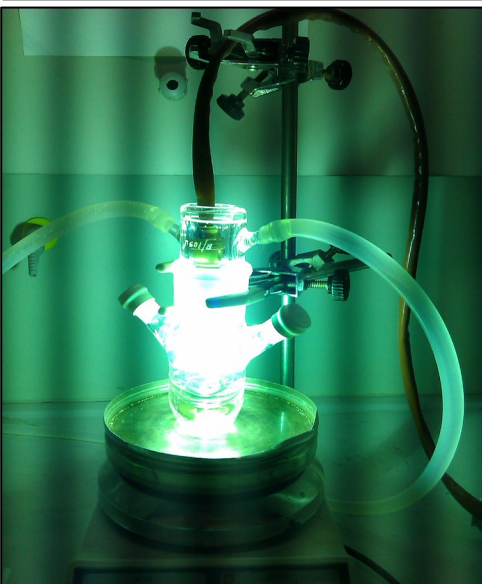
Modes of Energy Transfer for Chemical Reactions



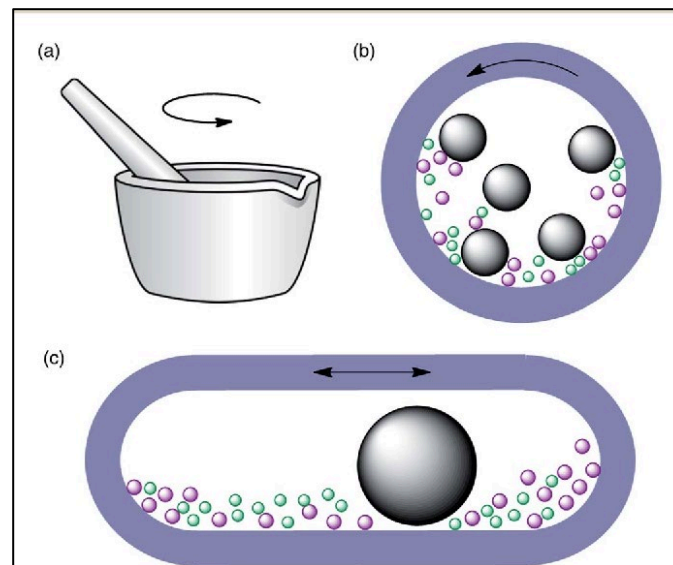
Thermochemistry



Electrochemistry



Photochemistry



Mechanochemistry

Defining Mechanochemistry

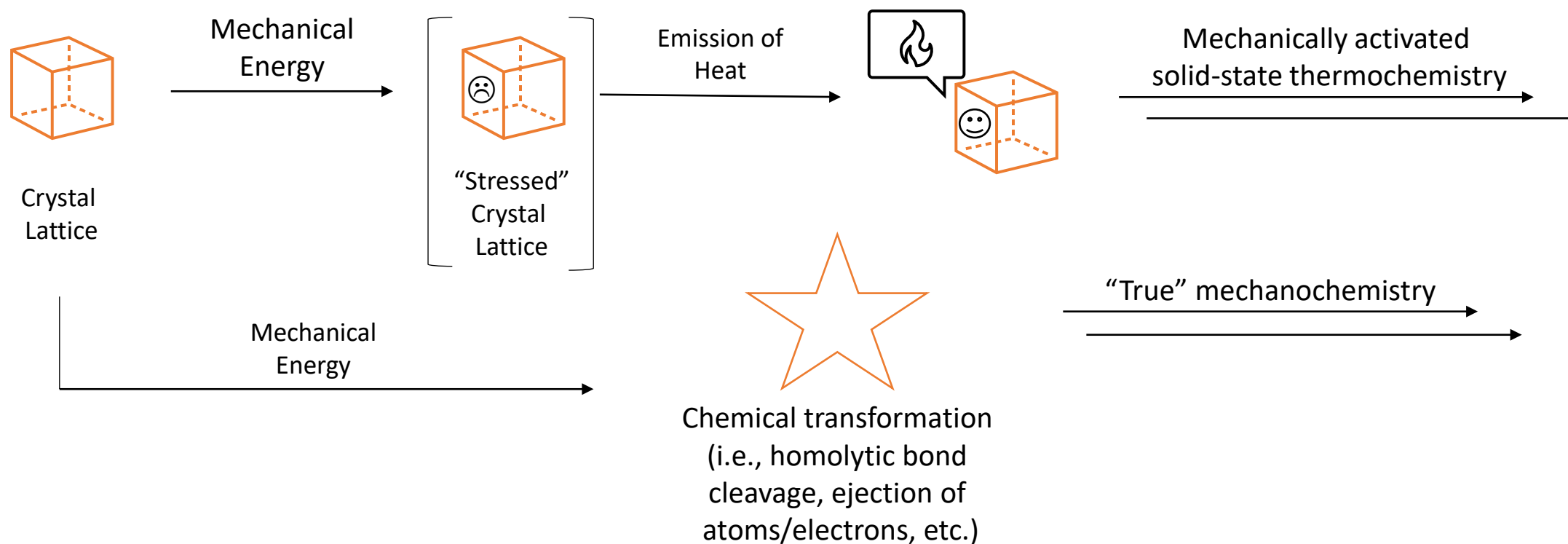
- IUPAC definition of a *mechano-chemical* reaction:
 - A chemical reaction that is induced by the direct absorption of mechanical energy
- Definition by Gerd Kaupp:
 - *“Mechanochemistry means mechanical breakage of intramolecular bonds by external force and must be differentiated from molecular solid-state chemistry, where contacts between micronized molecular solids are created by the mechanical action for mutual approach of the reacting centers”*



Gerd Kaupp

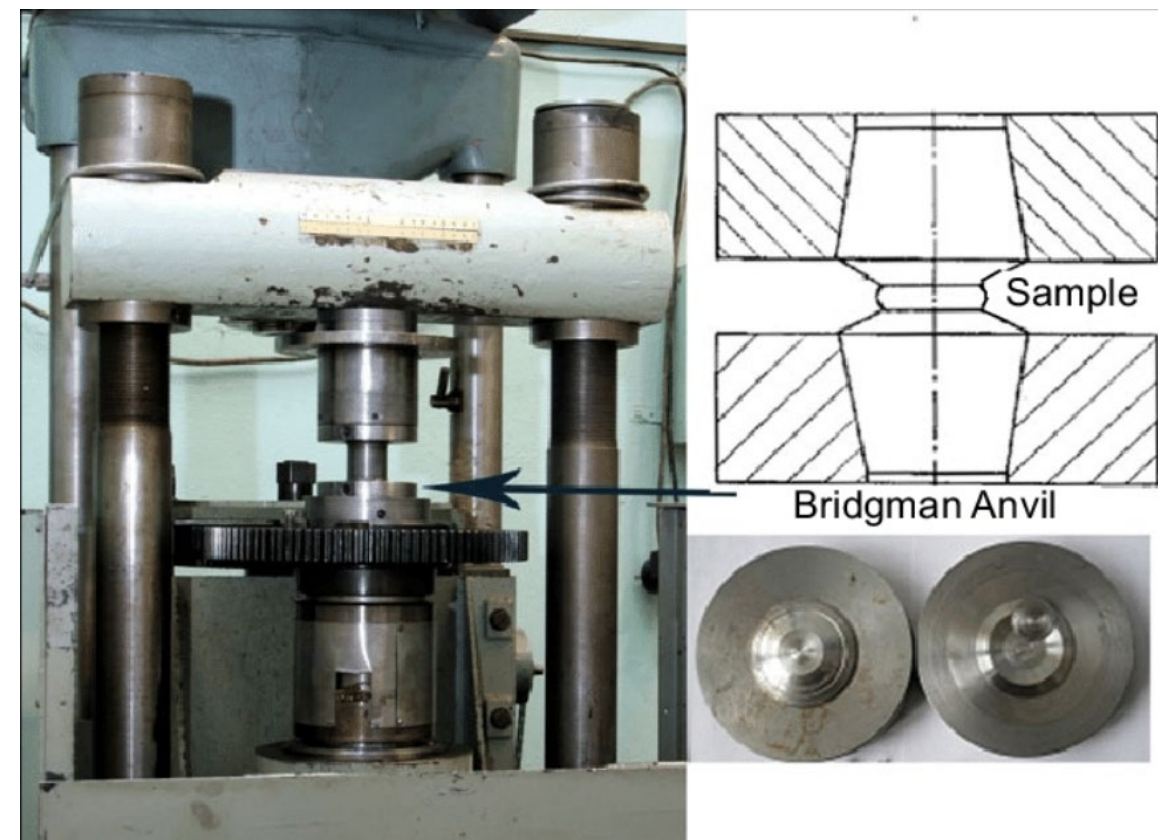
Elaborating on Kaupp's Definition

- Mechanical degradation results in an increase in surface area, but only has a 10% increase in reactivity
 - Reactivity arises from accumulated surface energy in the crystal lattice defects



A Note on “True” Mechanochemistry

- Most mechanochemical reactions are not “true” mechanochemistry, as defined by Kaupp
 - Organic compounds with strong bonds will not be cleaved through mild mechanochemical reaction conditions (i.e., milling or grinding) and require stronger forces such as those provided by a Bridgman’s anvil
- Most mechanochemical reactions proceed through a mechanically-induced thermochemical reaction



Different Mechanochemical Reactor Vessels

- Mortar and pestle:

- Form of grinding
- First example of mechanochemical reaction performed by a student of Aristotle by grinding cinnabar with a brass mortar and pestle:

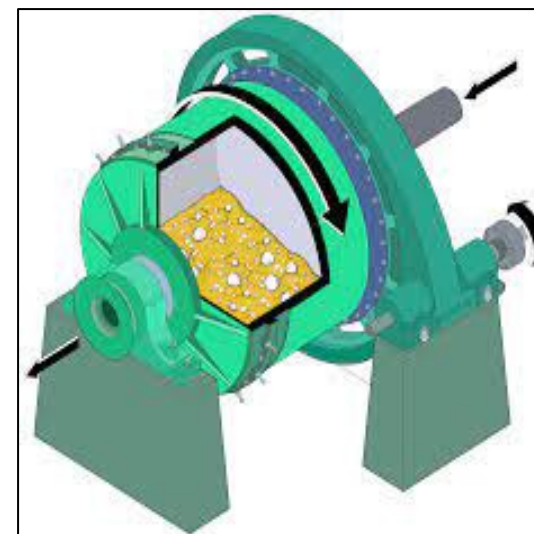


- Slow grinding due to low power input



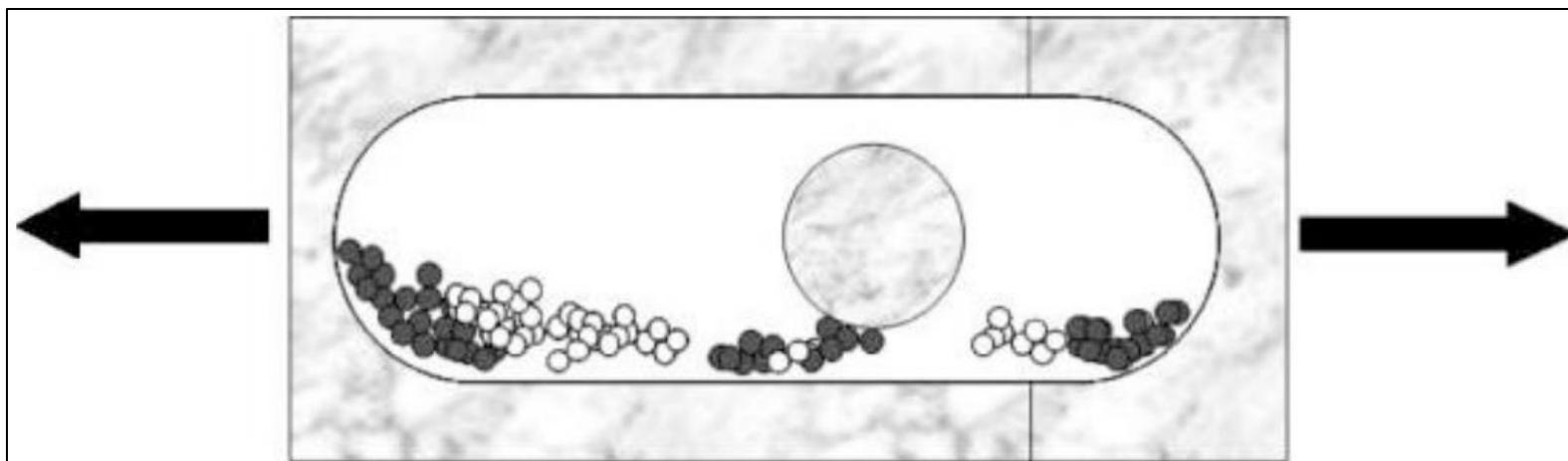
- Ball-mills:

- Form of milling
- Originally designed to break down metal ore to sub-millimeter size for industrial processing
- Uses dense balls or rods to break apart materials through continuous tumbling action



Types of Ball Mills

- Vibration ball mill:
 - Undergoes vibration in x-, y-, or z-axes individually or simultaneously
 - Less energetic option due to smaller travel distance of milling balls
 - https://youtube.com/clip/Ugkx1MH1a7bA2QvIdJa4U955L5XA_y6kOGvz



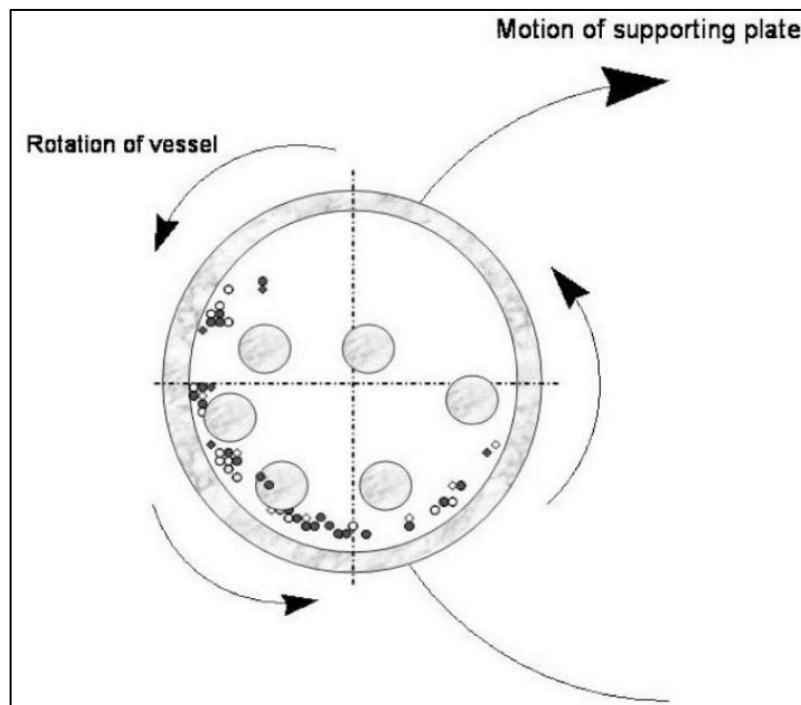
Types of Ball Mills

- Vibration ball mill:



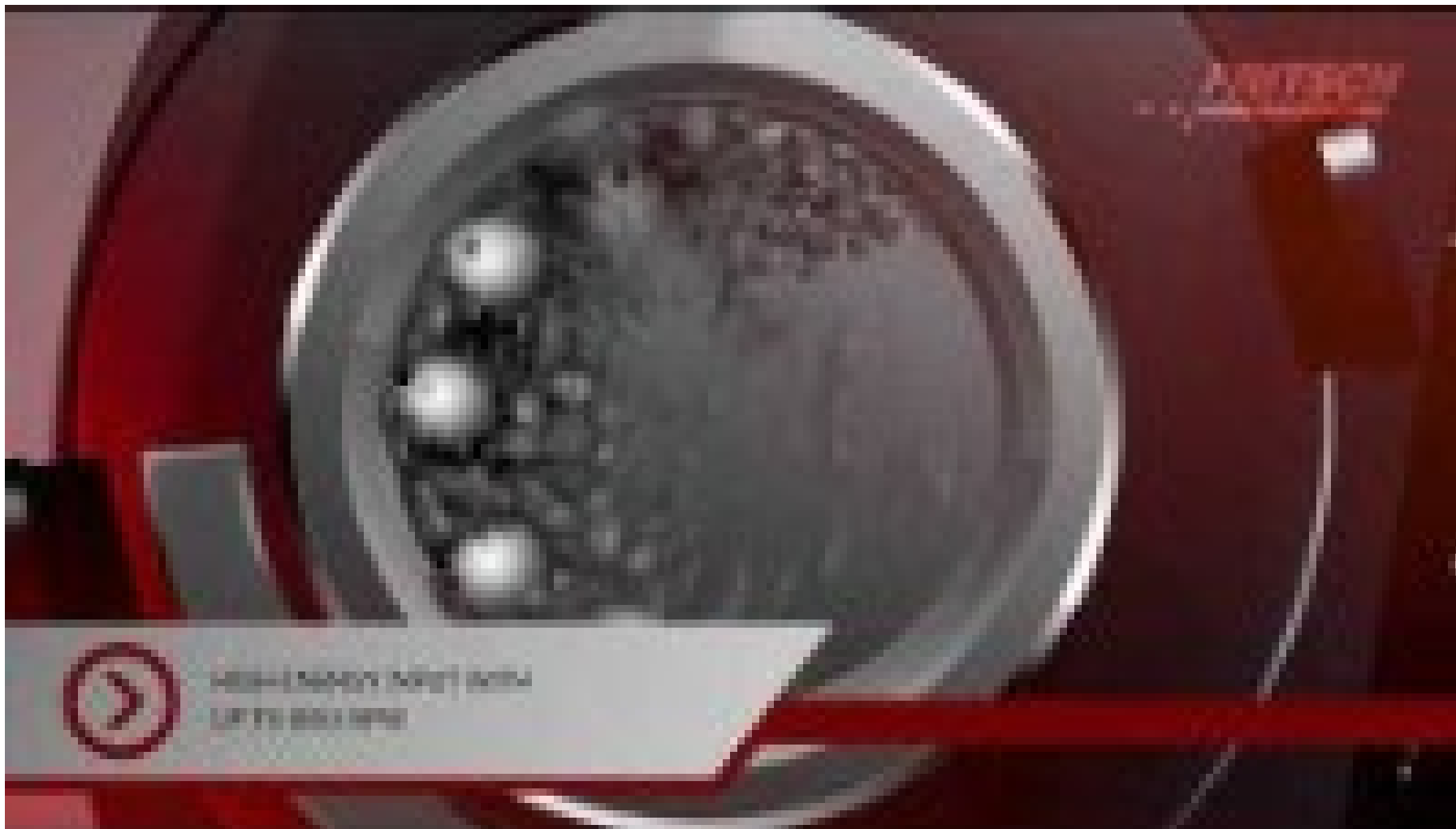
Types of Ball Mills

- Planetary ball mill:
 - Uses centrifuge to create a larger acceleration of gravity and imparts a larger impact force onto the sample
 - Considered the “workhorse” of modern laboratory mechanochemistry
 - <https://youtube.com/clip/UgkxNsr67qXJd0P2H2rWq31cmMcax6GyE5gB>



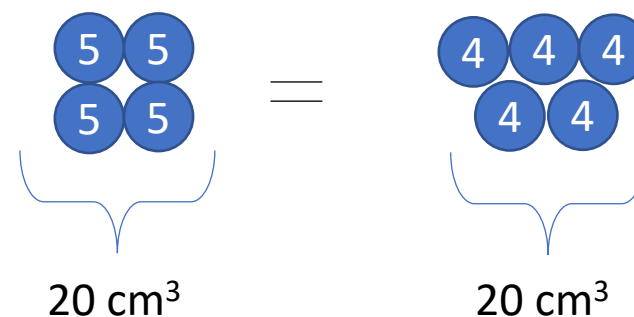
Types of Ball Mills

- Planetary ball mill:



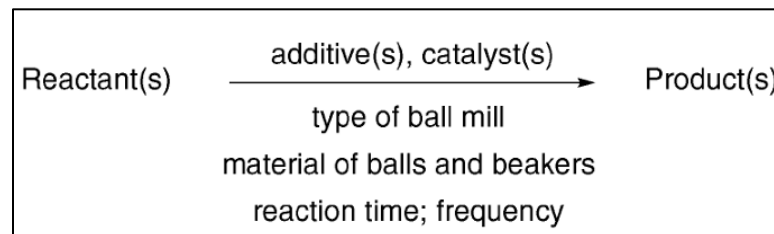
Parameters of Ball-Milling Reactions

- Besides the type of ball-mill, several other conditions determine the outcome of the mechanochemical reaction:
 - Rotation/oscillation frequency ($v_{\text{rot}}/v_{\text{osc}}$)
 - Milling time (t)
 - Density of milling material (ρ_{MB})
 - Size of milling balls (d_{MB})
 - Number of milling balls (n_{MB})
- Most important parameters are often frequency, milling time, and milling material:



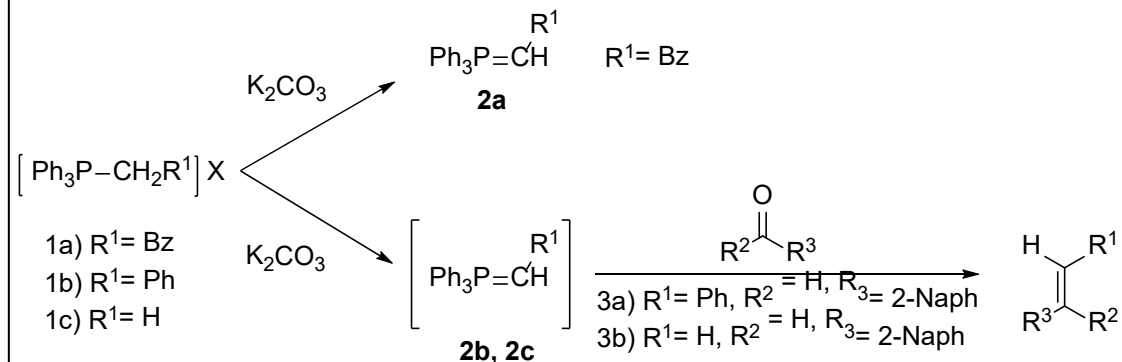
$$E_{\text{kinetic}} = 0.5I\omega^2 = 2\pi^2Iv^2$$

- General reaction diagram:

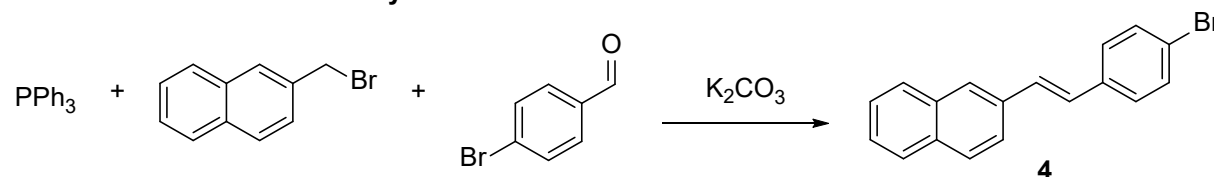


Solid-State Wittig Reaction

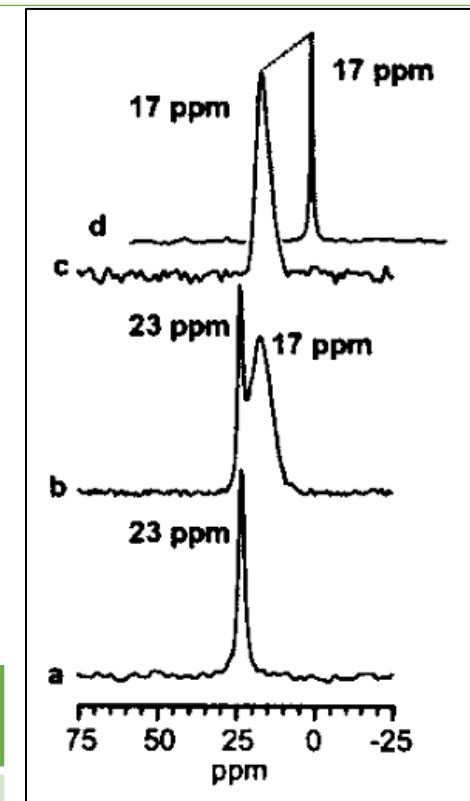
Mechanochemical Generation of Phosphoranes



"One-Pot" Mechanochemical Synthesis



Compound	Milling Time (h)	Yield (%)	E:Z Ratio
2a $\text{Ph}_3\text{P}=\text{CHBz}$	3	99	-
3a $\text{H}-\text{C}(\text{Ph})=\text{C}(\text{H})-\text{2-Naph}$	7	85	1.6:1
3b $\text{H}-\text{C}(\text{H})=\text{C}(\text{H})-\text{2-Naph}$	20	73	-
4 $\text{H}-\text{C}(\text{Ar})=\text{C}(\text{H})-\text{2-Naph}$	8	93	3.5:1



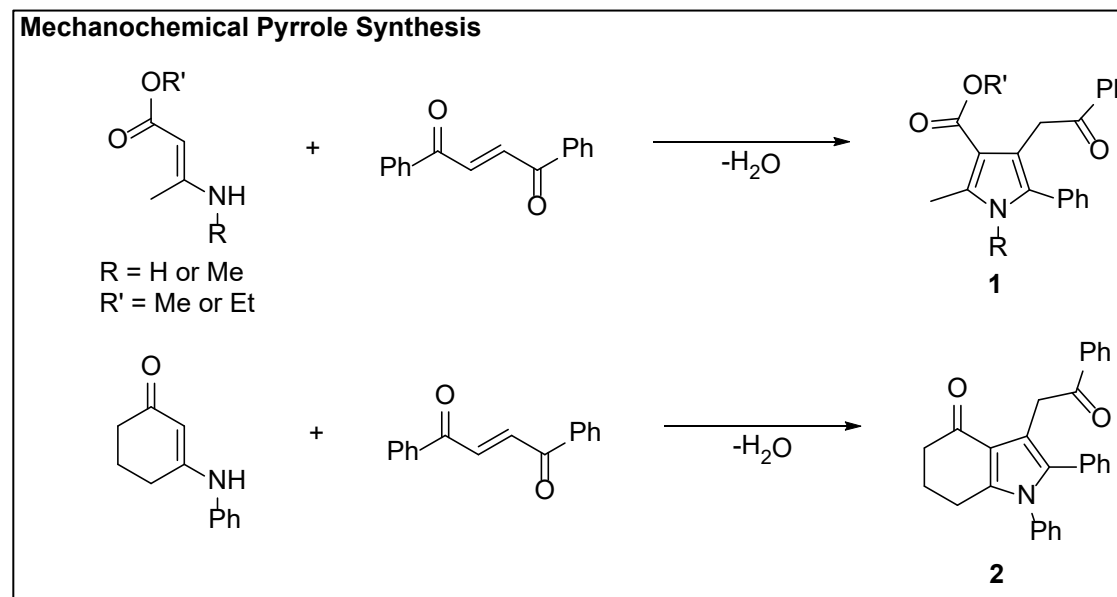
t=3h

t=1h

t=0h

Pyrrole Synthesis

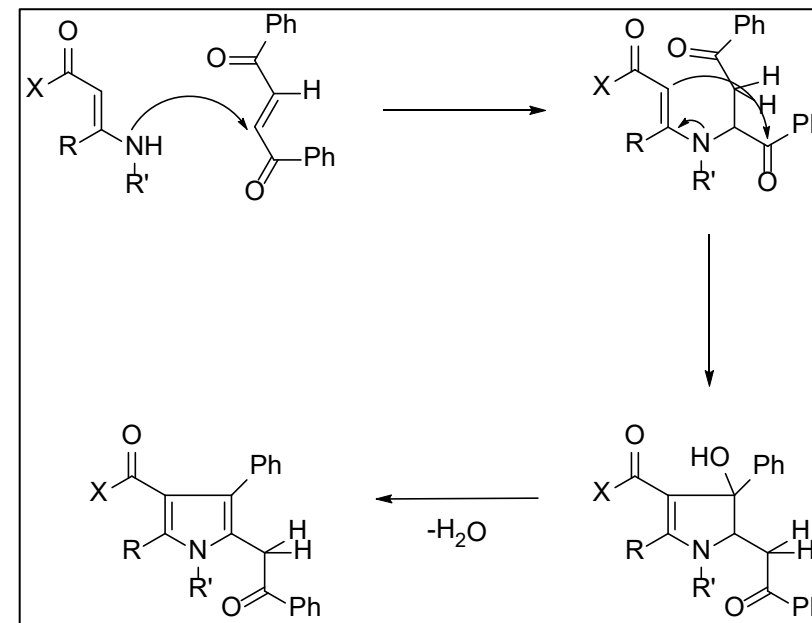
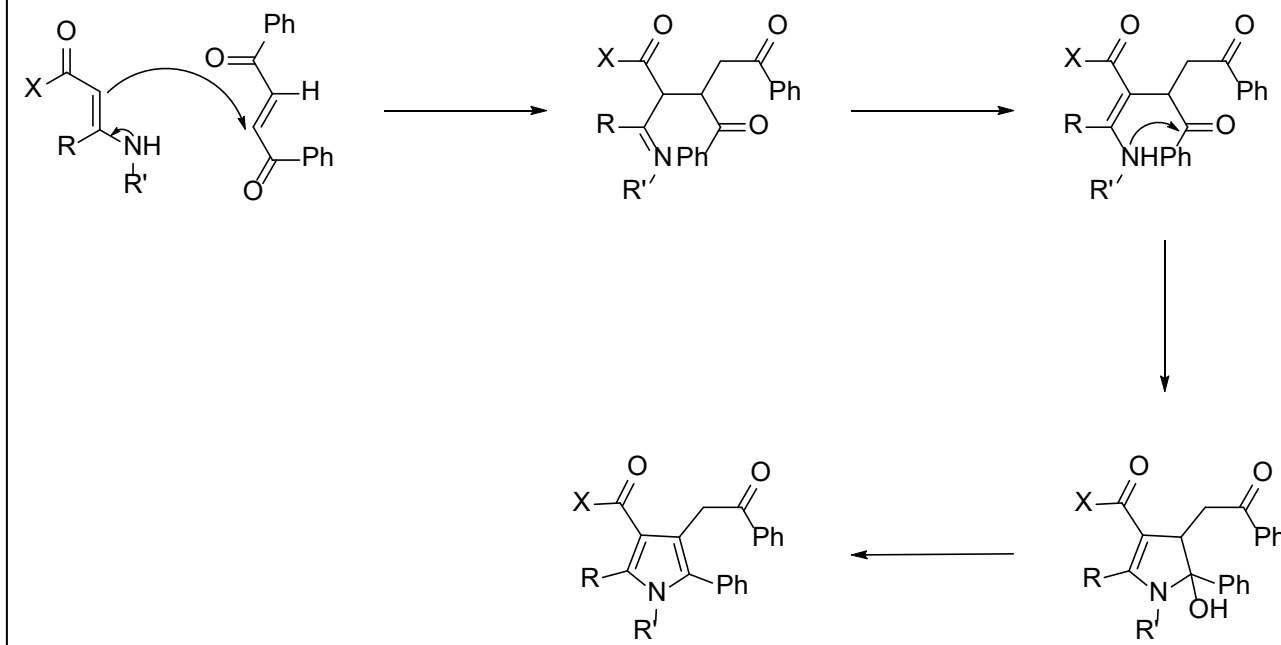
- Kaupp demonstrates solvent-free reactions benefit from crystal packing, leading to high selectivity
- Provides quantitative yields in 3 h of milling
 - Solution phase yields of 1 and 2 range from 46 – 81%



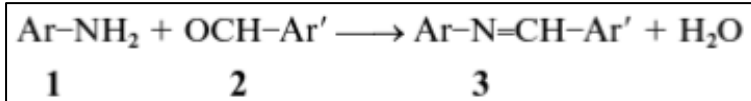
Pyrrole Synthesis

- Reaction shows strong preference for C-C bond formation, rather than C-N bond formation

C-C Selectivity vs C-N Selectivity



Macroscopic Insight



- “In the reactions of 1 and 2 it turns out that only the aldehydes 2 move into the lattice of the amines 1 in all the cases studied.”
- “A small crystal of *p*-chlorobenzaldehyde [$P2_1/a$,²⁵ lath-shaped crystals with rough (001) face] was laid down on the (100) surface of a single crystal of *p*-nitroaniline (system *k*; the initial roughness was $R_{ms} = 11.1 \text{ nm}$).”
 - “After several hours, the aldehyde crystal disappeared completely both by reaction and by sublimation”
- “Highly sensitive internal reflection SNOM gave no optical contrast that distinguished the material at the stumps from the one at the basic plane surface. This observation indicates that product formation had also occurred between the stumps in Fig. 1(b).”
 - “Apparently, ‘short distance sublimation’ of volatile *p*-chlorobenzaldehyde bridged the gap of roughly 100 nm between non-contacting surface areas.”

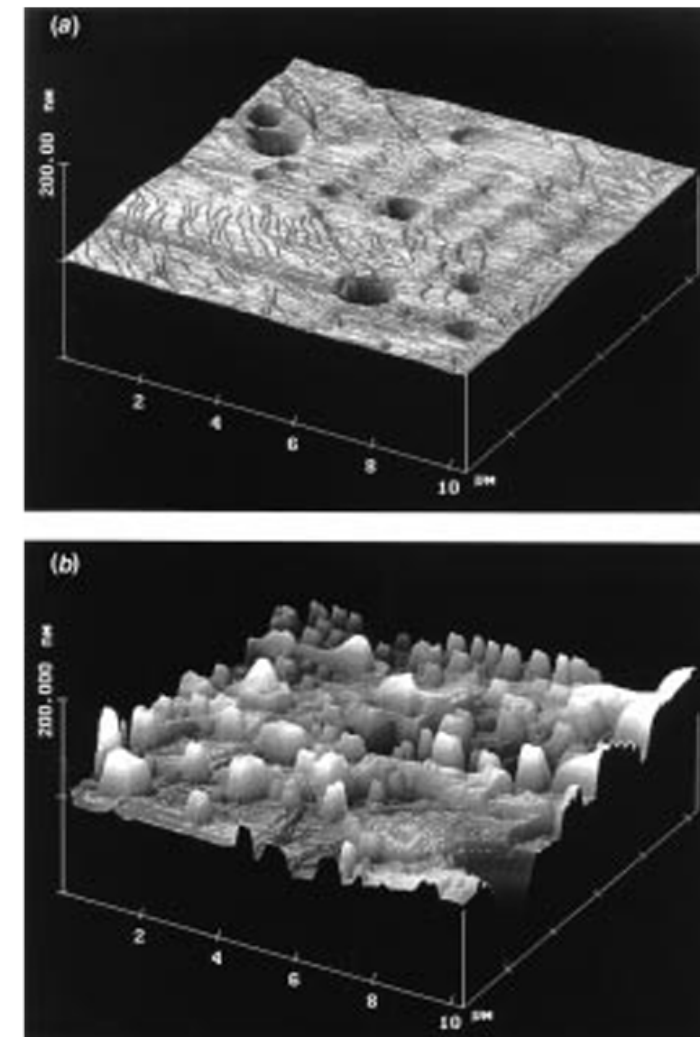
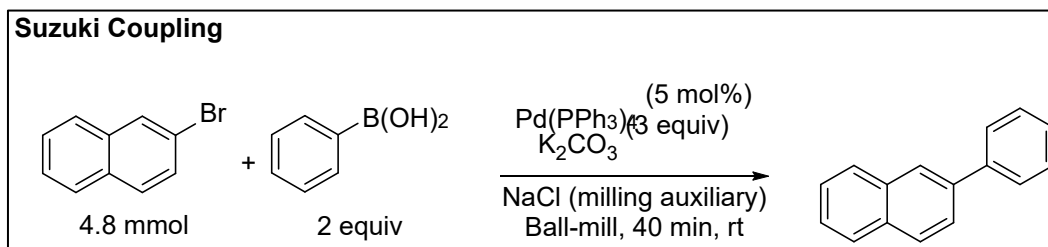


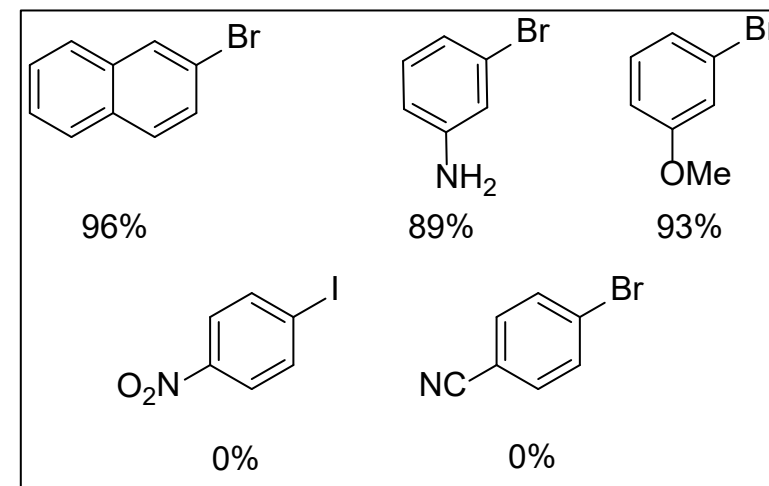
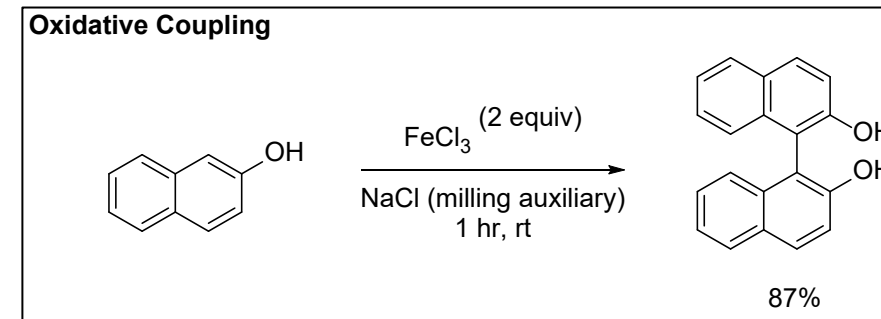
Fig. 1 AFM topographies of *p*-nitroaniline on (100); (a) pure and (b) after reaction with a tiny crystal (*ca.* 0.3 mg) of *p*-chlorobenzaldehyde, which had completely disappeared after 4 h, in the previously covered area. The sites of the same crystal species before and after reaction are not identical, but it has a fairly uniform appearance throughout.

Initial Endeavors of Solid-State Metal-Catalyzed C-C Bond Formation

- First solid-state coupling performed by Axelsson
- Prompted exploration of solid-state Suzuki coupling
 - Notable amount of homocoupling, which was attenuated by an excess of phenyl boronic acid



- Reactions used Pd^0 in an aerobic environment

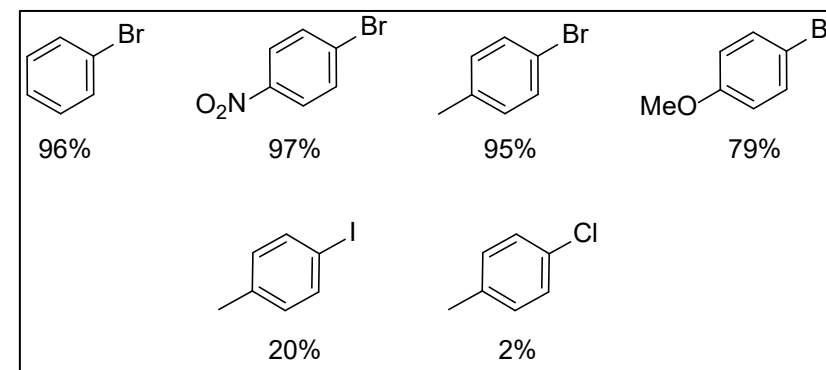
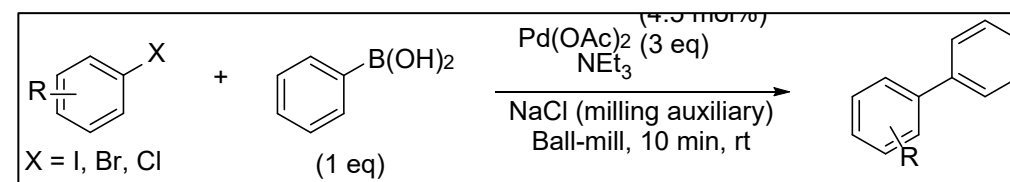


Expansion of the Solid-State Suzuki Coupling

- Klingensmith and Leadbeater decreased the loading of phenyl boronic acid to 1:1 and used NEt_3 as base

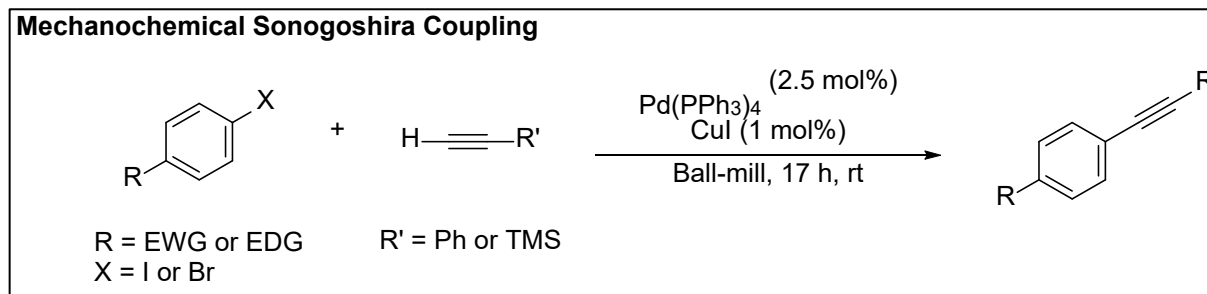
Entry	Reaction conditions	Yield (%) ^b
1	$\text{Pd}(\text{OAc})_2$, b = Na_2CO_3 , g.t. = 30 min	12
2	PdCl_2 , b = Na_2CO_3 , g.t. = 30 min	9
3	$\text{Pd}(\text{OAc})_2$, b = Na_2CO_3 , g.t. = 1 h	14
4	$\text{Pd}(\text{OAc})_2$, b = NEt_3 , g.t. = 30 min	95
5	PdCl_2 , b = NEt_3 , g.t. = 30 min	79
6	$\text{Pd}(\text{OAc})_2$, b = NEt_3 , g.t. = 10 min	95
7	$\text{Pd}(\text{OAc})_2$, b = NEt_3 , t = 16 h ^c	60

^a 1 mmol aryl halide, 1 mmol $\text{PhB}(\text{OH})_2$, 3 mmol base, 4.5 mol% Pd salt. b = base, g.t. = grind time, t = reaction time.
^b Isolated yields.
^c Stirred in a test tube.



An Interesting Report on the Ball-Milled Sonogoshira Reaction

- Initial success for mechanochemical Sonogoshira reaction



- Another example of Pd^0 in an aerobic environment
- Prompted the attempts of a copper-free Sonogoshira reaction

Table 2 “Copper-free” Sonogashira reactions of *p*-substituted benzene with trimethylsilylacetylene

X	R	Percent Yield ^a w/CuI	Percent Yield ^a “copper-free”
I	H	95	39
I	Me	84	17
I	Br	88	43
I	Cl	87	37
I	OMe	84	58
Br	CHO	87	44
Br	CHO ^b	89	46

^a Reported as isolated yields. ^b 1,2 disubstituted.

An Interesting Report on the Ball-Milled Sonogashira Reaction

Table 3 Sonogashira reactions of *p*-substituted benzene with trimethylsilylacetylene using a 3/32" copper ball in a stainless steel vial

X	R	Percent Yield ^a w/CuI	Percent Yield ^a w/Cu ball
I	H	95	87
I	Me	84	46
I	Br	88	31
I	Cl	87	52
I	OMe	84	40
Br	CHO	87	85
Br	CHO ^b	89	88

^a Reported as isolated yields. ^b 1,2 disubstituted.

Table 4 Sonogashira reactions of *p*-substituted benzene with trimethylsilylacetylene using a 3/32" copper ball in a copper vial

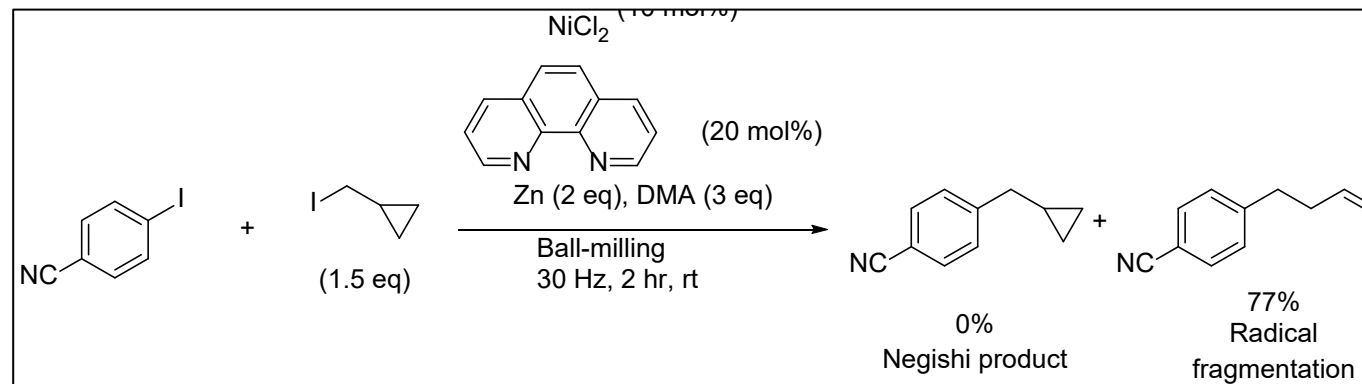
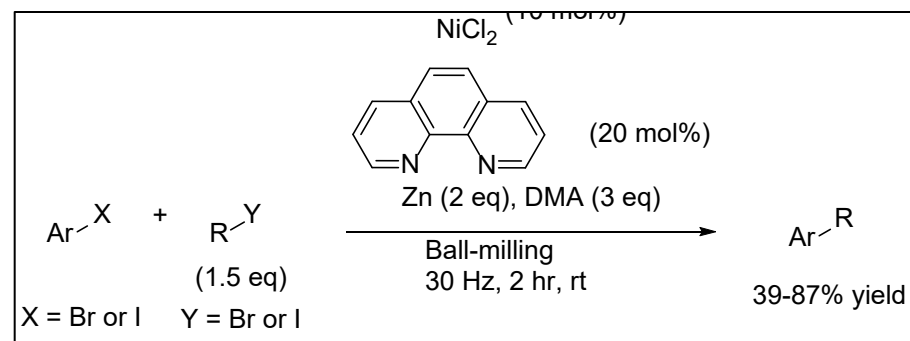
X	R	Percent Yield ^a w/CuI	Percent Yield ^a w/Cu ball and Cu vial
I	H	95	88
I	Me	84	83
I	Br	88	89
I	Cl	87	86
I	OMe	84	42
Br	CHO	87	84
Br	CHO ^b	89	90

^a Reported as isolated yields. ^b 1,2 disubstituted.

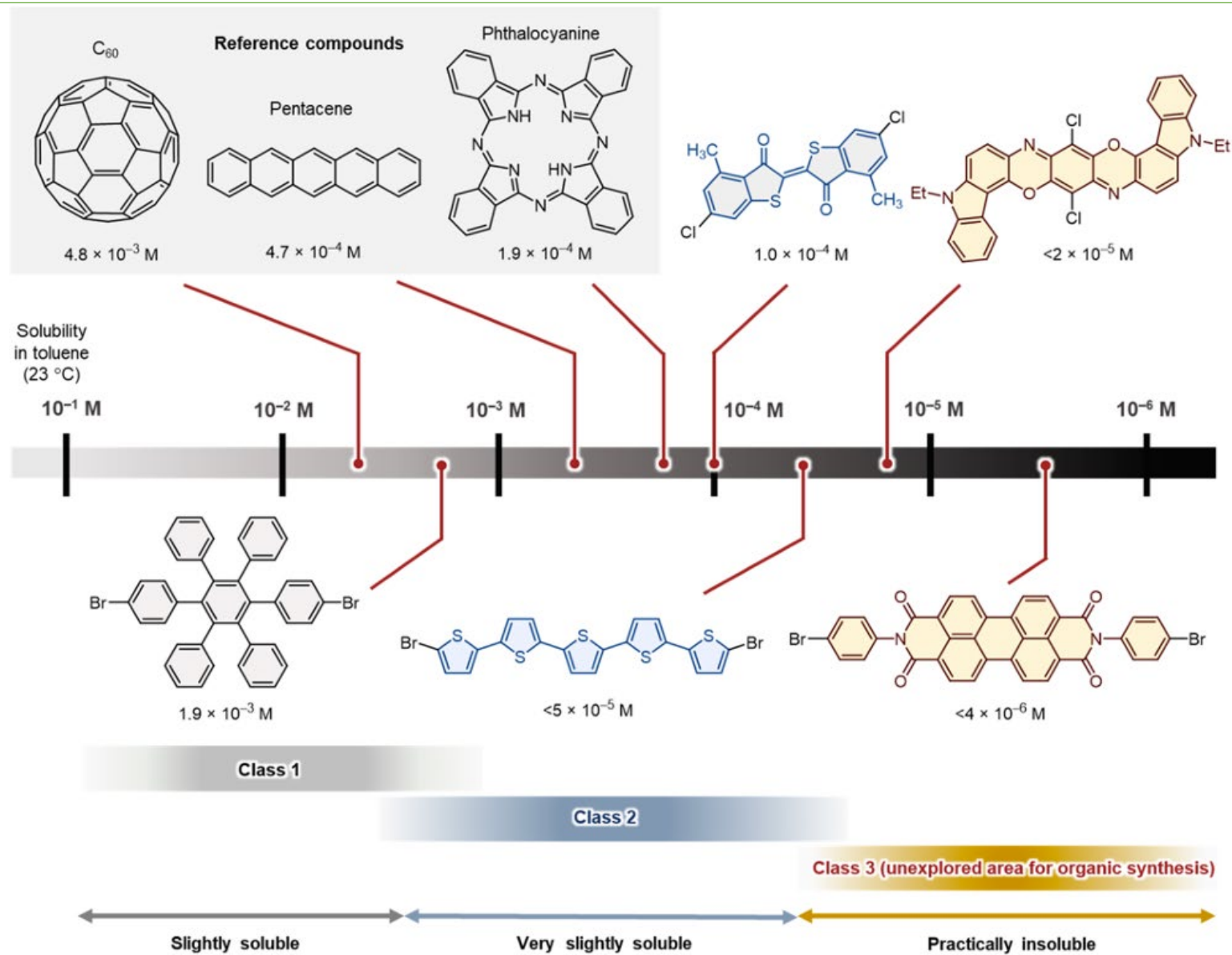
- No measurable mass loss of the copper ball and vial after each reaction
- No decrease in yield after continued use over a month

Mechanochemical Ni-Catalyzed Cross Electrophile Coupling

- Browne (2021):
 - Aerobic reaction conditions with short reaction times compared to solution phase
- Scalable with no change in yield or reaction time

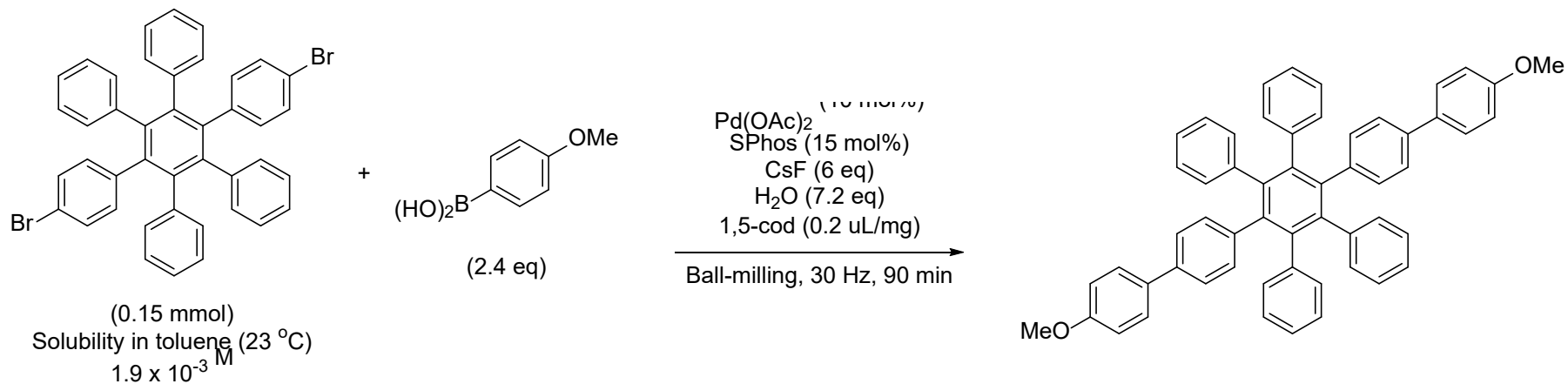
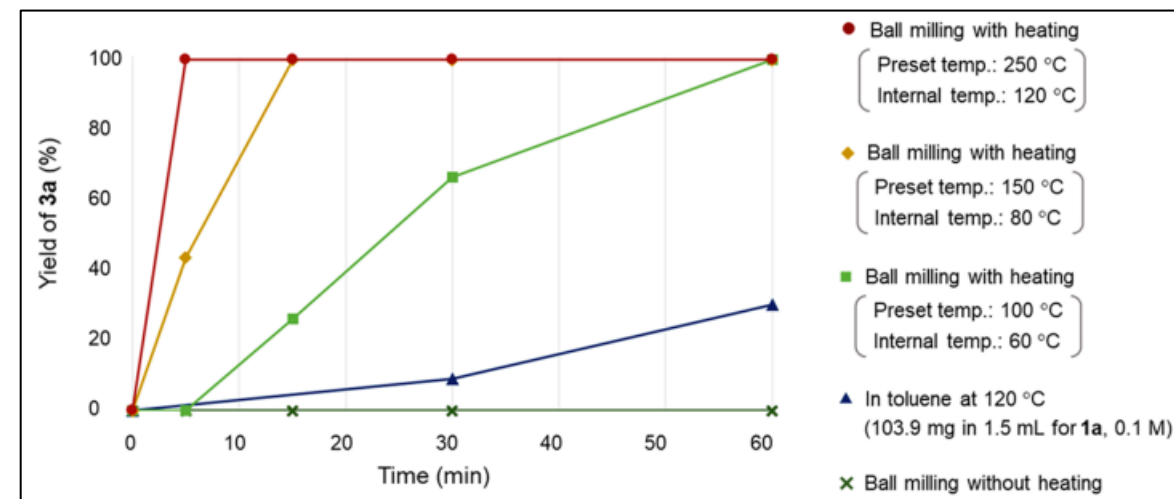


Cross-Coupling of Low Solubility Aryl Halides



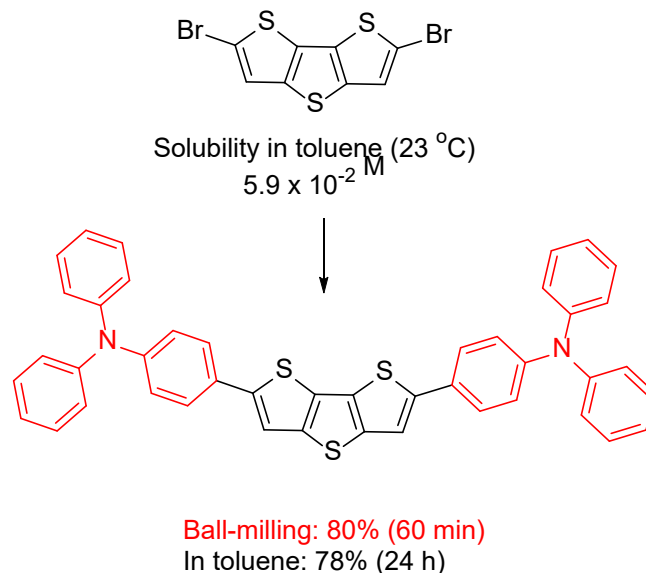
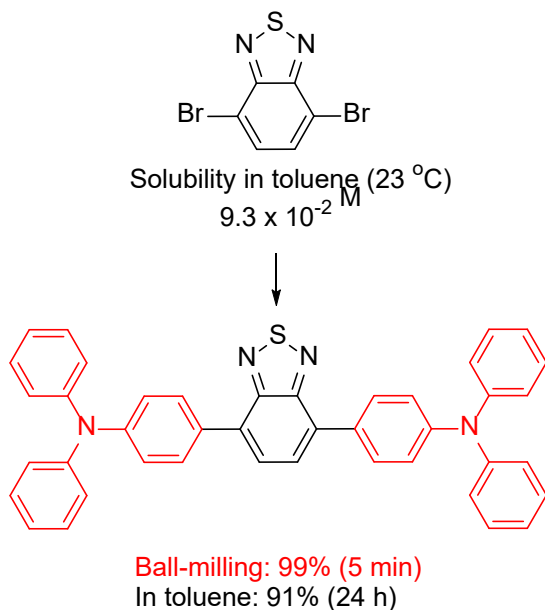
Cross-Coupling of Low Solubility Aryl Halides

- Ito (2021):
 - Can be performed with lower Pd loadings (3 mol%) and carried out on gram scale

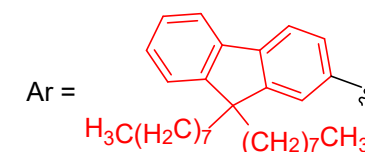
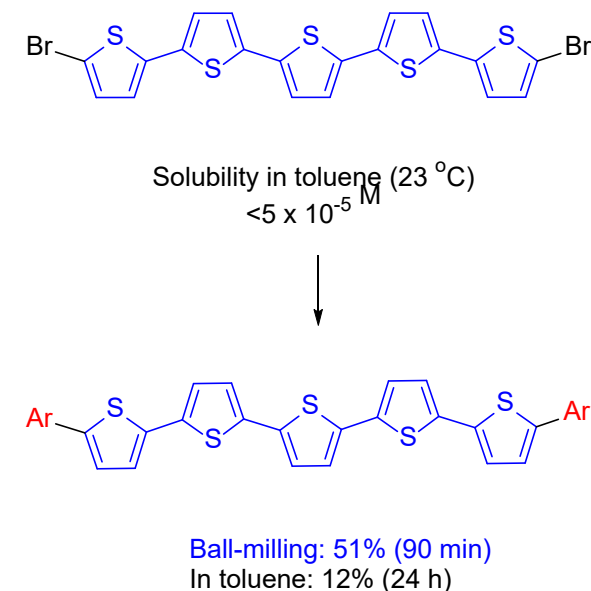
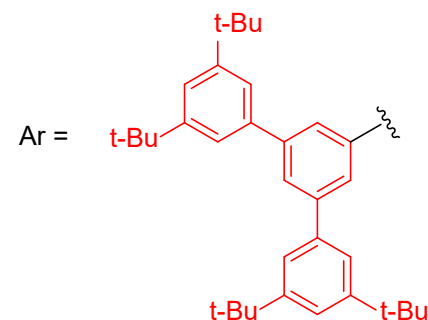
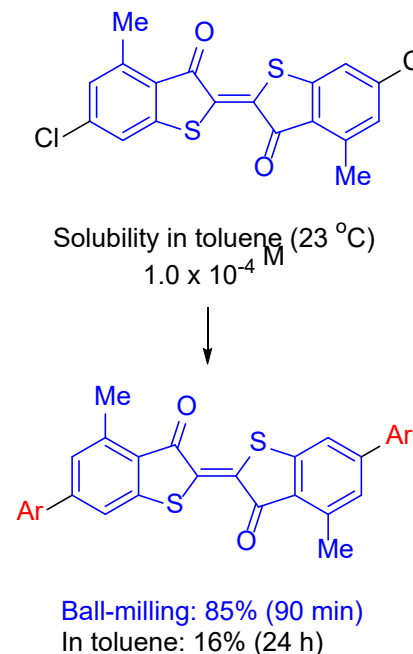


Cross-Coupling of Low Solubility Aryl Halides

Class 1: Slightly Soluble

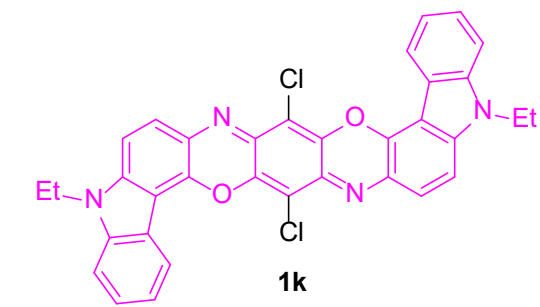


Class 2: Very Slightly Soluble

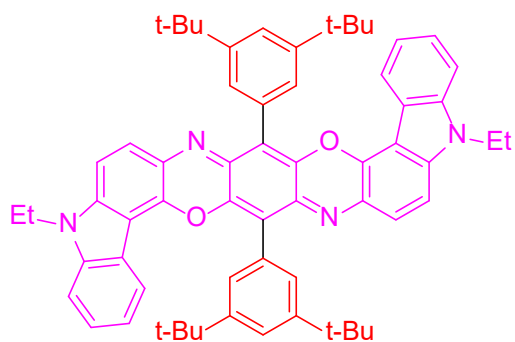


Cross-Coupling of Low Solubility Aryl Halides

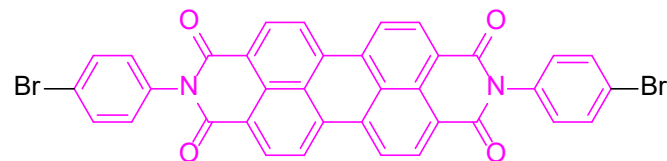
Class 3: Practically Insoluble



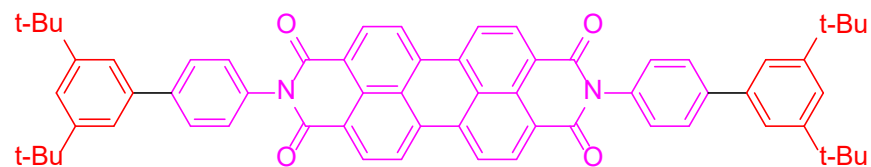
Solubility in toluene (23 °C)
 $< 2 \times 10^{-5} \text{ M}$



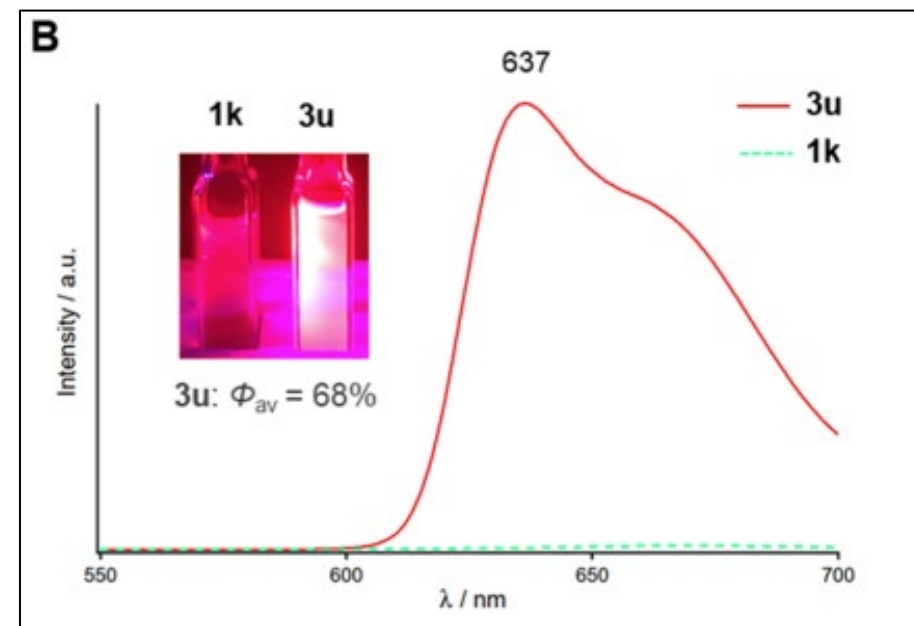
Ball-milling: 30% (90 min)
In toluene: No reaction (24 h)



Solubility in toluene (23 °C)
 $< 4 \times 10^{-6} \text{ M}$



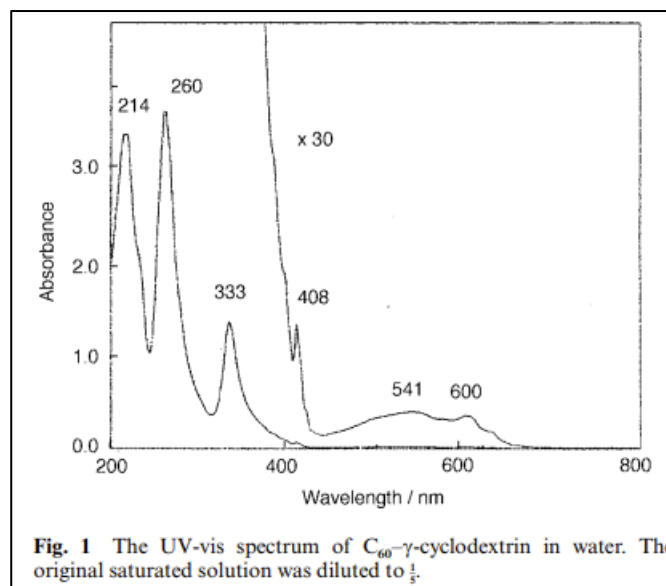
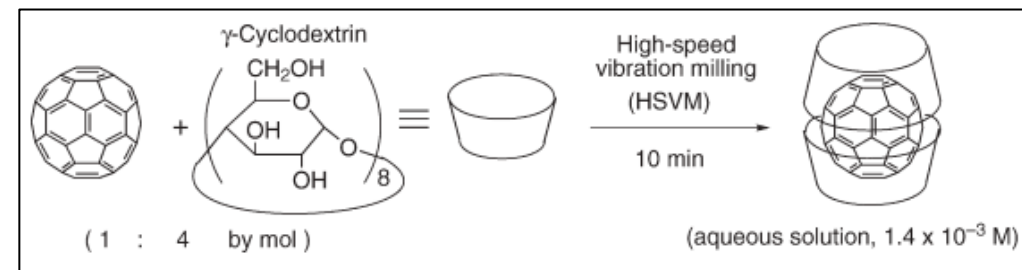
Ball-milling: 37% (90 min)
In toluene: No reaction (24 h)



Solubilization of C₆₀ in Aqueous Media

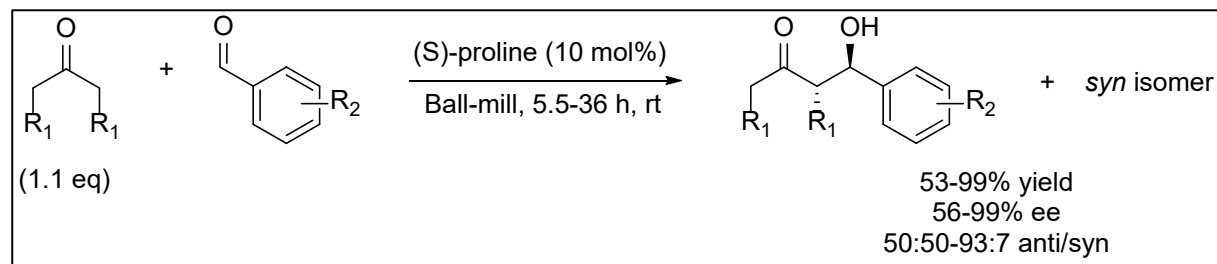
- Komatsu (1999):

- Expedited reaction time, compared to refluxing in water for 24 h and achieving solubilities of 8×10^{-5} M
- Nearly identical UV-Vis spectrum for C₆₀-complex than that of free C₆₀

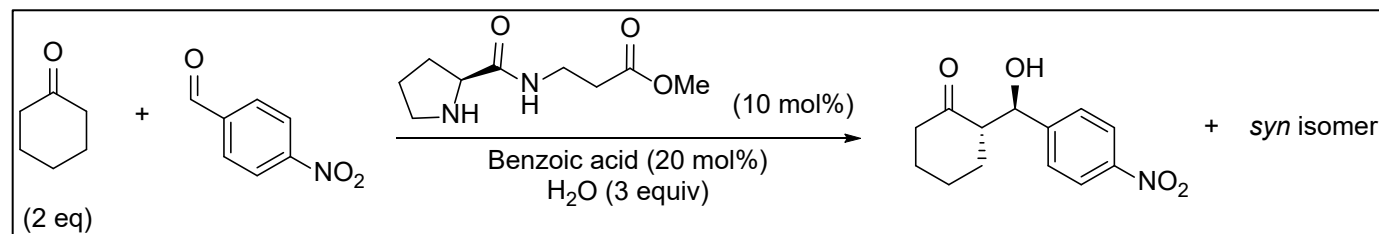


Mechanochemical Asymmetric Organocatalysis

- Bolm (2006):



- Juaristi (2015):

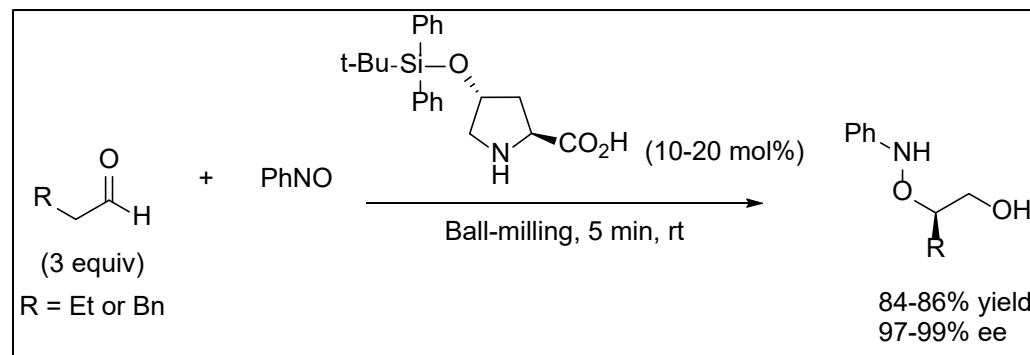


Solvent	Time (h)	Yield (%)	anti/syn	e.r.
None (milling)	0.5	94	90:10	91:9
H ₂ O (1 M)	48	99	80:20	84:16
THF (1 M)	240	95	45:55	50:50

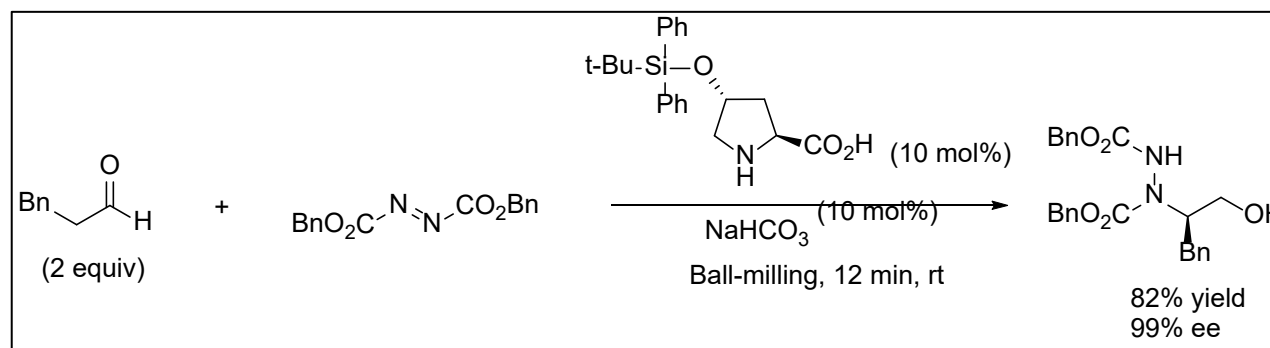
Mechanochemical Asymmetric α -aminooxylation and α -hydrazination

- Šebesta (2017):

- Similar yield and % ee than aqueous conditions, but 1/10 of the reaction time

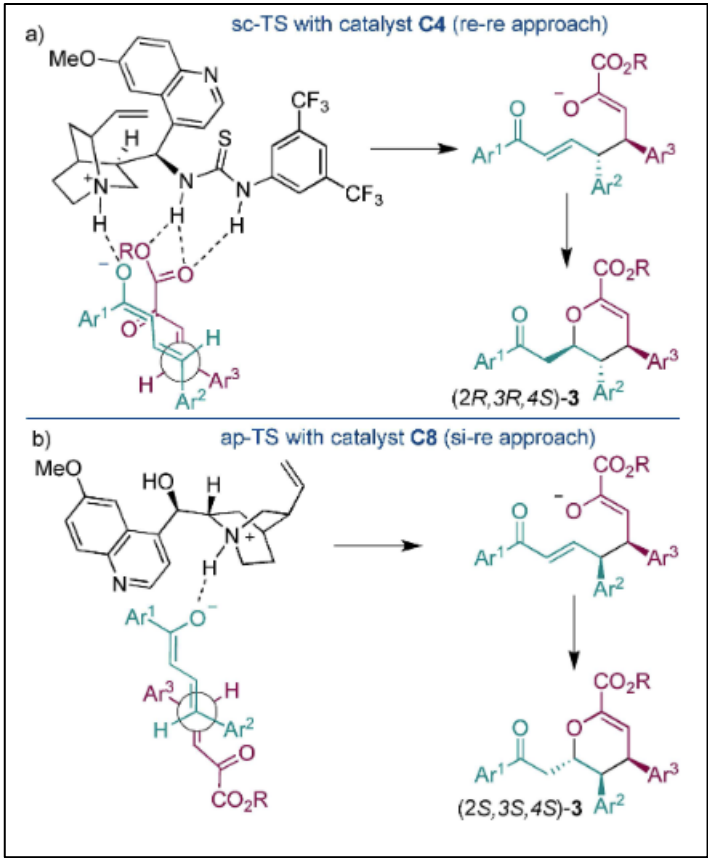
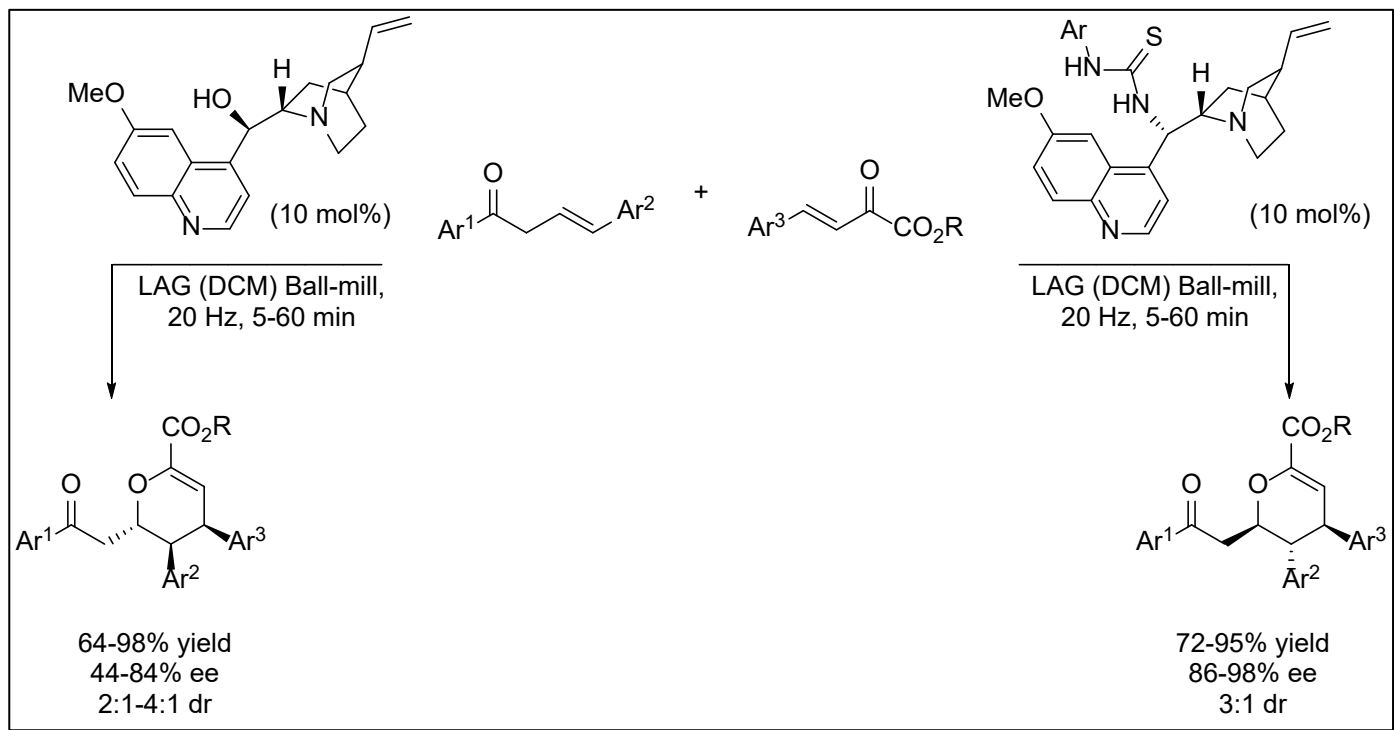


- Higher yield and shorter reaction times than aqueous conditions (1 h, 64% yield)



Mechanochemical Enantioselective Formal oxa-Diels-Alder

- Šebesta (2022):



Conclusions

- Environmentally sustainable approach to organic synthesis
 - Solvent minimization and low energy intensity
- Often provides shorter reaction times and simpler reaction setup
- May provide different selectivities and reactivities compared to solution phase chemistry
- Enables reactivity of traditionally “insoluble” compounds for solid-state conversion
- Improvement of technology to study macroscopic interactions