

Mechanochemistry

Green and sustainable way to known
and new compounds





Outline

Introduction

Definitions

History

Concepts & Milling Conditions

Areas of Application

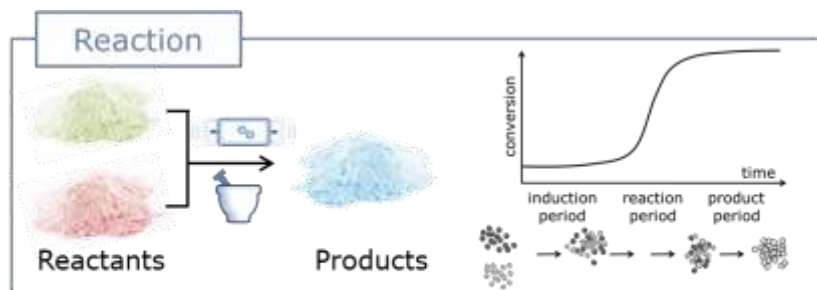
Understanding & Control

Conclusions & Prospects

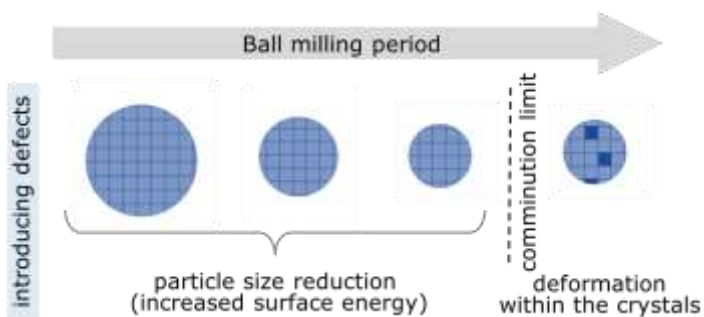


What is mechanochemistry?

Mechanochemistry is a branch of chemistry concerned with chemical and physico-chemical transformations of substances in all states of aggregation produced by the effect of mechanical energy.



particle size reduction
mixing
creation of active sites (defects)
generation of fresh active surfaces

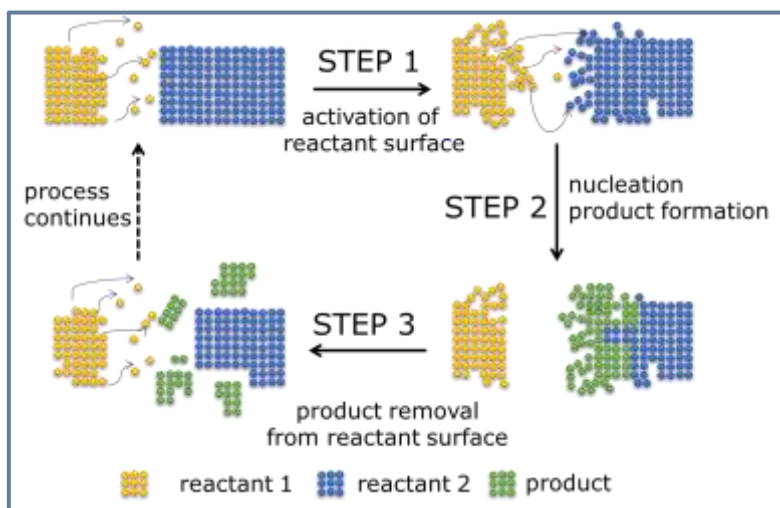


→ activation
→ chemical reaction
→ fast kinetics
→ new compounds
→ compounds with advantageous properties

G. Heinicke, Tribochemistry,
Akademie-Verlag, Berlin, 1986.



What is mechanochemistry?



IUPAC Chemical reaction that is induced by the **direct** absorption of mechanical energy.

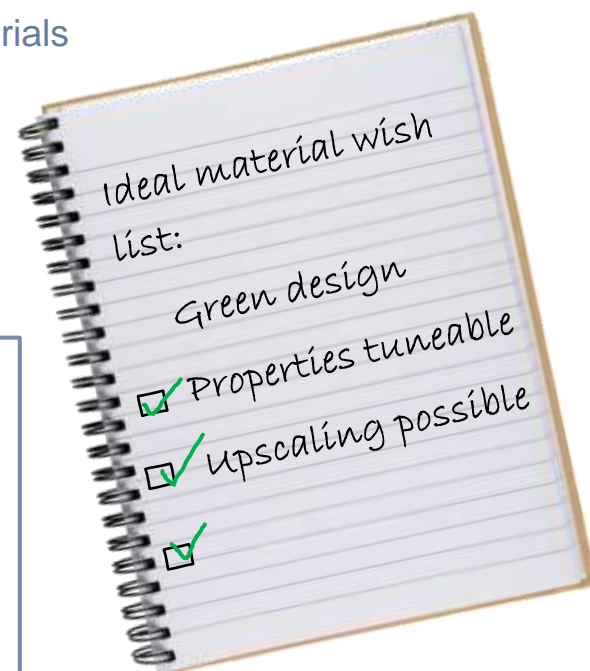
M. Nič, J. Jirát, B. Košata, A. Jenkins and A. McNaught, Eds., in IUPAC Compendium of Chemical Terminology, IUPAC, Research Triangle Park, NC, 2.1.0., 2009.



New/better materials – new/better synthesis routes



New materials needed



F. Gomollón-Bel,
Chem. Internat. 2019, 41, 12.

IUPAC names 10 chemistry innovations that will change the world:

5 Mechanochemistry and reactive extrusion

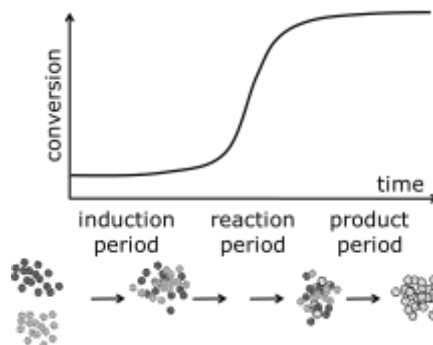
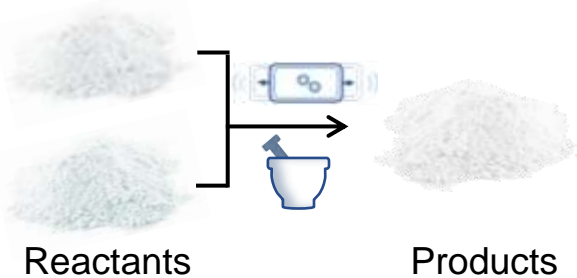
Mechanochemistry – including reactions through mechanical forces – sometimes **makes processes possible** that are hard to do by traditional solution synthesis. But scientists are still **struggling to understand** how the process works on a molecular scale.



I U P A C



Reaction



Devices



Materials

Advanced materials

MOFs

Pharmaceuticals

Organic compounds

Polymers

Cocrystals

Nanomaterials

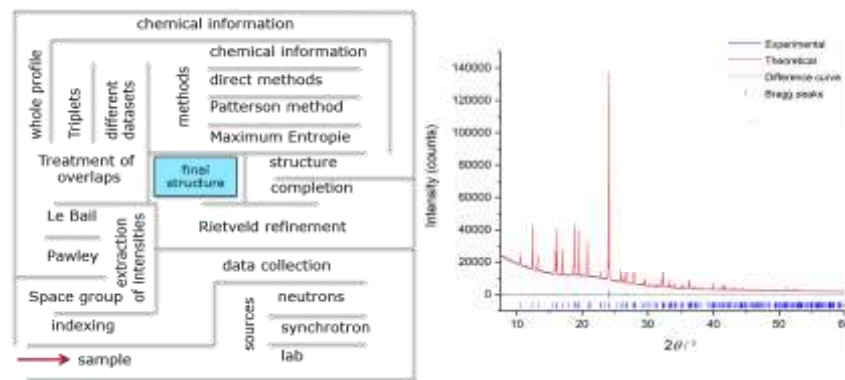
Nanocomposites

Intermetallics

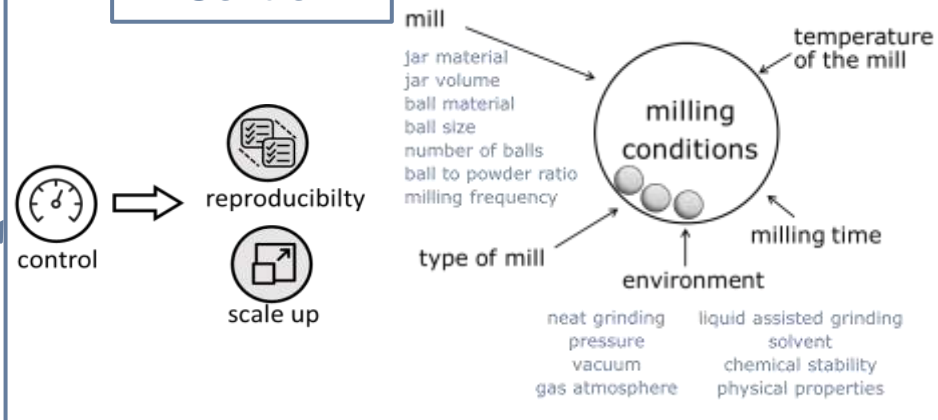




Structure solution from PXRD



Control

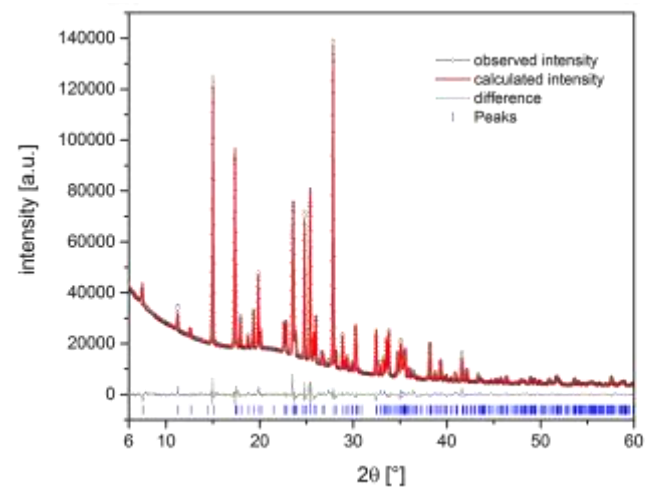
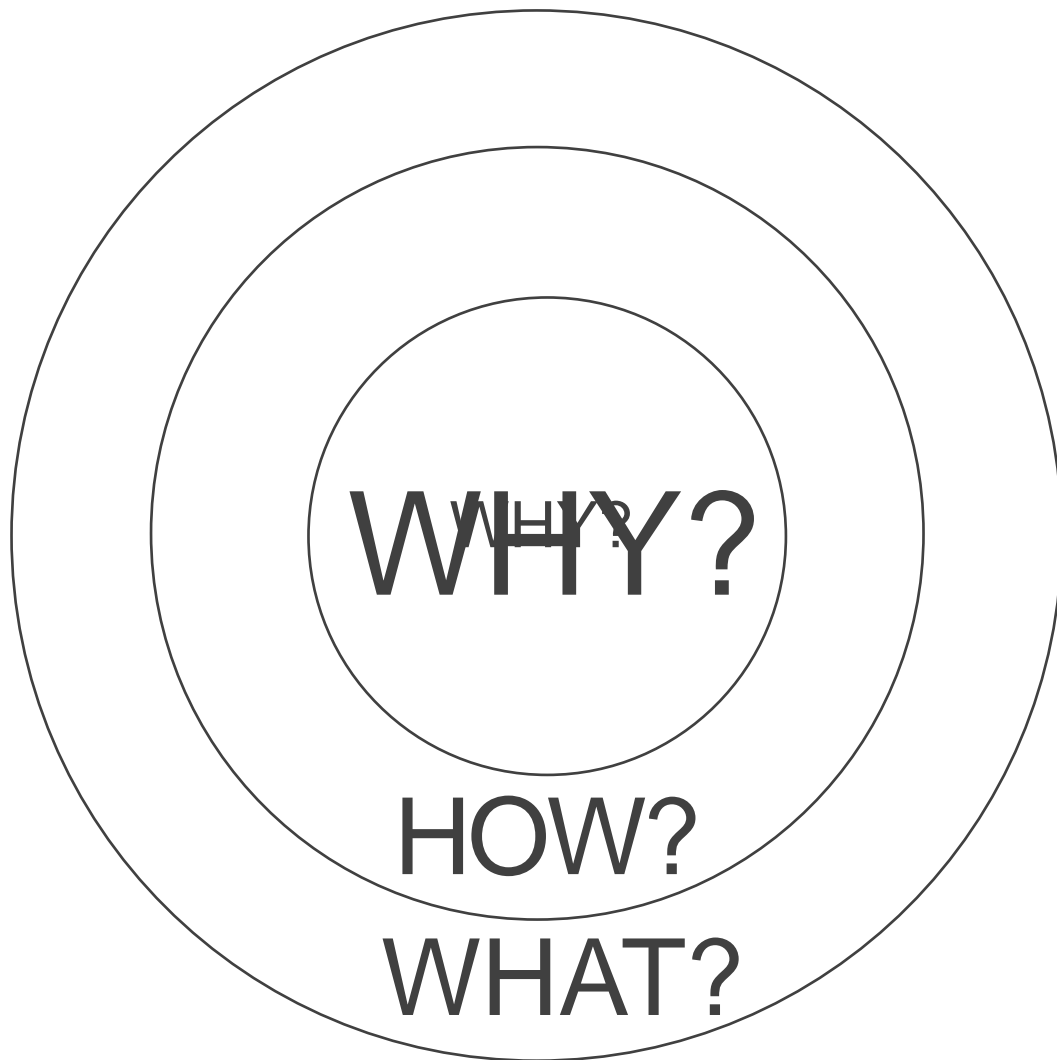


Solvent-based methods

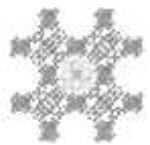
- ✗ High temperature
- ✗ Multiple steps (time-consuming)
- ✗ Large amounts of solvents
- ✗ Expensive
- ✗ Large amounts of liquid wastes
- ✓ Highly crystalline products
- ✓ Precise control of synthesis

Mechanochemical methods

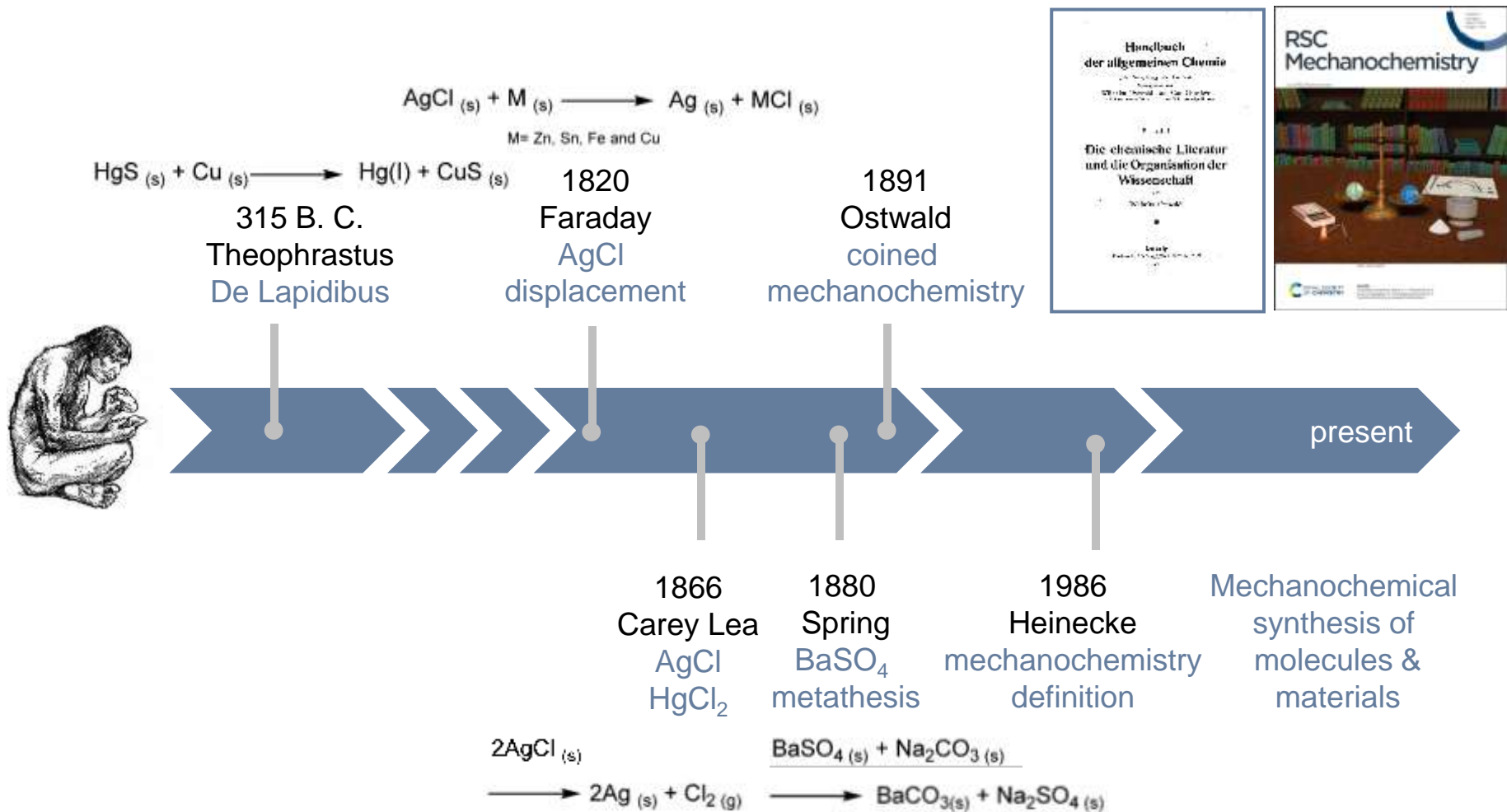
- ✓ Room temperature
- ✓ One-pot synthesis (faster)
- ✓ Solvent-free or small amounts of solvents
- ✓ Cost-effective
- ✓ Minimum wastes
- ✗ Powder/amorphization
- ✗ Precise control of synthesis is difficult



HISTORY



Mechanochemistry – something old



Early works – first publications

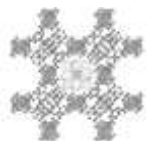
Unpublished



Published



The historical development of mechanochemistry
L. Takacs, Chem. Soc. Rev. 2013, 43, 7649

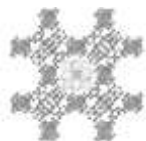
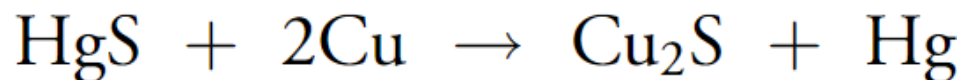


Exploring the ancient chemistry of mercury

Marianna Marchini^a, Massimo Gandolfi^a, Lucia Maini^{a,1}, Lucia Raggetti^b, and Matteo Martelli^{b,1}

Edited by Alexandra Navrotsky, Arizona State University, Tempe, AZ; received December 23, 2021; accepted

This paper explores the chemistry of mercury as described in ancient alchemical literature. Alchemy's focus on the knowledge and manipulation of natural substances is not so different from modern chemistry's purposes. The great divide between the two is marked by the way of conceptualizing and recording their practices. Our interdisciplinary research group, composed of chemists and historians of science, has set off to explore the cold and hot extraction of mercury from cinnabar. The ancient written records have been perused in order to devise laboratory experiments that could shed light on the material reality behind the alchemical narratives and interpret textual details in a unique perspective. In this way, it became possible to translate the technical lore of ancient alchemy into the modern language of chemistry. Thanks to the replication of alchemical practices, chemistry can regain its centuries-long history that has fallen into oblivion.



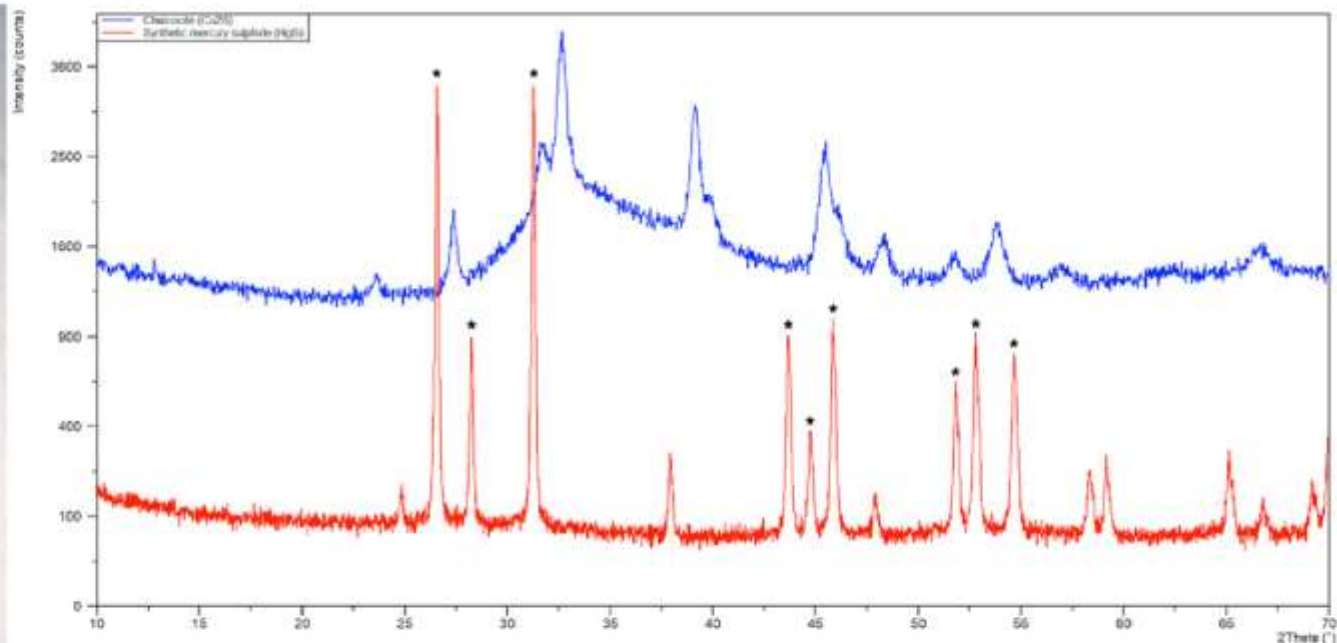


Fig. 1. *Left*, ceramic mortar in which HgS and copper powder were ground—droplets of mercury are visible at the bottom. *Right*, comparison between the XRPD pattern (blue solid line) of the residual powder obtained from the reaction of synthetic mercury sulfide and copper powder in the presence of acetic acid (reaction mixture ground with a ball mill for 4 h at 25 Hz; the high background in the pattern is due to the presence of the amorphous phase of metallic mercury in the final powder) and the XRPD pattern of synthetic mercury sulfide (red solid line). The asterisks in the red XRPD diffractogram indicate the peaks assigned to cinnabar. Phase identification was performed using the PDF 2 Release 2004 database.



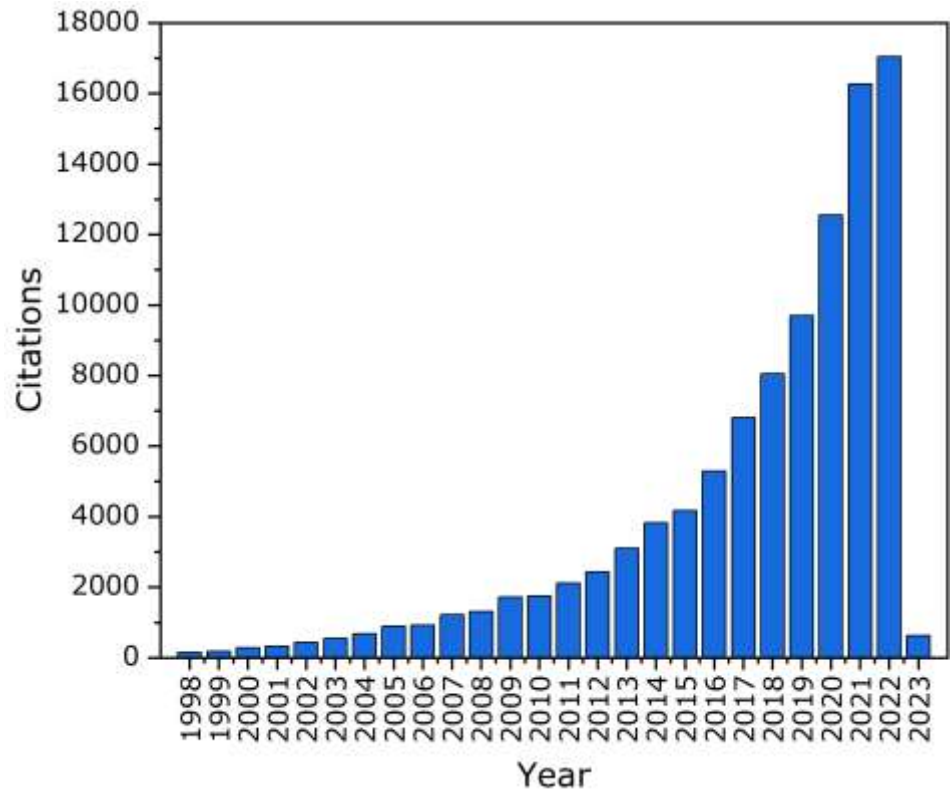
Mechanochemistry – something old



G. Agricola, De re metallica, 1556



F. Florinus, Oeconomus prudens et legalis, 1722



Handbuch der allgemeinen Chemie

Unter Mitwirkung vieler Fachleute
herausgegeben von
Wilhelm Ostwald und Carl Drucker
an. Prof. der Chemie in Leipzig an. Prof. an der Universität Leipzig

Band I

Die chemische Literatur und die Organisation der Wissenschaft

von
Wilhelm Ostwald



Leipzig
Akademische Verlagsgesellschaft m. b. H.
1919

1. Schwereenergie
2. Bewegungsenergie
3. Volumenergie
4. Flächenenergie
5. Formenergie
6. Wärmeenergie
7. Elektrische Energie
8. Magnetische Energie
9. Chemische Energie

Kapazität

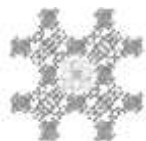
Gewichtsmenge
{Masse
{Moment
Volum
Fläche
Gestalt
Entropie
Elektrizitätsmenge
Magnetisierungszahl
Verbindungsmenge

Intensität

Schwerepotential
Quadrat d. Geschwindigkeit
Geschwindigkeit
Druck
Spannung
Elastizität
Temperatur
Potential
magn. Potential
Affinität

W. Ostwald, 1919:

Für die allgemeine Chemie kommen somit die Kombinationen der chemischen Energie mit den acht vorangehenden in Frage. Die fünf ersten mit den verschiedenen Formen der mechanischen Energie kann man dann noch zu dem allgemeinen Begriff der **Mechanochemie** verbinden, an welche sich dann die Thermochemie, die Elektrochemie und die Magnetochemie schließen. Das große Gebiet der chemischen Optik und der Photochemie ist ein Unterkapitel der letzten Abteilung, denn da die Lichterscheinungen als elektromagnetische Phänomene erkannt worden sind, so gehört nach der allgemeinen Systematik das Licht zunächst als eine Unterabteilung in die Lehre vom Magnetismus, wo sie als Produkt der gleichzeitigen Betätigung von magnetischer und elektrischer Energie und daher als eine Unterabteilung des allgemeineren Begriffs der elektromagnetischen Erscheinungen auftritt.



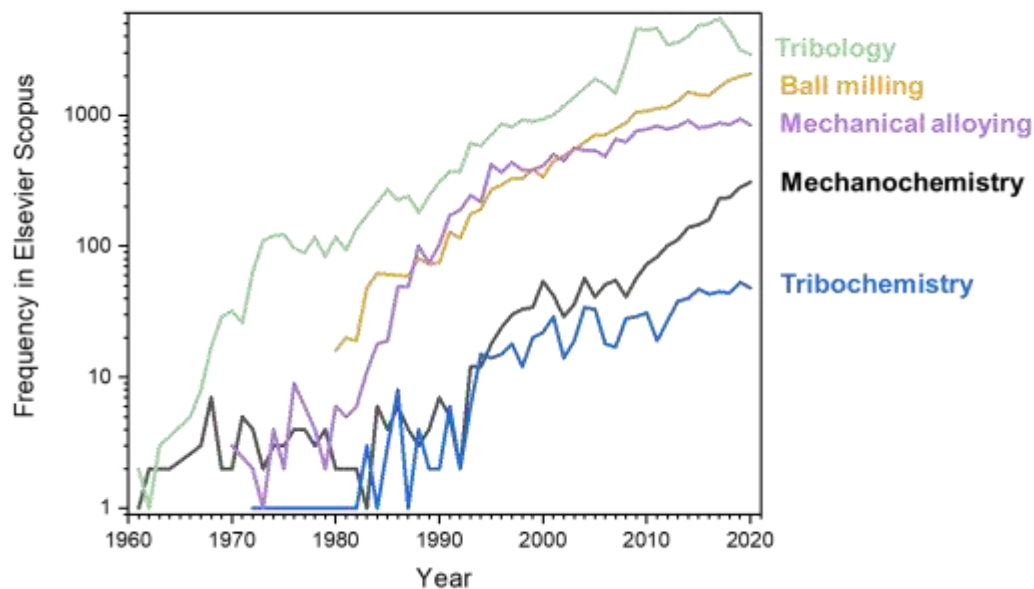
Tribochemistry

Tribochemistry studies chemical and physical changes of substances in **the solid state** under mechanical action.

Tribology, science uniting tribocchemistry and tribophysics.



Peter A. Thiessen,
1899-1990



Review Mechanically initiated chemical reactions in solids

1975

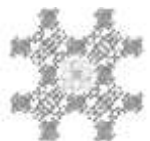
P. G. FOX

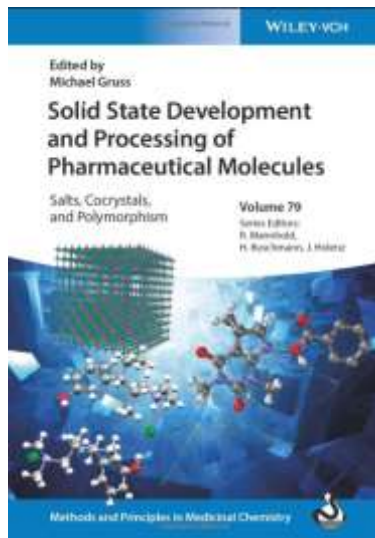
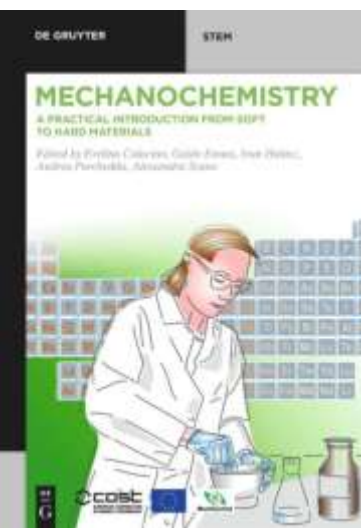
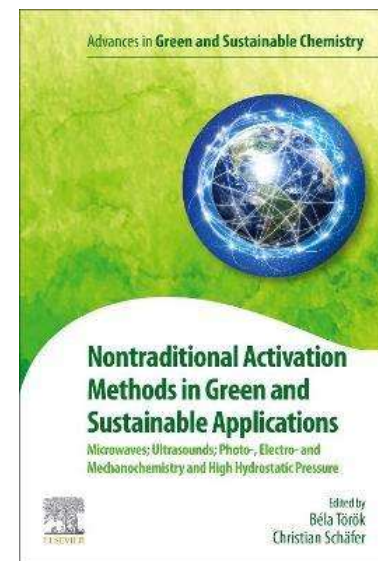
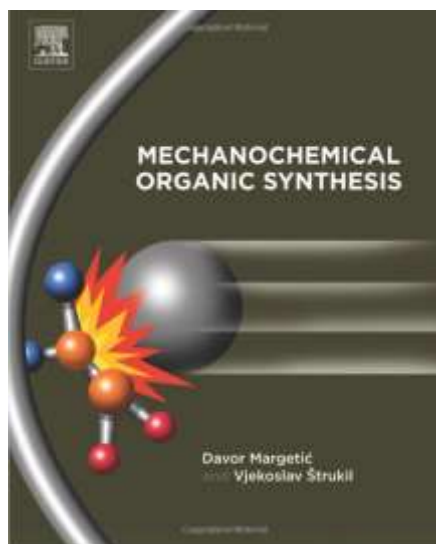
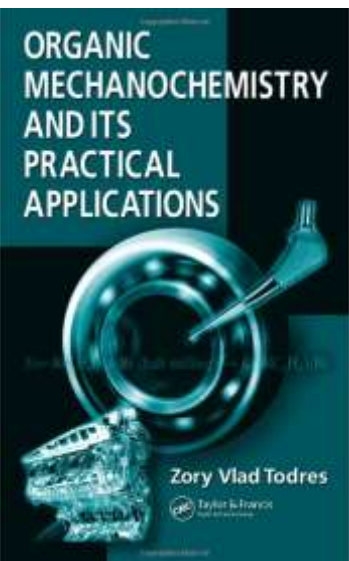
Department of Metallurgy and Materials Science, Nottingham University, Nottingham, UK

reaction. He further concluded that local heating facilitated the reaction which possibility had been ruled out by Carey-Lea on the grounds that the temperature rise could not be large enough to bring about decomposition in such thermally stable materials as the silver halides.

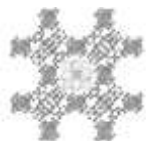
Since this early work, interest in this area has

been spasmodic, particularly in western countries where little seems to have been done except in the one area of mechanically initiated explosive reactions in solids, an interest stimulated by the last World War. The notable exceptions to this lie in the work of two schools, one in the Soviet Union whose results on the application of mechano-chemistry to such technological processes as leaching, decomposition and chemical synthesis, catalysis and mineral treatment processes has recently been summarized by Boldyrev and Аввакумов [6]. The second is the work of the East German group under the direction of Thiessen, whose work has also been reviewed [7].

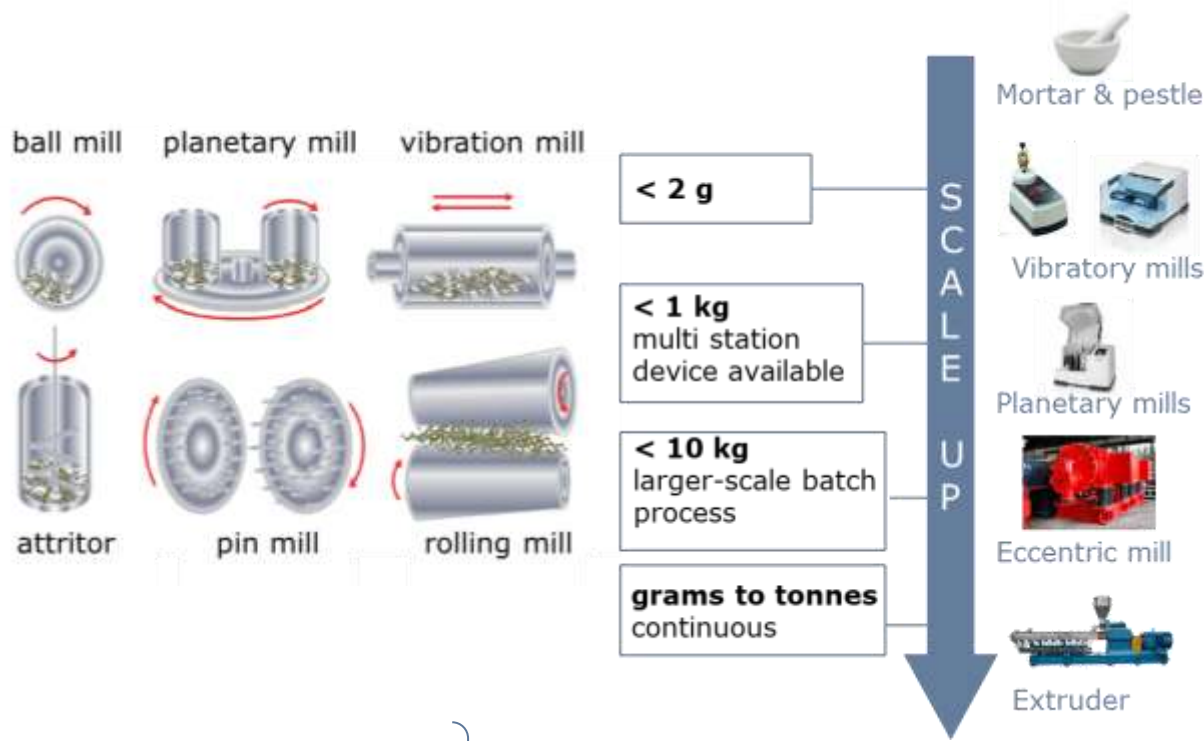




... and recent books



Milling conditions



jet mills
extruders
resonance acoustic mixing

} ball-free

Chemical parameters

type of chemical reaction
presence of catalysts or additives
the reagent ratio
presence of low amounts of liquid(s)

Technological parameters

type of ball mill
milling material
number, size of milling balls
filling degree of the milling vessels

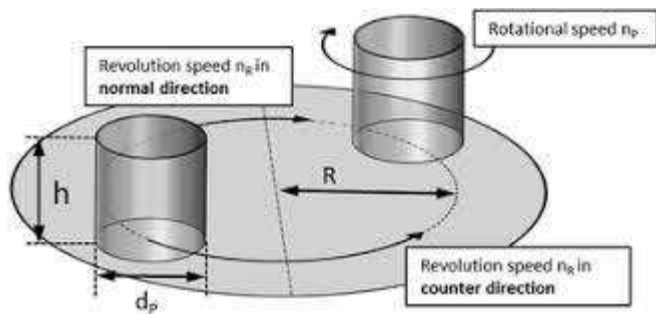
Process parameters

operating frequency
reaction time
reaction temperature

Chem. Soc. Rev., 2012, 41, 413.



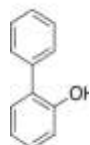
Type of mills



Why? → Green (Mechano)chemistry

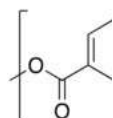
- The 12 Principles of Green Chemistry
1. Prevention
 2. Atom economy
 3. Less hazardous chemical syntheses
 4. Designing safer chemicals
 5. Safer solvents and auxiliaries
 6. Design for energy efficiency
 7. Use of renewable feedstocks
 8. Reduce derivatives
 9. Catalysis
 10. Design for degradation
 11. Real-time analysis for pollution prevention
 12. Inherently safer chemistry for accident prevention

#6 Design for energy efficiency



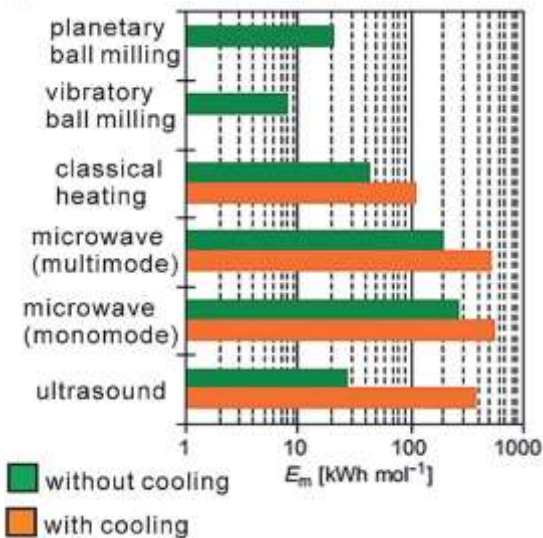
Mechano

#10 D



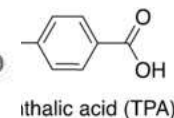
Polyethylene terephthalate (PET)

Comparison of the molar energy for the KMnO_4 -mediated oxidation of p-toluidine carried out with different methods of energy entry
 Depolymerization of waste materials such as polyethylene terephthalate (PET) under ambient reaction conditions

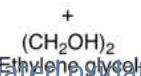


$$E_m = \frac{E_{\text{grid}}}{\sum_i n_{\text{product},i}}$$

higher yield



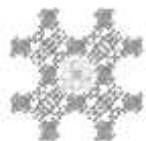
terephthalic acid (TPA)



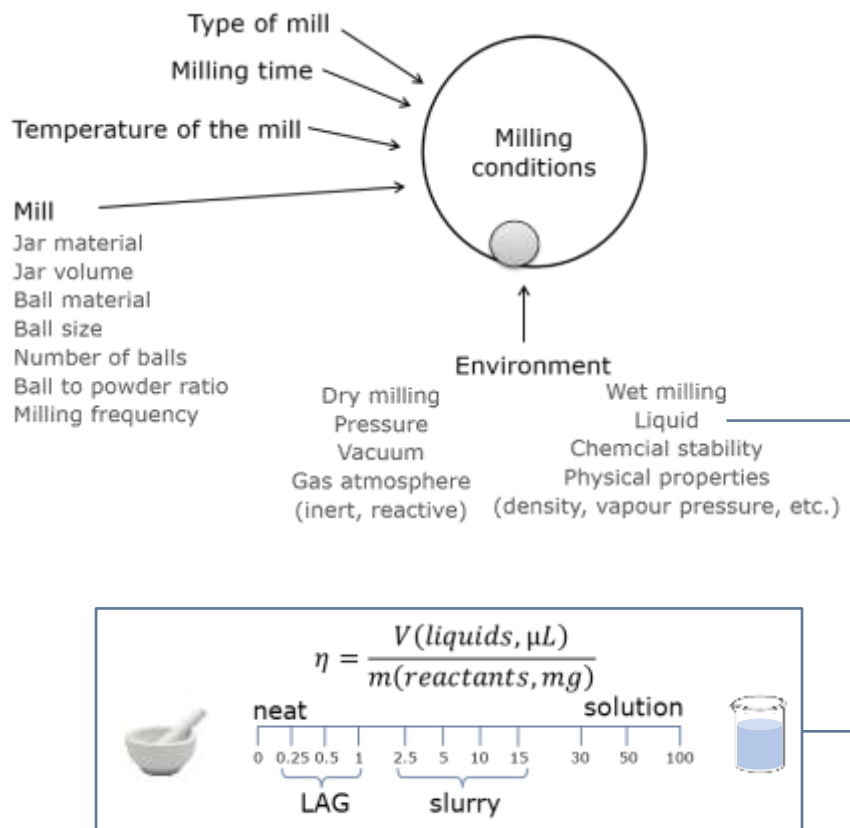
ethylene glycol

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press 1998, 30.

Stolle, A.; Ranu, B. C., Eds.; Technical Implications of Organic Synthesis in Ball Mills Royal Society of Chemistry: Cambridge, 2014.
 ChemSusChem 2021, 14, 2145.



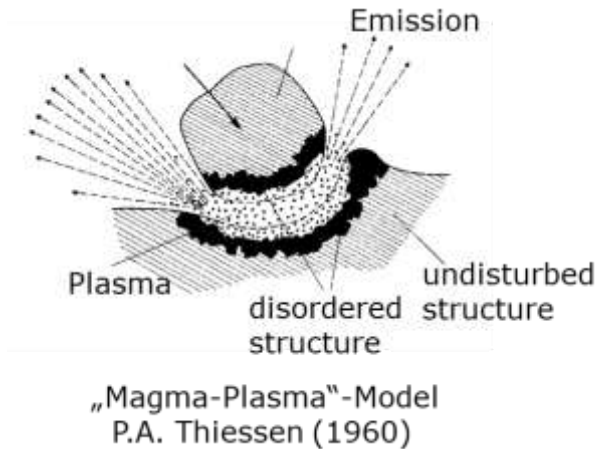
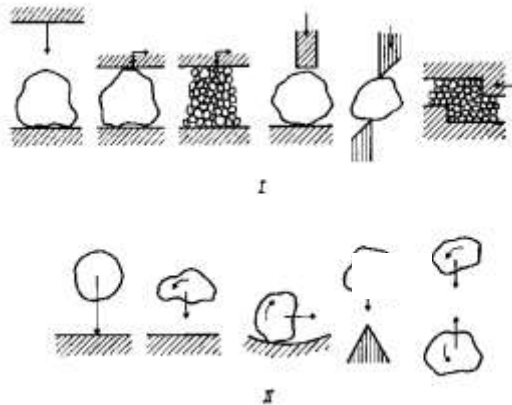
Liquid assisted grinding



Belenguer et al. JoVE, 2018, 131, E56824.



Structural changes of solids during milling



- Fresh, new surfaces
- Plastic deformations
- Material abrasion
- Amorphization, loss of translation symmetry
- Phase transformations
- Incorporation of impurities
- Accumulation of defects
- Effect on near and long-range order

- Emission of photons, electrons, lattice components

- Excitation of lattice vibrations local heating

- Formation / migration of lattice and electronic defects



Are we speaking the same language?

Primary Mechanochemical

Alloys	$2 \text{ Mg} + \text{ Si} \xrightarrow[\text{Ar}]{250 \text{ rpm}} \text{ Mg}_2\text{Si}$	$3 \text{ Ni} + \text{ Al} \xrightarrow[\text{Ar}]{200 \text{ rpm}} \text{ Ni}_3\text{Al}$
Metal oxides	$2 \text{ Al} + \alpha\text{-Fe}_2\text{O}_3 \xrightarrow[\text{atm}]{300 \text{ rpm}} 2 \text{ Al}_2\text{O}_3 + 2 \text{ Fe}$	$\text{h-BN} \xrightarrow[\text{H}_2]{90 \text{ rpm}} \text{dh-BN}$
Metal-organic	$\text{ZnO} + 2 \text{ (Methylimidazole)} \xrightarrow[\text{atm}]{30 \text{ Hz}, 20 \text{ min}} \text{ZIF-8}$	
Organic	$\text{carbamazepine (CBZ)} + \text{nicotinamide (NIC)} \xrightarrow[\text{atm}]{\text{H}_2\text{O}} \text{1:1 co-crystal (CBZ: NIC)}$	

Additive

Anything known about chemical conditions / reactivity (e.g. catalyst – dbu, PVP(water))

Additive (liquid, solid, polymer)








	Temperature	
	Parameters (e.g. time, frequency)	
		Atmosphere

Primary mechanical action

ACN $+45^\circ\text{C}$

\leftrightarrow 30 Hz 20 min

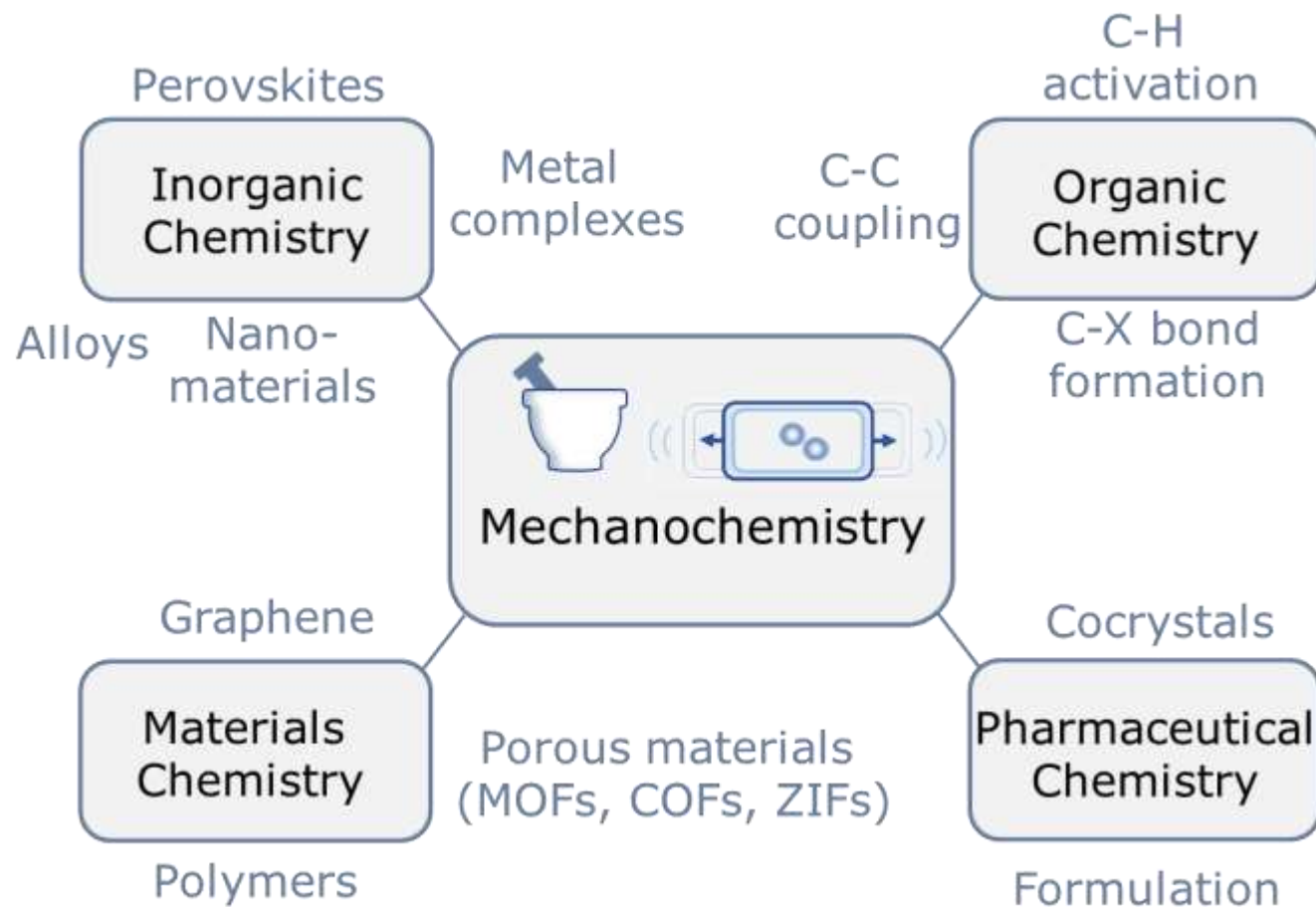
N_2

Neutral liquid		Heating		Ambient Atmosphere
Ionic liquid		Cooling		Dry Air
Solid additives		Self-Sustained Heating		Nitrogen Atmosphere
Polymer additives				Humid Atmosphere

Front. Chem. 2021, 9.



Applications

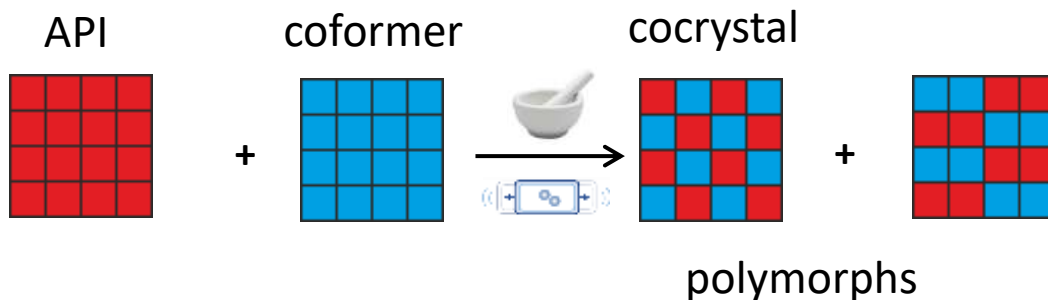


EXAMPLES

Cocrystals, MOFs, organic
compounds, metallic nanoparticles

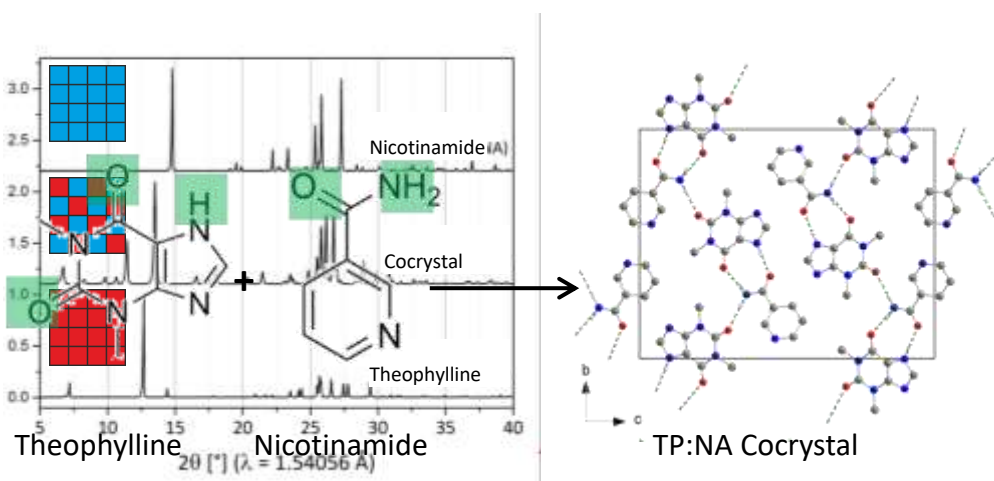


Cocrystals - a playground for crystal engineering



“...every compound has different polymorphic forms and... the number of forms known for a given compound is proportional to the time and energy spent in research on that compound.”

W. C. McCrone, in *Physics and Chemistry of the Organic Solid State*, Vol. 2, Wiley Interscience (1965).



→ New solid forms with enhanced properties



Mechanochemistry and cocrystals



XCVL.—*Halogen Derivatives of Quinone. Part III.* Derivatives of Quinhydrone.*

By ARTHUR R. LIND and JULIAN L. BAKER.

Introductory Remarks.

This history of quinhydrone is so well known that we need here but briefly refer to it. Since the discovery of the compound by Wiedemann in 1844 (*Annalen*, **51**, 153), various views have been advanced regarding its constitution, but no satisfactory hypothesis has yet been advanced, unless, indeed, the statement be accepted that it is a molecular compound of quinone and quinol.

* On reference to my paper "Halogen Derivatives of Quinone. Part I. (Trans., 1893, **61**, 572), I find that I have given the production of paradibromosulfolithionine from quinone tetrabromide when it is boiled with (Nef, *Ann. Chem. J.*, **19**, 463; and *J. pr. Chem.* [2], **48**, 161), as an intramolecular change. Such is, however, not the case, and my statement a misreading of Nef's work.—A. R. L.

J. Chem. Soc. Trans. 1893, 63, 1314.

Solid-State Reactivity of Picric Acid and Substituted Hydrocarbons

by B. F. Ezang¹ and N. B. Singh²

Department of Chemistry, Guelph University, Guelph, Ont., Canada (Received April 25, 1968)

The solid-state reactivity of picric acid + acrylonitrile, picric acid + β -naphthylamine, and picric acid + pyromellitic acid has been investigated. The results show that diffusion in the solid state is controlled by surface migration, in conformity with the earlier finding by Bostig and Singh. It is found that molecules having a smaller van der Waals radius having greater symmetry are more favorable for surface migration.




J. Phys. Chem. 1968, 72, 4446.

Pharmaceutical Research, Vol. 23, No. 16, October 2006 (10)

DOI: 10.1021/ps060116a

Research Paper

Cocrystal Formation during Cogrinding and Storage is Mediated by Amorphous Phase

Adityan E. Jayaraman,¹ Anoop Kumar Singh,^{1,2} Zeki J. Shou,³ and Nair Rodriguez-Hernandez^{1,4*}




Pharm. Res. 2006, 23, 2381.


COMMUNICATION

www.coc.org/crystengcomm | CrystEngComm

How does grinding produce co-crystals? Insights from the case of benzophenone and diphenylamine

Keith Chadwick,^a Roger Davey^a and Wendy Cross^{a*}

Received 26th March 2007, Accepted 26th June 2007
First published on the Internet Article on the web 06th July 2007
DOI: 10.1039/b61411h





CrystEngComm. 2007, 9, 732.

COMMUNICATION

First LAG Cocrystal Paper



Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics?

Ning Shan,^a Fumin Toda^b and William Jones^{a*}

^a Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW
E-mail: wj109@cam.ac.uk; Fax: 44 1223 336362; Tel: 44 1223 336468
^b Department of Chemistry, Faculty of Science, Obihiro University of Science, Okiyama, 770-0005, Japan

Received (in Cambridge, UK) 26th July 2002, Accepted 6th September 2002
First published on the Internet Article on the web 18th September 2002

We demonstrate that significant improvements in kinetics of co-crystal formation by grinding can be achieved by the addition of minor amounts of appropriate solvent. Co-crystallization by simple grinding is, however, successful. The co-crystal structure of CTA and 4,4'-biphenyl has been determined by single-crystal X-ray diffraction.

Chem. Commun. 2002, 2372.

Reviews

Recent Advances in Understanding the Mechanism of Co-crystal Formation via Grinding

Tomislav Friščić and William Jones^a

^a Department of Chemistry and Pfizer Institute for Pharmaceutical Materials Science, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

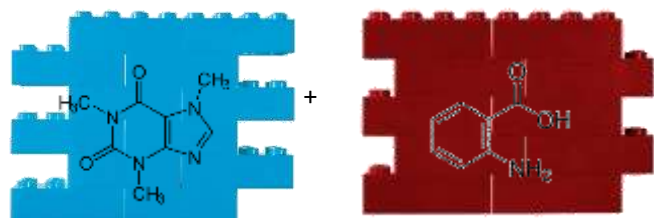
Received July 16, 2008

ABSTRACT: A brief and systematic overview of recent advances in understanding the mechanism of mechanochemical co-crystallization at macroscopic (bulk phase transformations) and microscopic levels (molecular recognition) is given. The review particularly addresses neat and liquid-assisted grinding approaches to co-crystal formation.

Cryst. Growth Des. 2009, 9, 1621.

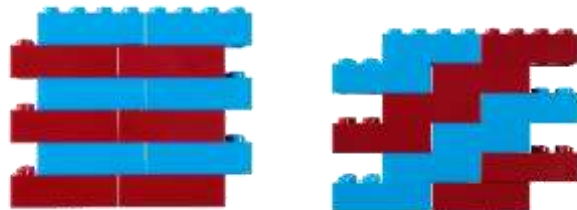


Caffeine:anthranilic acid cocrystal

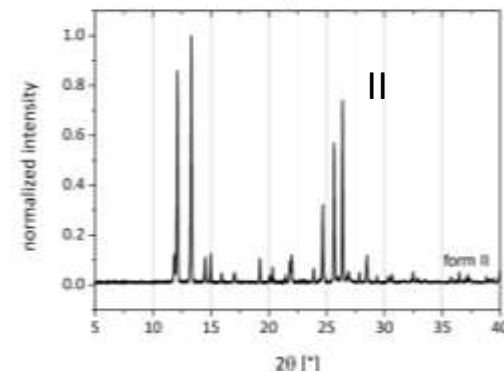
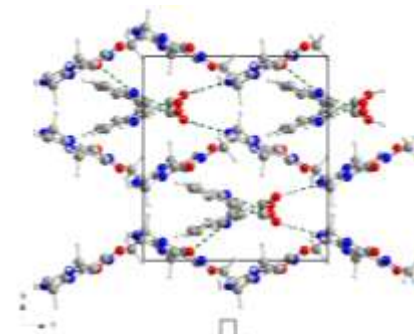
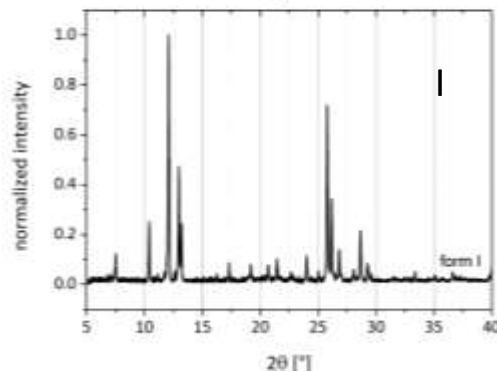
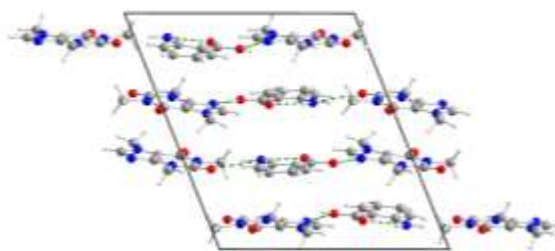


API

coformer



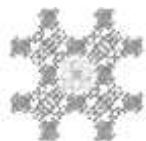
polymorphs
cocrystal



Acta Crystallogr., B 2014, 70, 72.

CrystEngComm, 2014, 16, 8272.

/41



How does grinding produce co-crystals?

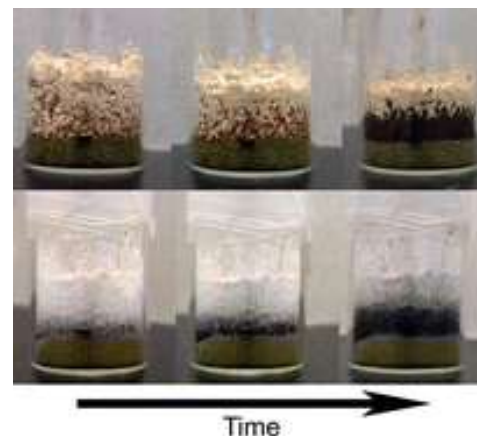


Insights from the case of
benzophenone and
diphenylamine

CrystEngComm, 2007, 9, 732.

Crystal to crystal transformation in the solid state

Either co-milling or simple mixing of benzoquinone and diol crystals of varied melting point temperature produces adduct crystals through very slow and gradual molecular diffusion processes **in the solid state**. Their formation process was compared and discussed based on the crystal structures of the starting diols and the diol-BQ adducts.

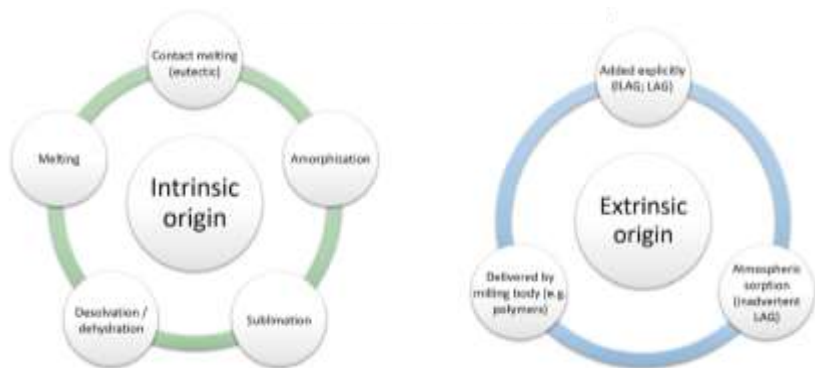


CrystEngComm, 2004, 6, 464.



What is the role of fluid phases?

- Liquid added from outside (solvent-drop grinding, kneading, solvent-assisted grinding, air humidity)
- Liquid appears via desolvation of one or both components of the mixture
- Melting
- Improving contacts and rheology of solid mixture
- Transfer of the reaction into fluid phase (at the contacts), precipitation from fluid phase
- Role in mass transfer of all or some of the components
- Hydrothermal conditions



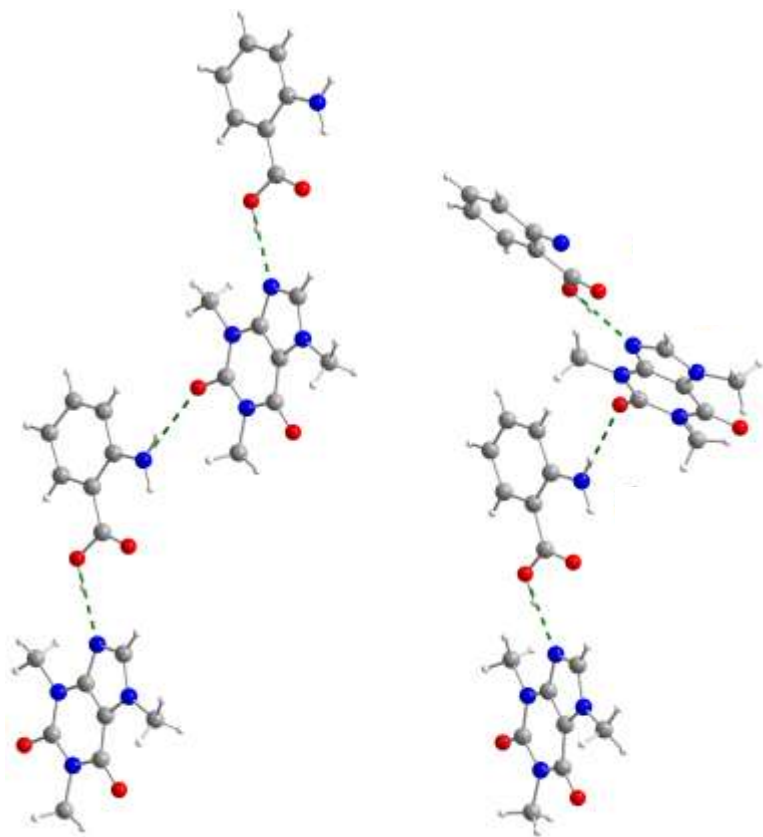
Belenguer et al. JoVE, 2018, 131, E56824.
Belenguer et al. Chemical Science, 2016, 7, 6617.



Solvent	Dipole moment [·10 ⁻³⁰ C·m]	Form	Solvent	Dipole moment [·10 ⁻³⁰ C·m]	Form
1,4-Dioxane	1.3	I	Methanol	5.5	I
2-Butanone	9.2	I	n-Heptan	0.0	I
Acetophenone	9.7	I	n-Hexan	0.0	I
Chloroform	3.7	I	n-Pentane	0.0	I
Cyclohexane	0.0	I	Nitromethane	10.3	I
Dichloromethane	6.0	I	THF	5.7	I
Diethyl ether	4.2	I	Acetone	10.0	II
Ethanol	5.7	I	Acetonitrile	11.7	II
Ethyl acetate	6.2	I	DMF	12.7	II
Ethylene glycol	6.7	I			

CrystEngComm, 2014, 16, 8272.





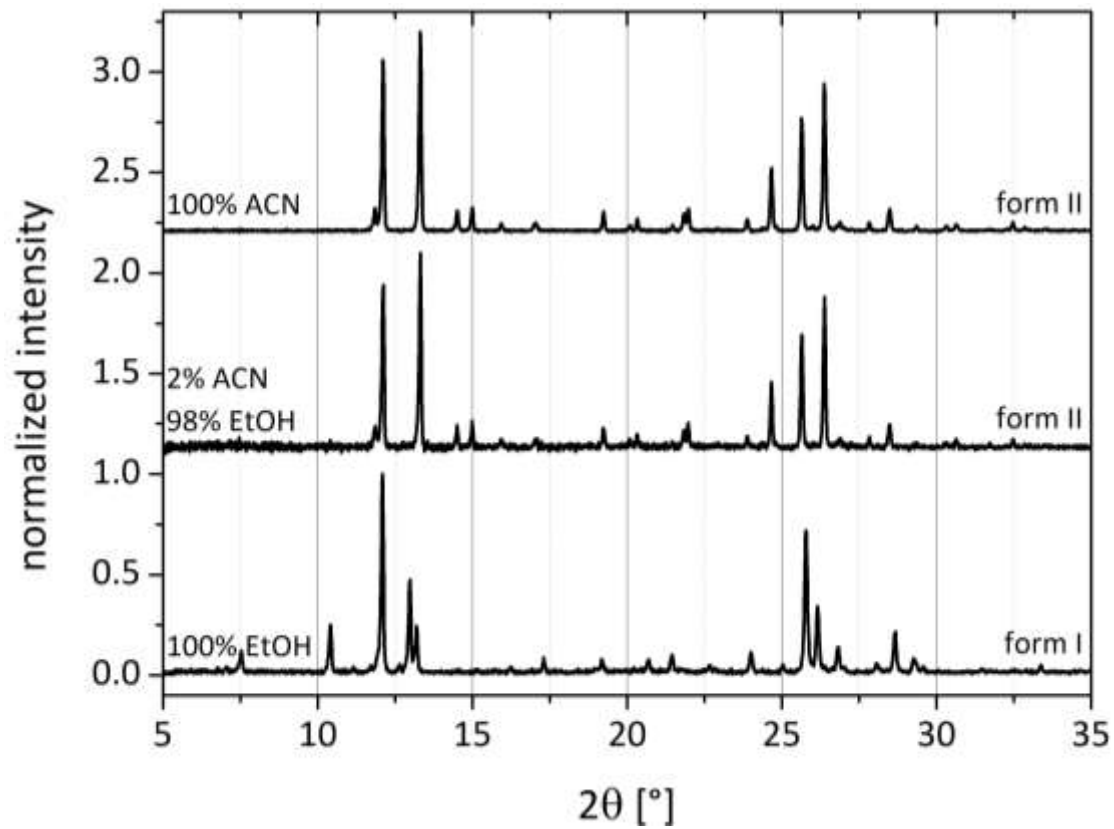
form I

form II

I: no interaction with solvent

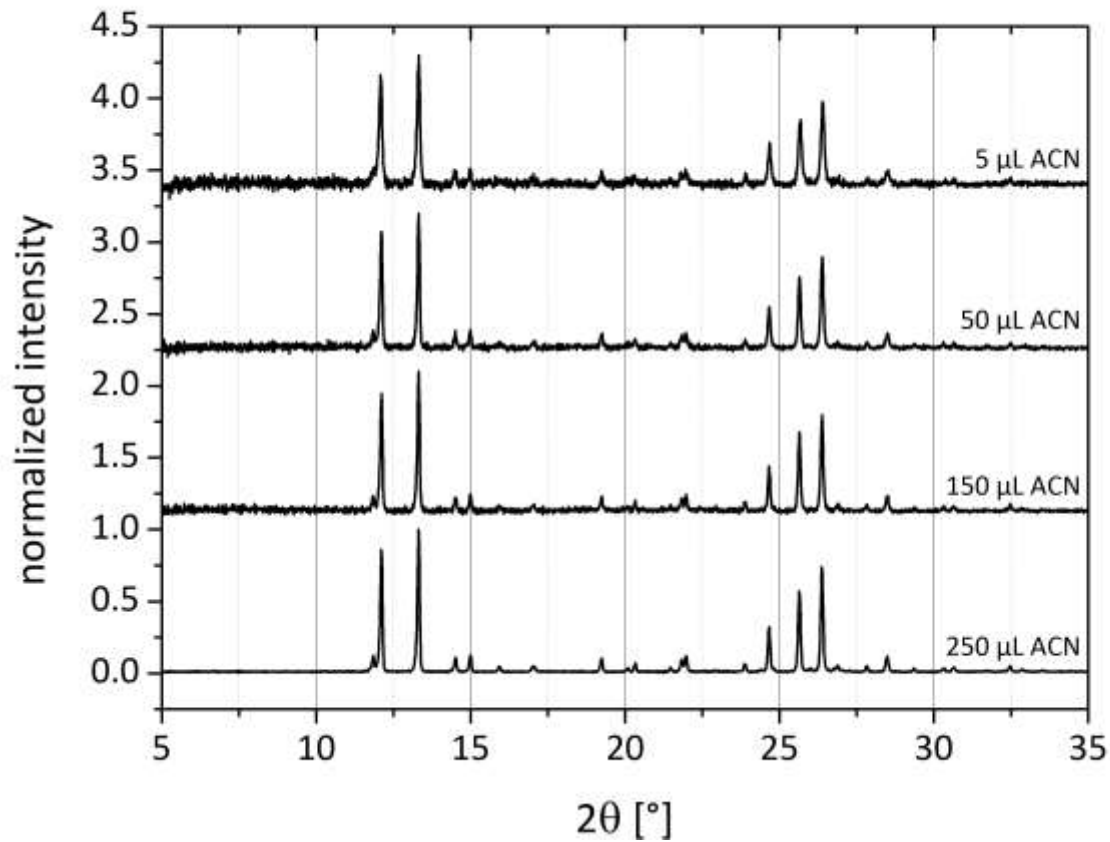
II: precoordination of solvent molecule with amino group of anthranilic acid → twisted moiety





acetonitrile (ACN) → form II



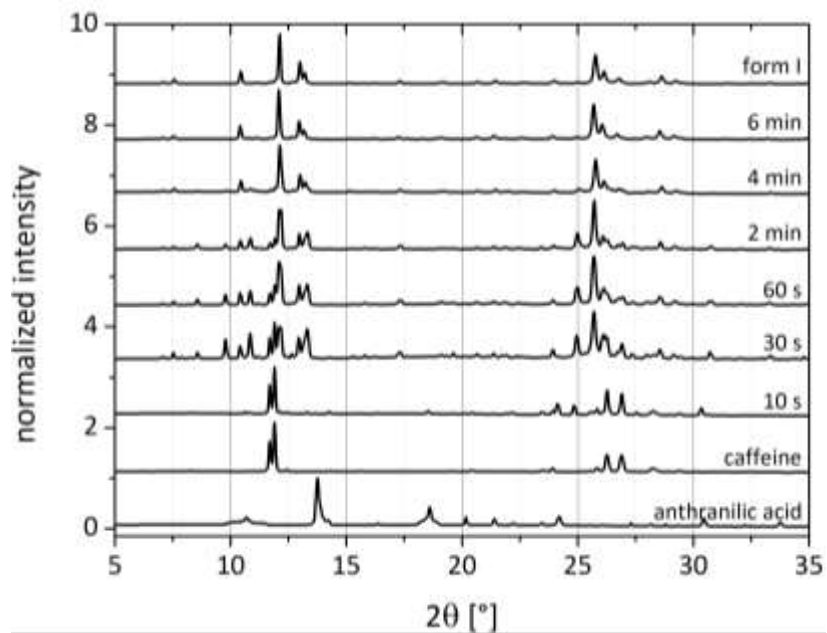


5 μL ACN sufficient for triggering the crystallization of form II



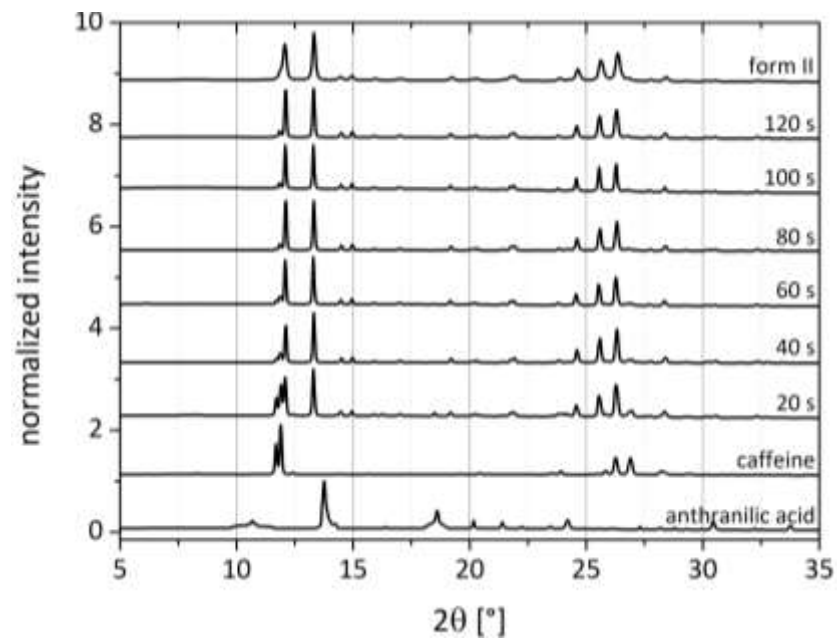
Ex situ data

Dioxan → form I



no reflections of reactants after 6 min

Acetonitrile → form II



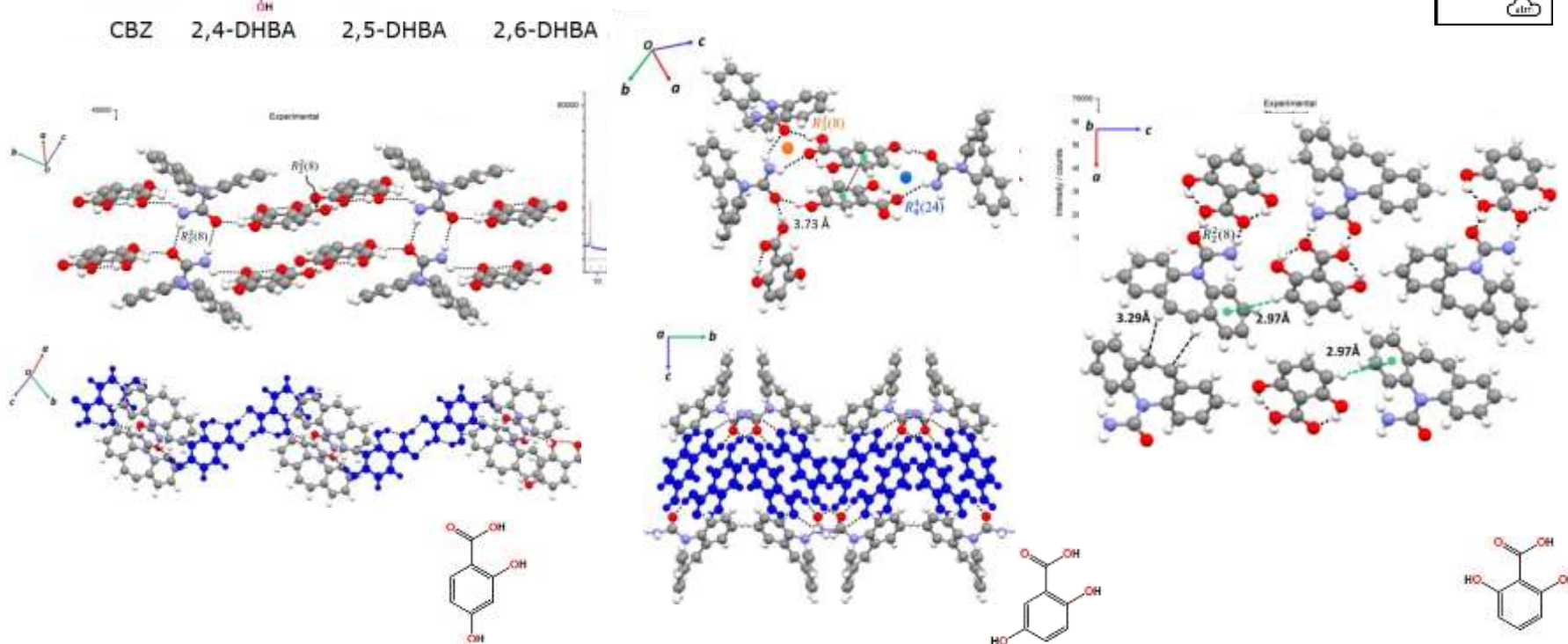
no reflections of reactants after 100 s



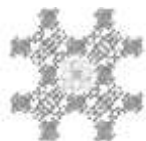
Packing interactions & reaction kinetics



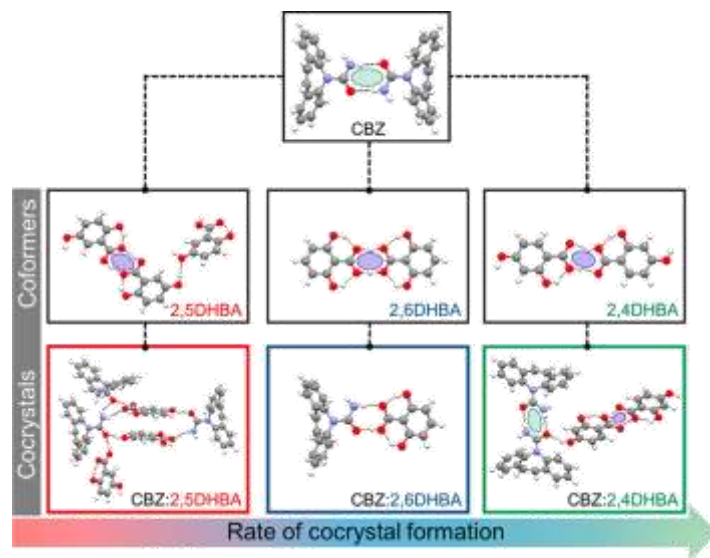
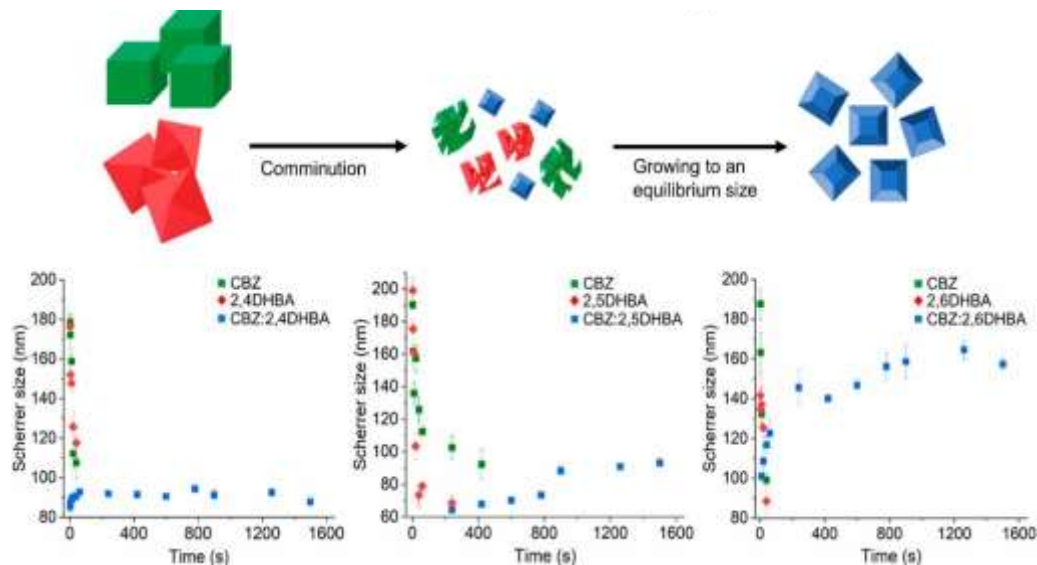
Carbamazepine & different dihydroxybenzoic acids as coformers → three new cocrystals



Cryst. Growth Des. 2021, 21, 6961.



Milling stopped after certain intervals → samples were measured directly → Rietveld refinement



→ CBZ:2,4DHBA & CBZ:2,6DHBA: Simultaneous comminution & start of cocrystallization
 → final crystallite size: 90 & 160 nm

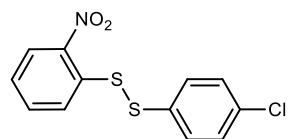
→ CBZ:2,5DHBA: Comminution phase more pronounced
 → final crystallite size: 90 nm

The rate of cocrystal formation seems to be correlated to the packing motif in the final product.

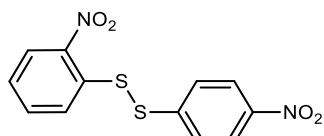
Cryst. Growth Des. 2021, 21, 6961.



Three polymorphs: quantitative reversible interconversion by grinding



2-nitrophenyl-4-chlorophenyl-disulfide



Works only with 1.5% mol/mol contaminant



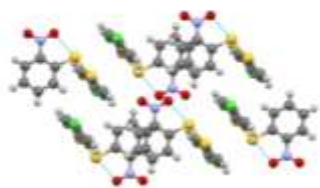
Form A



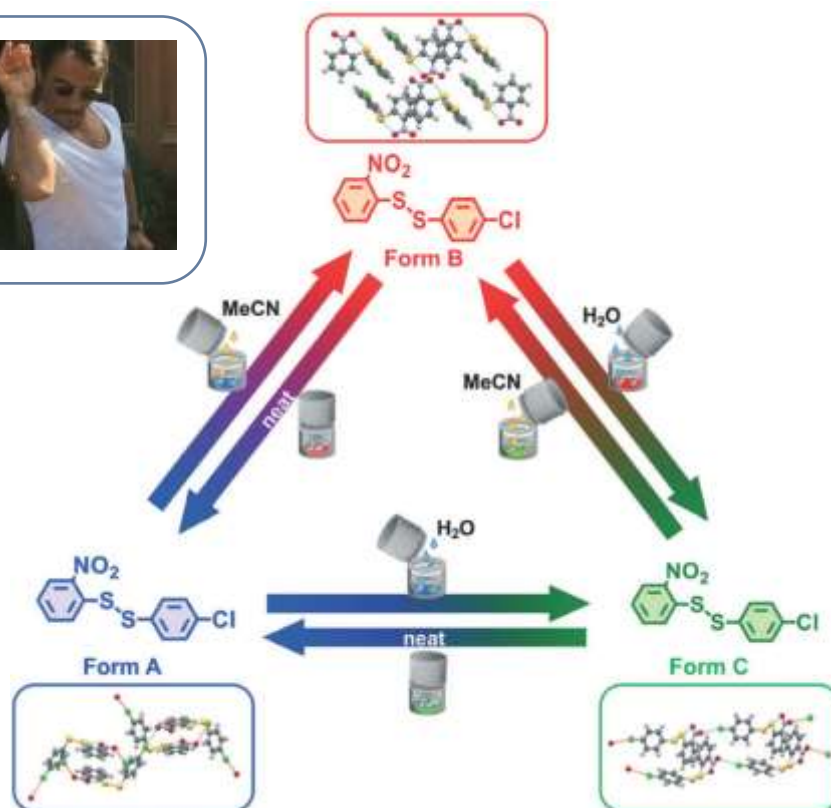
Form C



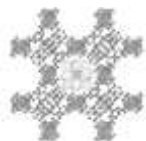
Form B

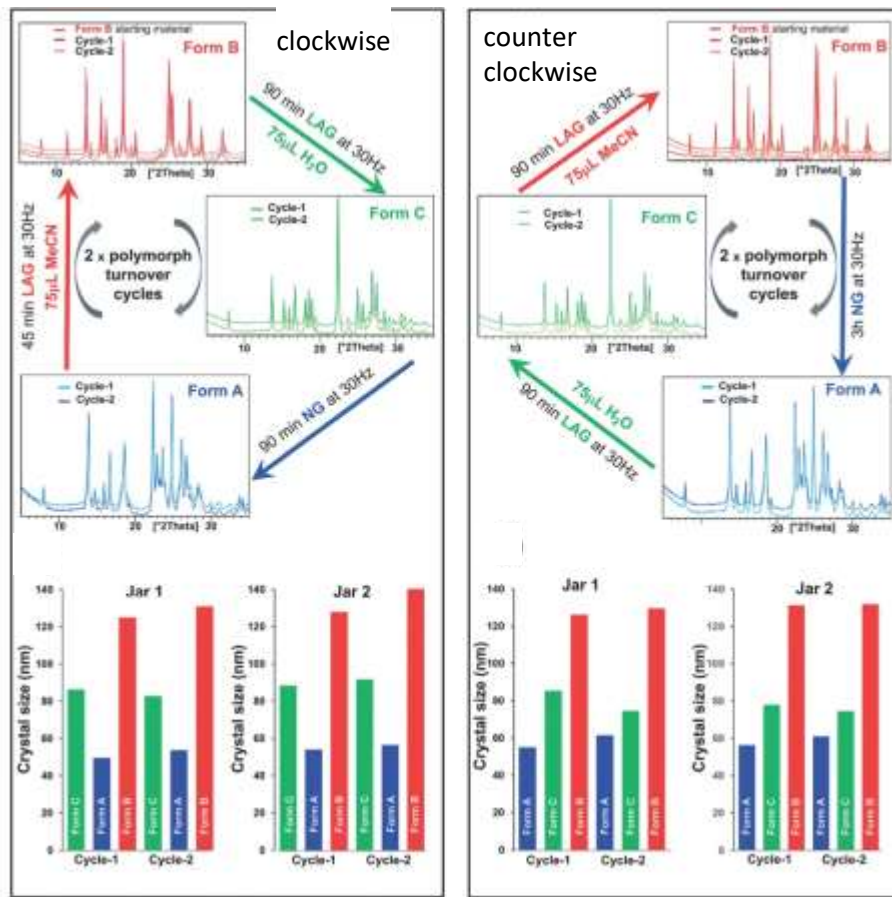


Form B > Form C > Form A



CrystEngComm, 2022, 24, 4256.



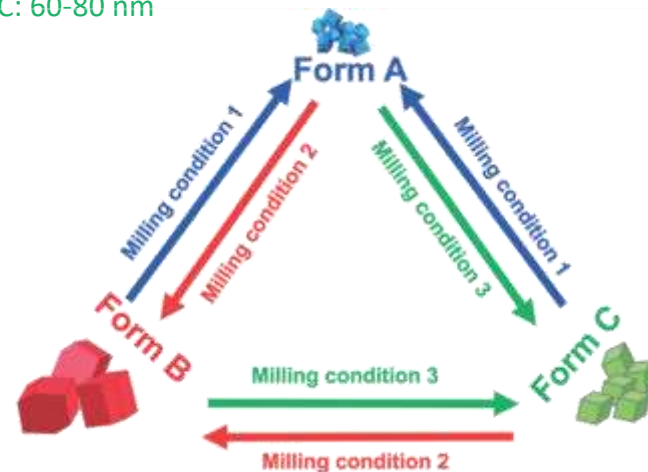


B → C → A → B

B → A → C → B

CrystEngComm, 2022, 24, 4256.

Form A: 50 nm
 Form B: 140 nm
 Form C: 60-80 nm



- High reproducibility & specificity of the crystallite size for each polymorph
- Polymorph stabilities are affected by crystal size and surface effects
- New polymorph (form C) has been prepared only via grinding



EX SITU VS IN SITU



Ex situ vs in situ

5216 *Chem. Mater.* **2010**, *22*, 5216–5221
DOI:10.1021/cm1012119

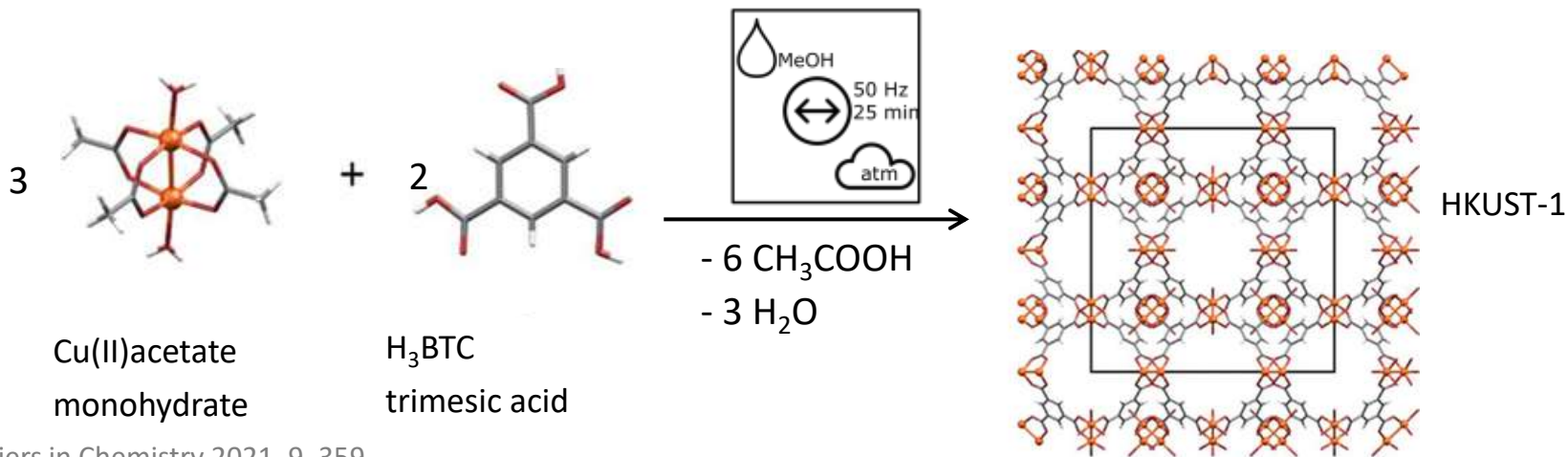
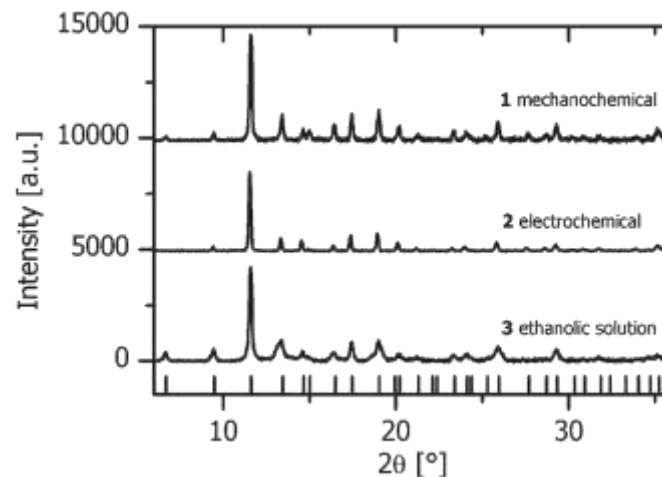
CHEMISTRY OF
MATERIALS
Article

Mechanochemical Synthesis of Metal–Organic Frameworks: A Fast and Facile Approach toward Quantitative Yields and High Specific Surface Areas

Maria Klimakow,[†] Peter Klobes,[‡] Andreas F. Thünemann,[†] Klaus Rademann,[‡] and Franziska Emmerling^{*,†}

[†]BAM Federal Institute for Materials Research and Testing, Richard-Willstätter-Strasse 11, 12489 Berlin, Germany, and [‡]Department of Chemistry, Humboldt-University, Brook-Taylor-Strasse 2, 12489 Berlin, Germany

Received April 29, 2010. Revised Manuscript Received August 2, 2010



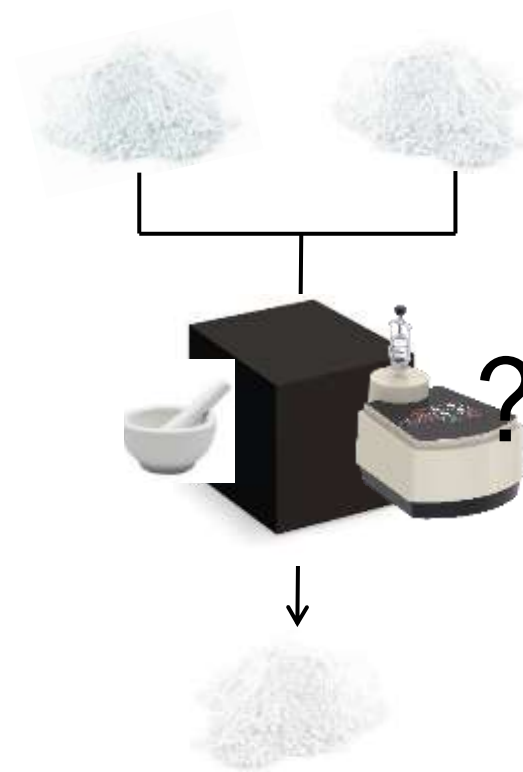
Frontiers in Chemistry 2021, 9, 359





IUPAC

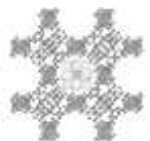
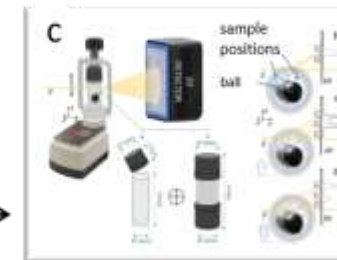
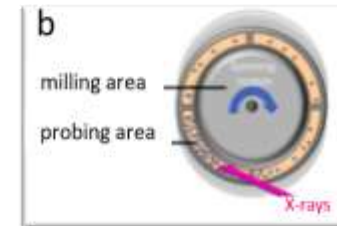
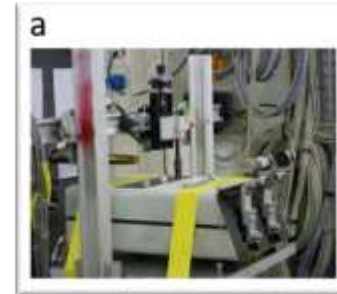
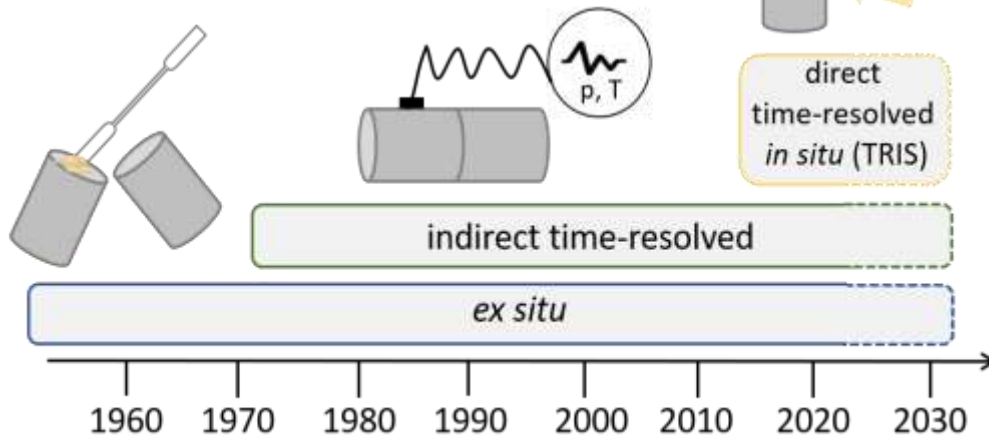
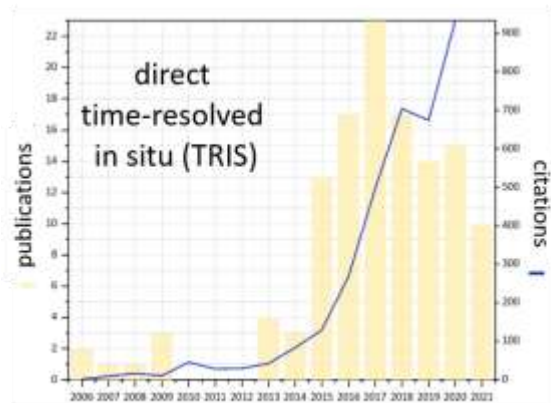
- Do we know what we are measuring?
- Do we know the experimental conditions?
- Is it a solid-state process?
- Which chemical species take part in the reaction?
- Which intermediates/products are formed?
- When are the products formed?
- What is the reaction rate?
- ...



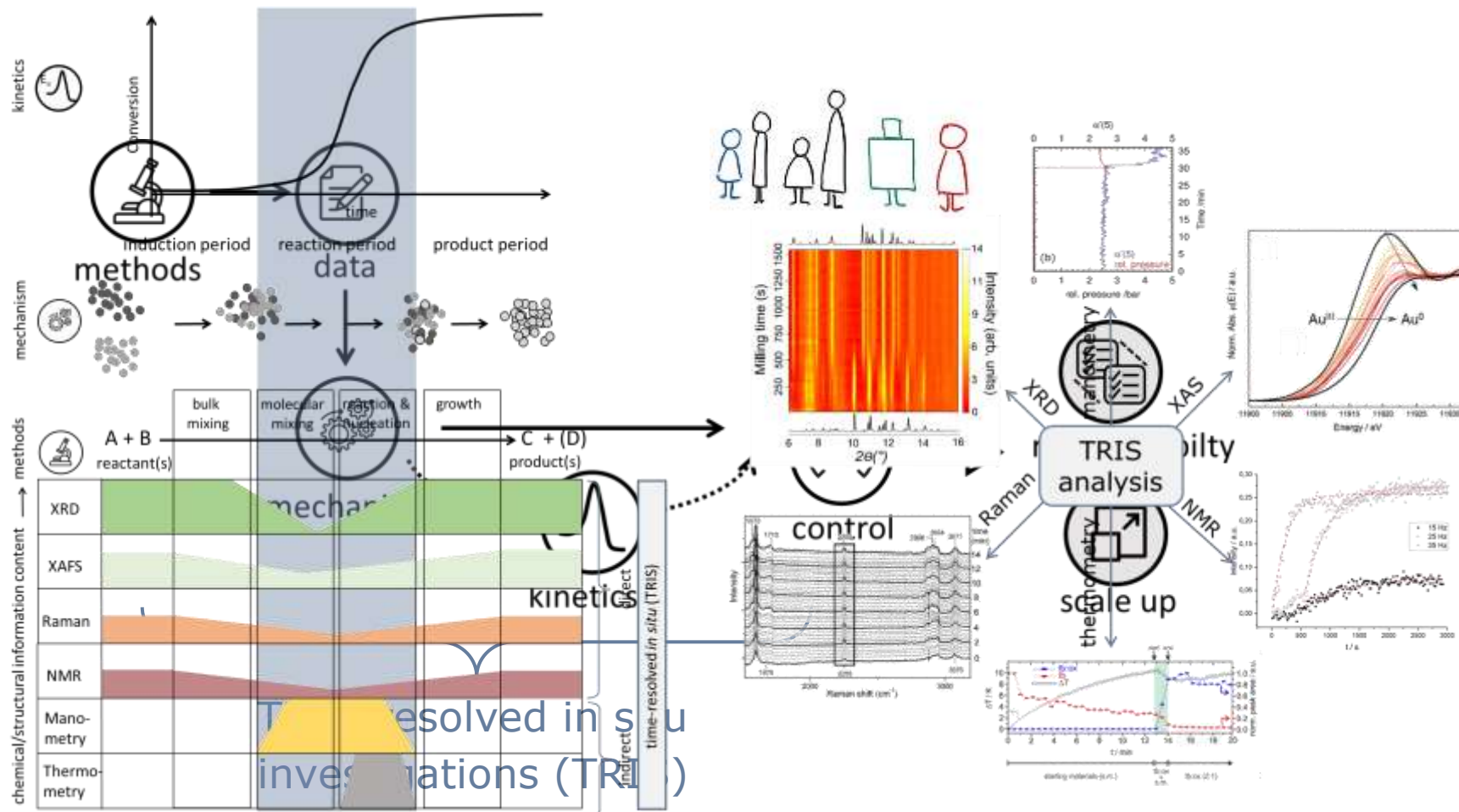
Gomollón-Bel, F. Chem. Int. 2019, 41 (2), 12-17.



Time-resolved in situ investigations



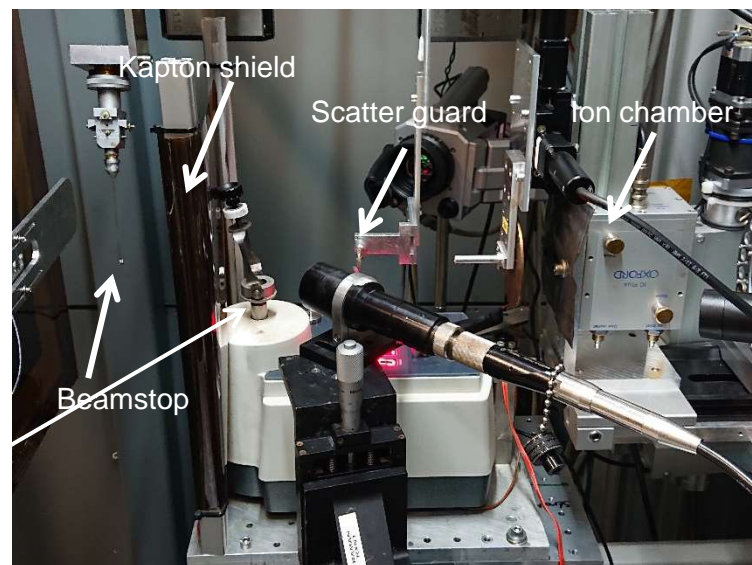
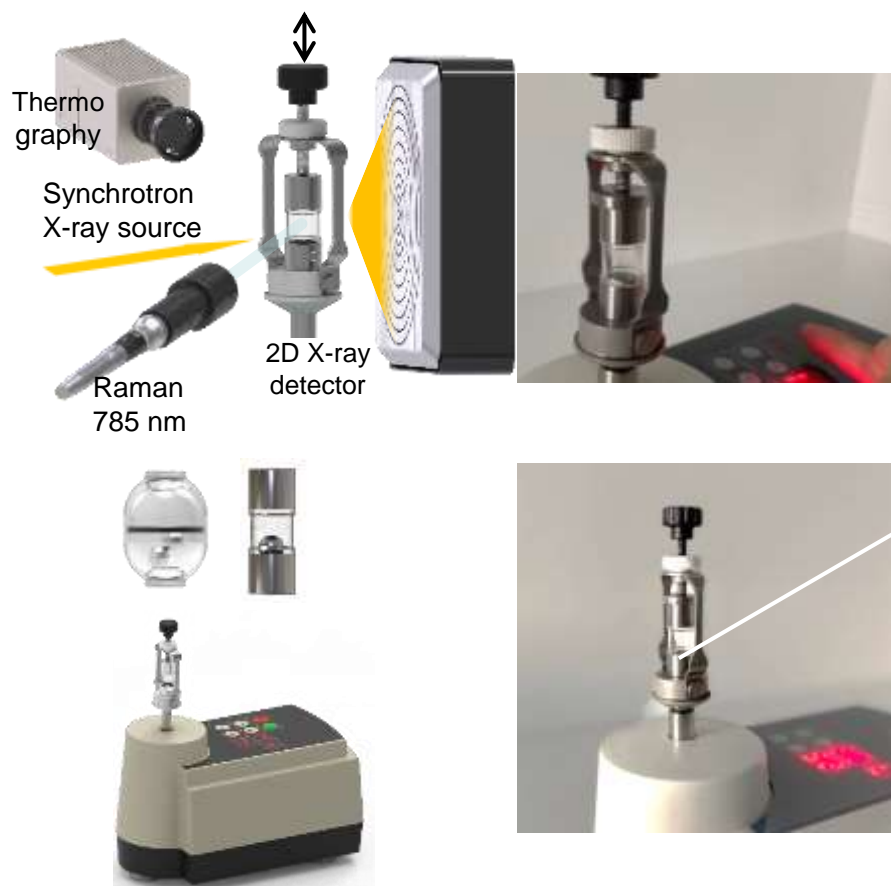
Where to? Understanding & Control



Angew. Chem. Int. Ed. 2022, 61, e20211727

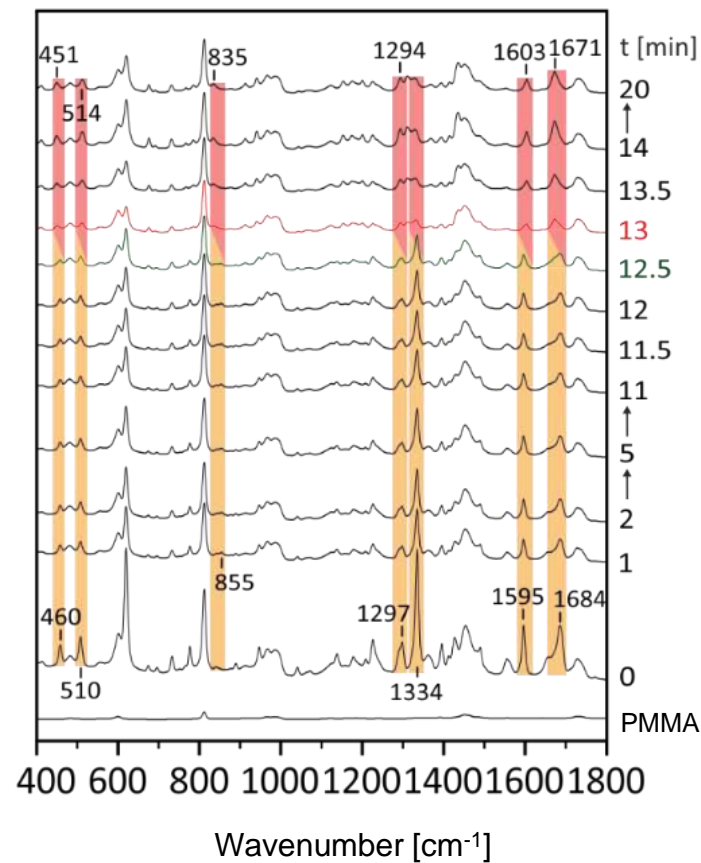
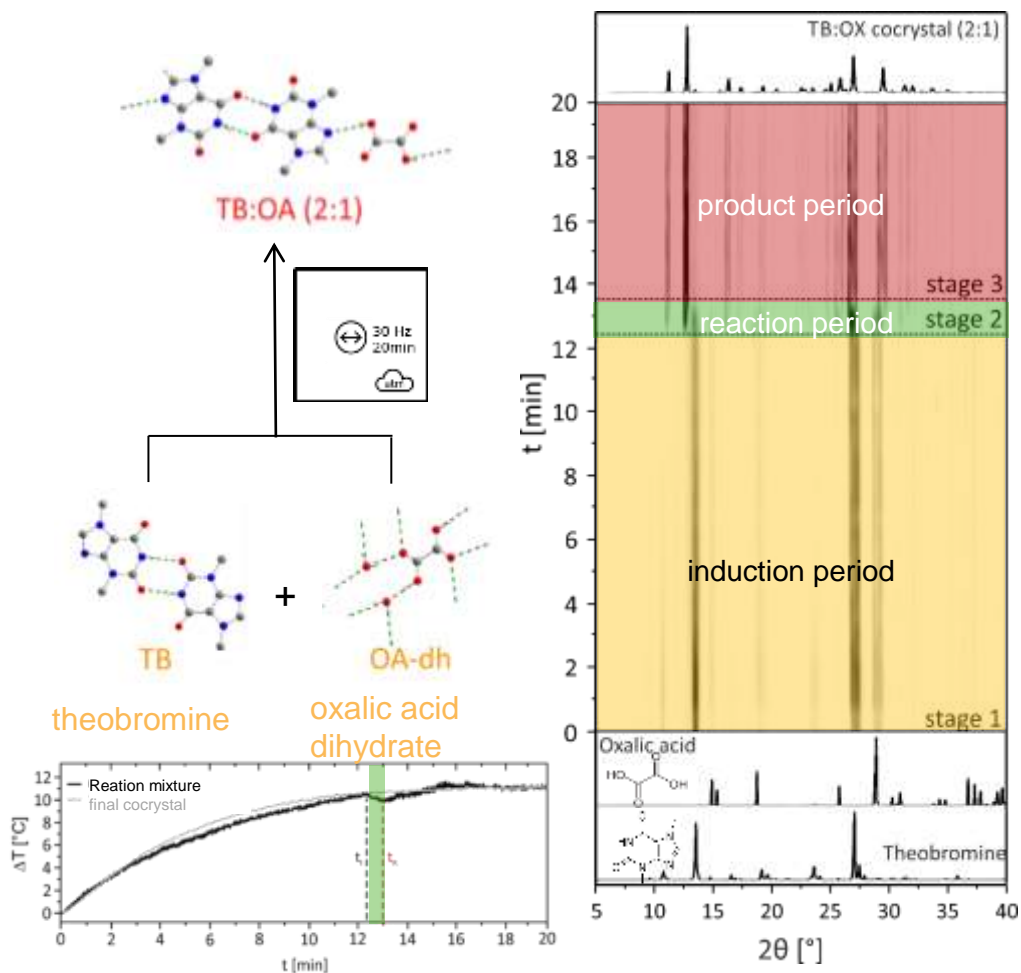


Time-resolved in situ investigation

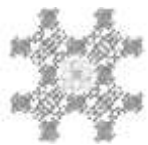


Angew. Chem. Int. Ed. 2015, 54, 1799.
Chem. Commun. 2017, 53, 1664.
Angew. Chem. Int. Ed. 2018, 57, 5930.
Nat. Commun. 2021, 12, 6134.

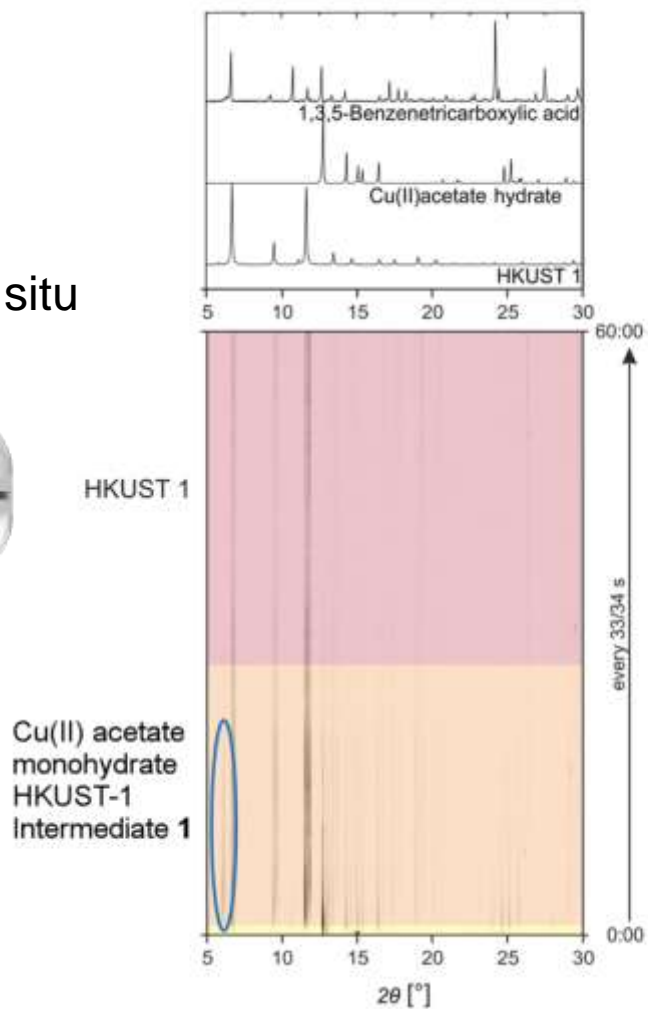




Angew. Chem. Int. Ed. 2018, 57, 5930.



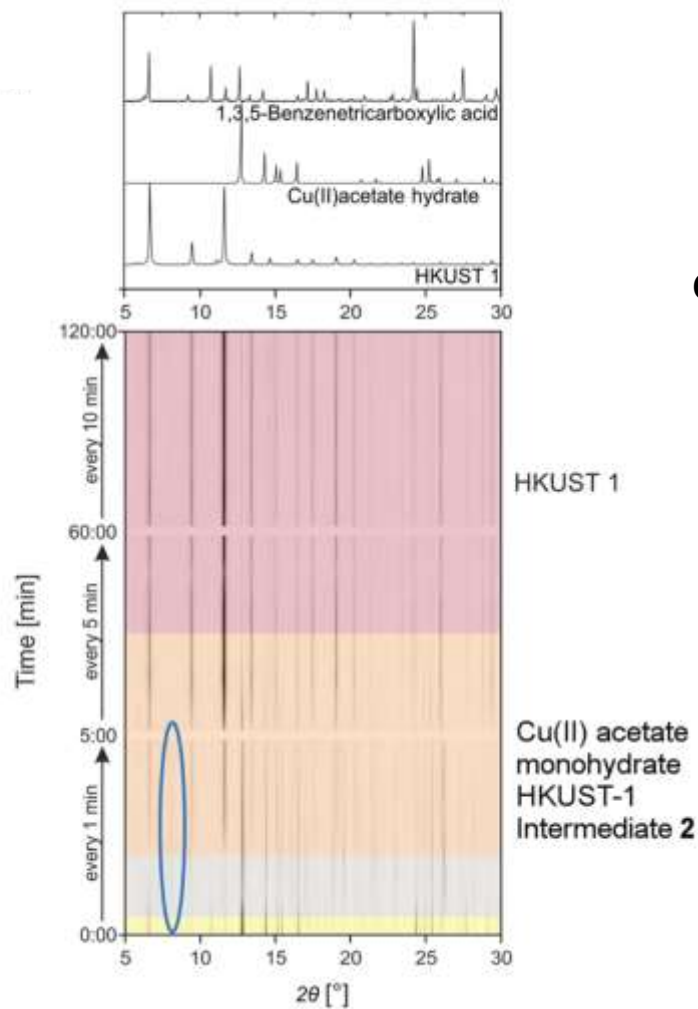
in situ



HKUST 1

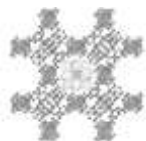
Cu(II) acetate monohydrate
HKUST-1
Intermediate 1

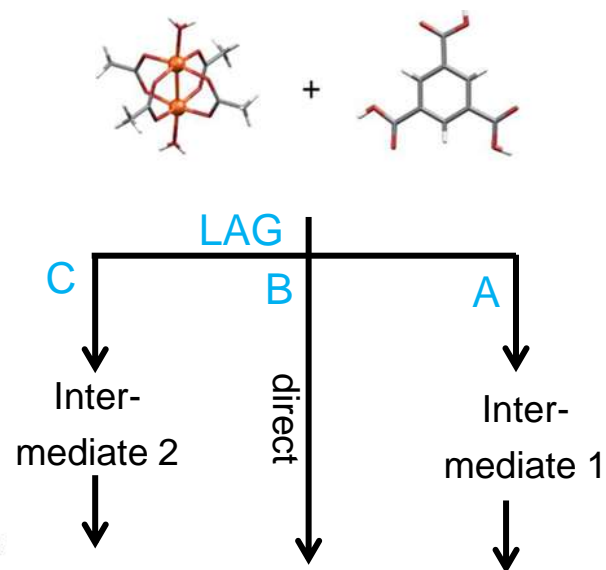
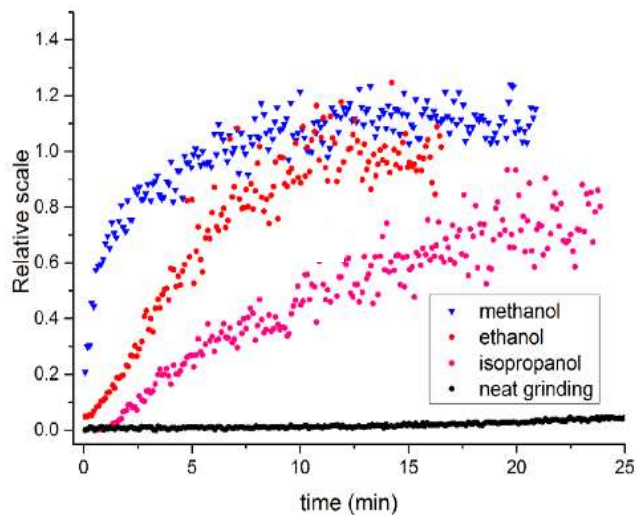
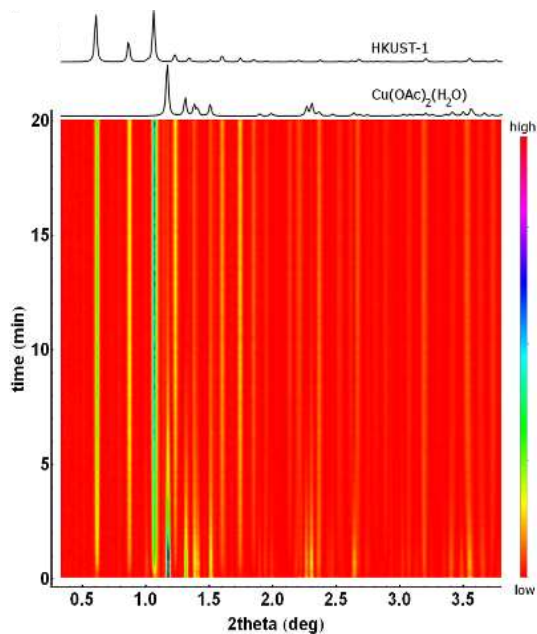
ex situ



HKUST 1

Cu(II) acetate monohydrate
HKUST-1
Intermediate 2



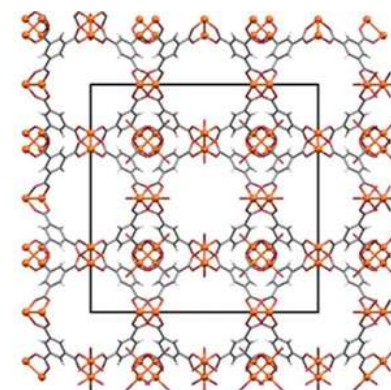
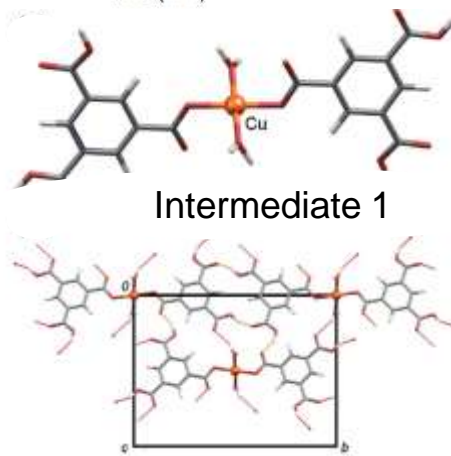


Choice of additive defines mechanism

A: solvents (long aliphatic chains)

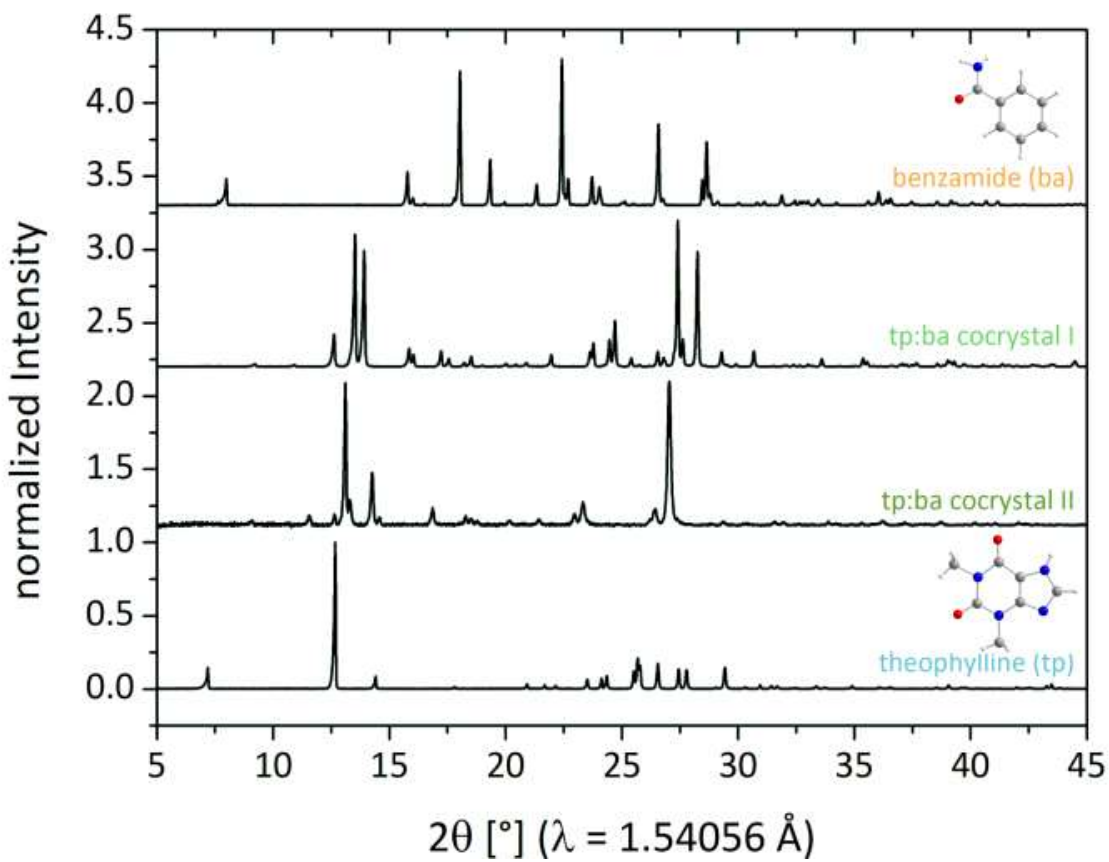
B: smaller solvent molecules

C: unpolar solvents

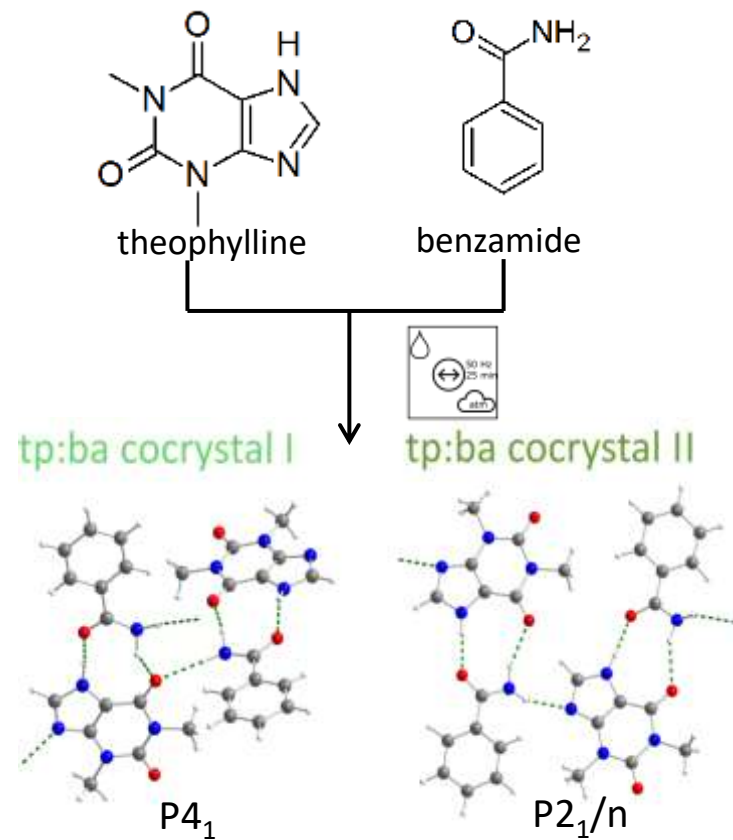


Inorg. Chem. 2017, 56, 6599.





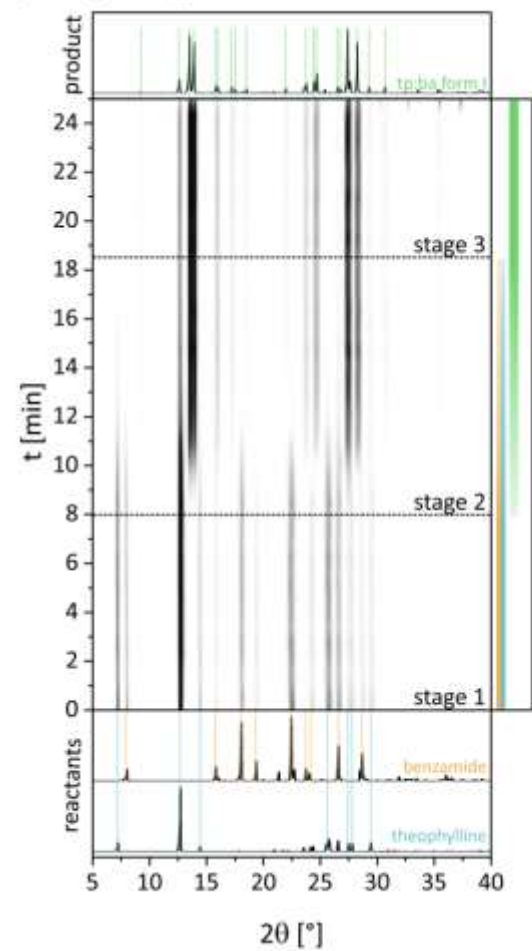
Cryst. Growth Des. 2016, 16, 1701.
Acta Cryst. 2016, C72, 217.



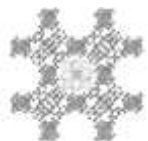
LAG liquid-assisted grinding
250 μl solvent
Screening 17 solvents

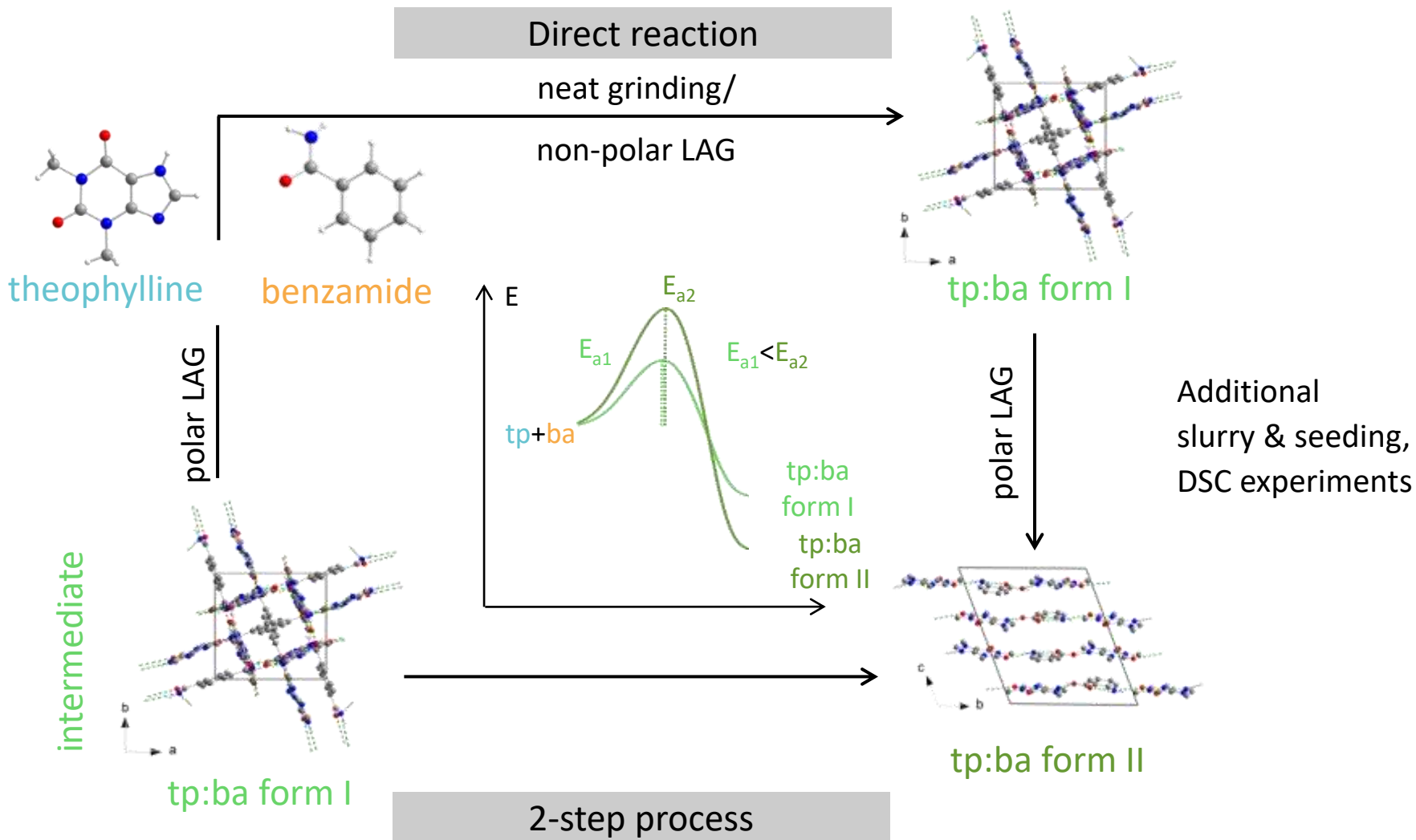


neat grinding form I

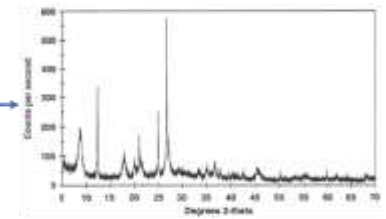
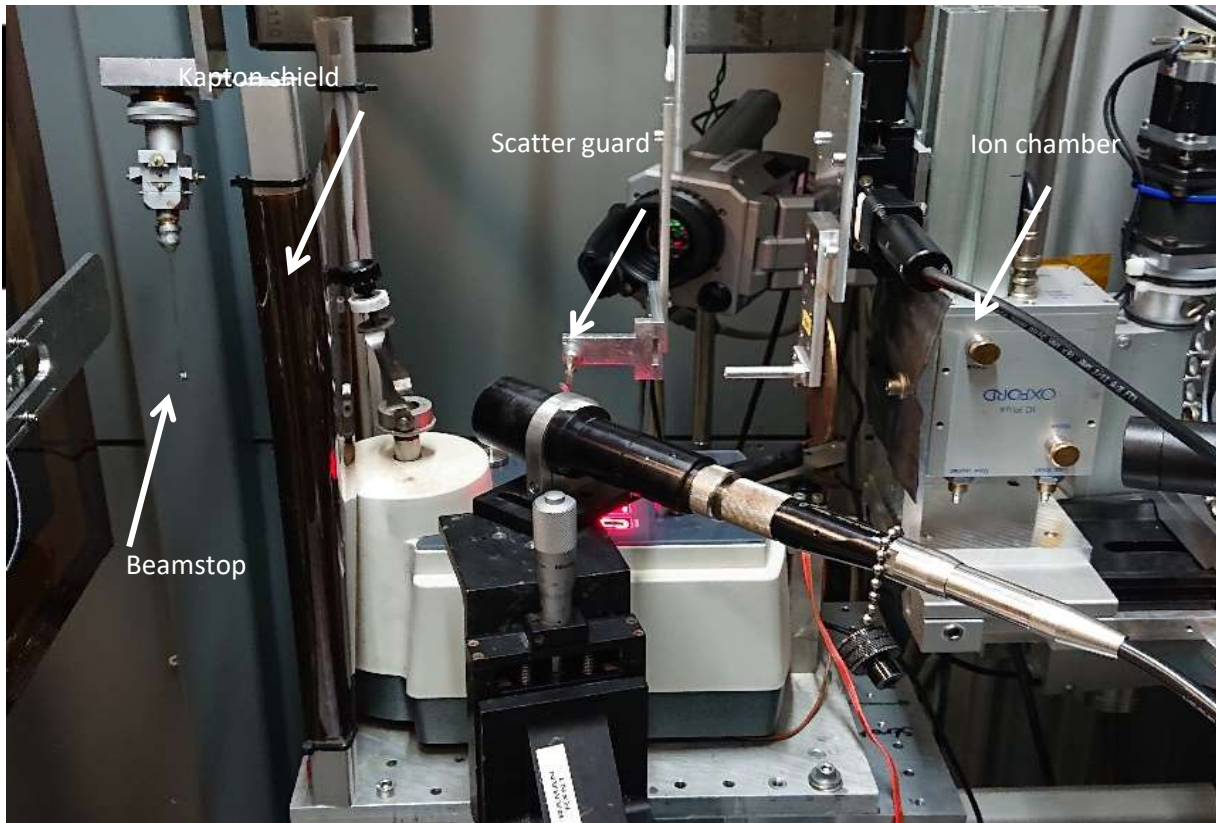


- reactants
- tp:ba form I
- tp:ba form II

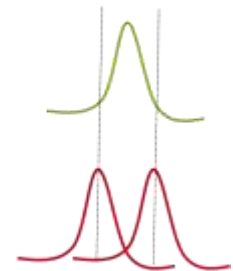


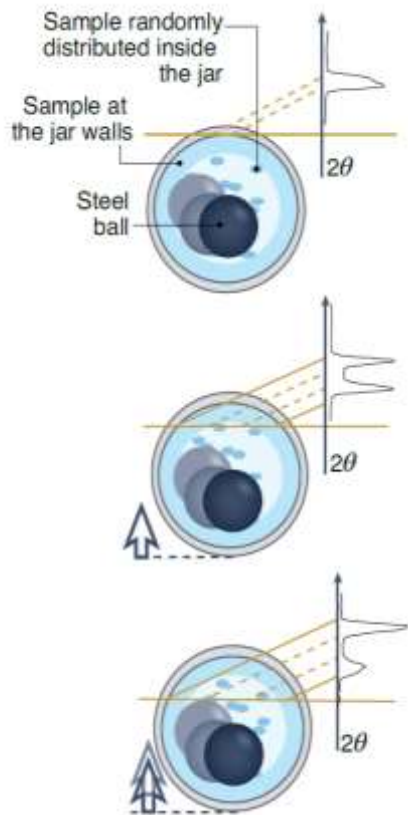


Optimizing the set-up for in situ milling



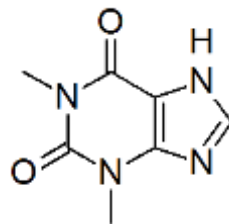
$$2\theta_2 \Rightarrow \tan(\theta_1) = \tan(2\theta_2)$$



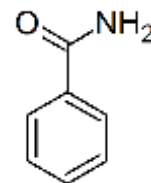


tp:ba
Form II

← LG
water

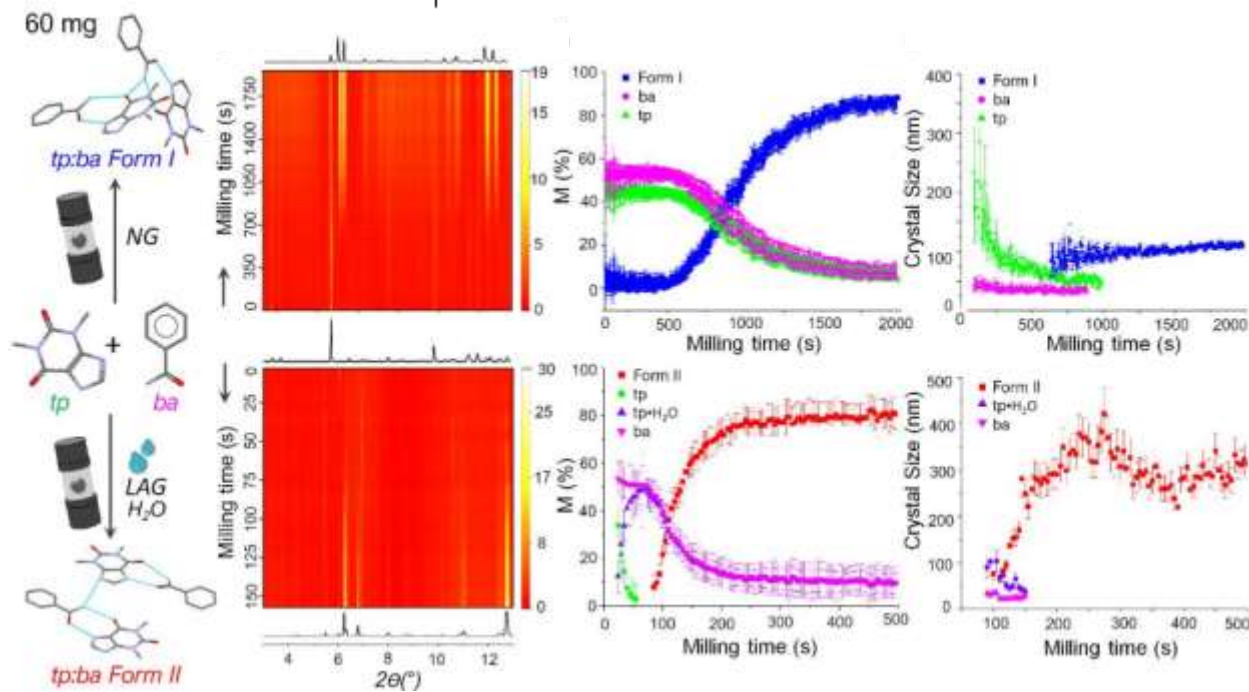


+

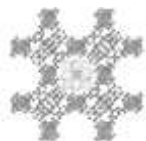


→ NG

tp:ba
Form I



Nat. Commun. 2021, 12, 6134.

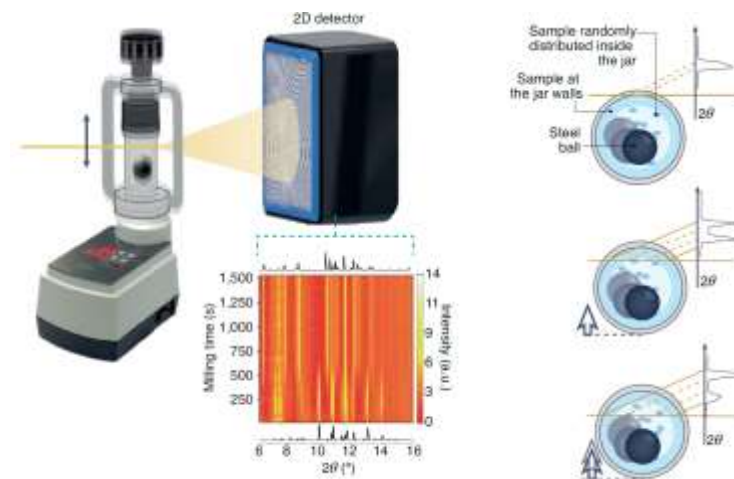
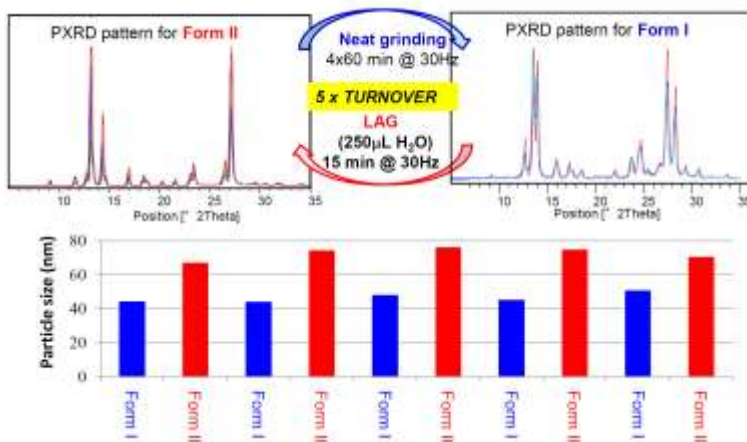




Cite this: Chem. Sci., 2016, 7, 6617

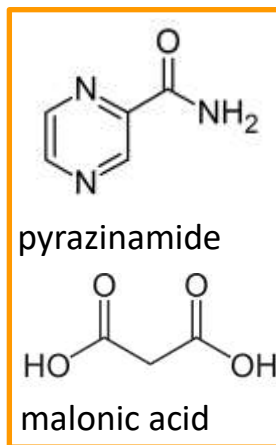
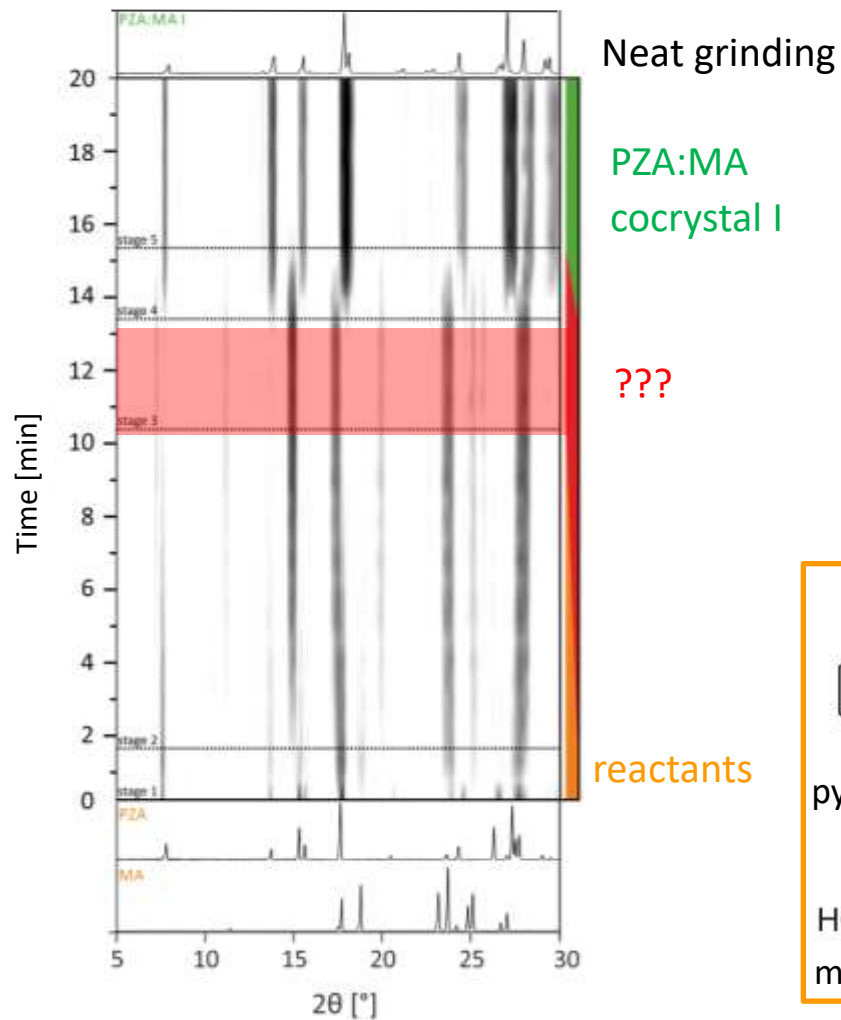
Solvation and surface effects on polymorph stabilities at the nanoscale†

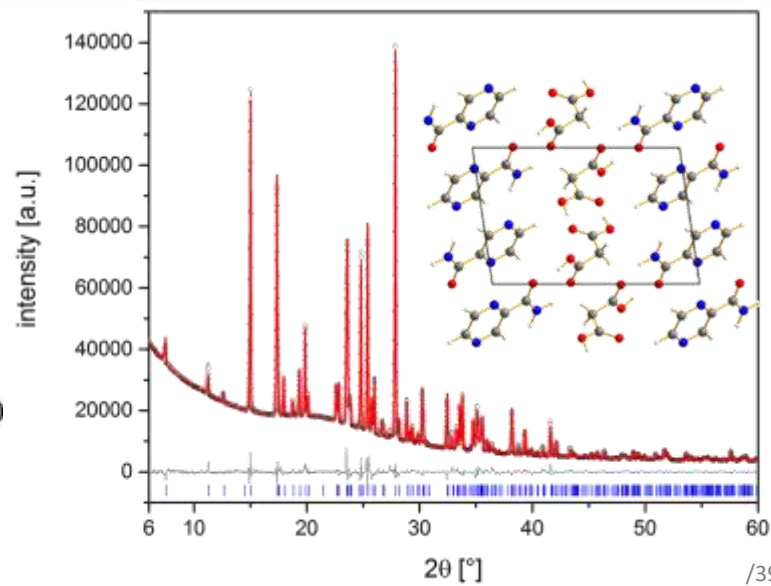
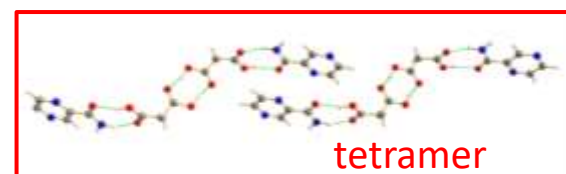
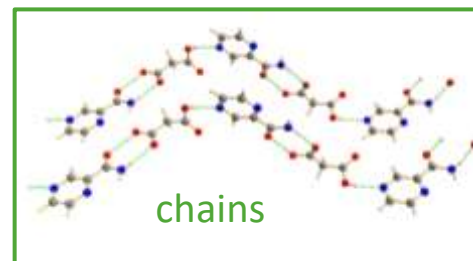
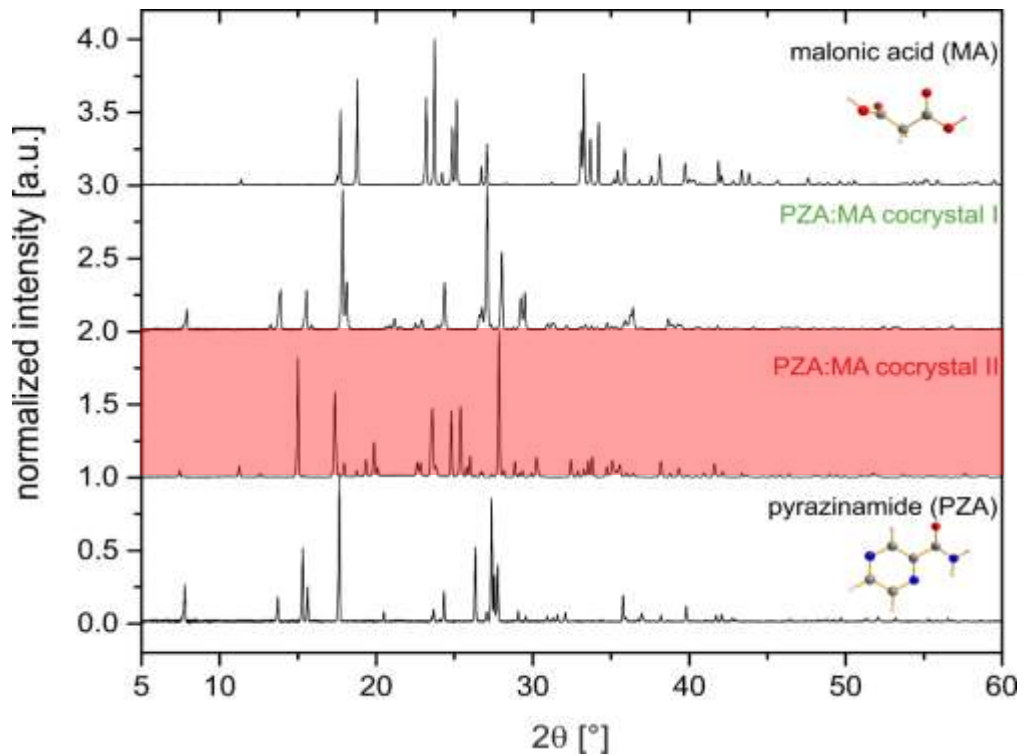
A. M. Belenguer,^{*a} G. I. Lampronti,^{ab} A. J. Cruz-Cabeza,^c C. A. Hunter^a and J. K. M. Sanders^{*a}



Nat. Commun. 2021, 12, 6134.



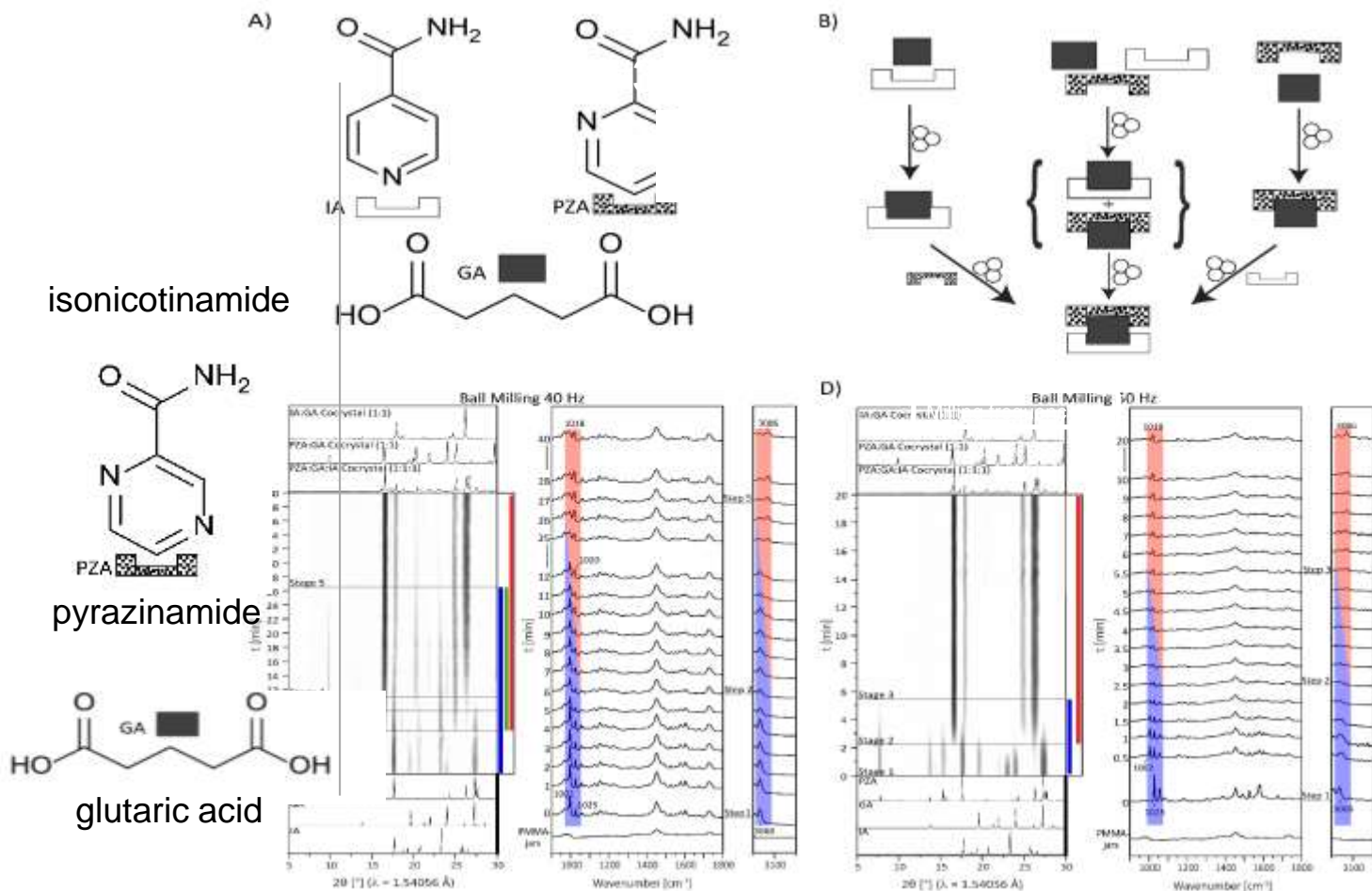




Cryst.Growth Des. 2017, 17, 1190.



Manipulating the Ternary Cocystal Formation



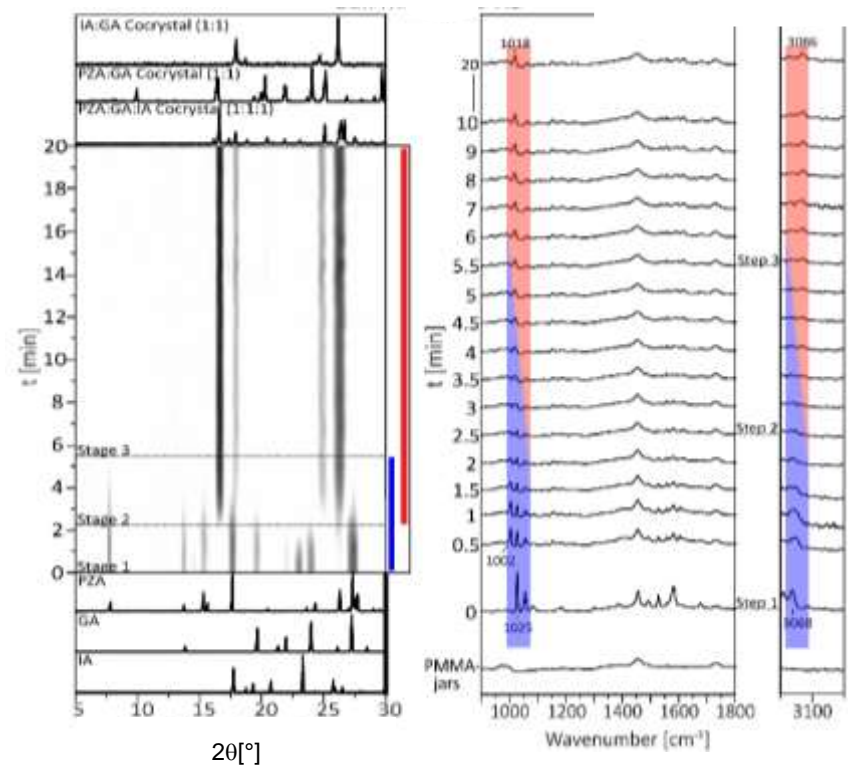
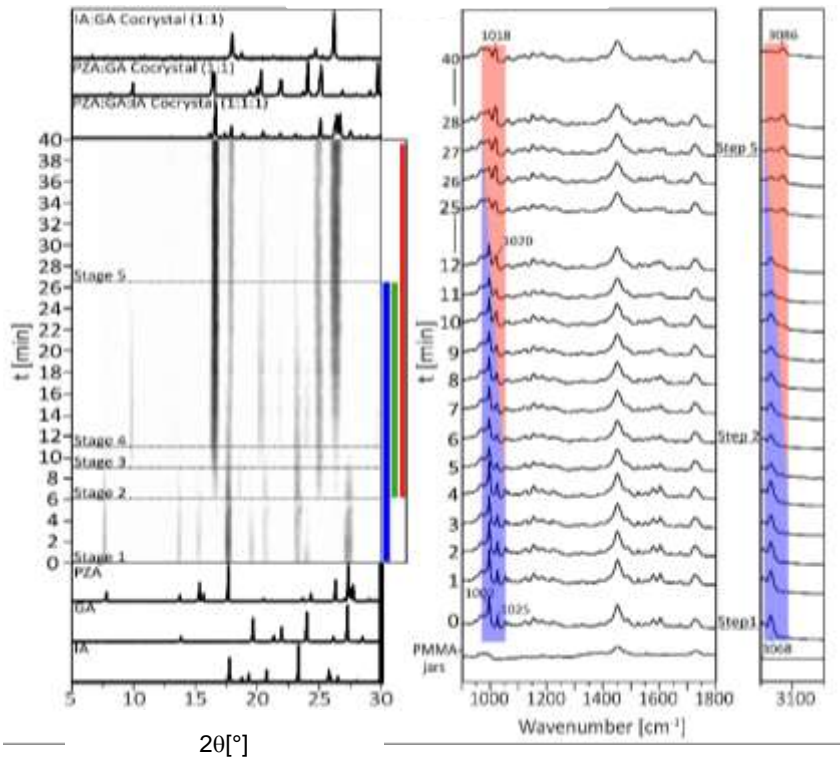
Chem. Commun. 2019, 55, 9793.



Reactants, binary cocrystal, ternary cocrystal

Ball mill 40 Hz

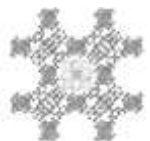
Ball mill 50 Hz



Lower frequency

→ lower mechanical impact

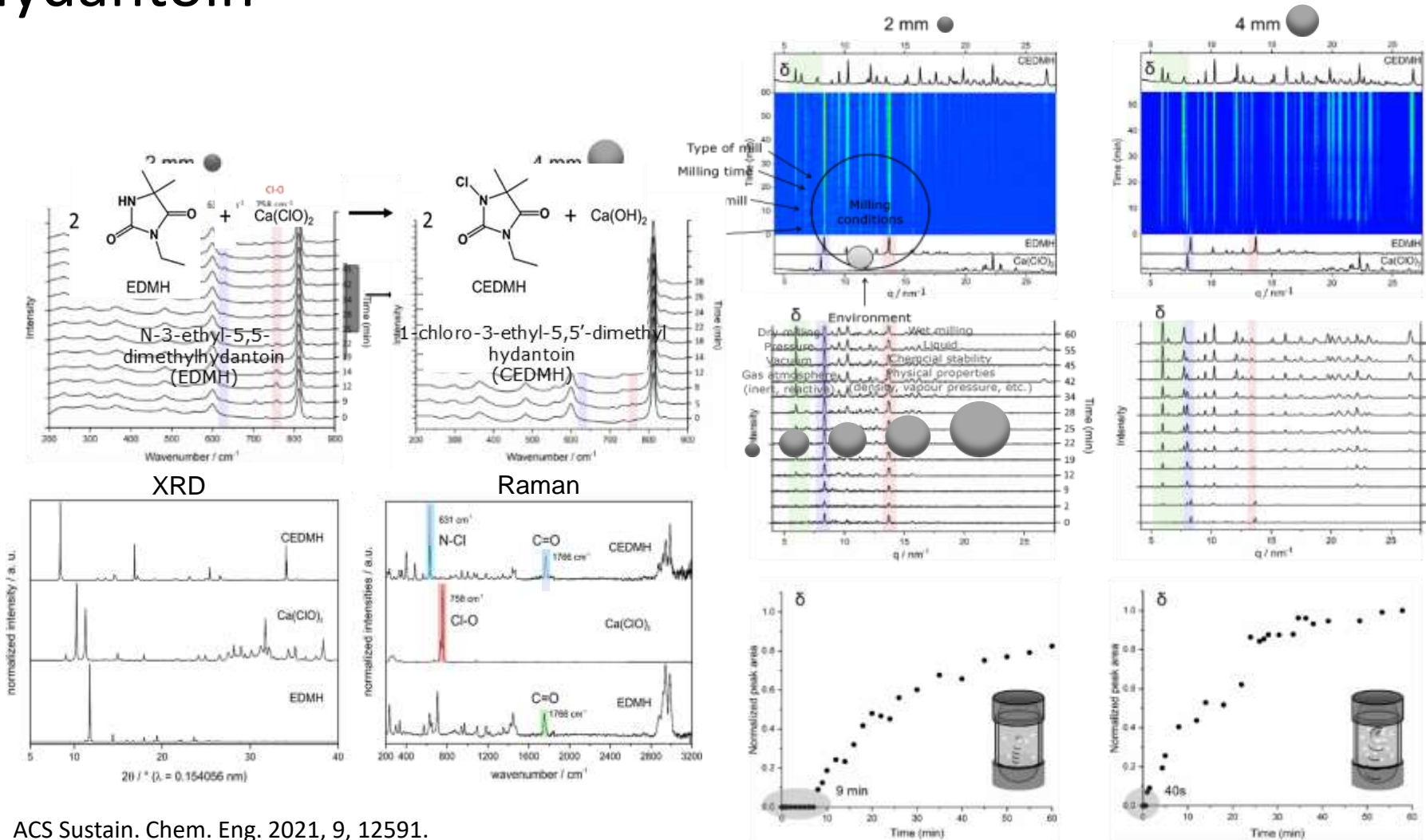
→ lower mixing intensity → → binary phase



ORGANIC CHEMISTRY

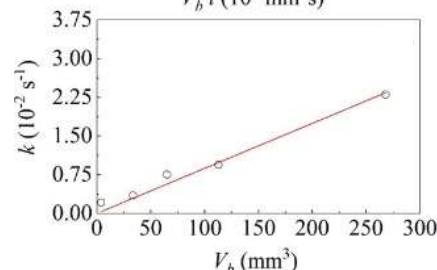
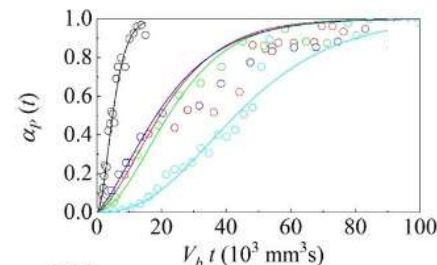
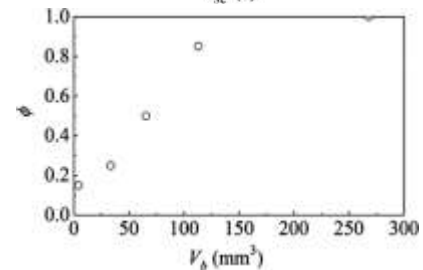
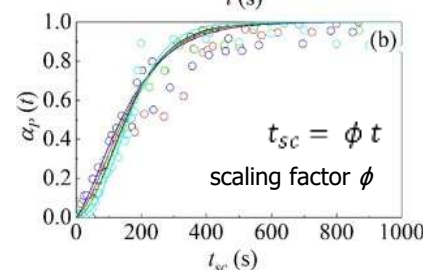
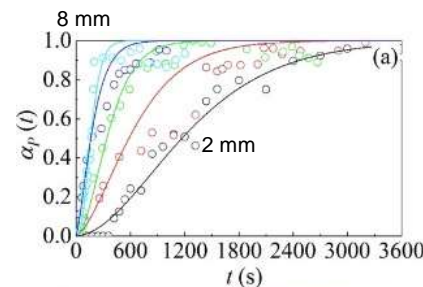
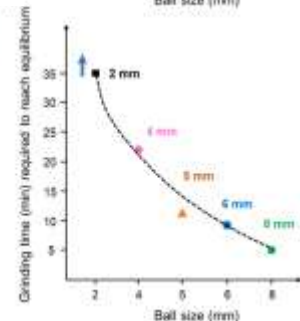
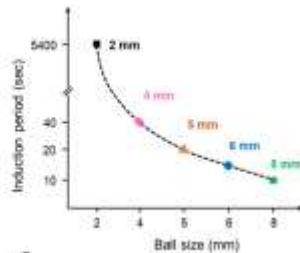
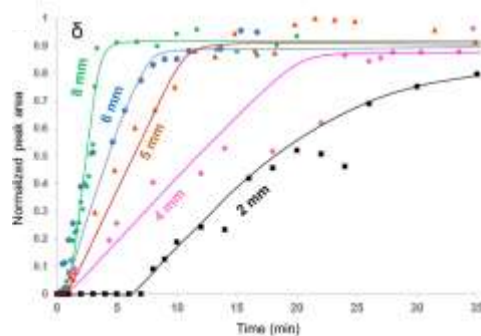
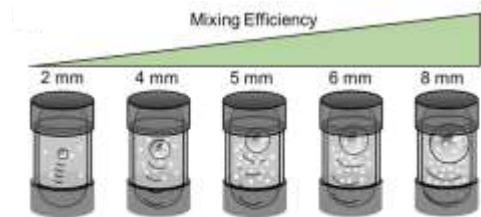


Mechanochemical N-Chlorination Reaction of Hydantoin



ACS Sustain. Chem. Eng. 2021, 9, 12591.





$$\alpha_p(t) = \sum_{i=1}^{\infty} \chi_i(t) \alpha_{p,i}$$

statistical factor

$$\chi_i(t) = [(k t)^i / i!] \exp(-k t)$$

chemical factor

$$\alpha_{p,i} = 1 - \left\{ [S_{in} \exp(r i) + (S_{fin} - S_{in})] / S_{fin} \right\}^{-\Pi S_{fin} / (r S_{ca} N_{in})}$$

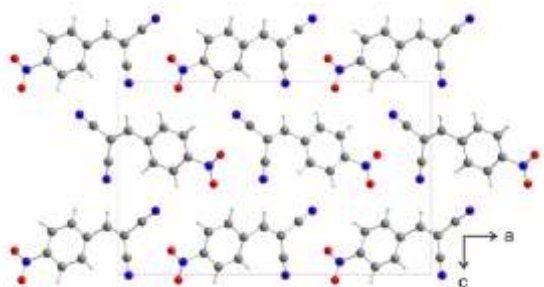
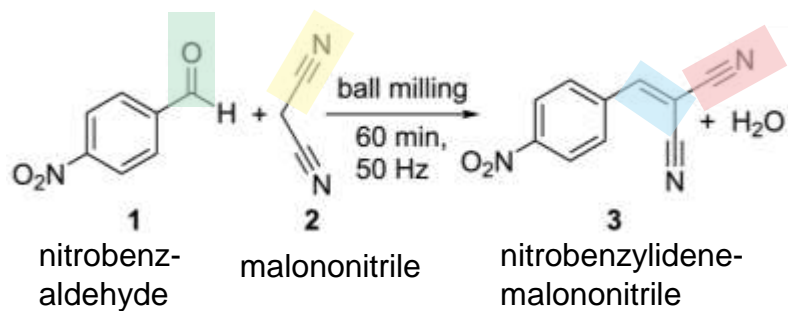
The chemical transformations activated with balls of different sizes exhibit isokinetic features.

Rate of the chemical transformations is governed by the amount of powder affected by critical loading conditions during individual impacts

Varies almost linearly with the ball volume

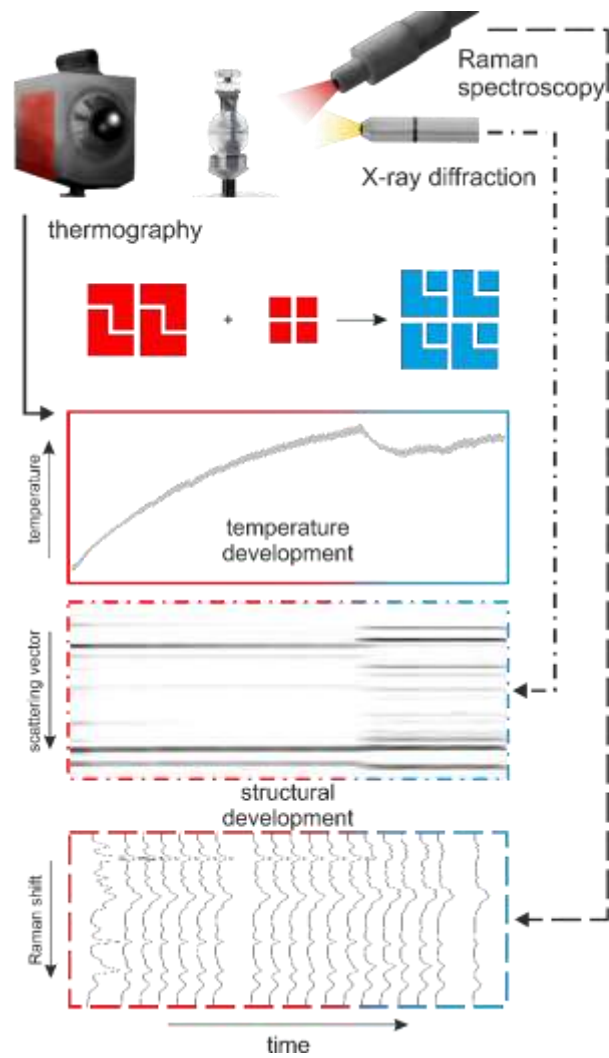
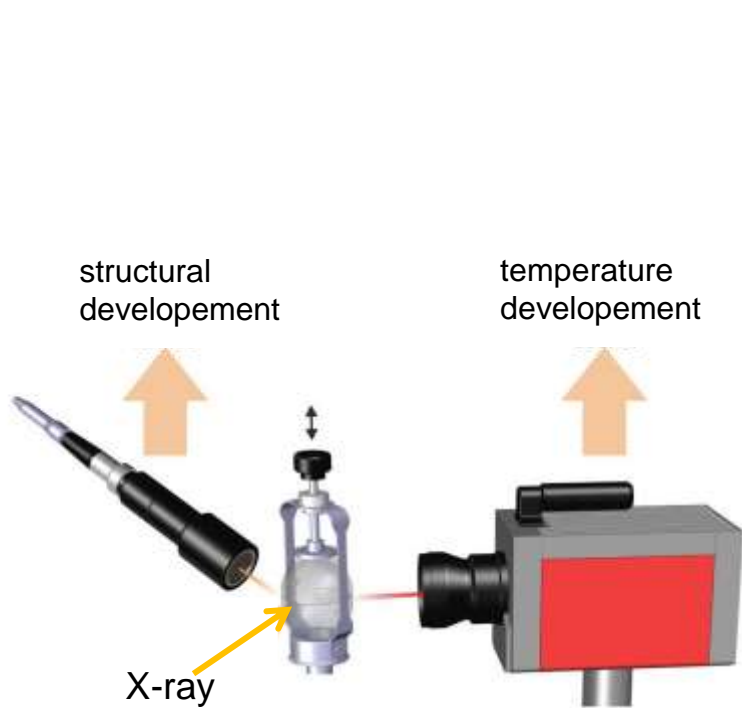


C-C Bonding Knoevenagel condensation



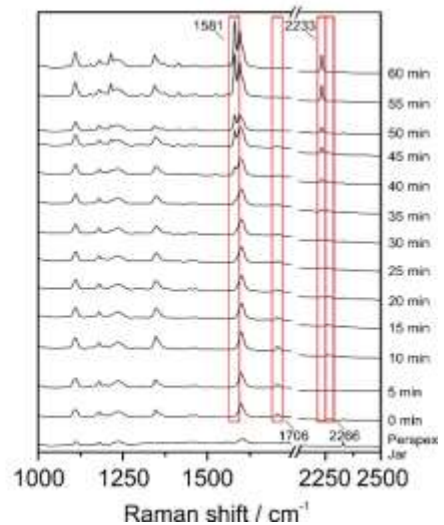
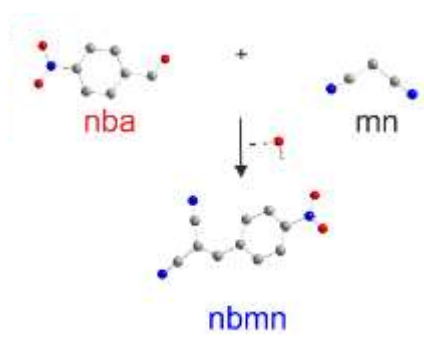
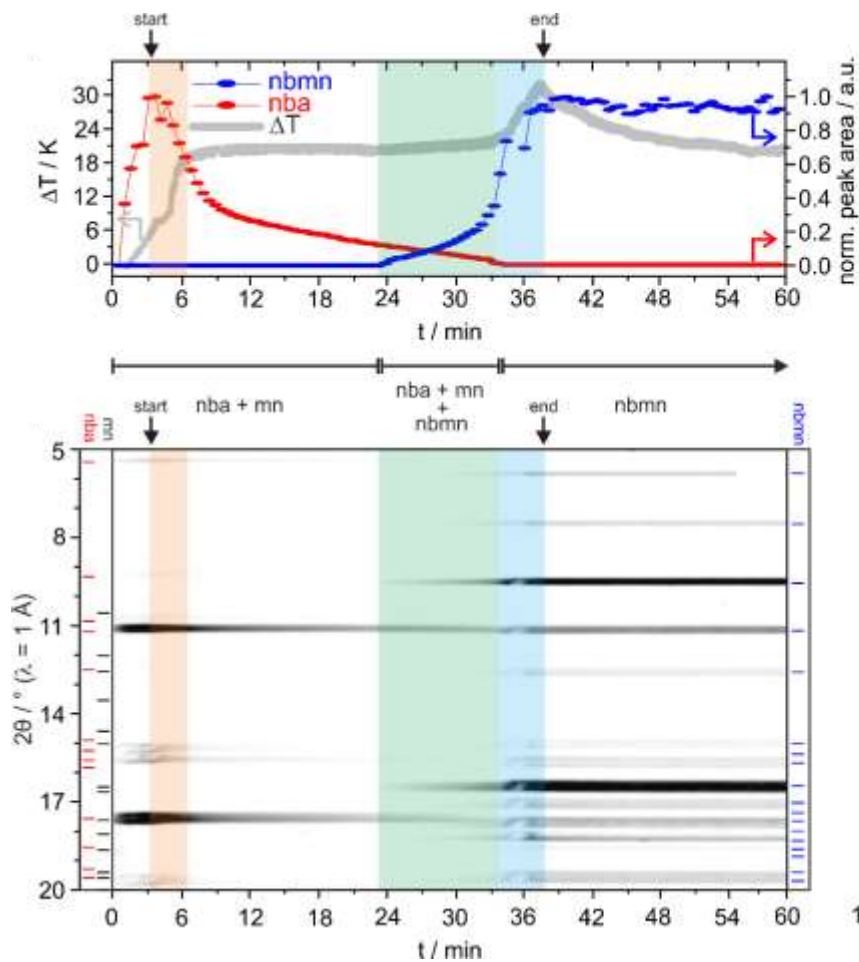
Beilstein J. Org. Chem. 2017, 13, 2010.





Chem. Commun., 2017, 53, 1664.
 Angew. Chem. Int. Ed. 2018, 57, 5930.

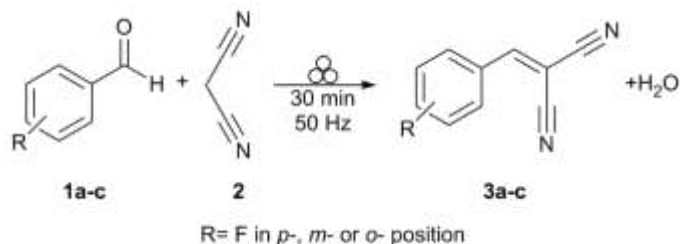




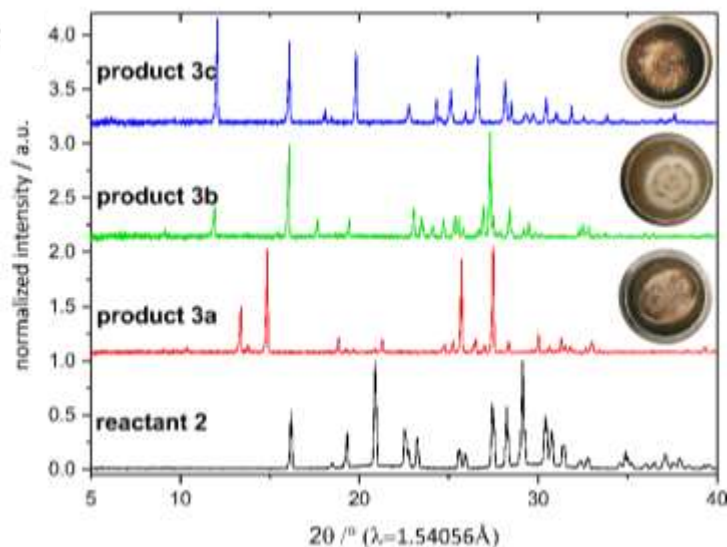
→ Information on crystalline, molecular, and temperature state

Chem. Commun., 2017, 53, 1664.
 Angew. Chem. Int. Ed. 2018, 57, 5930.



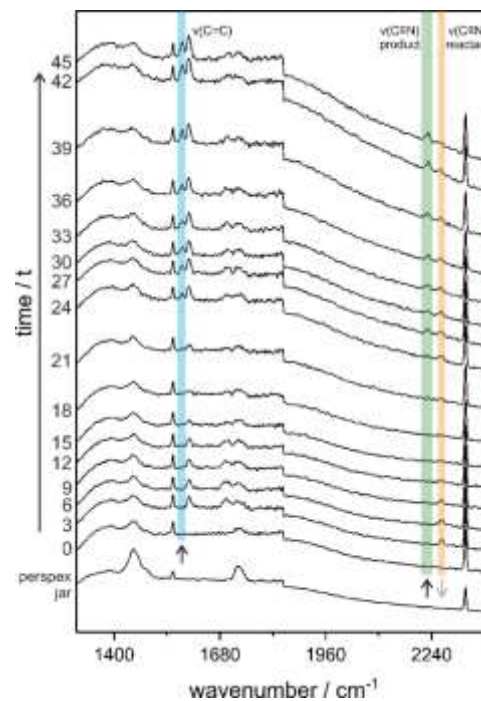
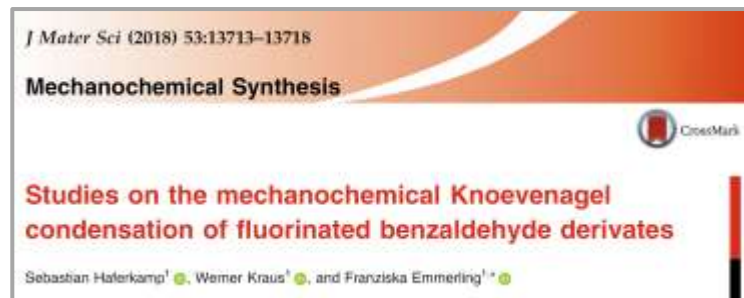


p-, *m*- and *o*-fluorobenzaldehyde



J. Mater. Sci. 2018, 53, 13713.

J. Org. Chem. 2019, 15, 1141.



→ Knoevenagel condensation works using liquid substrates in a mechanochemical reaction

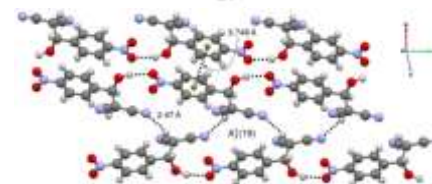
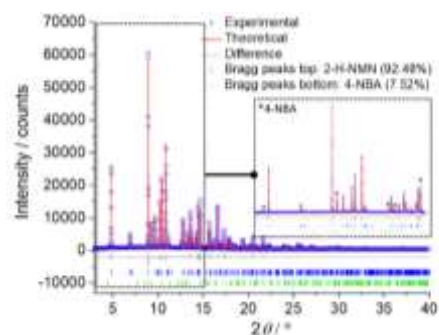
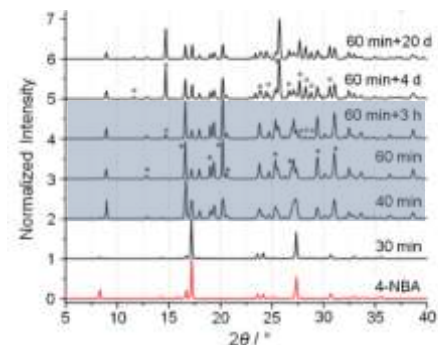
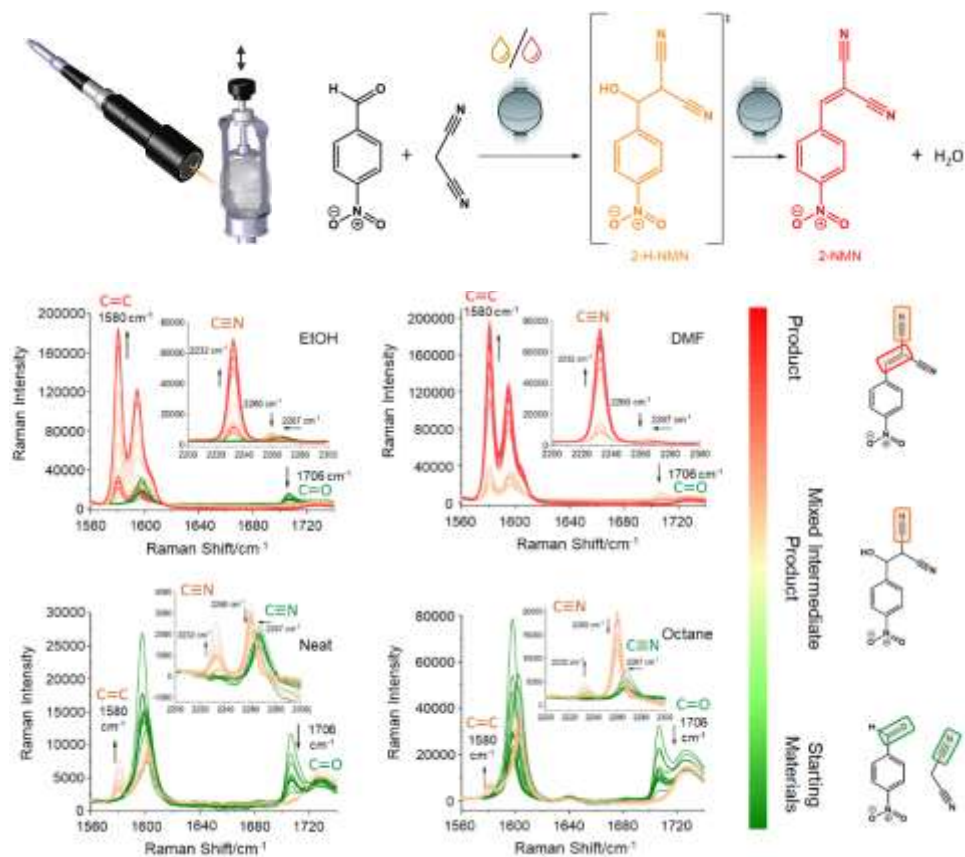
→ Suitable for single crystal X-ray analysis

→ In situ Raman spectroscopy reveals direct & complete conversion



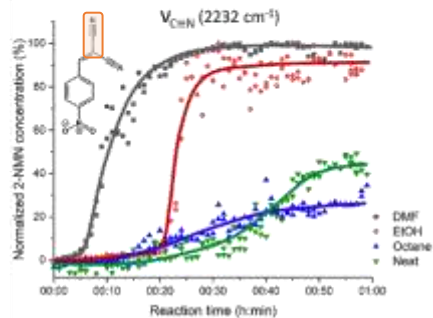
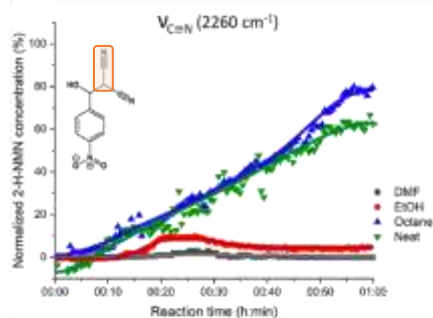
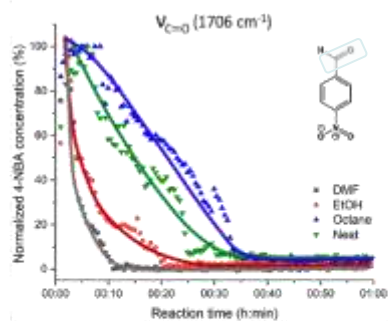
Role of solvent polarity

Trapping intermediate:
octane, lower frequencies (15 Hz)

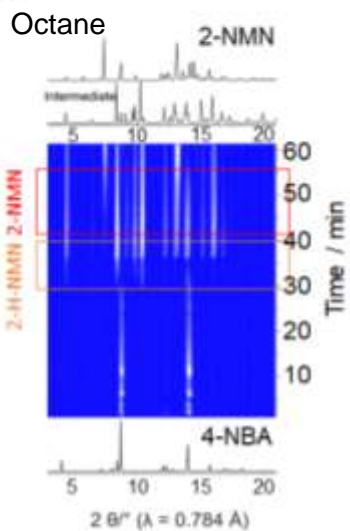
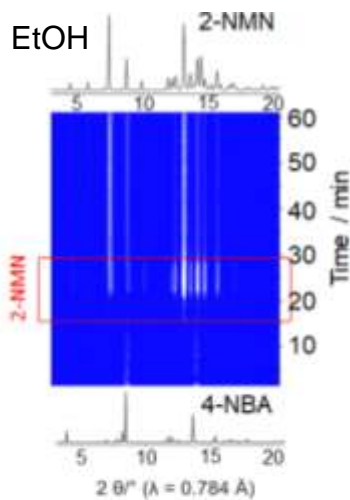


PCCP 2023, accepted.

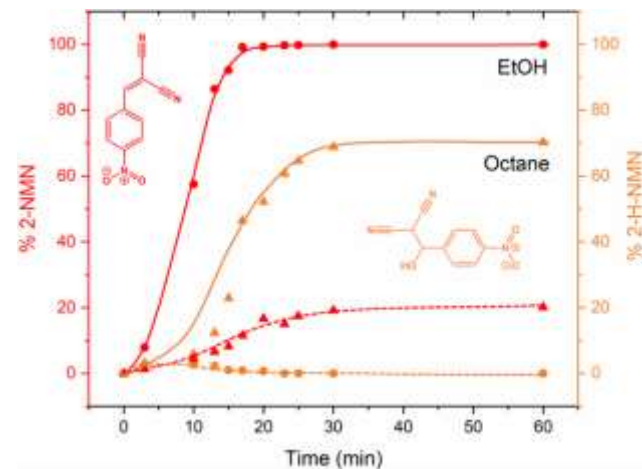




PCCP 2023, accepted



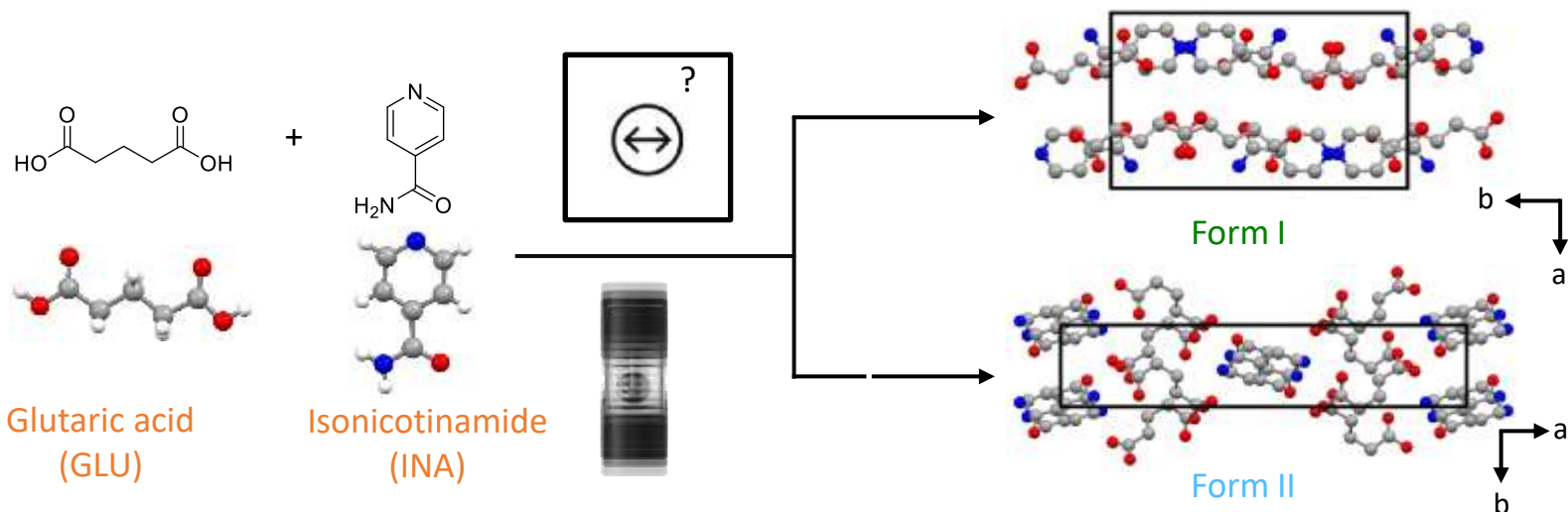
Ex situ XRD/Rietveld



- Use of EtOH and DMF resulted in faster reaction kinetics
- Neat grinding frequency 40 Hz → intermediate
- Octane & NG → formation of the intermediate 2-H-NMN, incomplete conversion to the product 2-NMN

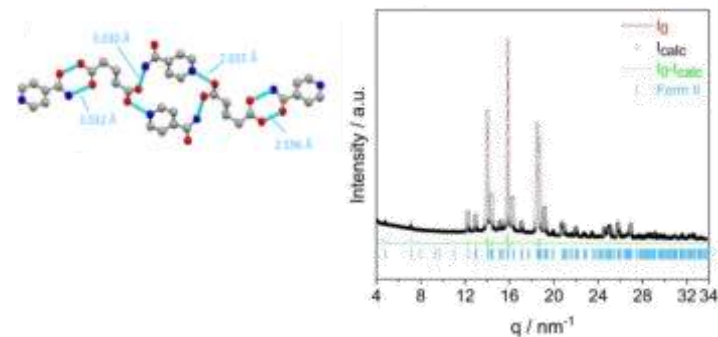


Controlling polymorphism by variable temperature ball milling



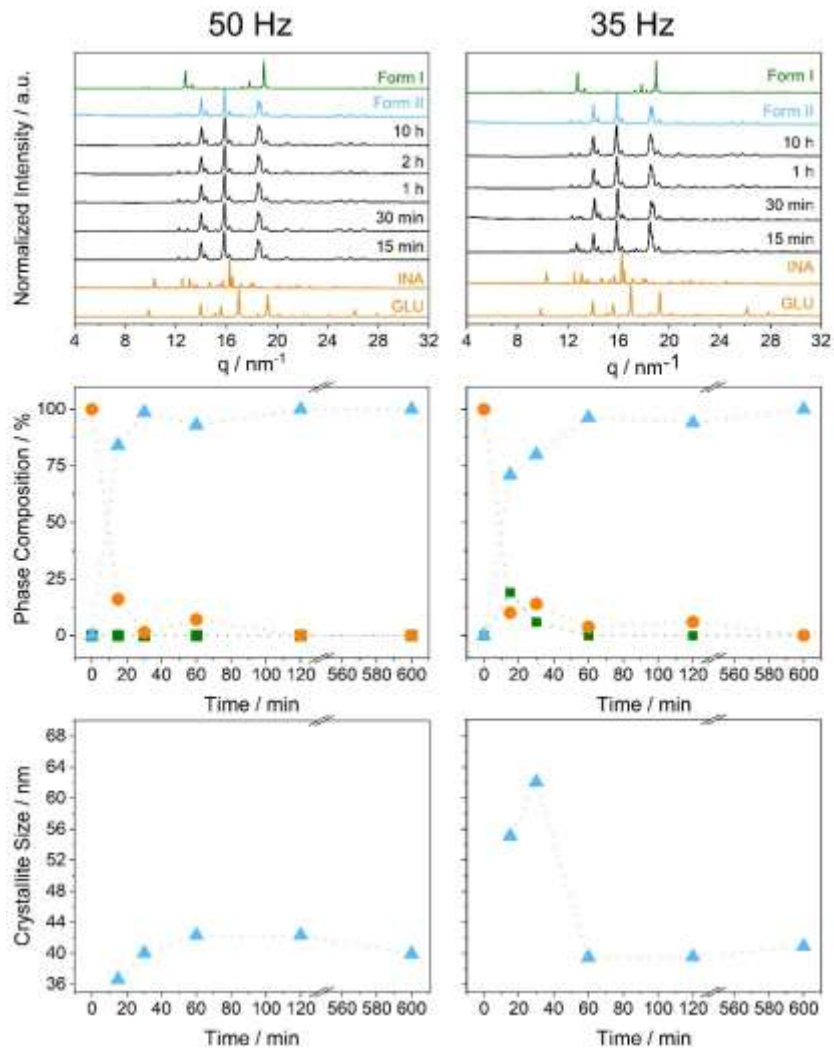
Form I is thermodynamically stable under ambient conditions.

Can polymorphism be controlled by variable temperature ball milling?

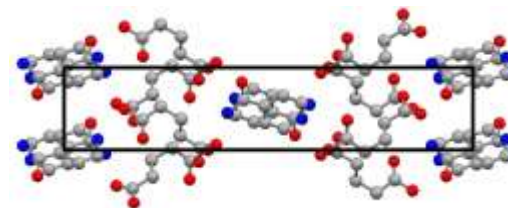


Faraday Discuss., 2023, 241, 178.





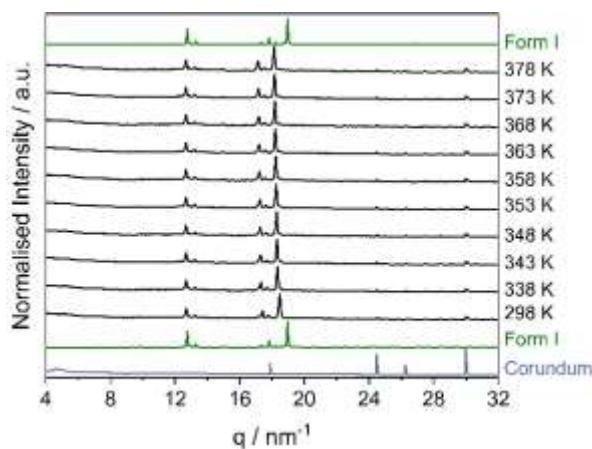
milling experiments at ambient temperature neat grinding



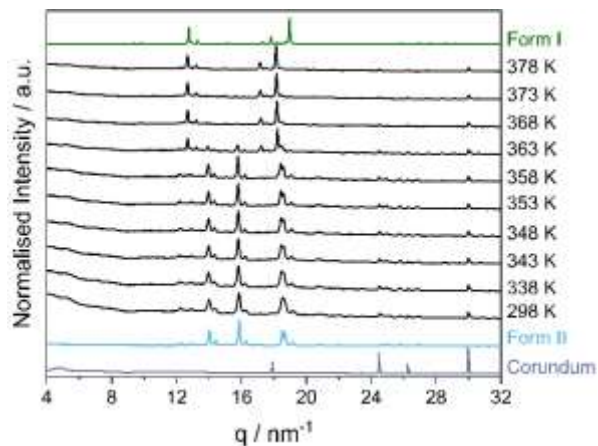
Stability of the polymorphs



Variable temperature PXRD up to 378 K

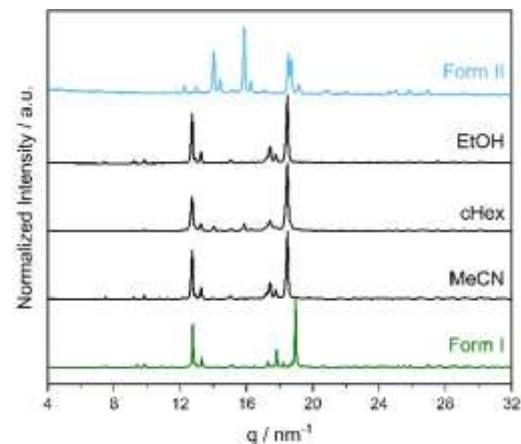


Starting with **Form I**
no conversion



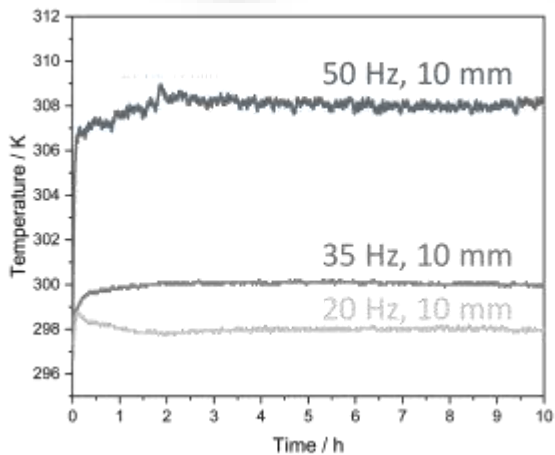
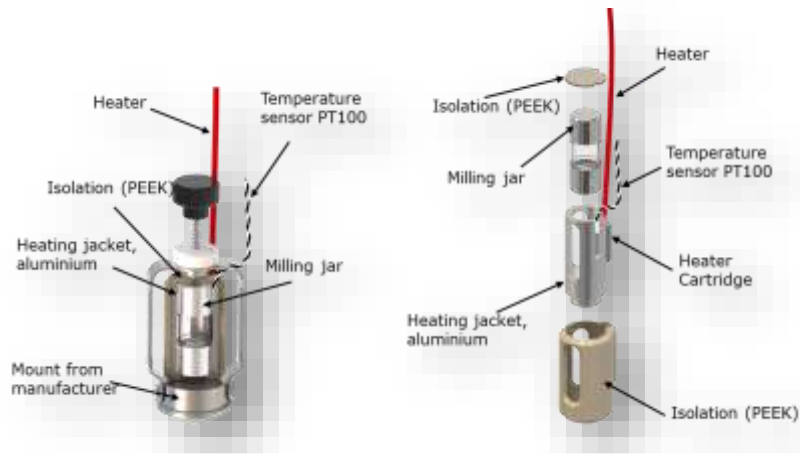
Starting with **Form II**
at 363 K: **Form II** → **Form I**

Slurry Experiments

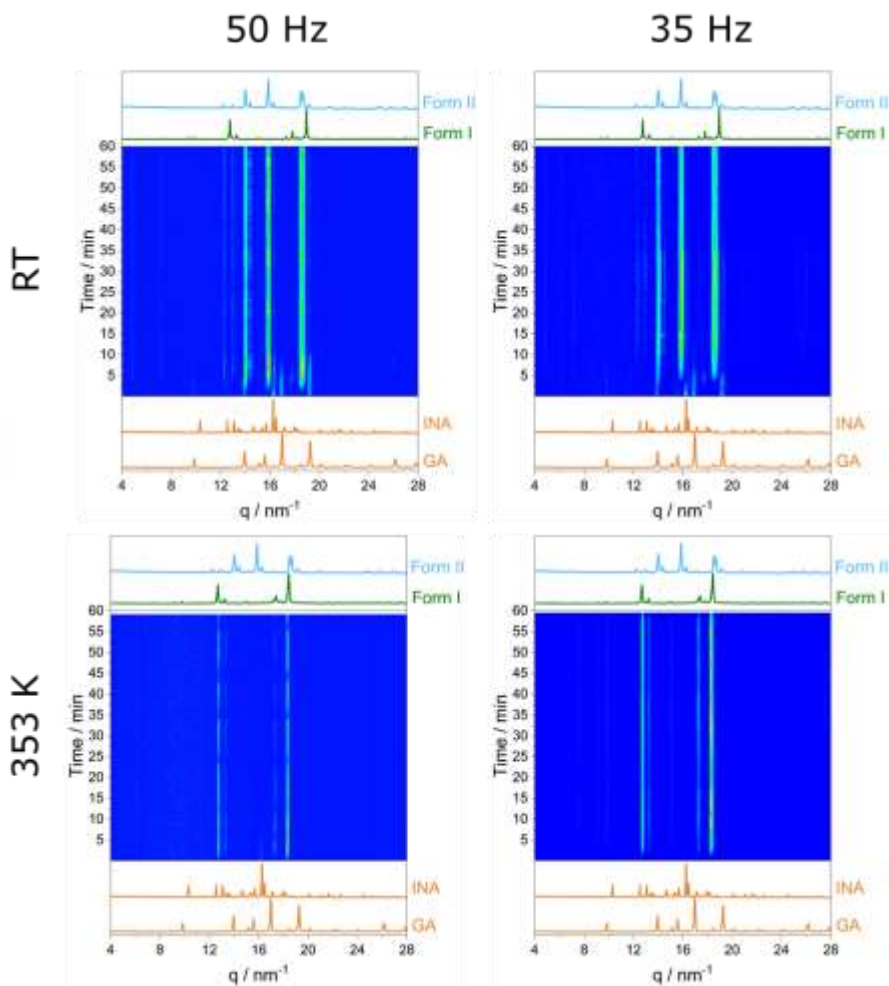


Faraday Discuss., 2023, 241, 178.





RT: Form II
 353 K: Form I



Faraday Discuss., 2023, 241, 178.

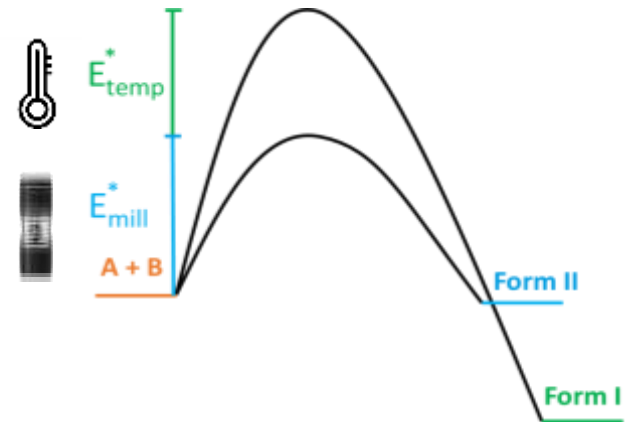


Temperature / K	Frequency / Hz
RT	Form II
313	Form II (15 min)
323	Form II (120 min)
	Form II (15 min)
333	Form II (120 min)
	Form I or Form II (15 min)
337	Form I or Form II (120 min)
	Form I and traces of Form II (15 min)
343	Form I (120 min)
	Form I (30 min)
	Form I (80 min)
345	Form I (85 min)
	Form II (95%) + Form I (5%) 90 min
348	Form I or Form II 120 min
353	Form I (120 min)
353	Form I (120 min)

Metastable
Form II

Polymorphic
outcome
stochastic

Form I



Combination of temperature and milling
energy can overcome activation energy for
transformation

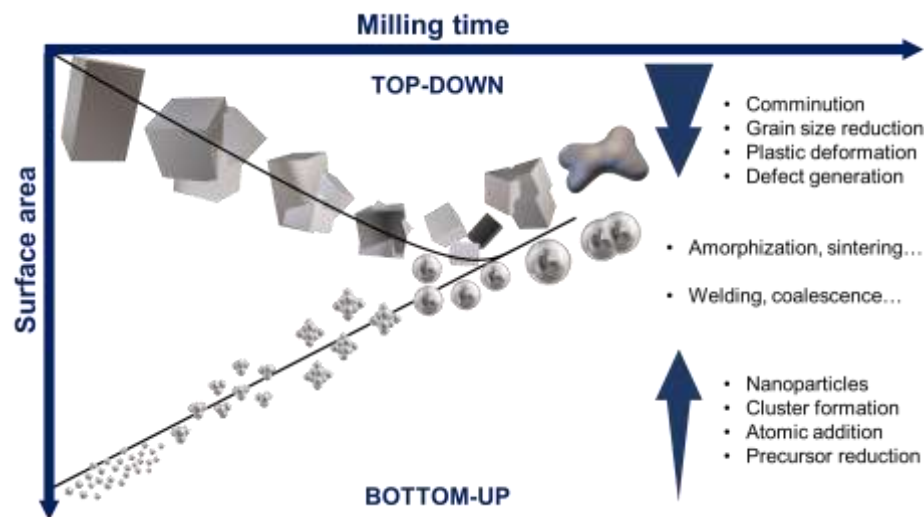
Faraday Discuss., 2023, 241, 178.



INORGANIC MATERIALS



Mechanochemical synthesis of noble metal nanoparticles



Check for updates

Cite this: *J. Mater. Chem. A*, 2020, 8, 16114

Challenges and opportunities in the bottom-up mechanochemical synthesis of noble metal nanoparticles

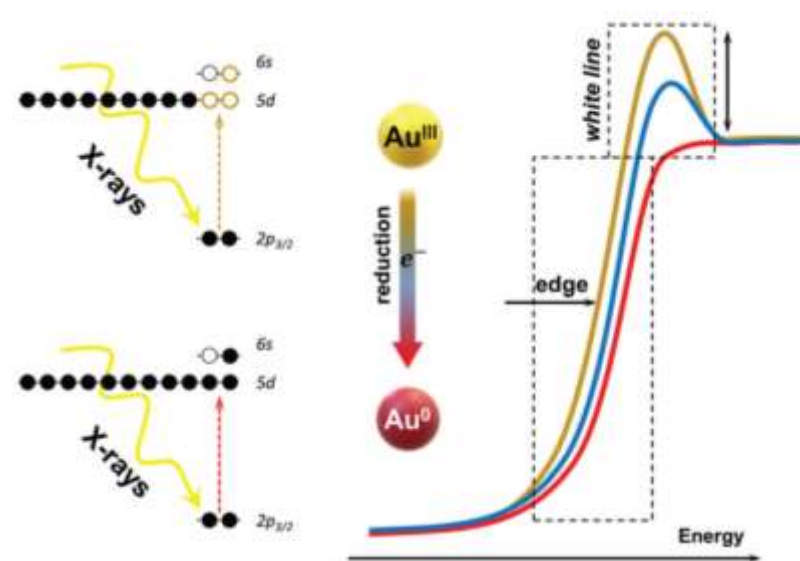
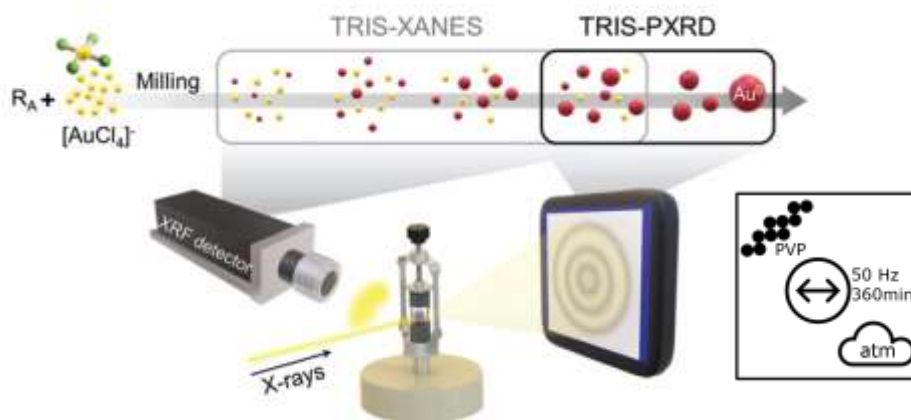
Paulo F. M. de Oliveira,^{ab} Roberto M. Torres,^a Franziska Emmerling^{ab} and Pedro H. C. Camargo^{bc}

Table 4 Practical guidelines for the mechanochemical synthesis of noble metal NPs

Parameter	Effect
Milling/grinding time	Long milling duration tends to increase the particle size, yet small NPs are possible at high conversions of the metal precursor for protected NPs. A compromise in between milling time and conversion of the precursor is necessary in the case of surfactant free NPs.
Milling/grinding bodies	Nonmetallic milling assembly (jar + balls, or mortar and pestle) are preferred to avoid contamination (ZrO ₂ , agate, PTFE, etc.) The use of metallic milling set can be beneficial if a galvanic replacement can take place, dismissing the use of common reducing agents.
Capping agent	For synthetic polymers (e.g., PVP), a high molecular mass provides a better stabilization and afford smaller NPs.
Reducing agent	Capping agents can be dismissed in the case for supported NPs. Not yet investigated in detail. Similar to solution, strong reducing agents such as NaBH ₄ or H ₂ (after dispersion of the precursor and support by grinding) tends to generate smaller NPs. Protecting agents such as PVP or PEG, and supporting materials (e.g. Lignin) can also play the role of reductants.
Metal salt precursor	Organic volatile precursors tend to yield smaller NPs. The chemical nature/affinity of the salt determines the NP distribution face to the supporting material, when employed.



New tandem approach: XANES & XRD

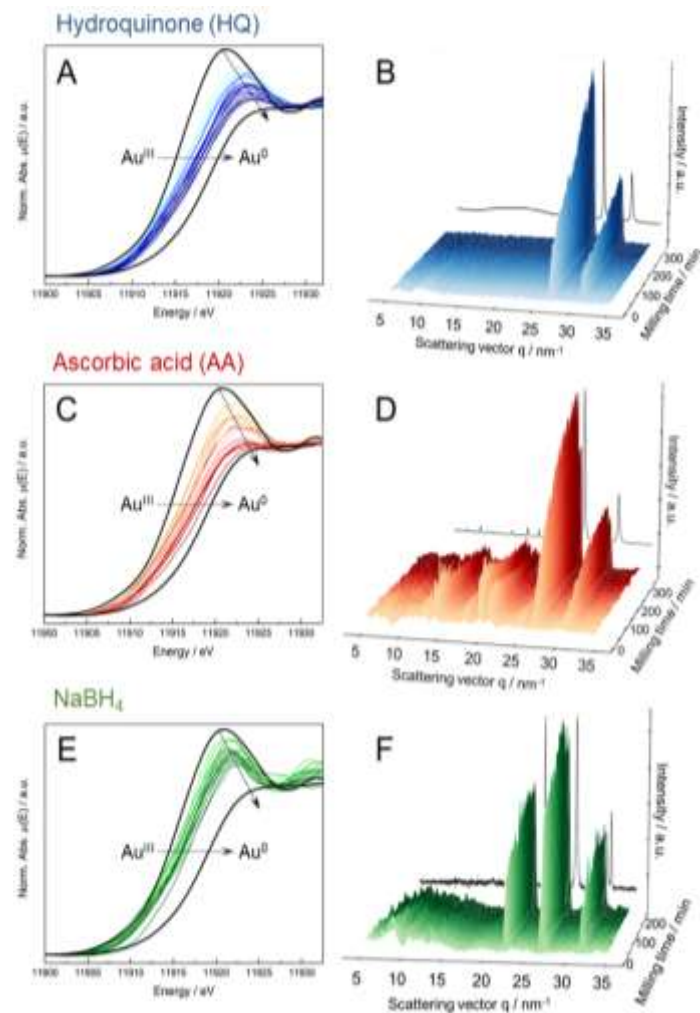
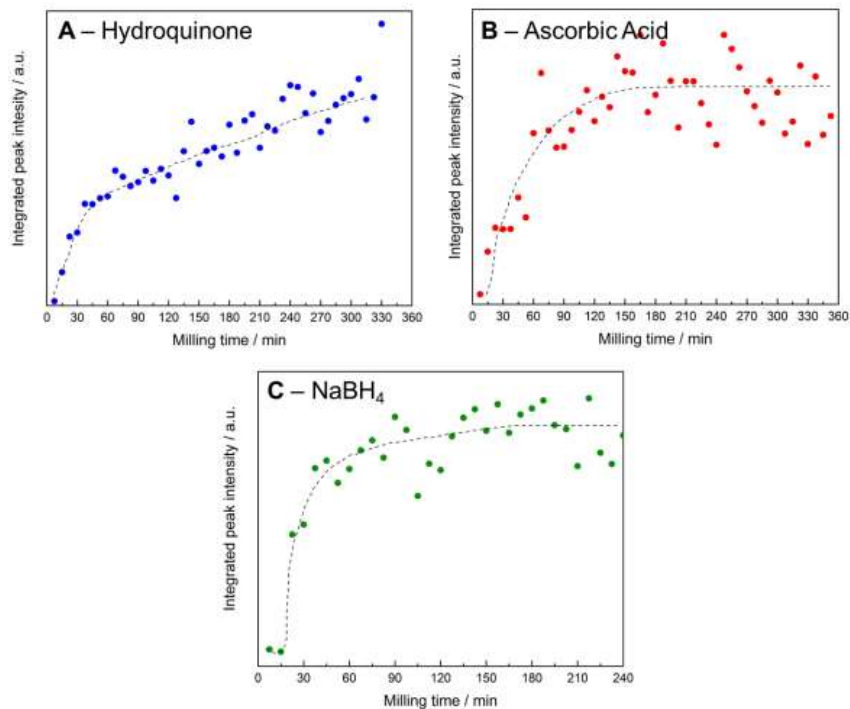


X-ray absorption spectroscopy → electronic structure
X-ray diffraction → crystalline structure

Correlations of milling parameters with mechanism of NP nucleation & growth

Chem. Commun. 2020, 56, 10329.





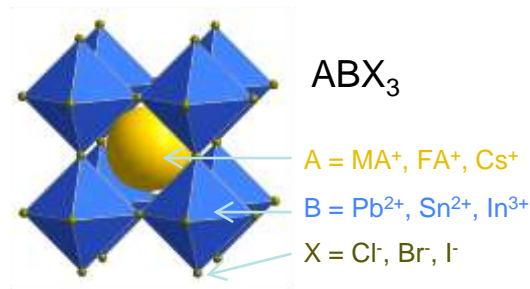
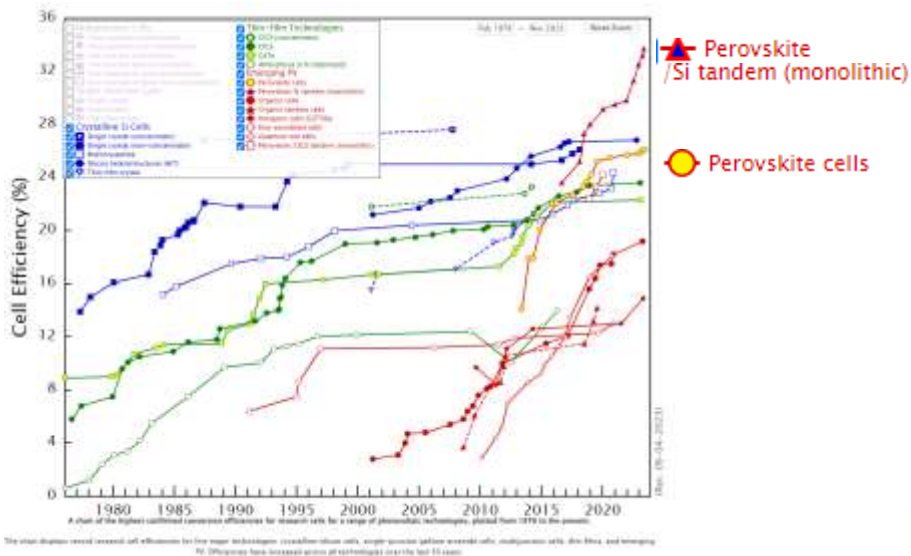
Mechanochemical synthesis of Au MPs/NPs follow a general kinetics profile

Pronounced differences to solution chemistry
Setup approach for OLA nanoparticle investigations

Chem. Commun. 2020, 56, 10329.



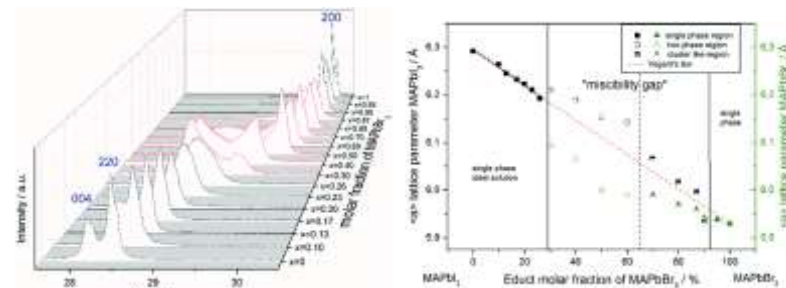
Mechanosynthesis of mixed halide perovskites



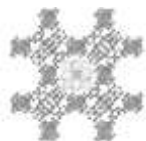
$MAPb(I_{1-x}Br_x)_3$ $r_{Br^-} = 182$ pm, $r_{I^-} = 206$ pm
 ~ 18% difference
 2.4 eV ($MAPbBr_3$) 1.6 eV ($MAPbI_3$)

miscibility gap between $0.29 \leq x \leq 0.92$

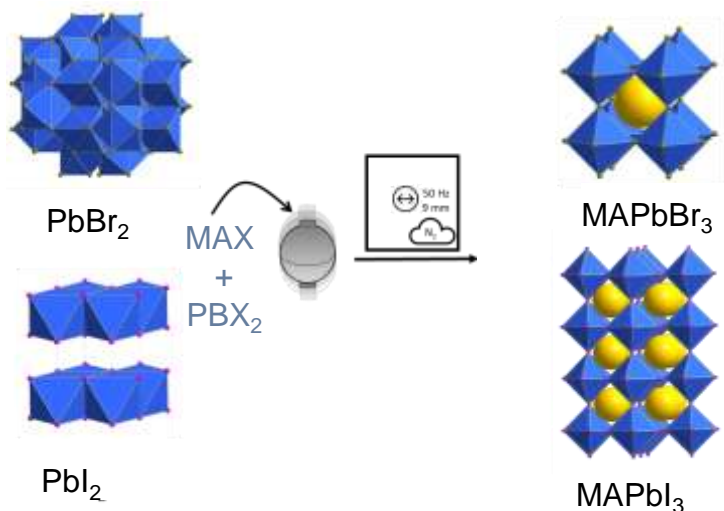
Perovskite solar cells (PSCs) reaching over 26.1% (33,7%) power conversion efficiency



RSC Adv., 2019, 9, 11151.



Mechanosynthesis of mixed halide perovskites



MA = methyl ammonium

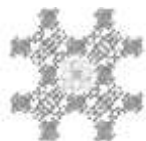
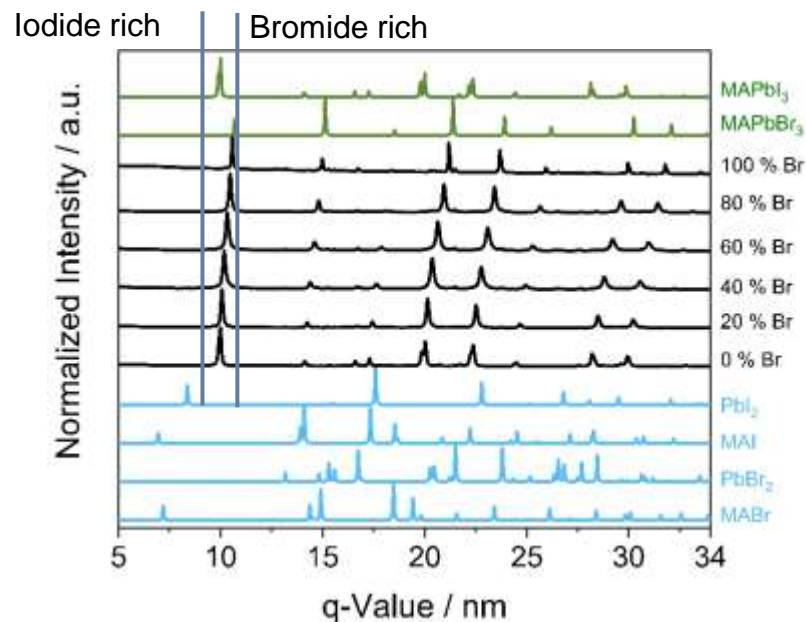
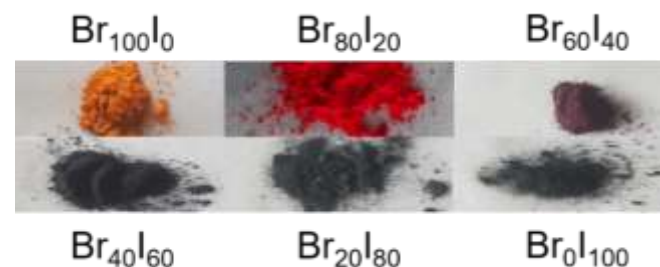
Other examples of mechanochemical synthesis of halide hybrid perovskites:

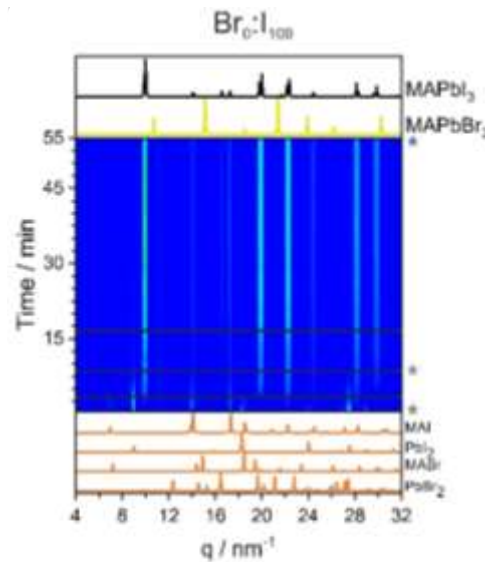
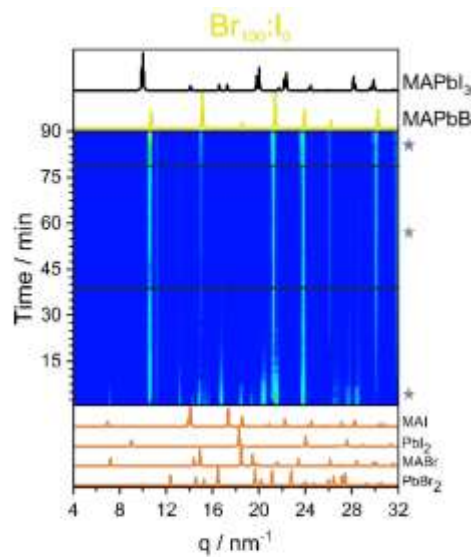
Chem. Eur. J. 2018, 24, 17701.

Chem. Sci. 2018, 9, 3080.

Chem. Eur. J. 2021, 27, 5.

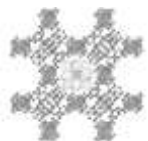
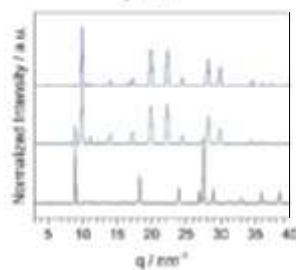
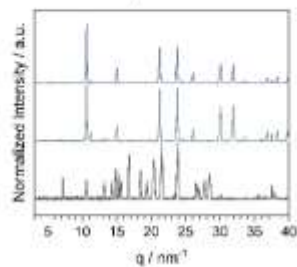
Adv. Energy Mater. 2020, 10, 1902499.

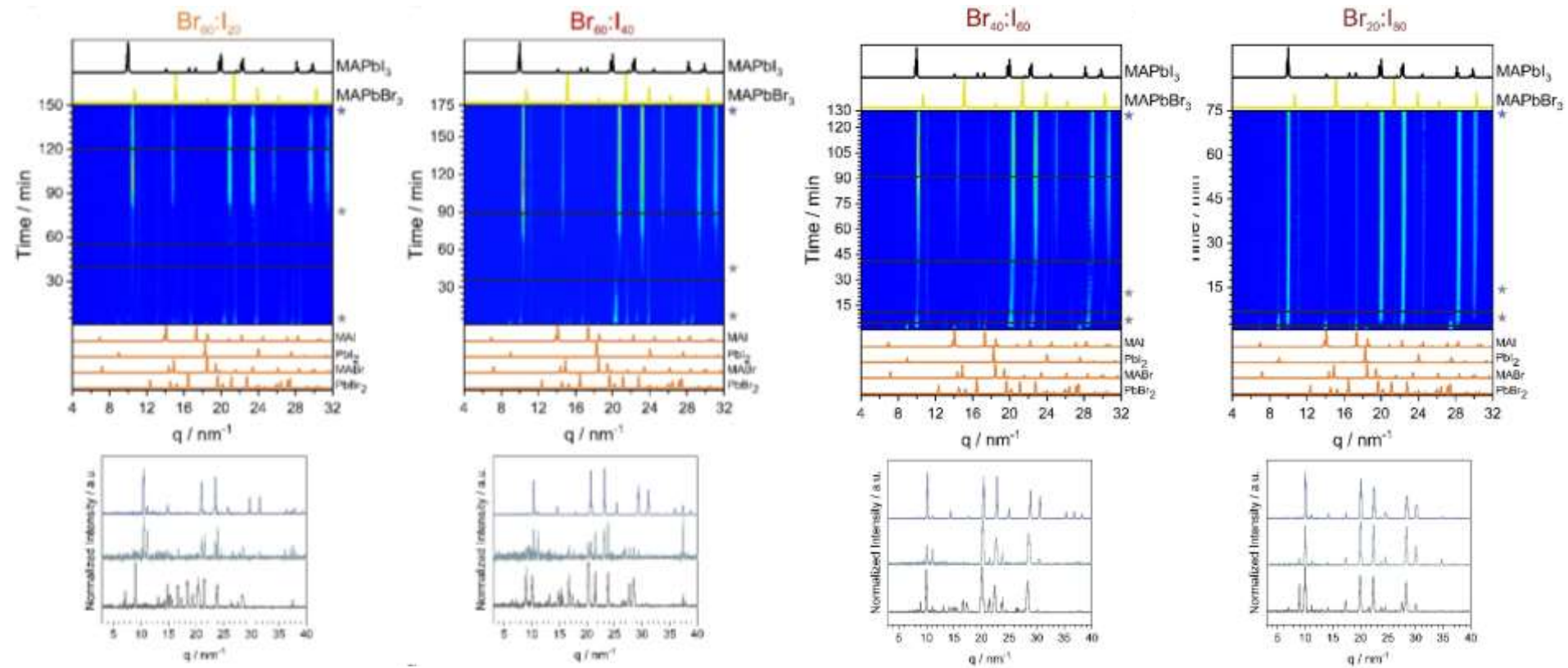




→ Pure phases MAPbBr₃ and MAPbI₃ form directly from starting materials

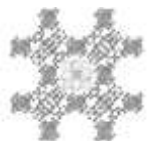
→ Crystallinity increases during prolonged milling

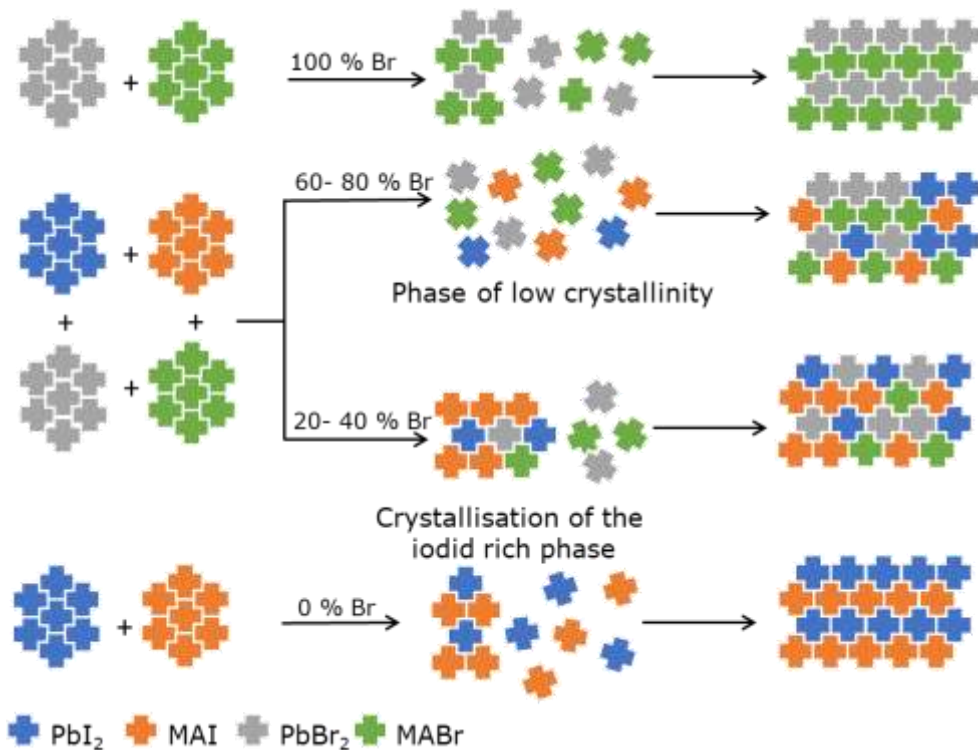




→ 80-60% Br: intermediate phase of lower crystallinity during formation of final structure

→ 60-80% I: initial formation of I-rich phase followed by slow incorporation of Br





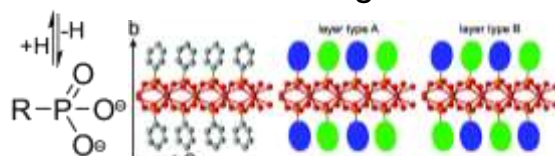
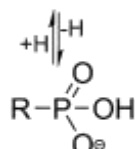
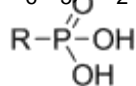
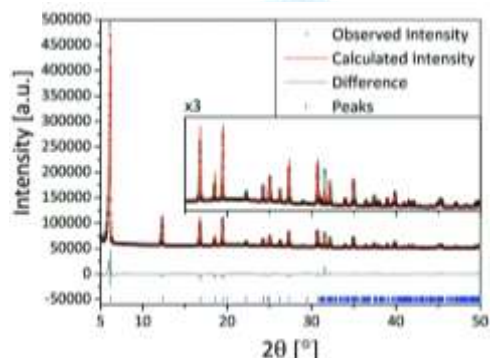
- Mechanochemistry overcomes drawbacks of solution chemistry
- Greater control over stoichiometry & purity
- Three different formation pathways



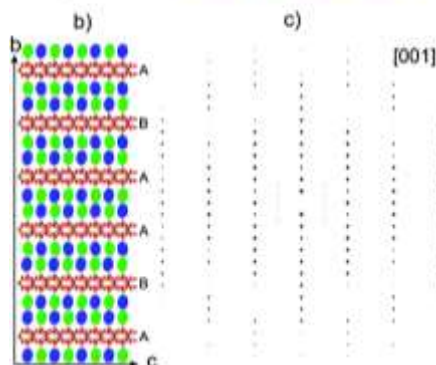
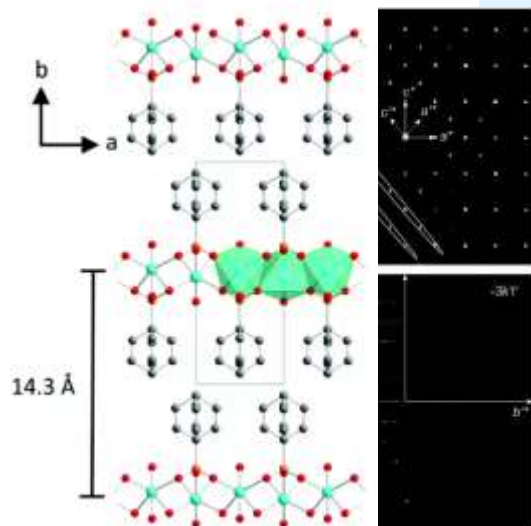
METAL PHOSPHONATES



Metal phosphonates



- ✓ chemical and thermal stability (stable C-P bond)
- ✓ flexible coordination environment
- ✓ high insolubility in many solvents (hard character of the phosphonate oxygen atoms & high coordination affinity for metal atoms)



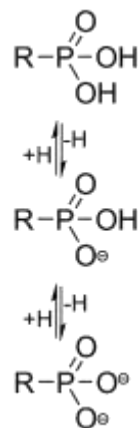
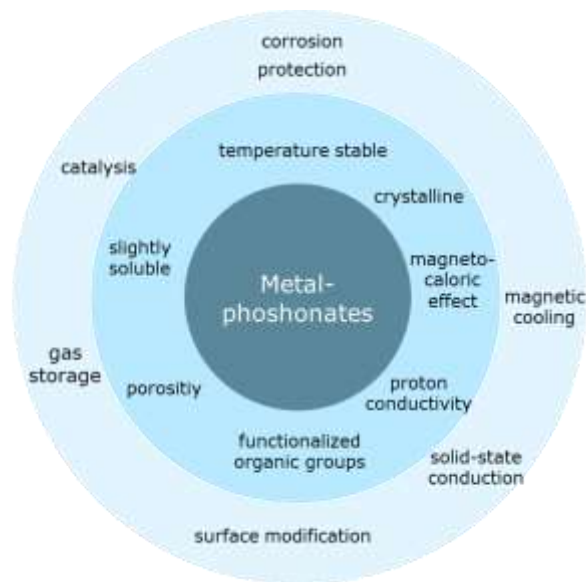
Electron diffraction
in collaboration with
Prof Ute Kolb, Mainz



RSC Adv., 2016, 6, 36011. Dalton Trans., 2016, 45, 9460.

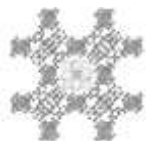
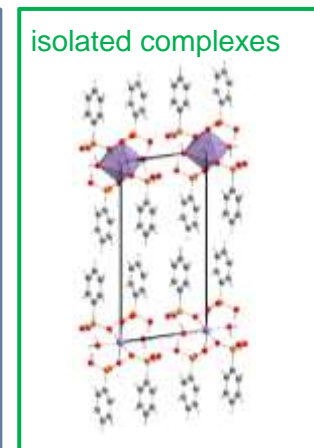
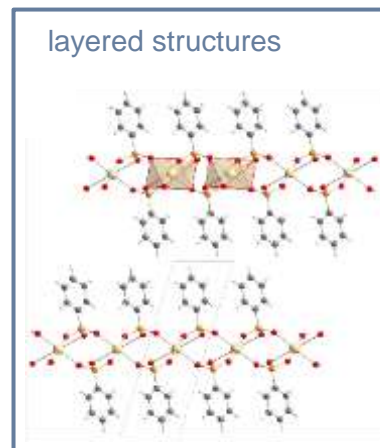
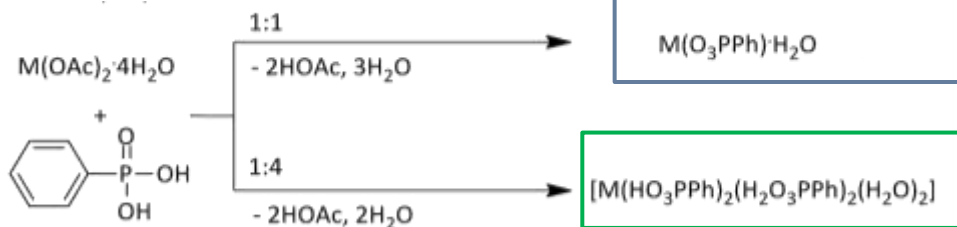


Metal phosphonates

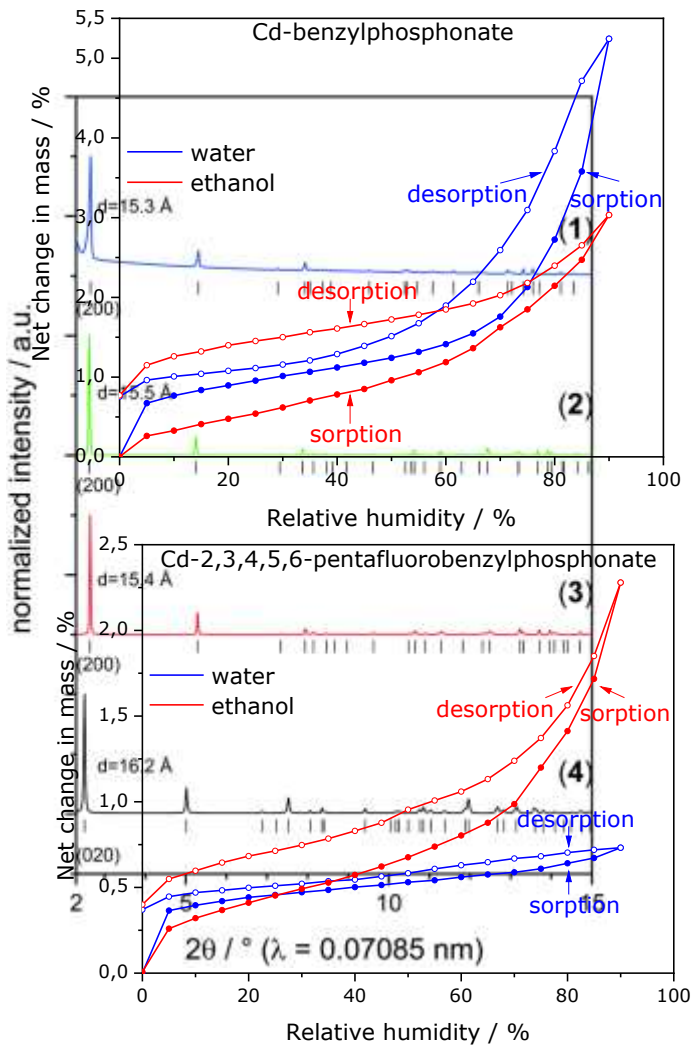
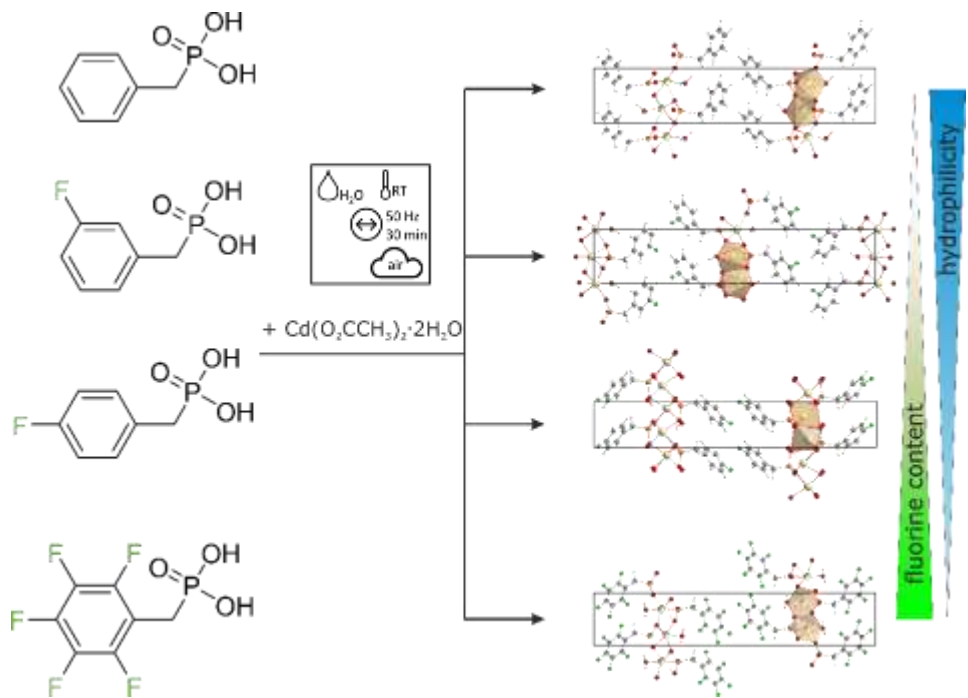


- ✓ stoichiometric control
- ✓ crystalline powder
- ✓ new crystalline (metastable) phases
- ✓ quantitative reactions

M= Zn, Mn, Fe, Co, Ni, Cu



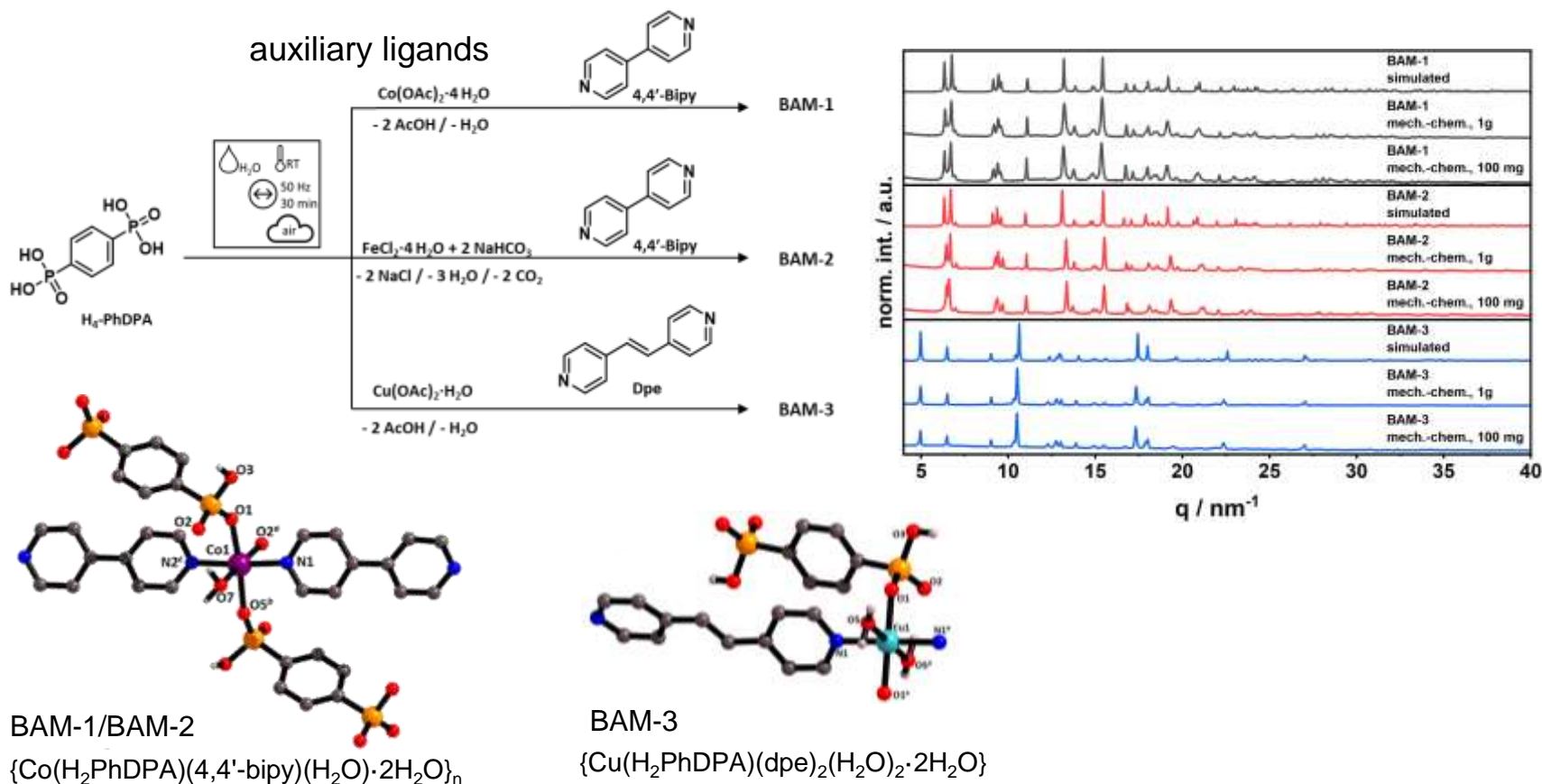
Cadmium benzylphosphonates



CrystEngComm, 2019, 21, 5958.



Metal phosphonates as proton conductors

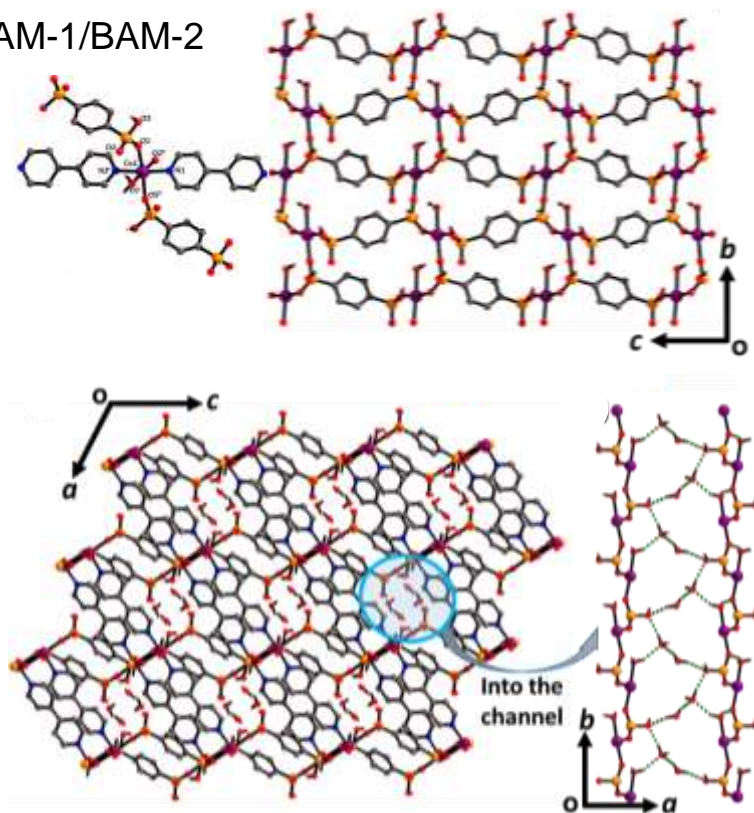


Inorganic. Chem., Inorg. Chem. 2022, 61, 28, 10801–10809.

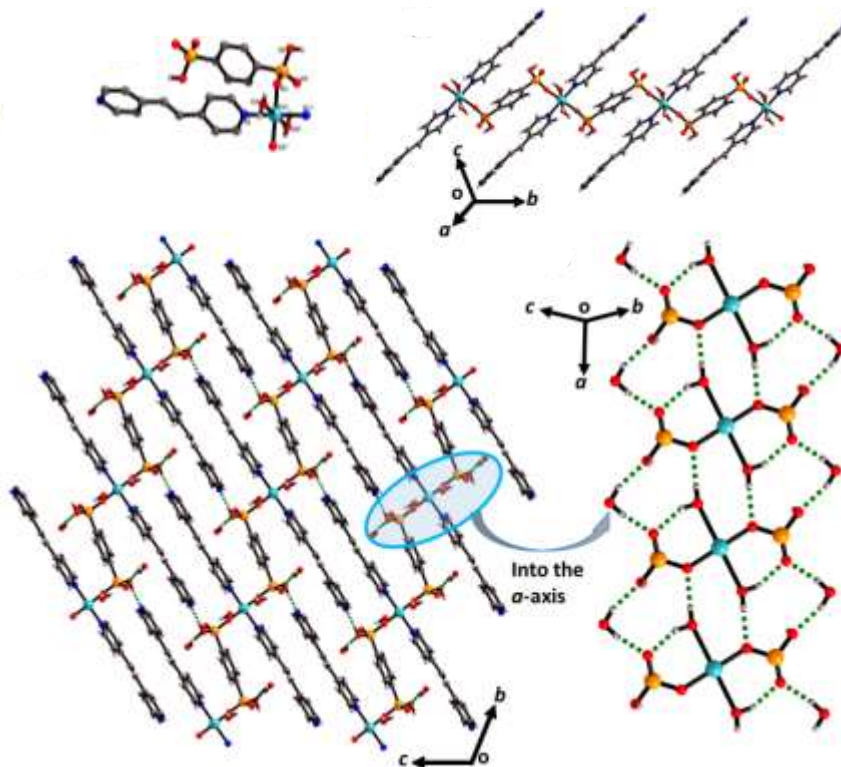


Metal phosphonates

BAM-1/BAM-2

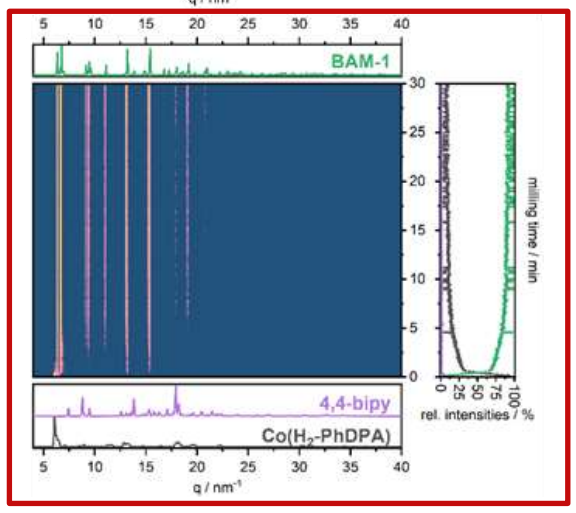
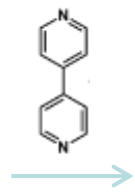
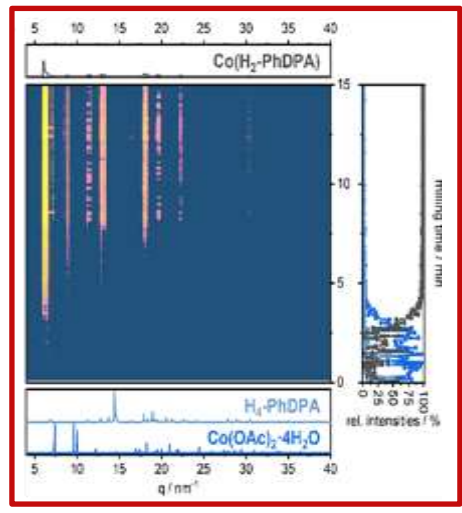
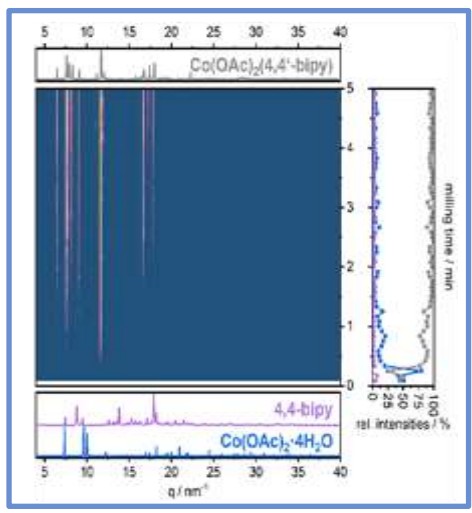
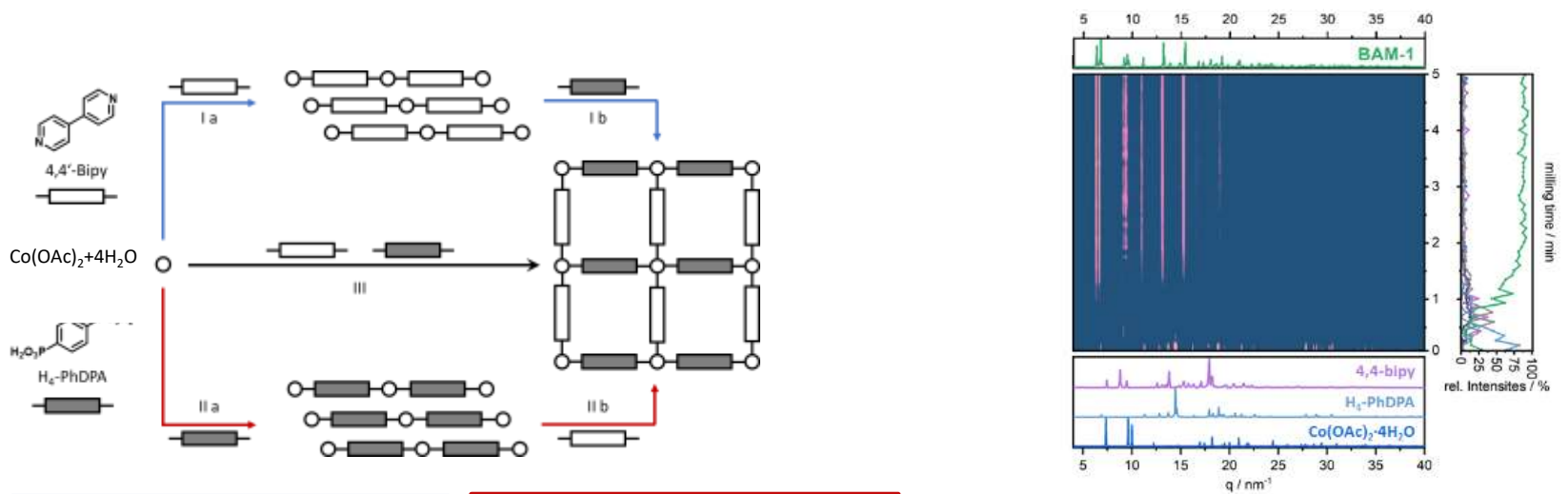


BAM-3

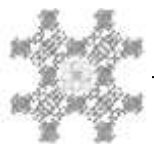


Inorganic. Chem., 10.1021/acs.inorgchem.2c01023.

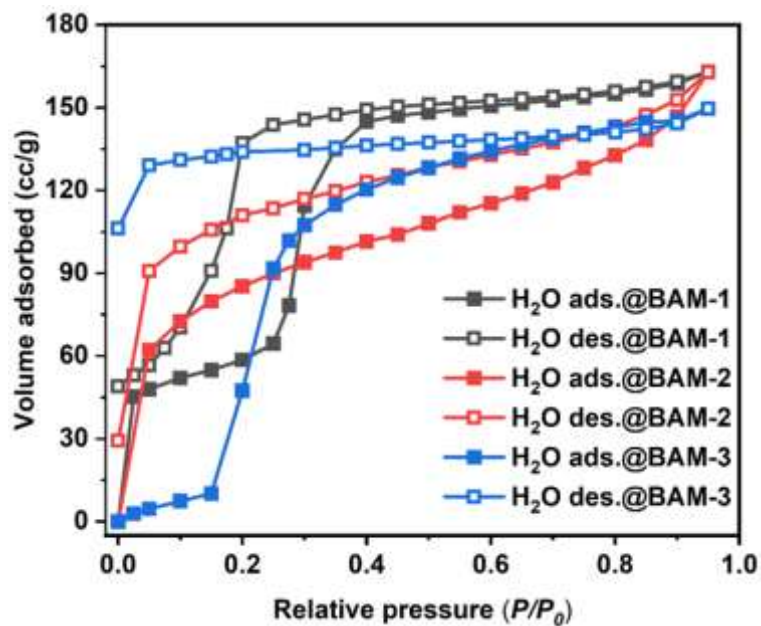




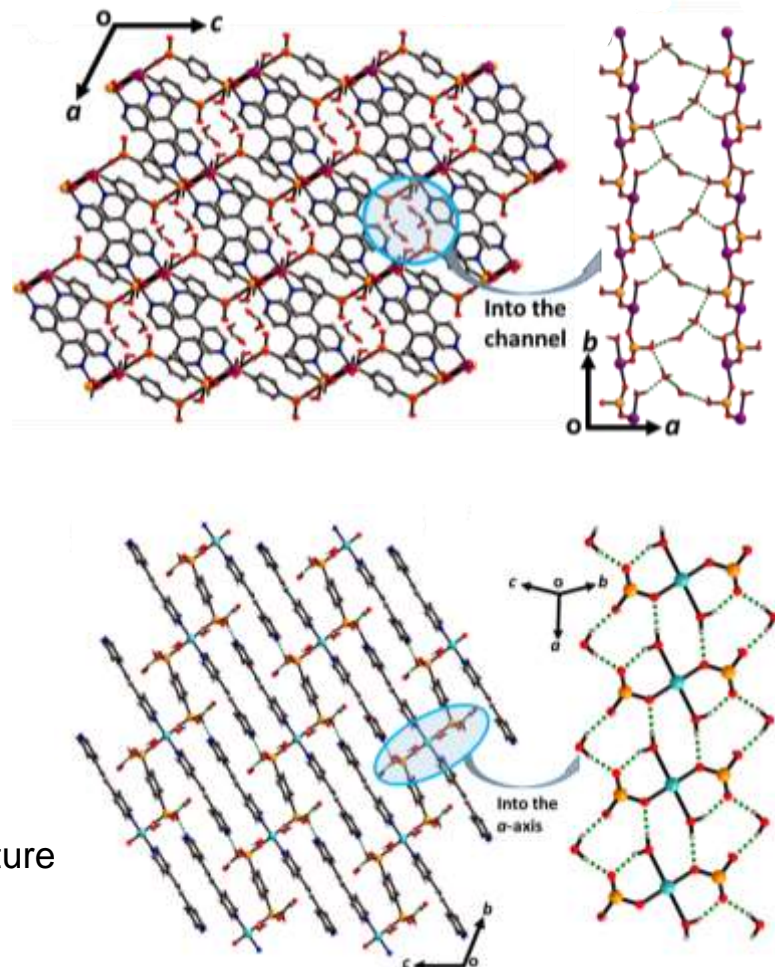
Crystengcomm, under revision



Water uptake

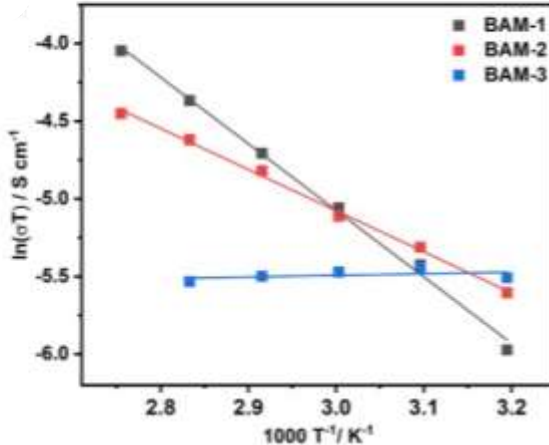
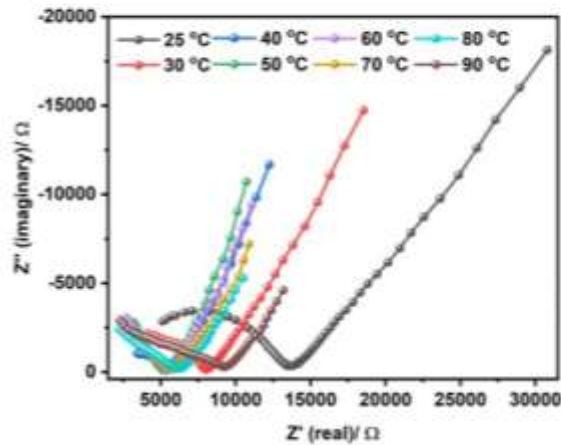
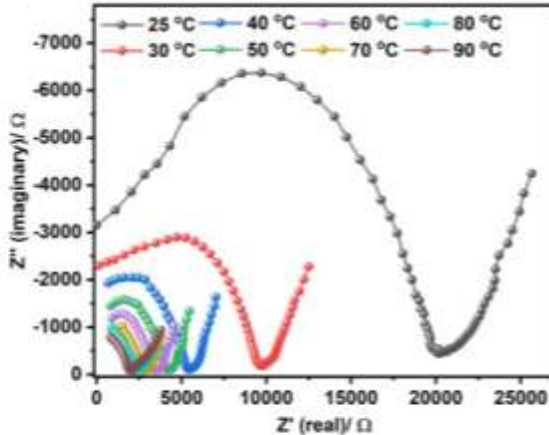
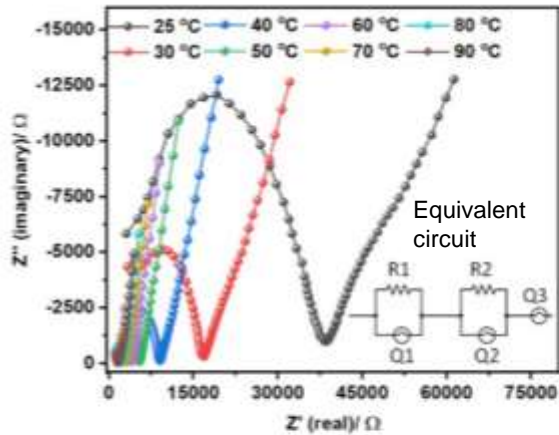


- strong water affinity
- different adsorption isotherms reflect the flexible nature of the frameworks



Inorganic. Chem., 10.1021/acs.inorgchem.2c01023.



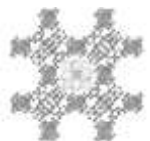


- poor proton conductivity at 25°C & low RH
- increasing conductivity with increasing RH
- at constant RH=98% increasing conductivity with increasing temperature

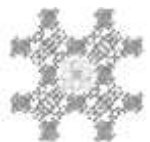
- BAM-1: $4.9 \times 10^{-5} \text{ S cm}^{-1}$
- BAM-2: $4.4 \times 10^{-5} \text{ S cm}^{-1}$
- BAM-3: $1.5 \times 10^{-5} \text{ S cm}^{-1}$

- E_a values below 0.4 eV → proton transfer via proton hopping (Grotthuss mechanism)

Nyquist Plots at 98% RH



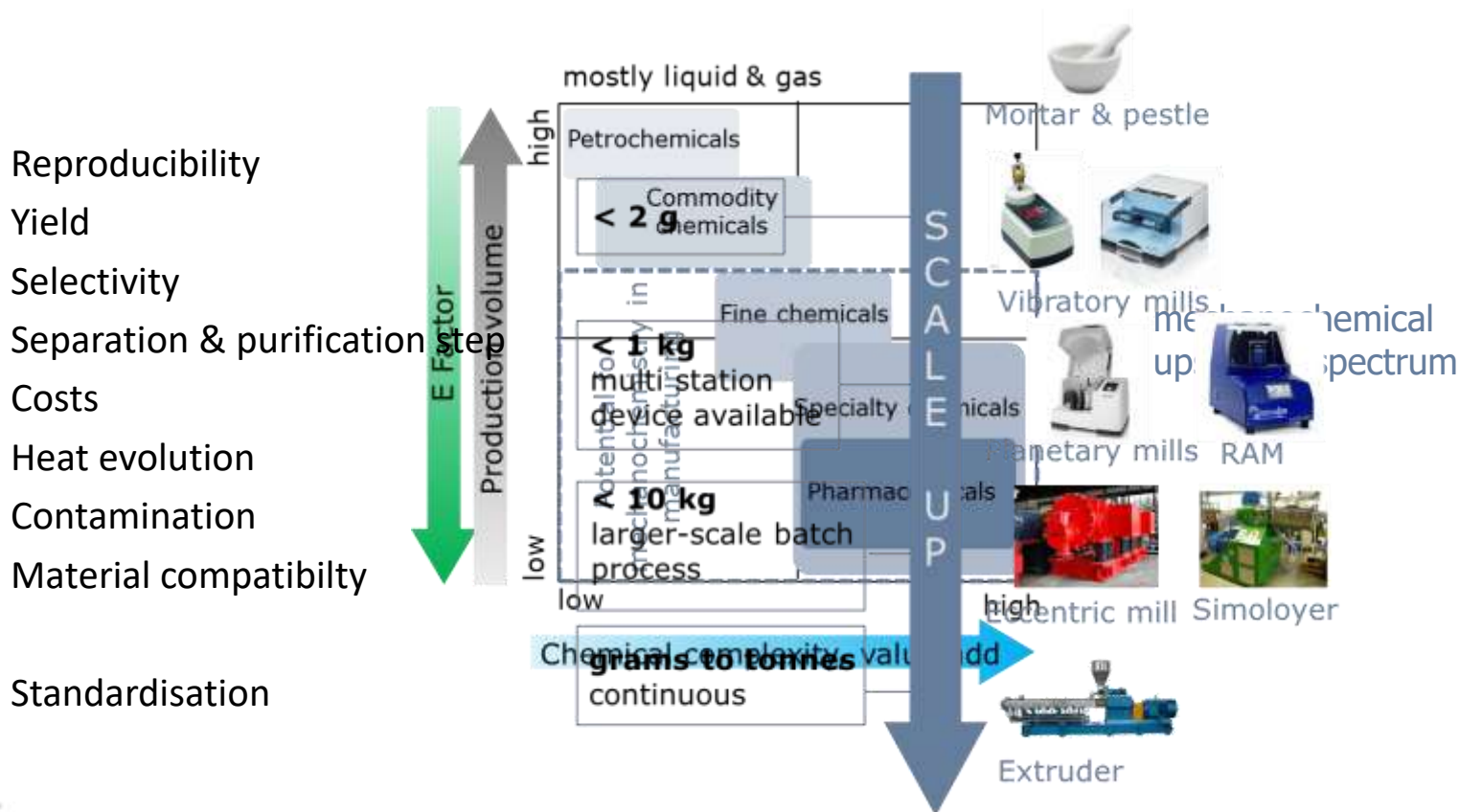
UPSCALING

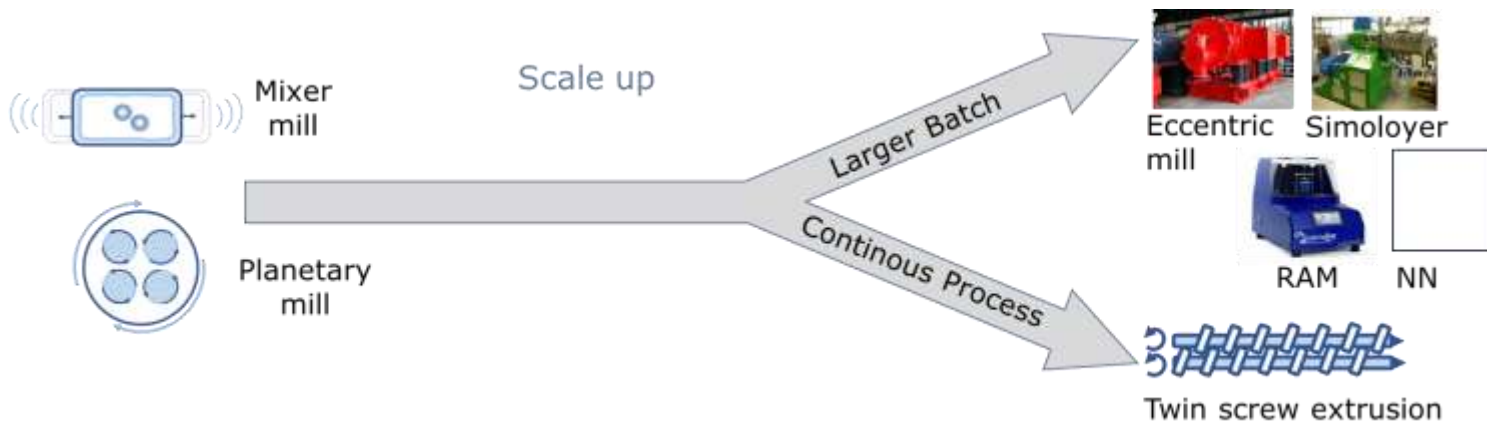


Vision: Sustainable advanced manufacturing

Leveraging and scaling up mechanochemistry for materials synthesis, while effectively addressing the core challenges of sustainability and efficiency.

Innovation in the chemical space by providing an alternative for the synthesis of (new) advanced materials.





Bigger ball mills might not be the answer....

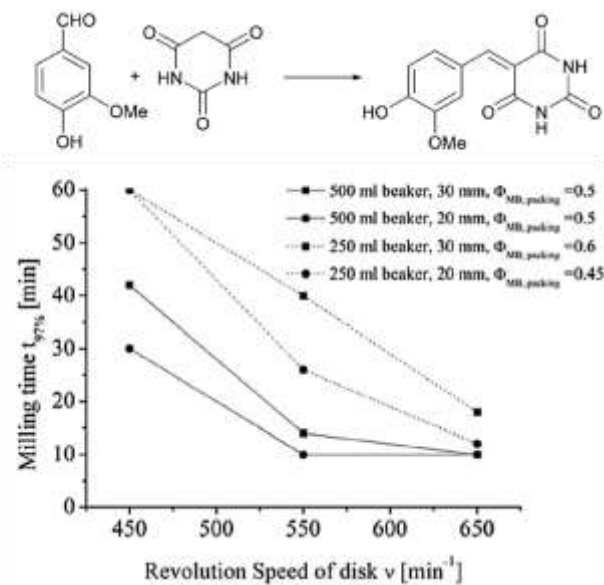
Analysed time to reach 97% yield

Increasing number of balls slows the reaction

→ Less impact energy

Increasing jar volume (fixed powder mass) increases rate

→ More impact energy



Chemical parameters

type of chemical reaction
presence of catalysts or additives
the reagent ratio
presence of low amounts of liquid(s)

Technological parameters

type of ball mill
milling material
number, size of milling balls
filling degree of the milling vessels

Process parameters

operating frequency
reaction time
reaction temperature

A. Stolle et al. Faraday Discuss., 2014, 170, 267



ZIF-8 - a famous MOF

PNAS

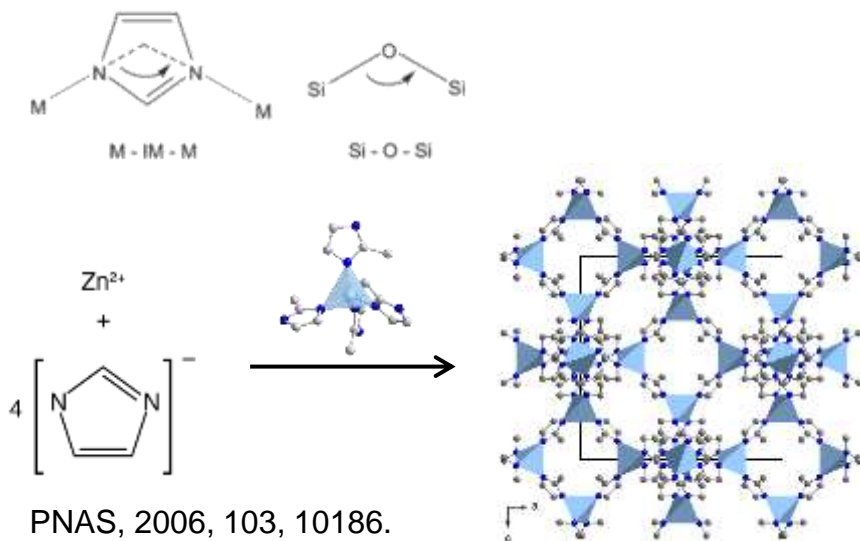
Exceptional chemical and thermal stability of zeolitic imidazolate frameworks

Kyo Sung Park^{*1}, Zheng Ni^{*1}, Adrien P. Côté^{*1}, Jae Yong Choi¹, Rudan Huang⁵, Fernando J. Uribe-Romo^{*2}, Hee K. Chae³, Michael O'Keeffe⁵, and Omar M. Yaghi^{*1}

¹Department of Chemistry and Biochemistry, Center for Reticular Materials Research at California NanoSystems Institute, University of California, Los Angeles, CA 90095; ²Department of Chemistry Education, Seoul National University, Seoul 151-748, Korea; ³Institute for Chemical Physics, School of Science, Beijing Institute of Technology, Beijing 100081, People's Republic of China; and ⁴Department of Chemistry, Arizona State University, Tempe, AZ 85287

Edited by Jack Halpern, University of Chicago, Chicago, IL, and approved May 22, 2006 (received for review March 26, 2006)

Typical ZIF Synthesis. (ZIF syntheses are exemplified here by the synthesis of ZIF-8; see Section S1 in *Supporting Appendix* for detailed synthetic procedures for all ZIFs.) A solid mixture of zinc nitrate tetrahydrate $\text{Zn}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (0.210 g , $8.03 \times 10^{-4} \text{ mol}$) and 2-methylimidazole (H-MeIM) (0.060 g , $7.31 \times 10^{-4} \text{ mol}$) was dissolved in 18 ml of DMF in a 20-ml vial. The vial was capped and heated at a rate of $5^\circ\text{C}/\text{min}$ to 140°C in a programmable oven and held at this temperature for 24 h, then cooled at a rate of $0.4^\circ\text{C}/\text{min}$ to room temperature. After removal of mother liquor from the mixture, chloroform (20 ml) was added to the vial. Colorless polyhedral crystals were collected from the upper layer, washed with DMF ($10 \text{ ml} \times 3$), and dried in air for 10 min (yield: 0.032 g , 25% based on H-MeIM). The product was formulated by using elemental microanalysis as $\text{Zn}(\text{MeIM})_2 \cdot (\text{DMF}) \cdot (\text{H}_2\text{O})_3$ ($\text{C}_{11}\text{H}_{23}\text{N}_5\text{O}_4\text{Zn}$; Calcd. C, 37.25; H, 6.54; N, 19.74. Found. C, 37.69; H, 5.22; N, 19.58). The purity of ZIF-8 product has also been confirmed by PXRD analysis (see Section S3 in *Supporting Appendix*).



→ Approx 30 h, DMF, CHCl_3
Yield: 25%

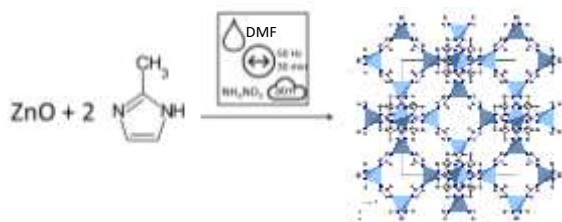


ZIF-8 & mechanochemistry



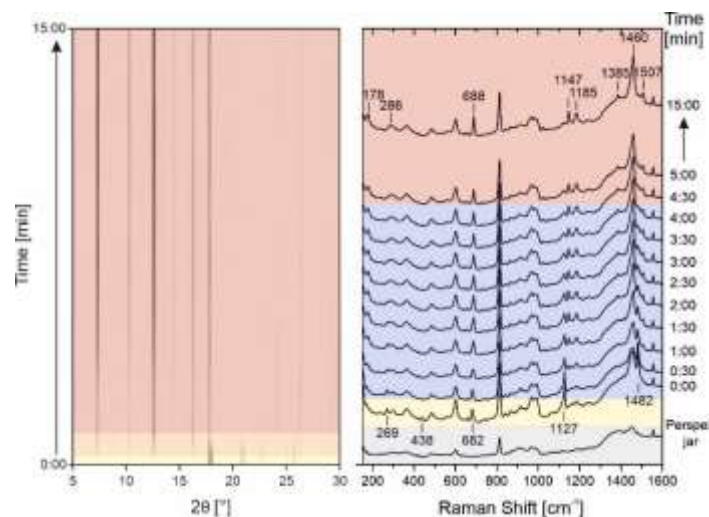
First setup

1 g



ZnO, 2-methylimidazole

ILAG conditions

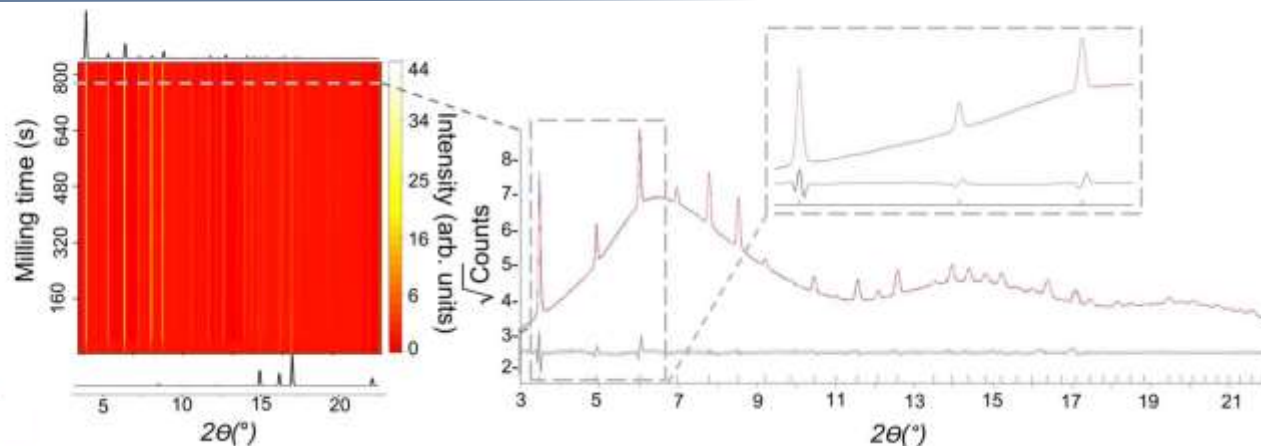


Angew. Chem. Int. Ed. 2015, 54, 1799.

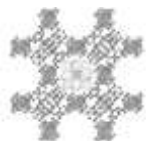


Optimized setup

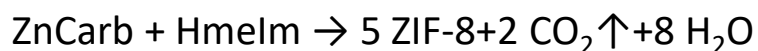
70 mg



Nat. Commun. 2021, 12, 6134.

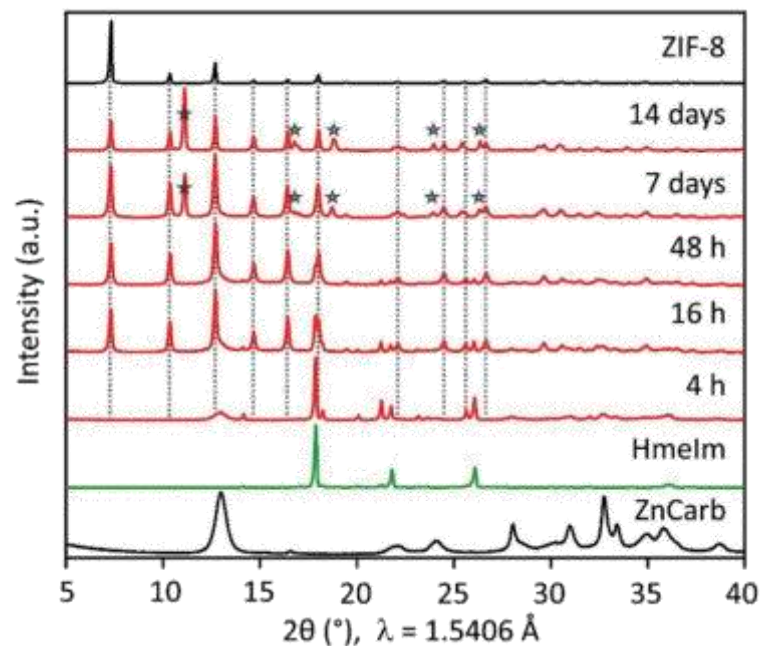
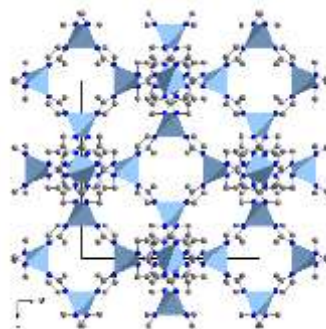


„Mix and wait“ synthesis of ZIF-8



Hmelm = 2-methylimidazole ($\text{C}_4\text{H}_6\text{N}_2$)

ZnCarb = $\text{Zn}_5(\text{CO}_3)_2(\text{OH})_6$

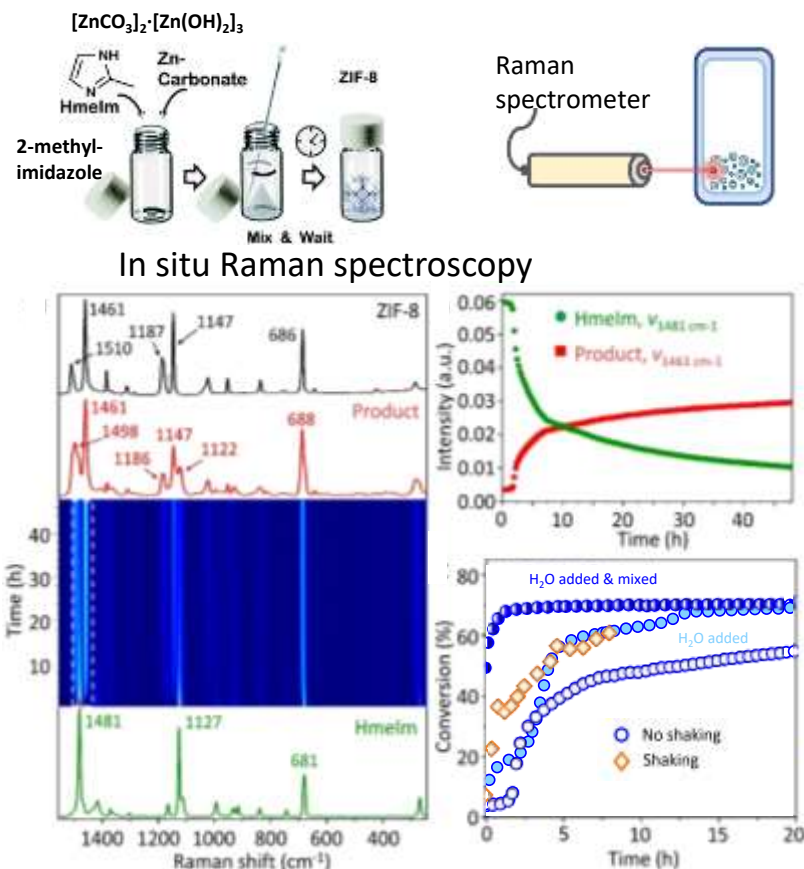


Side phase ★ $\text{Zn}(\text{melm})_2 \cdot \text{ZnCO}_3$

RSC Adv., 2022, 12, 8940.

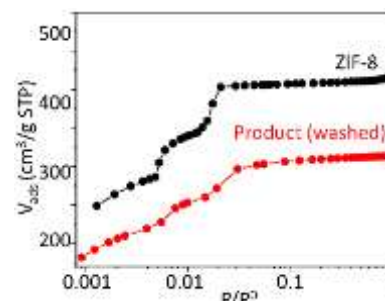


Mix and wait – synthesizing MOFs

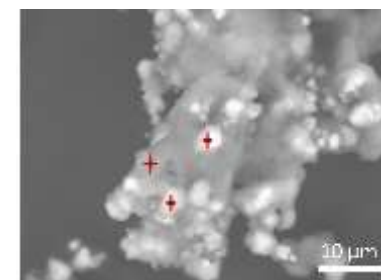


RSC Adv., 2022, 12, 8940.

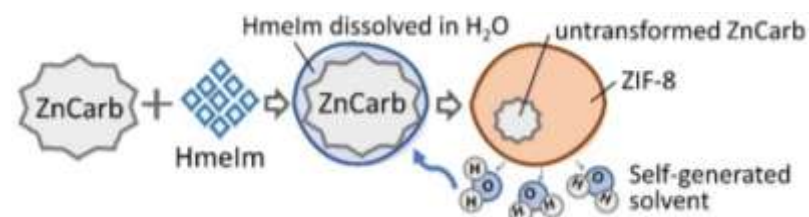
N₂ adsorption



SEM with EDX



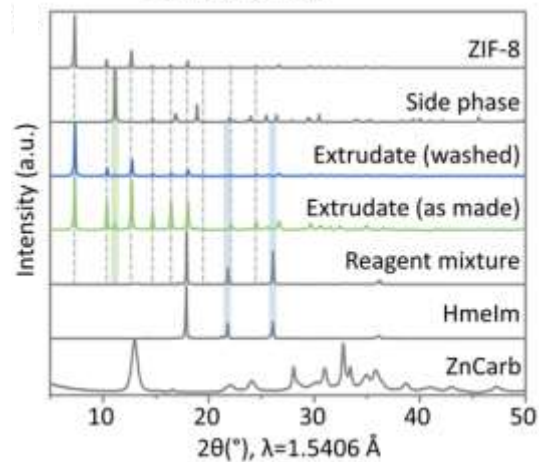
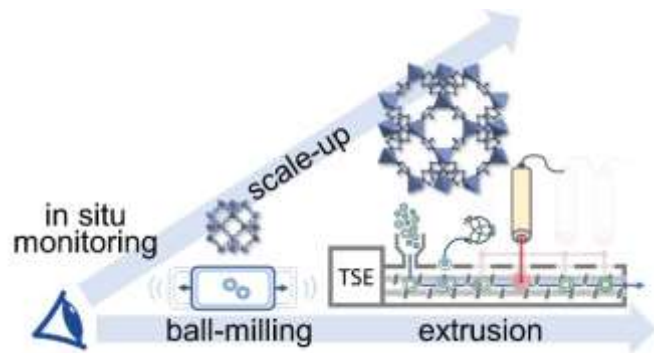
Suggested mechanism



→ Reaction accelerated by released water acting as solvent for Hmem

→ Shaking & addition of water increase reaction rate & minimise t_{ind}





Batch reaction

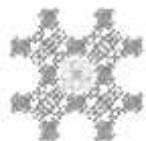


Continuous process

PMMA laser-transparent windows

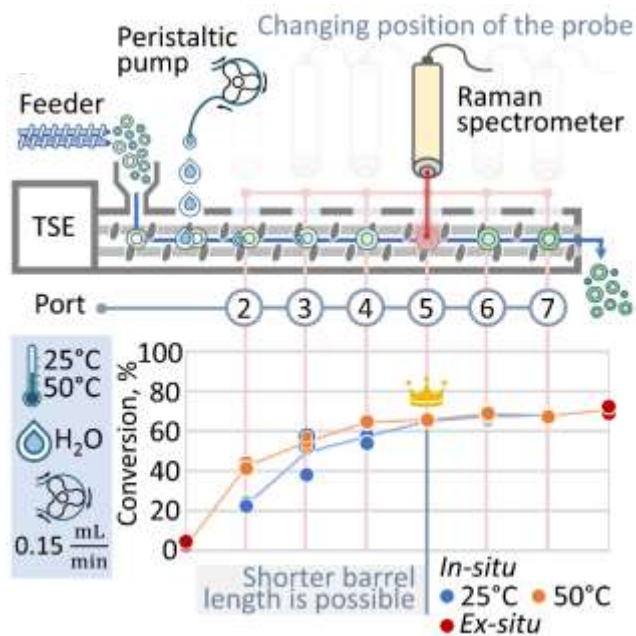


ACS Sust. Chem. Eng. 2023, 11, 13, 5175–5183.

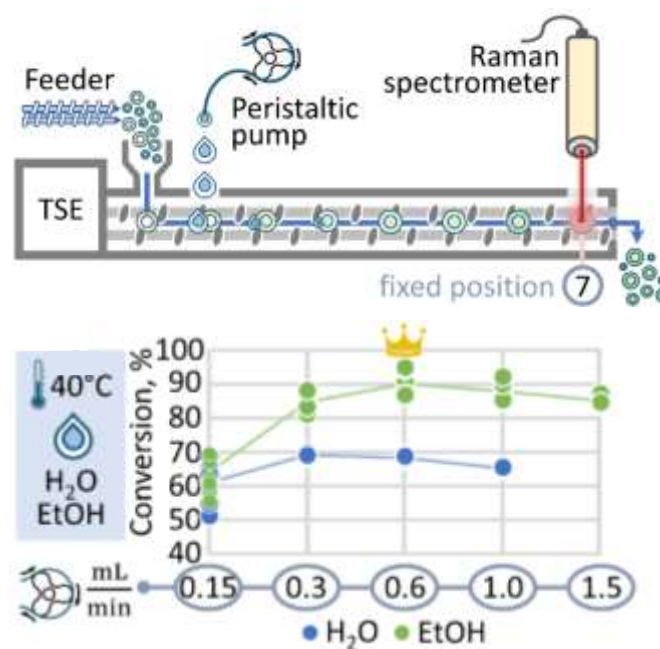


Optimization of the ZIF-8 extrusion

Effect of the barrel length



Effect of the liquid

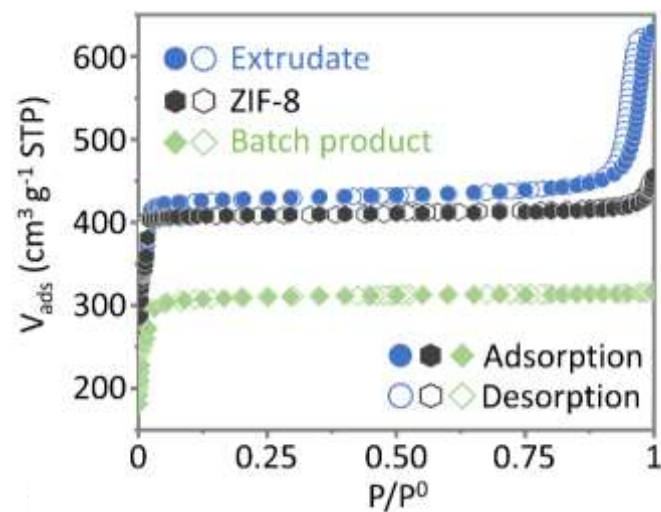
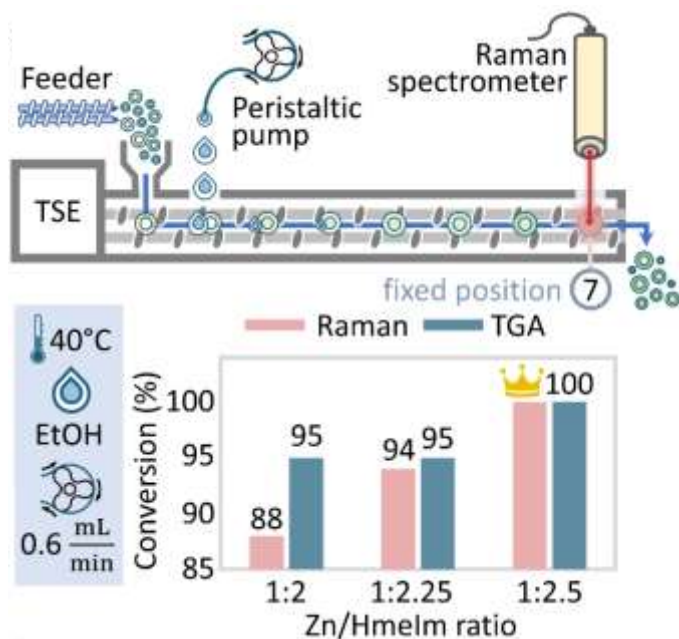


EtOH no side phase and higher conversion

ACS Sust. Chem. Eng. 2023, 11, 13, 5175–5183.

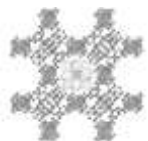


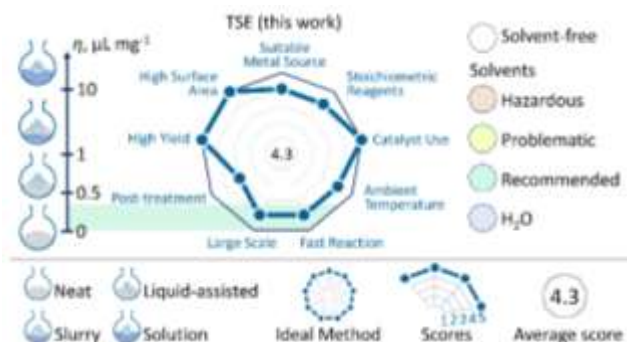
Optimization of the ZIF-8 extrusion



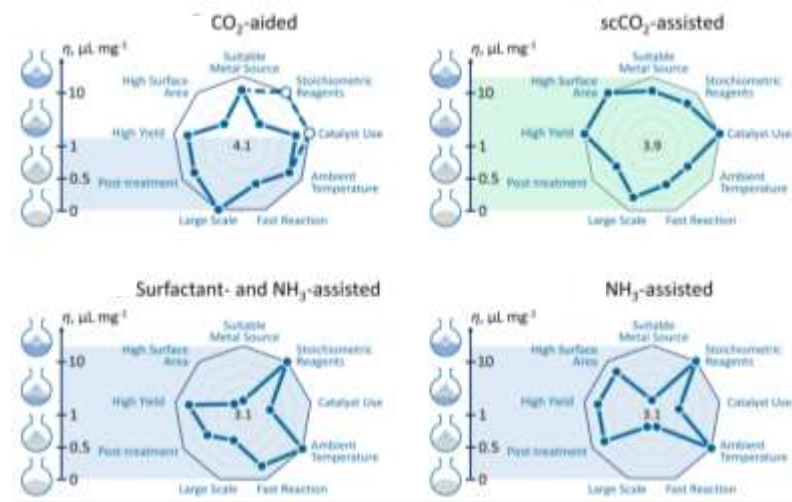
- ✓ Production rate: 2 g/min or 2.9 kg/day
- ✓ BET surface area 1816 $\text{m}^2 \text{g}^{-1}$
- ✓ Quantitative yield

ACS Sust. Chem. Eng. 2023, 11, 13, 5175–5183.

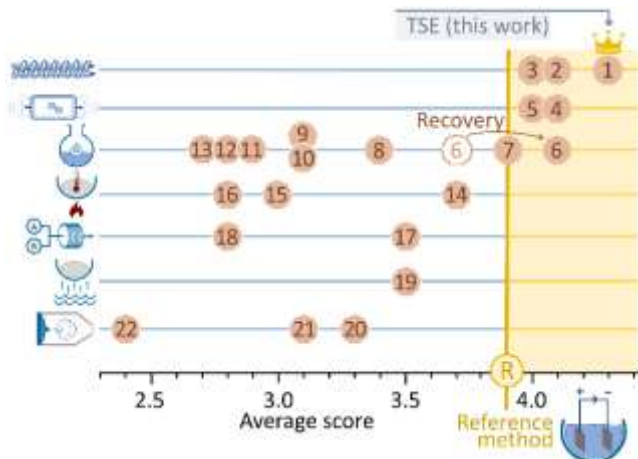




Solvent-based batch reactions

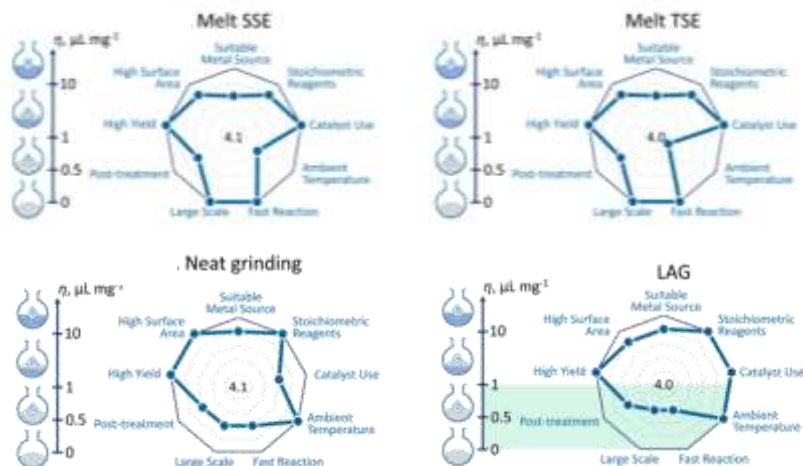


Charts for comparing the environmental friendliness and scalability of different synthetic approaches



Extrusion

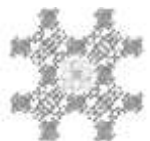
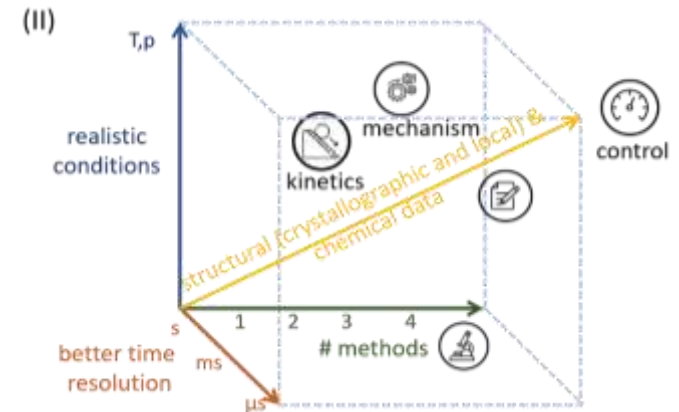
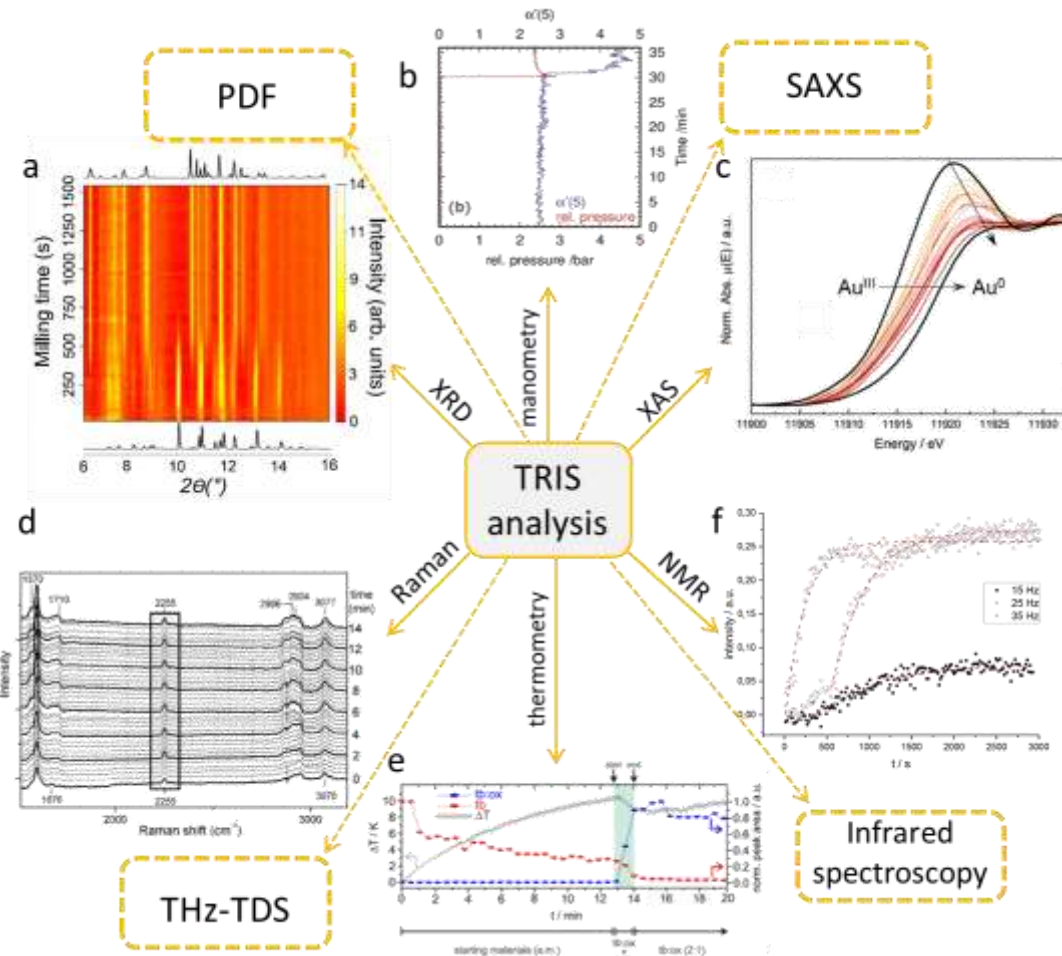
Ball-milling



ACS Sust. Chem. Eng. 2023, 11, 13, 5175–5183.



Future steps?



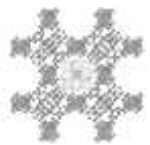
Where are we now? - Main achievements

- ✓ A large variety of reactions has been documented: highly selective, with yields approaching 100%, ecologically friendly, economically acceptable
- ✓ Examples of successful scaling-up and industrial applications
- ✓ New instrumentation has been developed time resolved *in situ* monitoring of
- ✓ Organic mechanochemistry seems to be now more “fundamental” than the “classical” inorganic mechanochemistry
- ✓ Mechanochemistry is established in chemistry, materials science, pharmaceutical industry, catalysis, green chemistry, etc. (ACIE, Nature, Science, ChemSci, JACS, RSC journals and many other).



Conlusions & Perspective

- There is still a lot to learn. Factors influencing mechanisms and rates of solid-phase reactions are complex.
- Time resolved in situ methods will (& must) continue to develop.
- New techniques will broaden the available toolbox.
- Refined sampling procedures & data collection strategies and will provide new and additional information for understanding mechanochemical processes.
- The full potential of mechanochemical methods will be realised... and will change the world.



Topics for student talks

- PET Recycling -> New Polymorphs
- MOF Synthese
- Mechanochemical Synthesis of APIs
- -...

