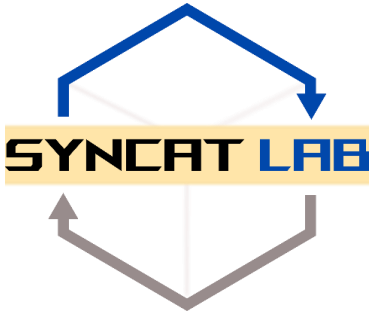
IASOC - Ischia Advanced School of Organic Chemistry

September 17-21, 2026



Shaping the Future of Mechanochemistry with High-Throughput Experimentation and Machine Learning

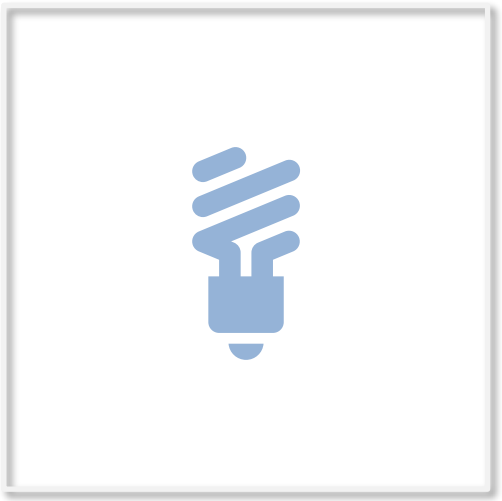
Luca Capaldo

Dept. of Chemistry, Life Sciences and Environmental Sustainability
University of Parma (UNIPR)

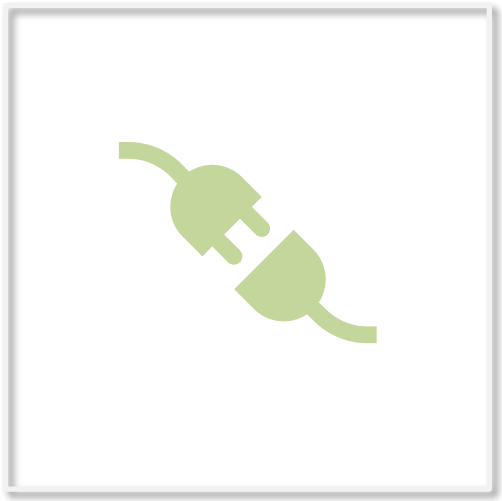
luca.capaldo@unipr.it

Research at SynCat Lab

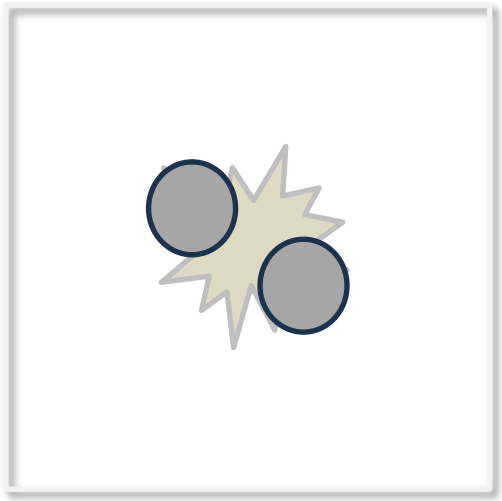
Develop synthetic methodologies driven by sustainable energy



JACS Au **2025**, *5*, 3491–3499
Green Chem. **2025**, *27,* 14799-14806
Nat. Commun. **2024**, *15*, 4028
Chem. Sci. **2024**, *15*, 14844-14850
JACS **2023**, *145*, 991–999



ACIE **2023**, *62*, e202315881
CC **2021**, *57*, 4424-4427



Nat. Commun. **2026**, *17*, 8559
CSC **2025**, *18*, e202500461
CSC **2025**, *18*, e202500211

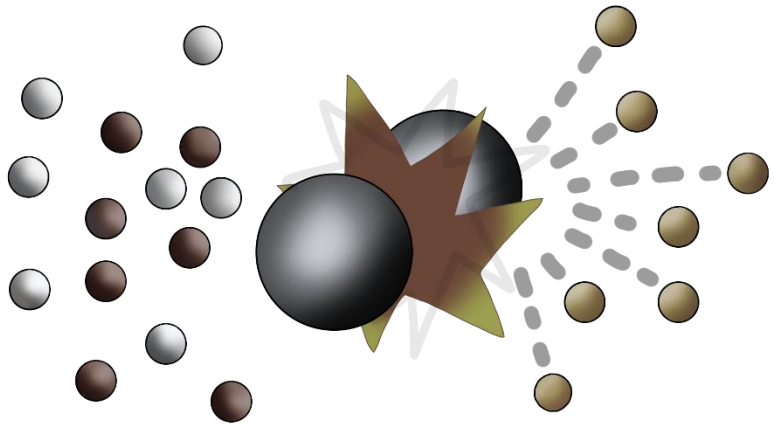
Mechanochemistry

Mechanochemistry studies the effects of mechanical energy forces on physicochemical changes and transformations.

NEWS

lupac names 10 chemistry innovations that will change the world

BY KATRINA KRÄMER | 3 APRIL 2019



Solvent minimization

Unconventional reactivity

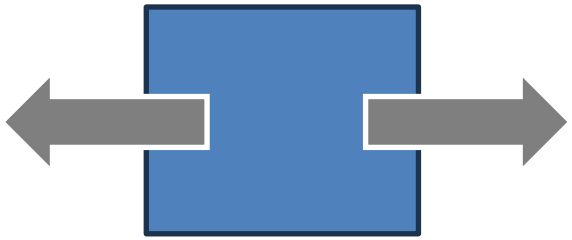
Alternative selectivity

Faster reactions

Insoluble reactants

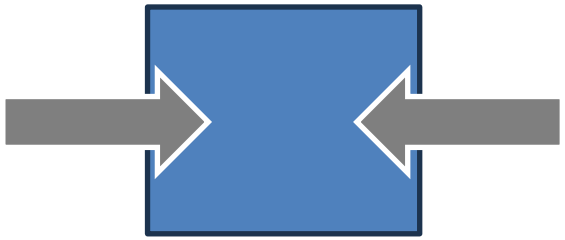
Friščić: *ACIE* **2020**, 59, 1018 | Emmerling: *ACIE* **2024**, 63, e202414745 | Uzarevic: B., *Nat. Rev. Chem.* **2023,** 7, 51 | James: *Chem. Soc. Rev.* **2012**, *41*, 413

Mechanical forces



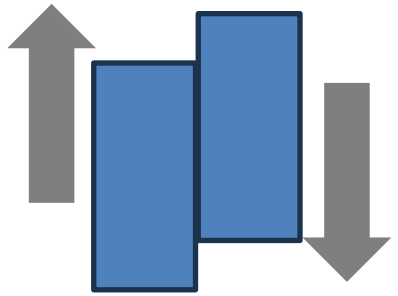
Pulling forces

(sonication)



Compressing forces

(ball milling)



Shearing forces

(friction)

The tools of a mechanochemist



Mortar & pestle

Simple
Low cost

Intermittent operation
Reproducibility
scalability



Mixer mill

High energy input
Automated operation
High reproducibility

Moderate cost
Expensive jars
Scalability



Planetary mill



Twin screw extruder

Scalability
Automated operation
Adjustable temperature

High cost
Torquing out

The tools of a mechanochemist



Mortar & pestle

Simple
Low cost

Intermittent operation
Reproducibility
scalability



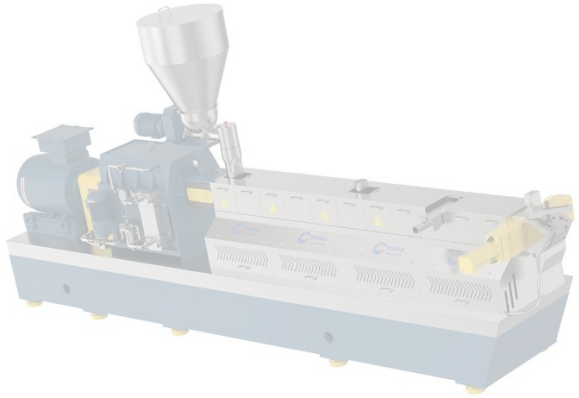
Mixer mill

High energy input
Automated operation
High reproducibility

Moderate cost
Expensive jars
Scalability



Planetary mill



Twin screw extruder

Scalability
Automated operation
Adjustable temperature

High cost
Torquing out

Ball mills are a standard equipment for inorganic synthesis





Weigh

Load the jar

Seal the jar

Shake

Work-up

Lenghty structural analysis

Ball mills are a standard equipment for ~~in~~organic synthesis?





Weigh

Load the jar

Seal the jar

Shake

Work-up

fast analysis

X 50

Key disconnect remains between this growing potential and the workflows used for reaction development

Critical challenges

Solution-phase synthesis uses HTE, while mechanochemistry is conducted via through sequential, low-throughput workflows.

Renders mechanochemistry less competitive than other enabling technologies.

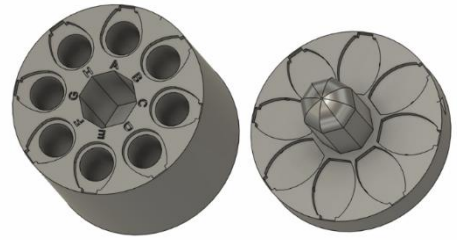
Hampers integration with automation and machine learning capabilities

Severely impacts reaction optimization and time-resolved studies (kinetic studies)



Active Learning

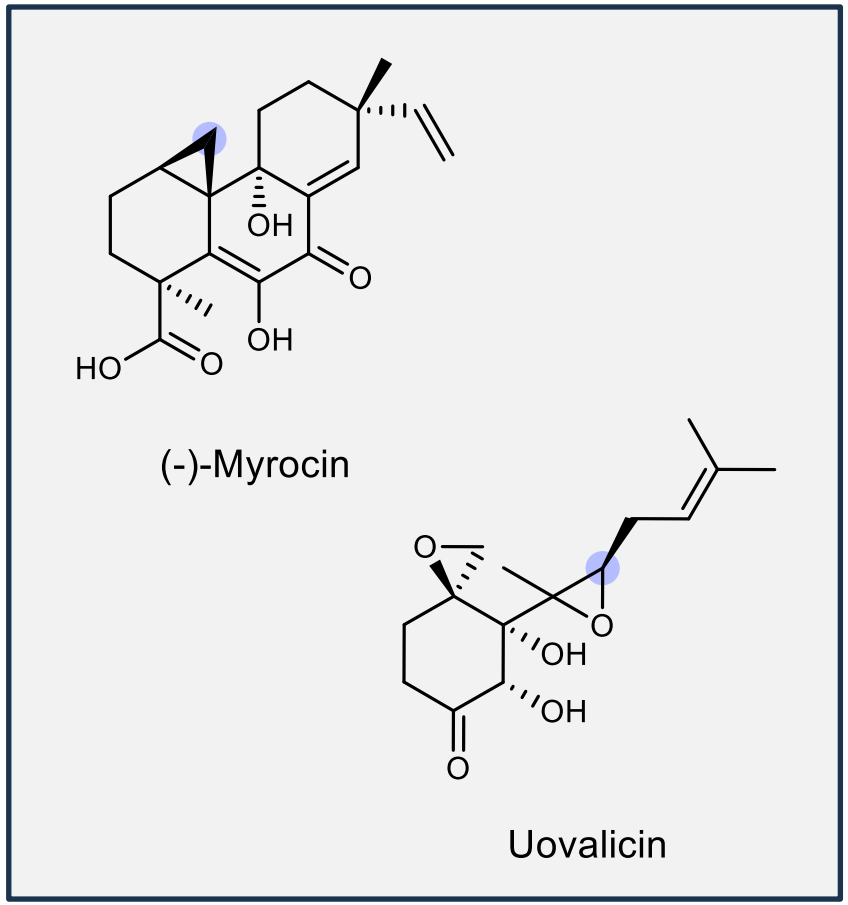
Nat. Commun. **2026**, *17*, 8559

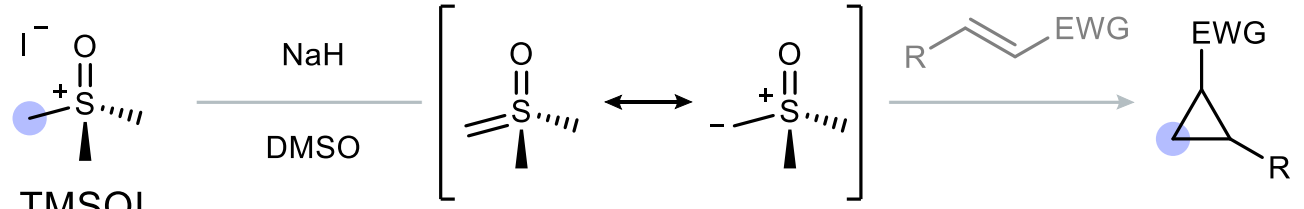


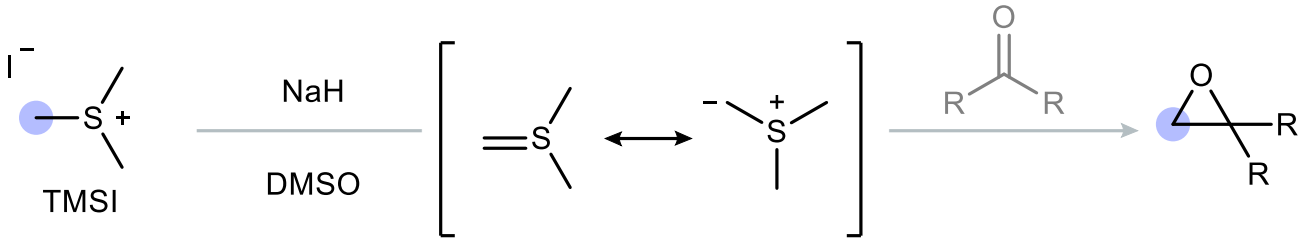
Miniaturized milling

ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

The Johnson-Corey-Chaykovsky reaction







Key limitation using solution chemistry

high-boiling solvent explosive mixture

pre-formation of ylide long reaction time

NaH/DMSO system

Corey, Chaykovsky: *JACS* **1962**, *84*, 866 | For a P-ylide mechanochemical process see: Templ, Schnürch: *ACIE* **2024**, *63*, e202411536

Active learning for reaction optimization

LAG agent

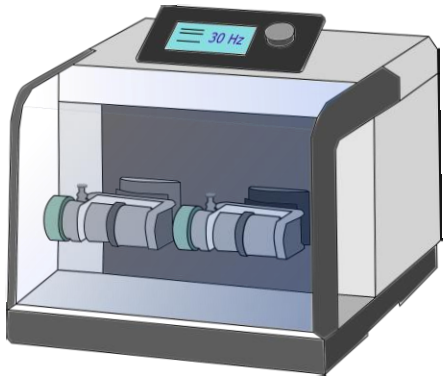
Grinding agent

Frequency

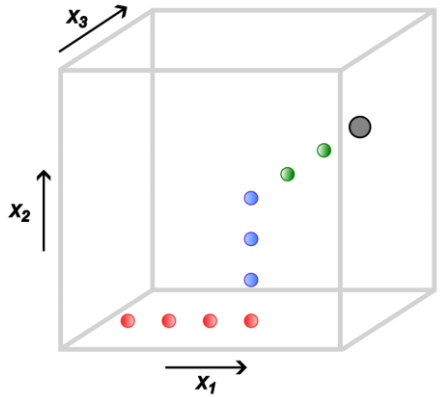
Jar & ball materials

Reaction time

Stoichiometry



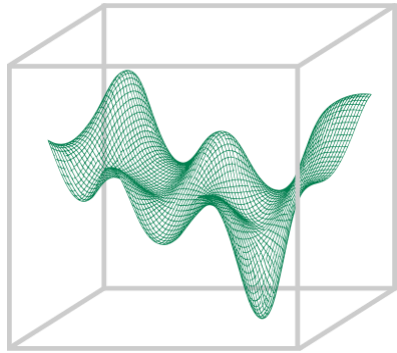
OVAT approach



Empirical optimization
Suboptimal reaction conditions

[State-of-the-art]

Bayesian Optimization



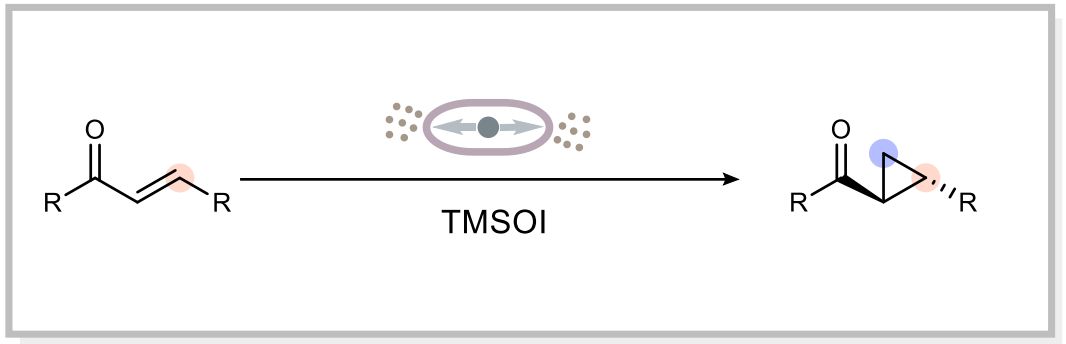
Data-driven reaction optimization
Unbiased exploration of reaction space

[Underexplored]

Strategy: instead of screening everything, which single experiment will teach us the most?

Model	Selection	Experiment	Update
Predict outcome + uncertainty	Most informative condition	Run the suggested experiment	Retrain the model

Optimization of the JCC cyclopropanation



Yield

PMI value

Reaction parameters

Base type ('KOH' or 'KO^{t}Bu')

Base loading (0-2 equiv.)

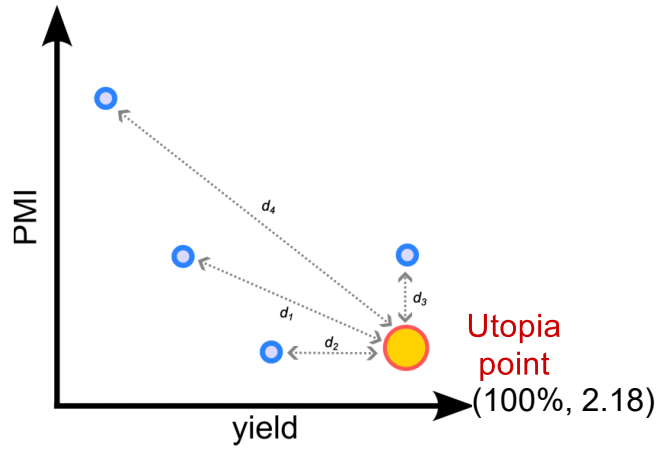
Reaction time (0-300 s)

Frequency (3-30 Hz)

LAG ('CH_3CN' or 'DMSO')

Amount of LAG (0-1 μL/mg)

Utopia Point Bayesian Optimization (UPBO)

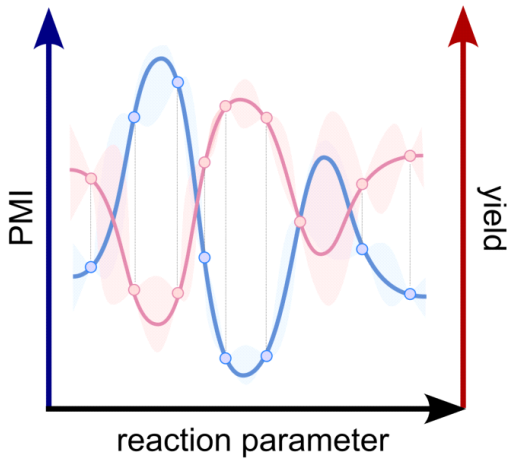


$d = f(x) = \sqrt{(x-x')^2 + (y-y')^2}$

$x^* = \text{argmin}(d)$

vs

Multiobjective Bayesian Optimization (MOBO)



$x^* = \text{argmin}(PMI)$

$x^* = \text{argmax}(yield)$

Optimization of the JCC cyclopropanation

UPBO
Utopia Point Bayesian Optimization

Pros
- Simple and intuitive
- Converts multiple objectives into one

Cons
- Sensitive to scaling/normalization
- Hides trade-offs between yield and PMI

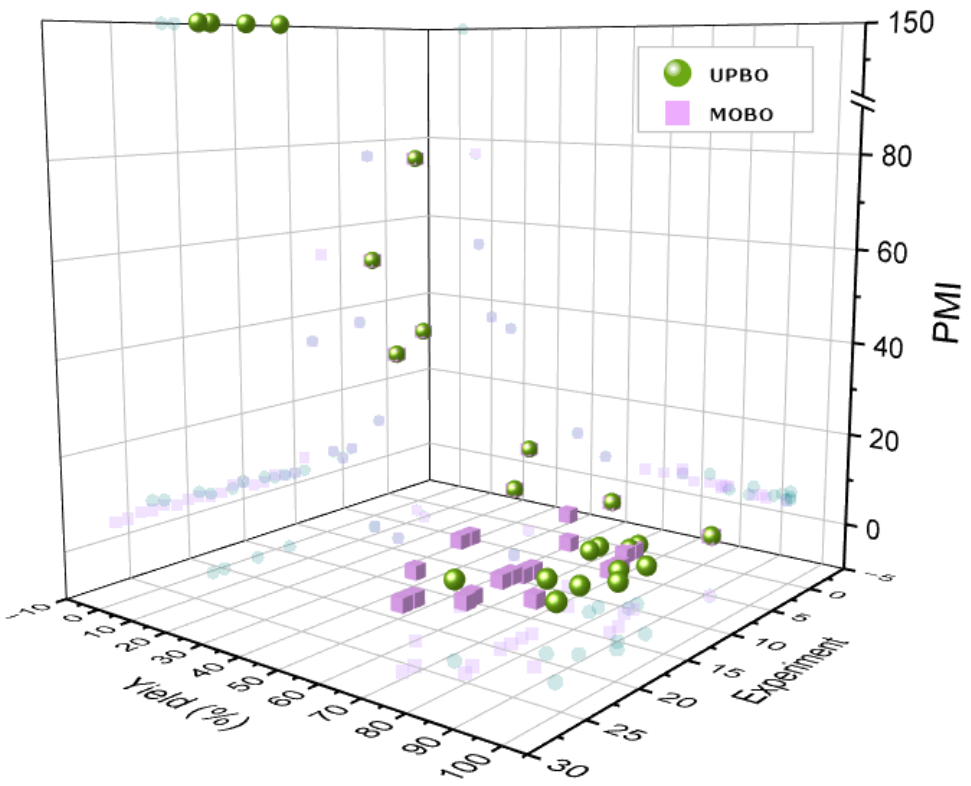
MOBO
Multi-Objective Bayesian Optimization

Pros
- Optimizes yield and PMI separately
- Reveals trade-offs

Cons
- Relatively higher computational resources

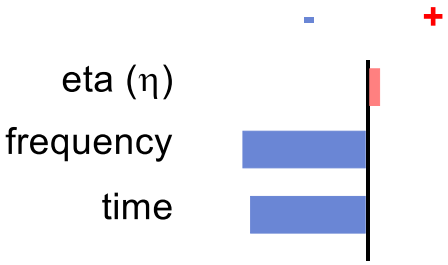
8 initial experiments were identified by **Latin Hypercube Sampling**

Optimization of the JCC cyclopropanation



UPBO

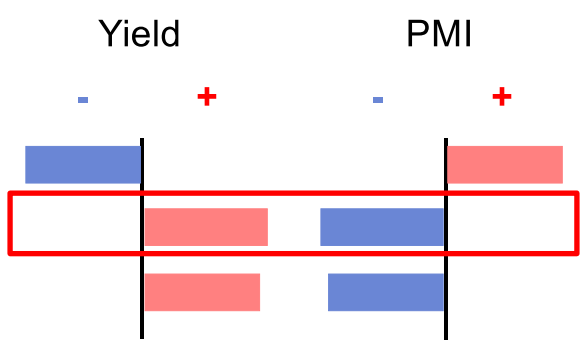
Euclidean distance



Base type: KOH
Base loading (0.9 equiv.)
Reaction time (2.5 min)
Frequency (30 Hz)
LAG (DMSO, 0.4 μL/mg)

Yield	PMI
92%	3.21

MOBO

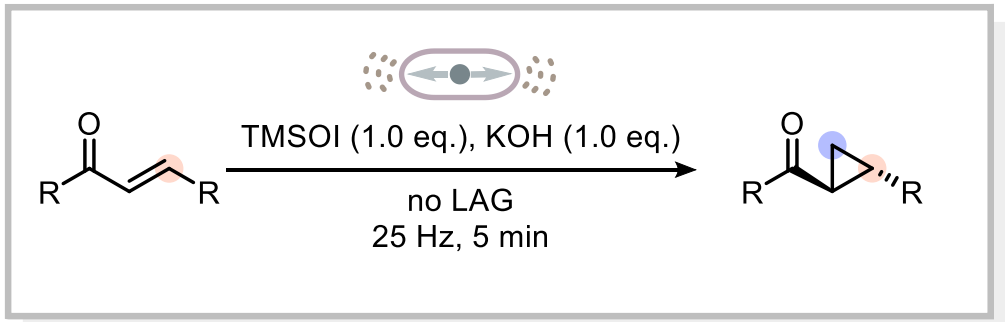


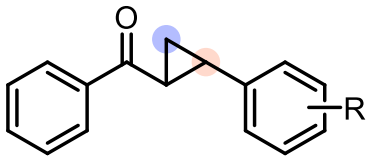
Base type: KOH
Base loading (1.0 equiv.)
Reaction time (5 min)
Frequency (21.5 Hz)
LAG (n. a.)

Yield	PMI
86%	2.54

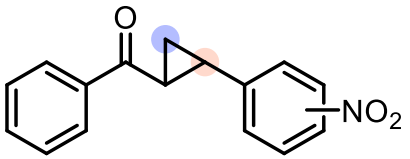
@25 Hz: 96%, 2.28

Scope of the mechanochemical JCC cyclopropanation

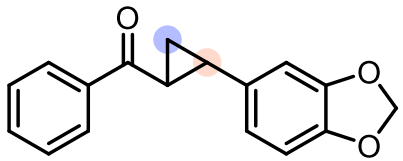




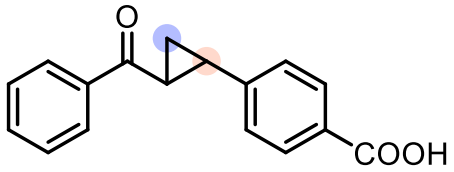
R=H, 96%
R=*para*-Br, 95%



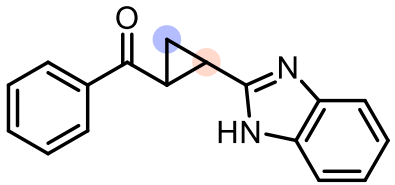
para, 76%
meta, 70%



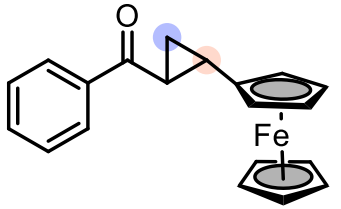
51%



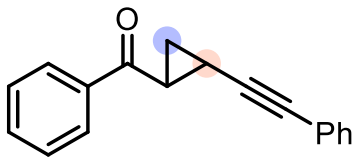
88%



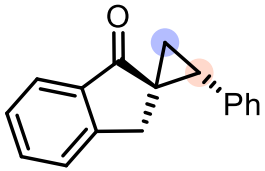
95%



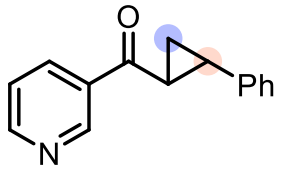
81%



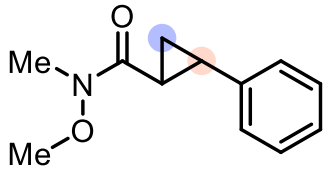
49%



92%

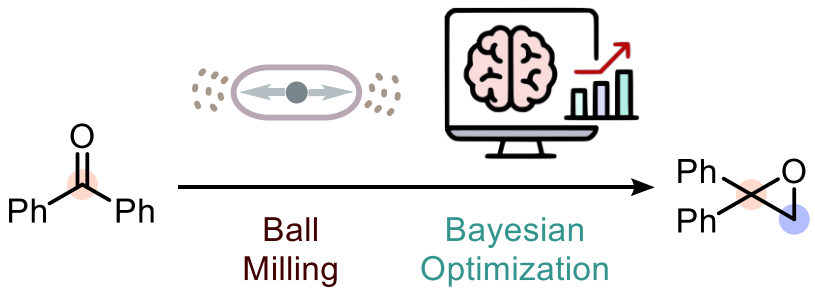


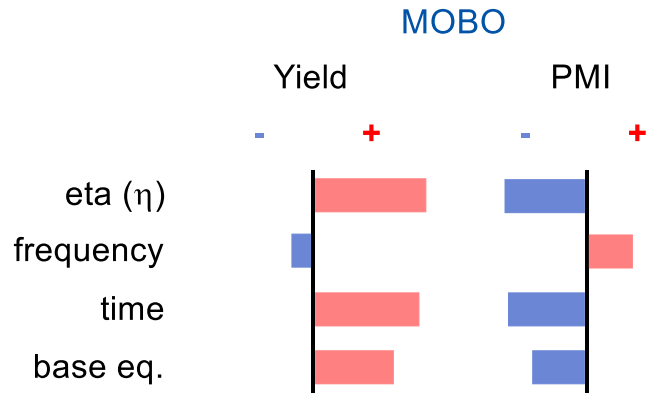
82%



55%

Mechanochemical JCC epoxidation

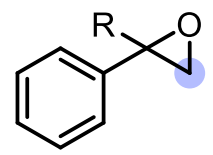




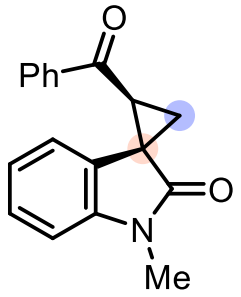
Sulfur salt: TMSI (1.0 equiv.)
Base type: KOH
Base loading (1.5 equiv.)
Reaction time (55 min)
Frequency (14 Hz)
LAG (DMSO, η = 0.6)

Yield	PMI
97%	4.11

from ketones

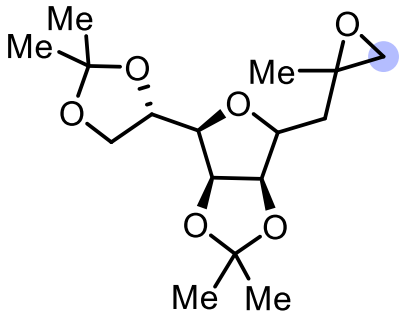


R=Ph, 96%
R=Me, 53%



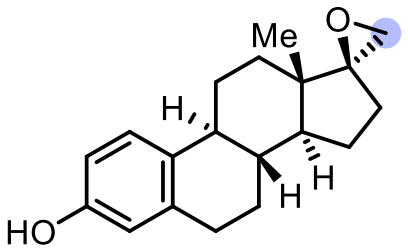
from N-methyl isatin

52%
dr 5:1



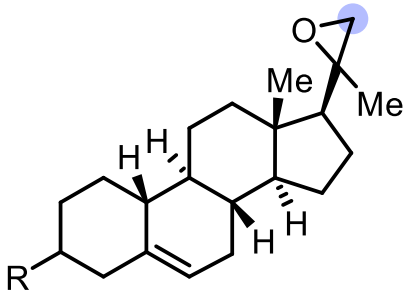
from D-mannose

45%
dr 1:1



from estrone

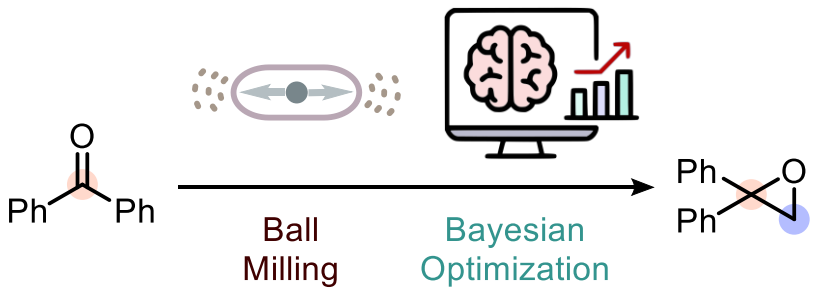
68%[a]
dr > 20:1

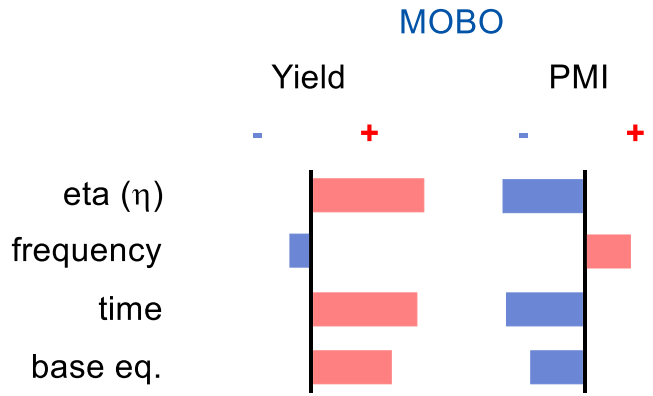


from pregnenolone

R= *OAc*, 40%
R=*OH*, 35%
dr 10:1

Mechanochemical JCC epoxidation

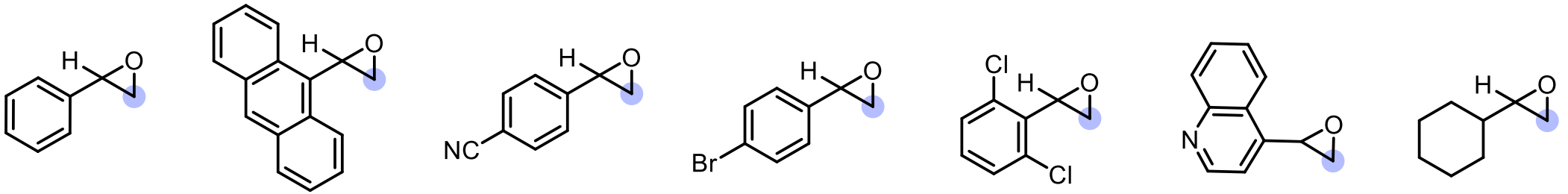




Sulfur salt: TMSI (1.0 equiv.)
Base type: KOH
Base loading (1.5 equiv.)
Reaction time (55 min)
Frequency (14 Hz)
LAG (DMSO, η = 0.6)

Yield	PMI
97%	4.11

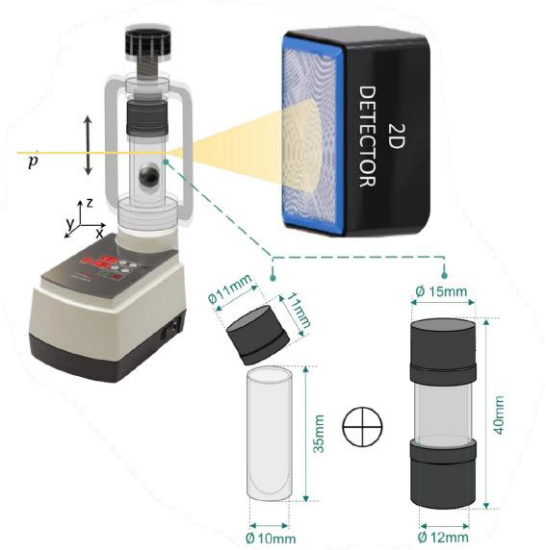
from aldehydes

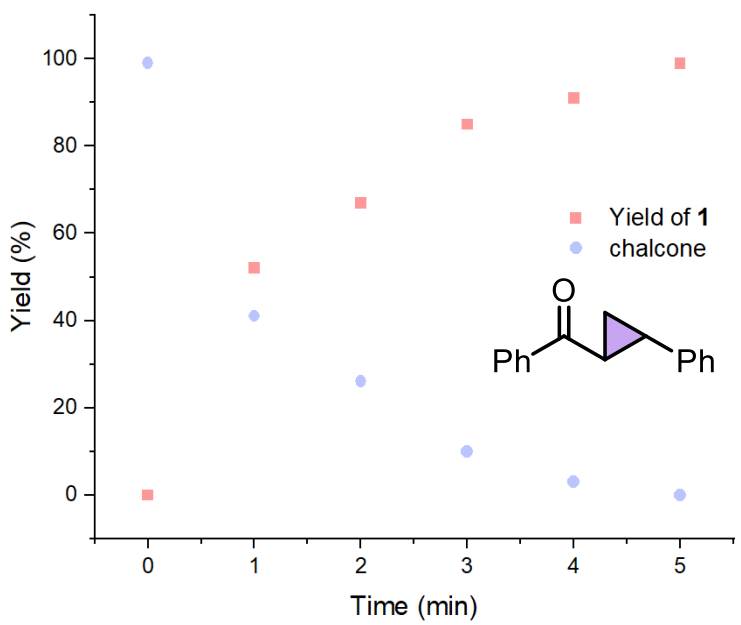


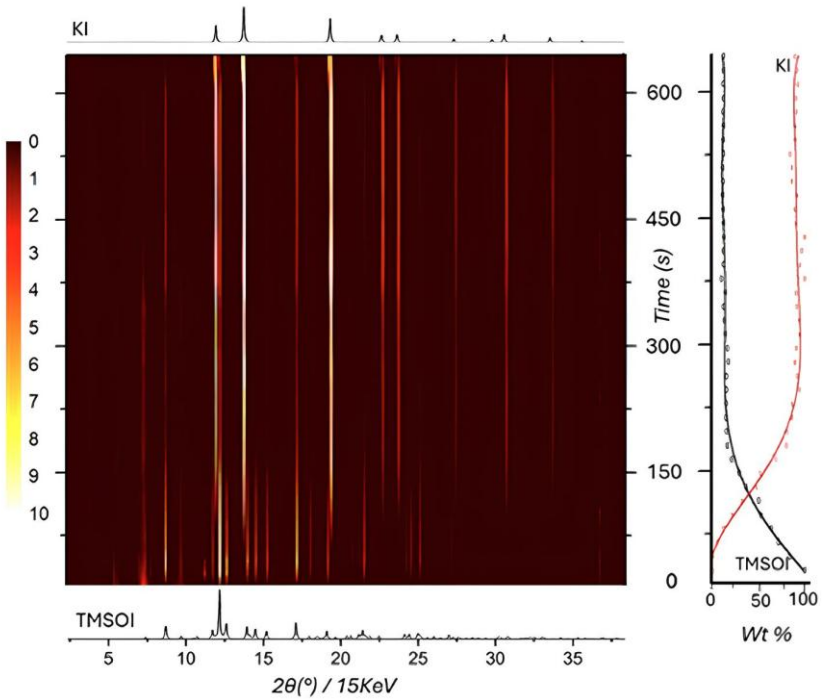
75% 80% 32% 35% 50% 63% 51%

Kinetic studies, upscale and biorelevant scaffolds









w/ P. P. Mazzeo

Critical challenges

Solution-phase synthesis uses HTE, while mechanochemistry is conducted via sequential, low-throughput workflows.

Renders mechanochemistry less competitive than other enabling technologies.

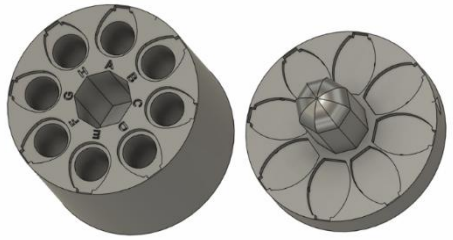
Hampers integration with automation and machine learning capabilities

Severely impacts reaction optimization and time-resolved studies (kinetic studies)



Active Learning

Nat. Commun. **2026**, DOI: 10.1038/s41467-026-75499-3



Miniaturized milling

ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

Miniaturizing mechanochemistry



standard milling jars

2-6 jars in parallel
100s of mg/jar
>500 €/jar
typically jar volume: 10-30 mL

Sufficient energy input?

Minimum viable scale



Revolver
3D-printable design
2 €

polypropylene milling vials



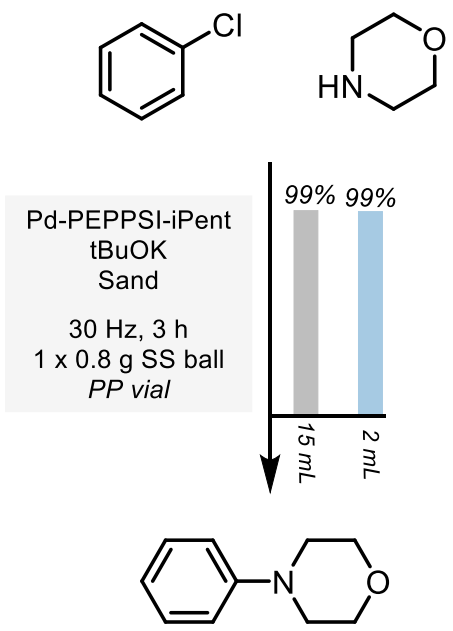
up to 20 in parallel
mgs/vial
~0.1 €/jar
2 mL vial volume

Positional reproducibility

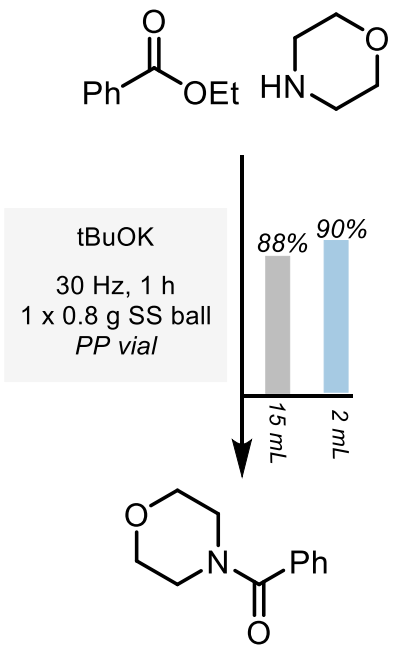
Reaction generality

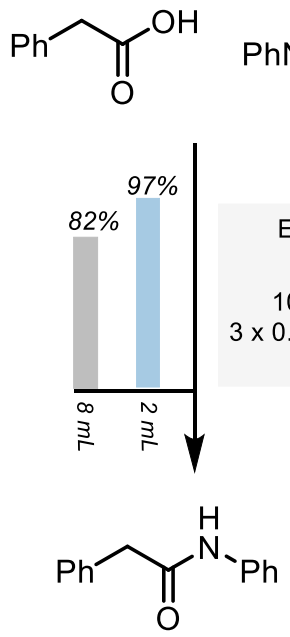
Reaction generality (selected examples)

Buchwald-Hartwig Amination

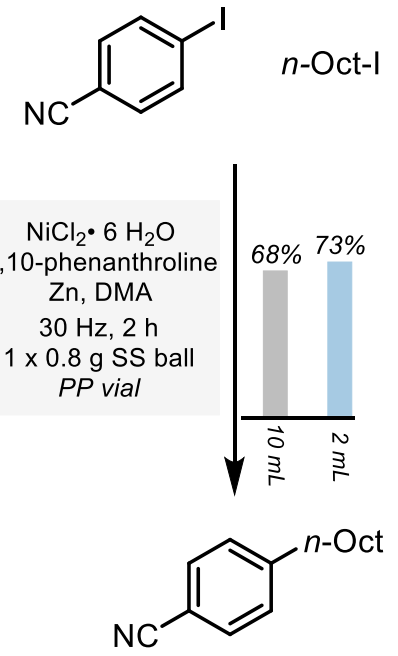


Amidation





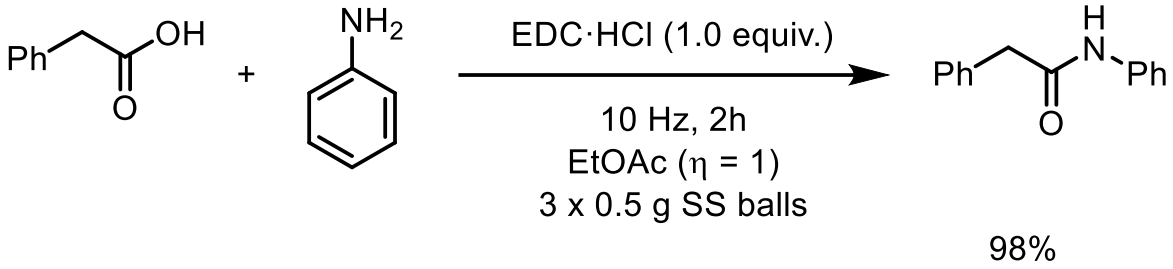
XEC



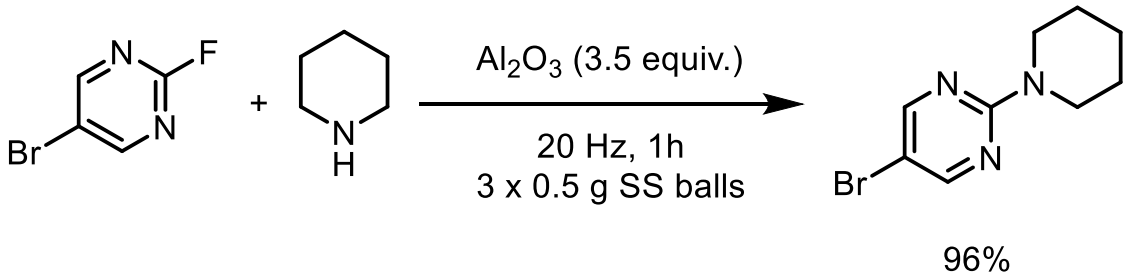
w/ D. L. Browne: ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

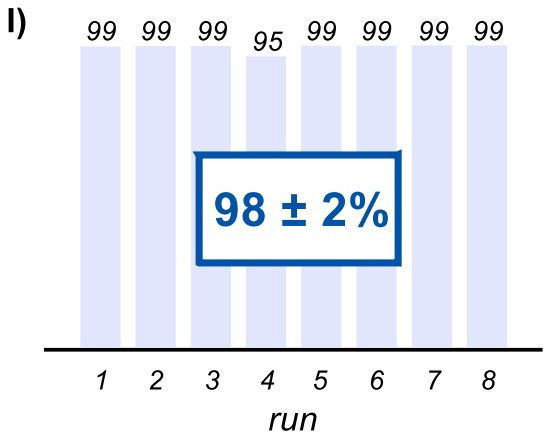
Time-course analysis via miniaturized milling

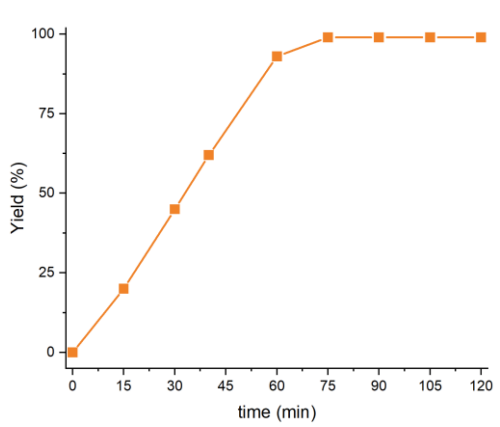
Amide coupling

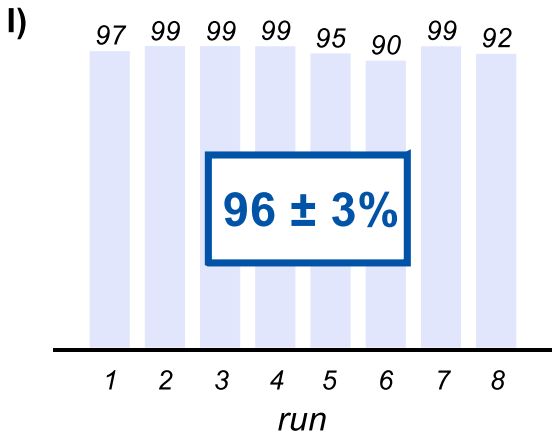


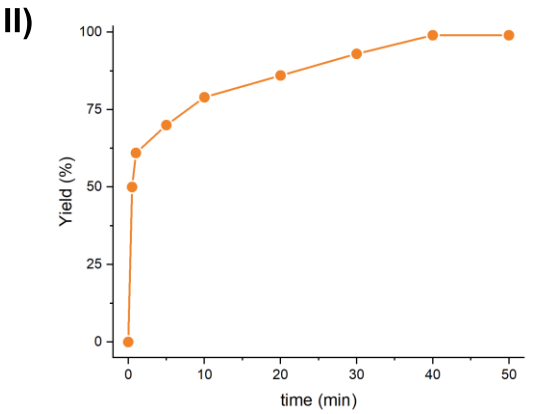
Nucleophilic Aromatic Substitution





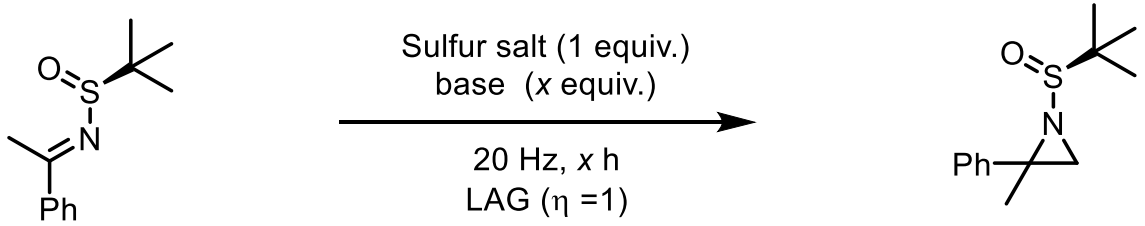


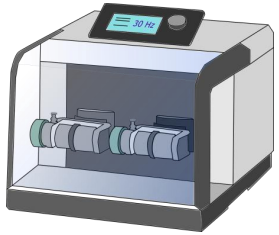


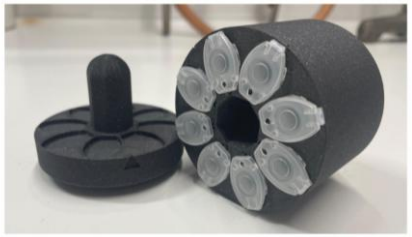


ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

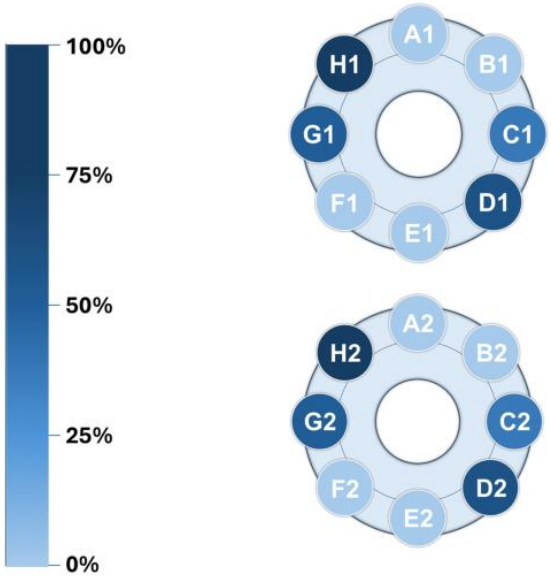
Full reaction discovery, optimization and development







A) Mill 1: reaction optimization

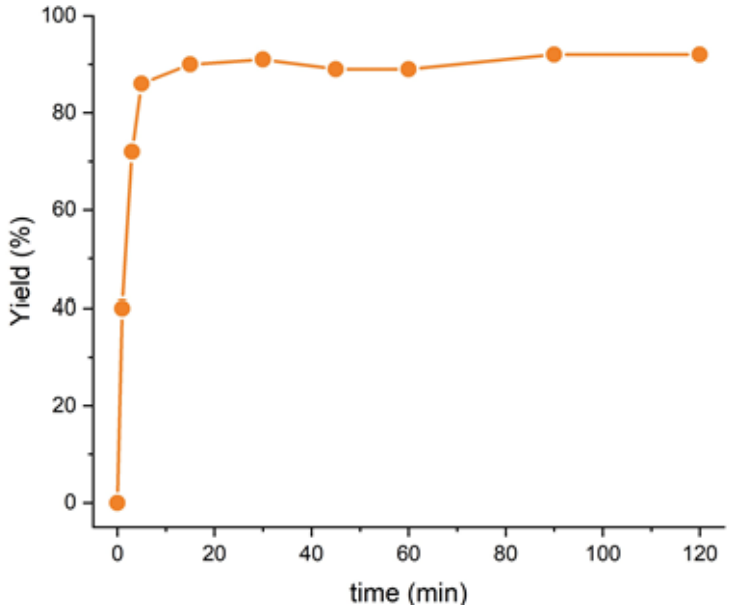


Best yield: H1 = 92%

Entry	Base	Eq. Base	Salt	η (DMSO)
A1	KOH	1	TMSI	0
B1	"	"	"	1
C1	"	"	TMSOI	0
D1	"	"	"	1
E1	"	2	TMSI	0
F1	"	"	"	1
G1	"	"	TMSOI	0
H1	"	"	"	1

Entry	Base	Eq. Base	Salt	η (DMSO)
A2	KO^{t}Bu	1	TMSI	0
B2	"	"	"	1
C2	"	"	TMSOI	0
D2	"	"	"	1
E2	"	2	TMSI	0
F2	"	"	"	1
G2	"	"	TMSOI	0
H2	"	"	"	1

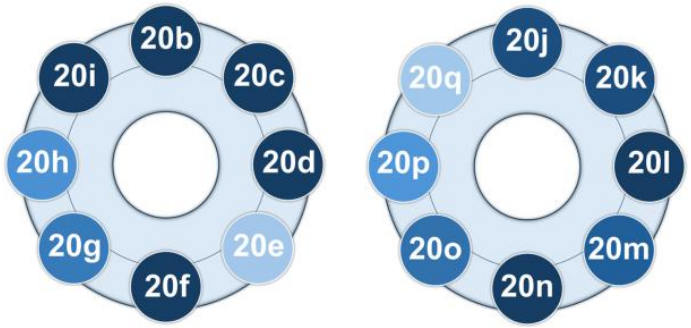
B) Mill 2: Time-course profile

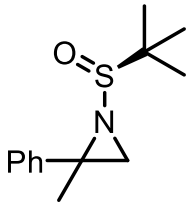


ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

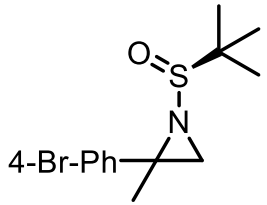
Full reaction discovery, optimization and development

C) Mill 3: Chemical space sampling & scope evaluation

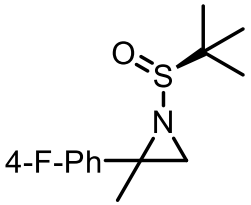




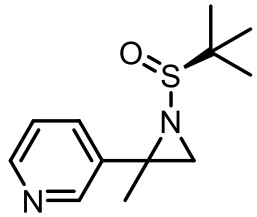
91% (96%)
dr 5:1



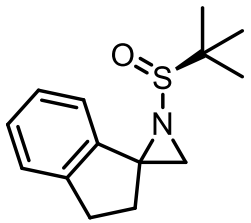
92%
dr 6:1



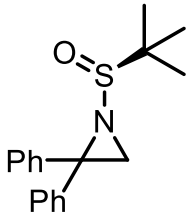
98%
dr 6:1



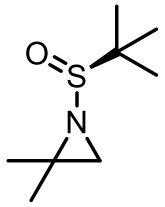
77%
dr 5:1



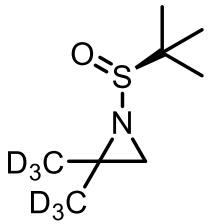
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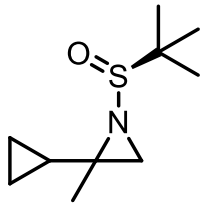
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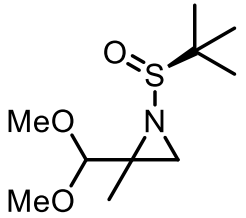
40%



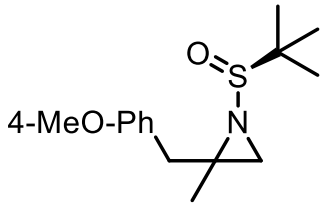
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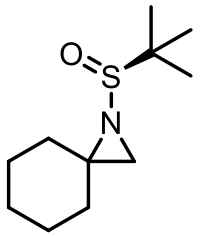
69%
dr 10:1



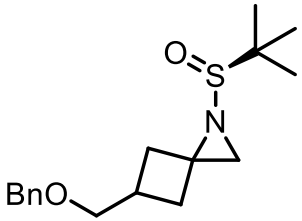
59%
dr 10:1



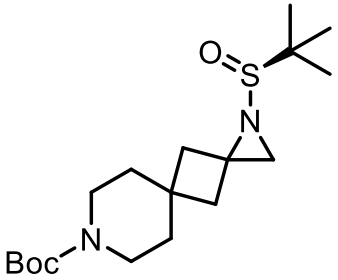
89%
dr 2.5:1



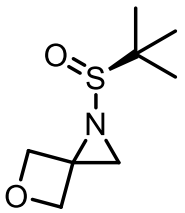
74%



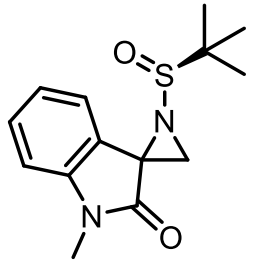
48%



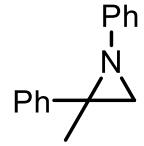
79%



43%



25% (40%)



traces

ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205

Take-home message

Mechanochemistry is reshaping the way we perform organic synthesis

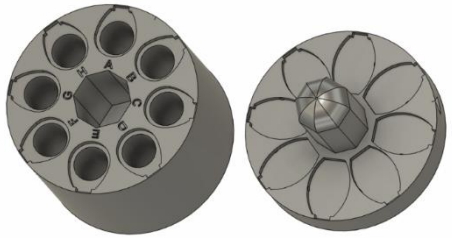
Ball mills are no longer niche instruments—they are becoming mainstream

But our experimental workflows remain stuck in the past



Active Learning

Nat. Commun. **2026**, DOI: 10.1038/s41467-026-75499-3



Miniaturized milling

ChemRxiv **2026**, DOI: 10.26434/chemrxiv.15005205



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Ministero dell'Università e della Ricerca

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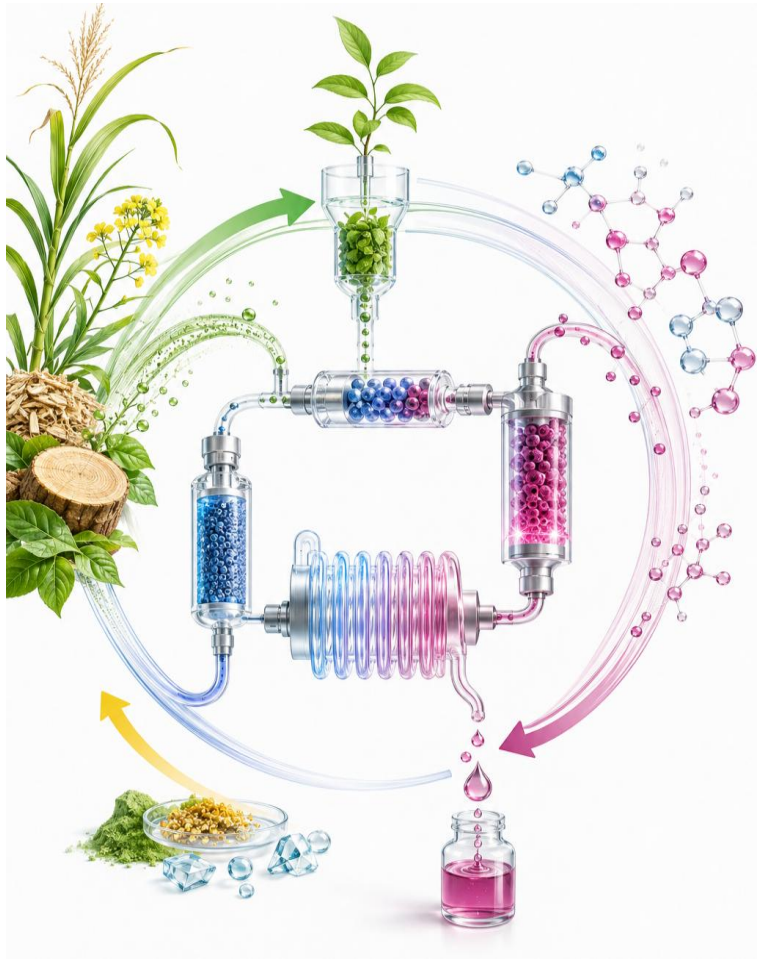
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  Procos
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