Mechanochemistry in Organic Synthesis

Iakovos Saridakis

MacMillan research group
Group meeting Literature Talk
Nov 22nd, 2024

Brief tutorial introduction on Mechanochem (<u>generally</u>)

History

Mechanistic aspects

Mechanical actions and mechanoreactors

Reaction Monitoring

Why mechanochemistry?

Mechanochemical vs. solution-based reactions

Medicinal mechanochemistry

“Mechanochemistry 2.0”

Mechanoredox

Electrochemistry

Photochemistry

Thermal chemistry

Electrical potential

Photonic energy

Heat

Mechanochemistry

Electrochemistry

Electrical potential

Photochemistry

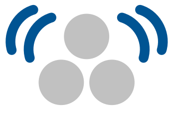
Photonic energy

Thermal chemistry

Heat

Mechanochemistry in Organic Synthesis

Definition



Mechanochemistry

"Chemistry induced by input of mechanical energy"

Electrochemistry

Electrical potential

Photochemistry

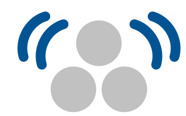
Photonic energy

Thermal chemistry

Heat

Mechanochemistry in Organic Synthesis

Terminology & subcategories



Mechanochemical reaction according to IUPAC:
'Chemical reaction that is induced by the direct absorption of mechanical energy'*

** 'Shearing, stretching, and grinding are typical methods for the mechano-chemical generation of reactive sites […].'*

Mechanochemistry in Organic Synthesis

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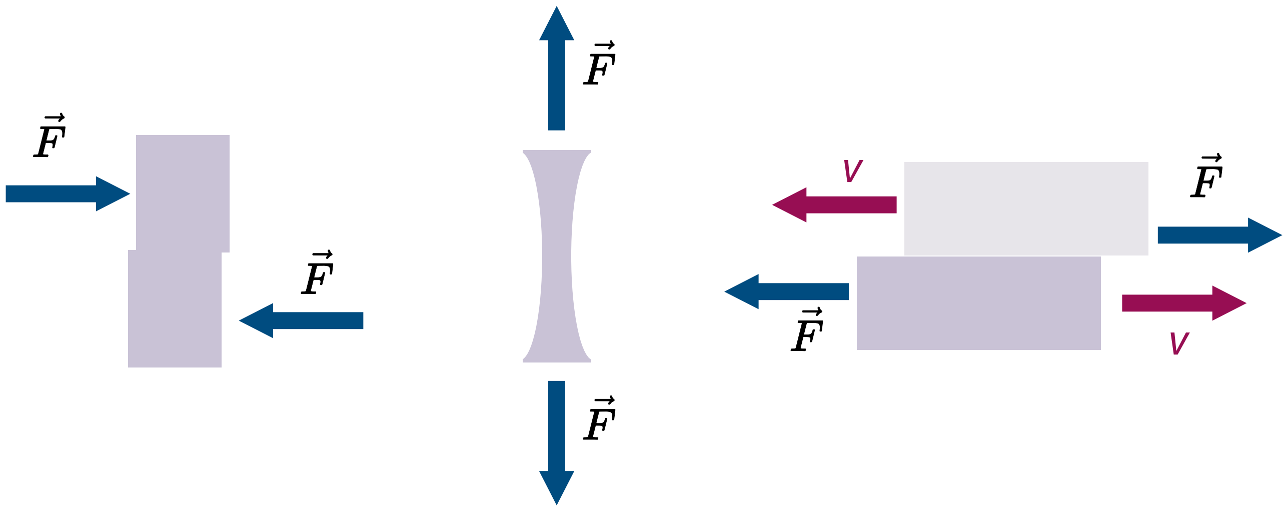
Shearing *Stretching* *Friction*



Mechanochemistry in Organic Synthesis

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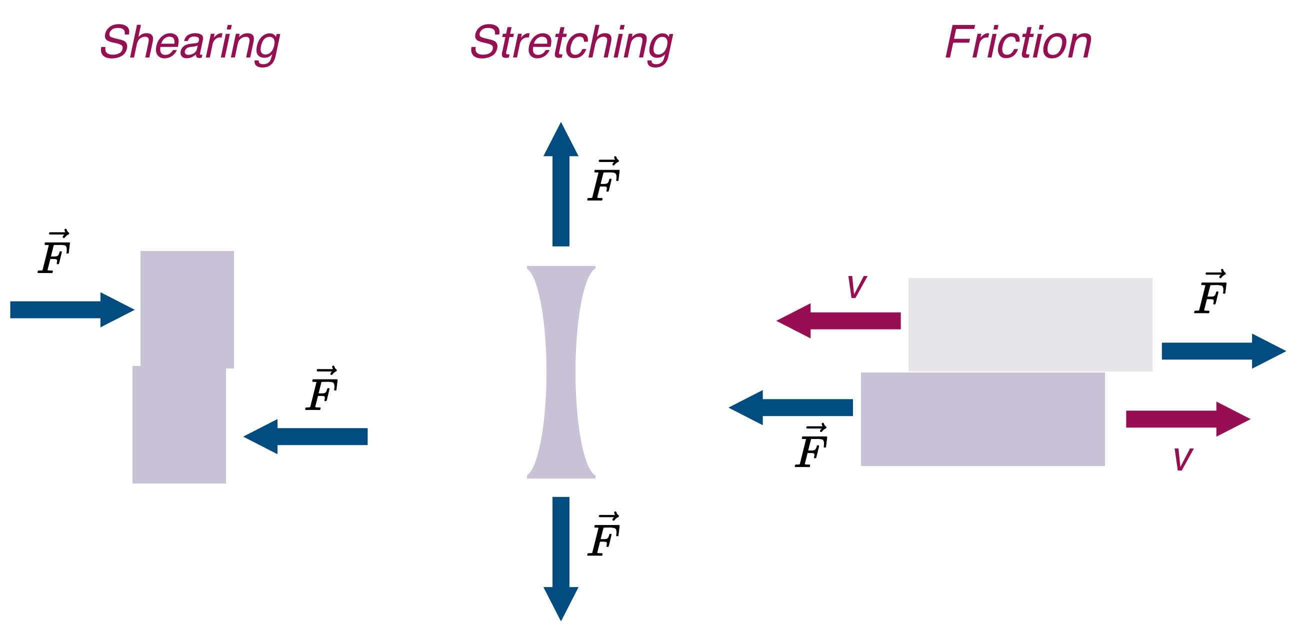


Other popular term:

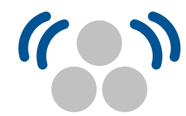
*1970: **<u>Tribo</u>chemistry** (chemistry by friction)*

- Materials
- Polymer Chemistry
- Organic Chemistry
- Inorganic Chemistry

Inter-discipline miscommunication and debates

Mechanochemistry in Organic Synthesis

Terminology & subcategories



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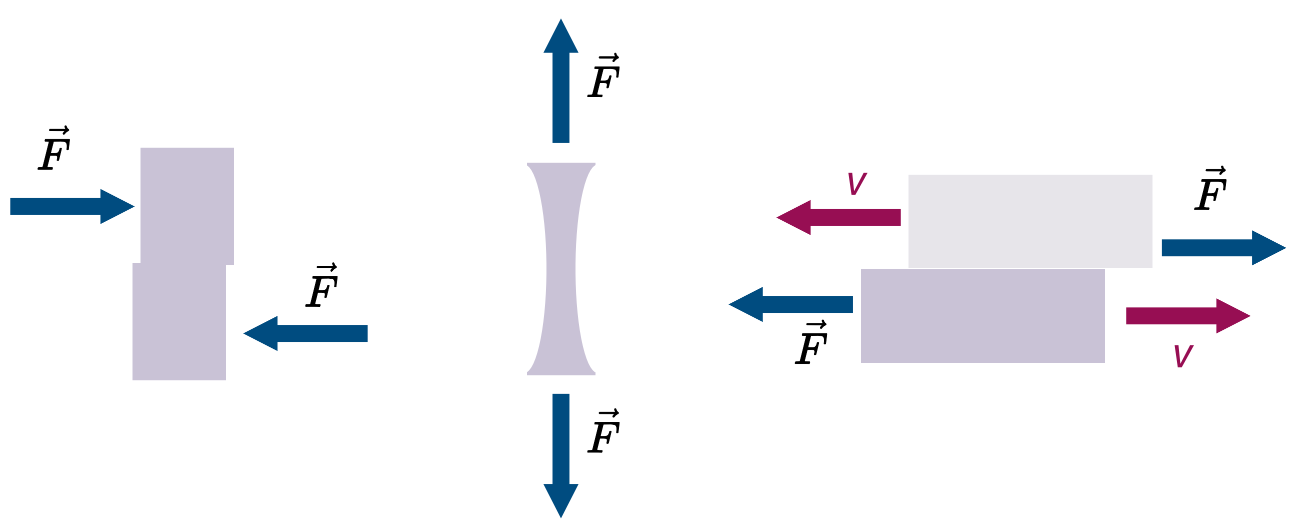

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Inter-discipline miscommunication and debates

"***Mechanochemistry***" as the "common language"

Mechanochemistry in Organic Synthesis

History of Mechanochemistry

Cinnabar

$HgS \xrightarrow[\text{AcOH}]{\text{Made of Cu}} Hg^0$

Theophrastus of Eresus
Book: "On Stones", 315 BC

Stuart L. James et al., *Chem. Soc. Rev.* **2012**, *41*, 413–447.

315 BC

Mechanochemistry in Organic Synthesis

History of Mechanochemistry

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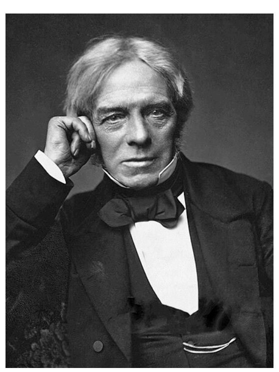


M. Faraday

$AgCl \xrightarrow{\text{Zn}} Ag^0$

*"if dry chloride of silver in powder be triturated in a mortar with zinc filings, the two bodies immediately act [...] **in the dry way**"*

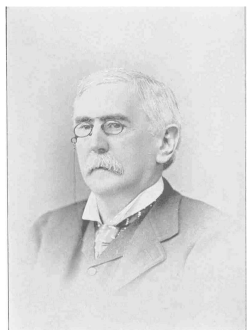
M. Faraday Q. *J., Sci. Lit. Arts* **1820**, *8* , 374; L. Takacs *J. Therm. Anal. Calorim.* **2007**, *90*, 81.

315 BC

1820

Mechanochemistry in Organic Synthesis

History of Mechanochemistry



M. Carey Lea

HgX_n → Hg^0

AgX → Ag^0

Heating alone:
Decomposition

L. Takacs, *J. Mater. Sci.*, **2004**, *39*, 4987

315 BC

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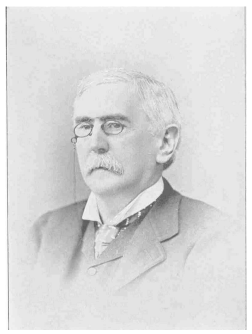
Mechanochemistry in Organic Synthesis

History of Mechanochemistry



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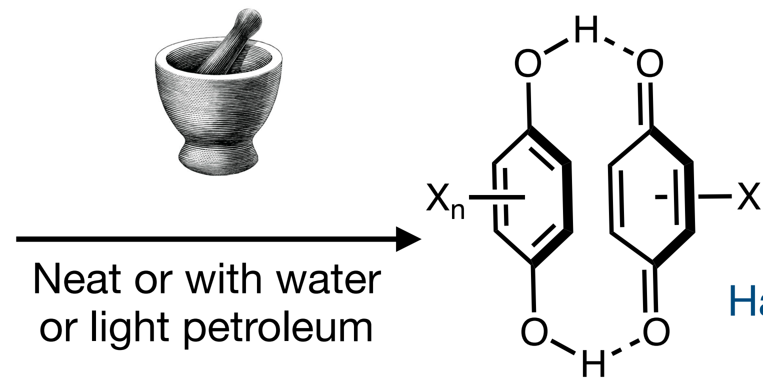

Neat or with water or light petroleum

Halogen derivatives of quinhydrone

A. R. Ling and J. L. Baker, *J. Chem. Soc., Trans.*, **1893**, *63* , 1314

315 BC

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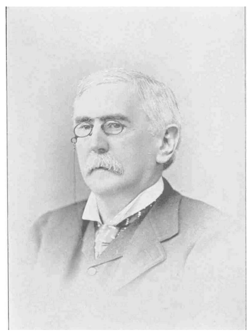
Mechanochemistry in Organic Synthesis

History of Mechanochemistry



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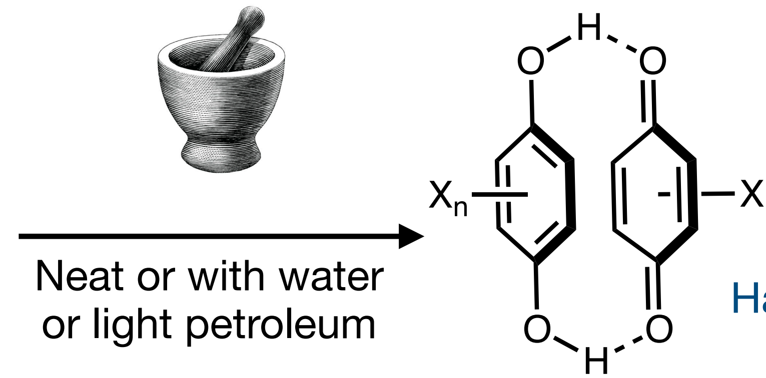

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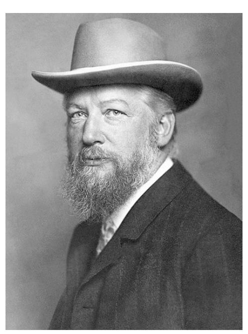

Wilhelm Ostwald

Nobel Prize in Chemistry 1909
(For unrelated research)

1919: Coined "**mechanochemistry**"

Stuart L. James et al., *Chem. Soc. Rev.* **2012**, *41*, 413–447.

315 BC — 1820 — 1866 — 1893 — 1919

Mechanochemistry in Organic Synthesis

History of Mechanochemistry

IUPAC Top Ten Emerging Technologies in Chemistry 2019

Gomollón-Bel, *F. Chem. Int.* **2019**, *41*,12–17.

315 BC 1820 1866 1893 1919 2019-2024

Mechanochemistry in Organic Synthesis

History of Mechanochemistry

IUPAC INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

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ROYAL SOCIETY OF **CHEMISTRY**

RSC Mechanochemistry

2022

315 BC | 1820 | 1866 | 1893 | 1919 | 2019-2024

Mechanochemistry in Organic Synthesis

History of Mechanochemistry

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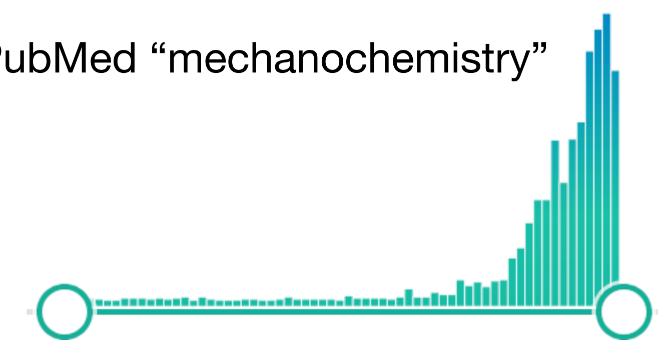

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Mechanochemistry in Organic Synthesis

“How does this work?”

Mechanochemistry in Organic Synthesis

"How does this work?"

Diversity of reaction types, conditions, materials, inhomogeneity → Debates and different mechanistic models → Each has limited area of applicability, many models can apply at once

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Mechanochemistry in Organic Synthesis

"How does this work?"

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Most accepted approaches
(Yet, debated)

Hot-spot theory

Magma-plasma model

Stuart L. James et al., *Chem. Soc. Rev*. **2012**, *41*, 413–447.

Mechanochemistry in Organic Synthesis

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Friction

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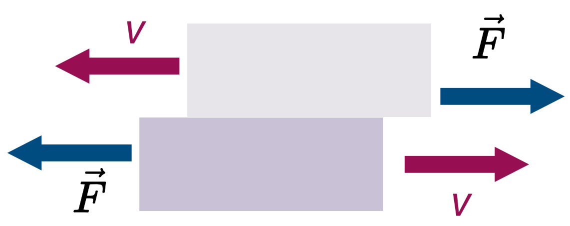
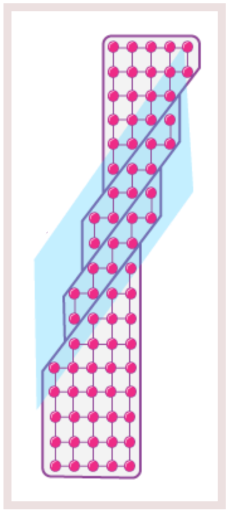


Plastic deformation



Irreversible bond cleavage/formation upon stress

Bowden, F. P. et al., *Proc. R. Soc. Lond. Ser. A Math. Phys. Sci.* **1947**, *188*, 329–349.

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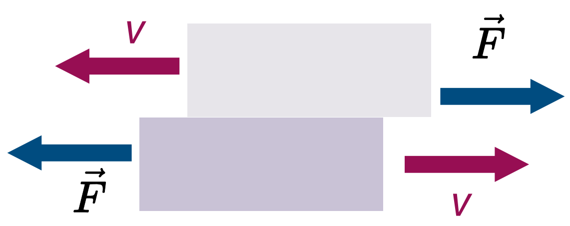

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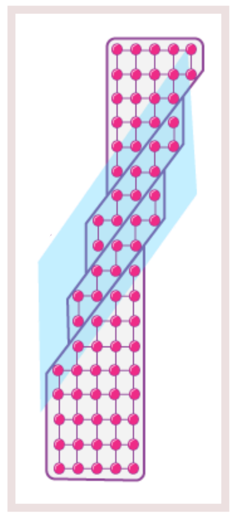
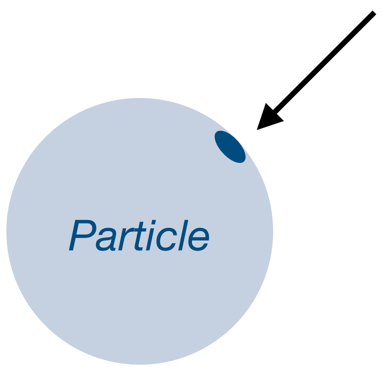


Irreversible bond cleavage/formation upon stress

Local heat



Approx. 1 μm²

1000 °C for 0.1–1 ms

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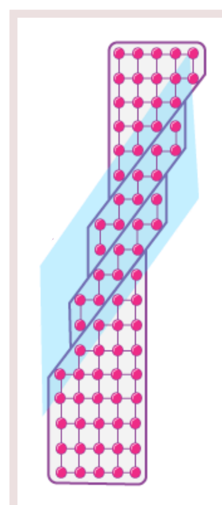

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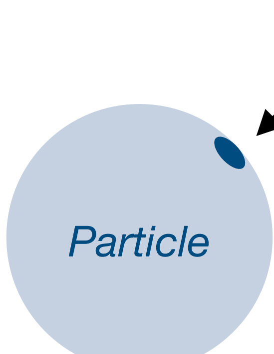

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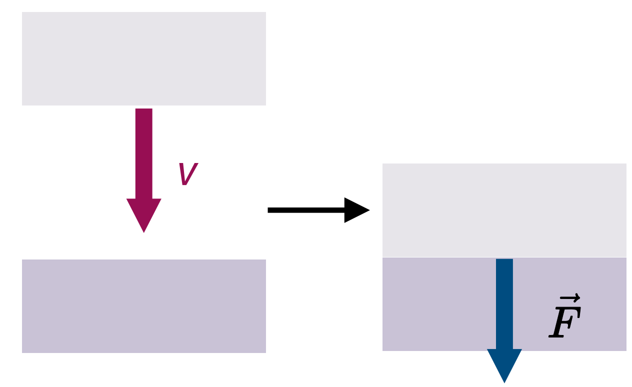
Magma-plasma model

Impact



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Mechanochemistry in Organic Synthesis

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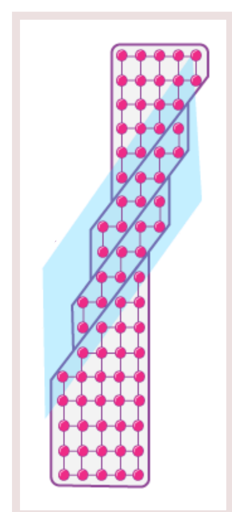
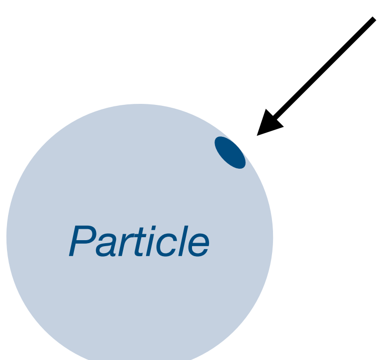


Irreversible bond cleavage/formation upon stress

Local heat



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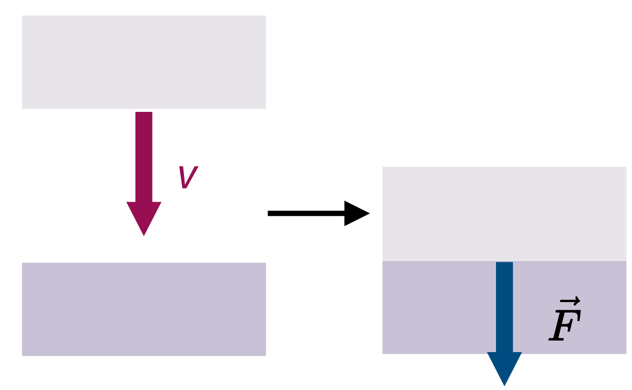
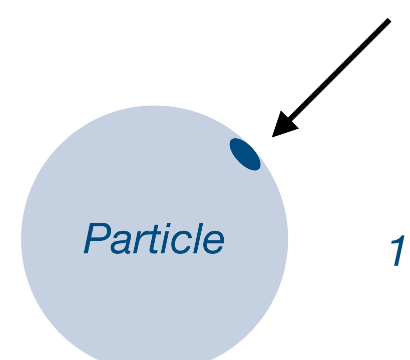


Point of impact



Transient plasma

10000 °C for 0.1–1 ms

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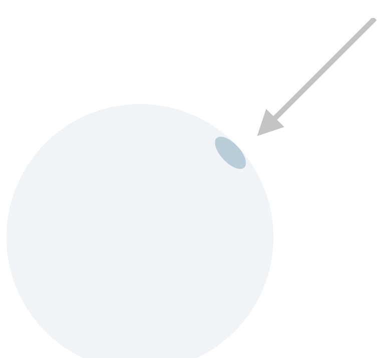
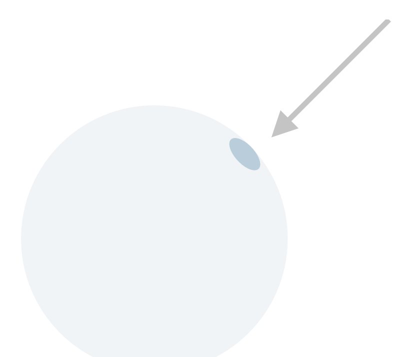
Mechanochemistry in Organic Synthesis

"How does this work?"

Both for inorganic materials

Do not apply generally for organic mechanochemistry





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Mechanochemistry in Organic Synthesis

"How does this work?"

Both for inorganic materials

<u>Do not apply generally for organic mechanochemistry</u>

- Hot-spots would result in decomposition
- Could exist only for negligible time periods

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Mechanochemistry in Organic Synthesis

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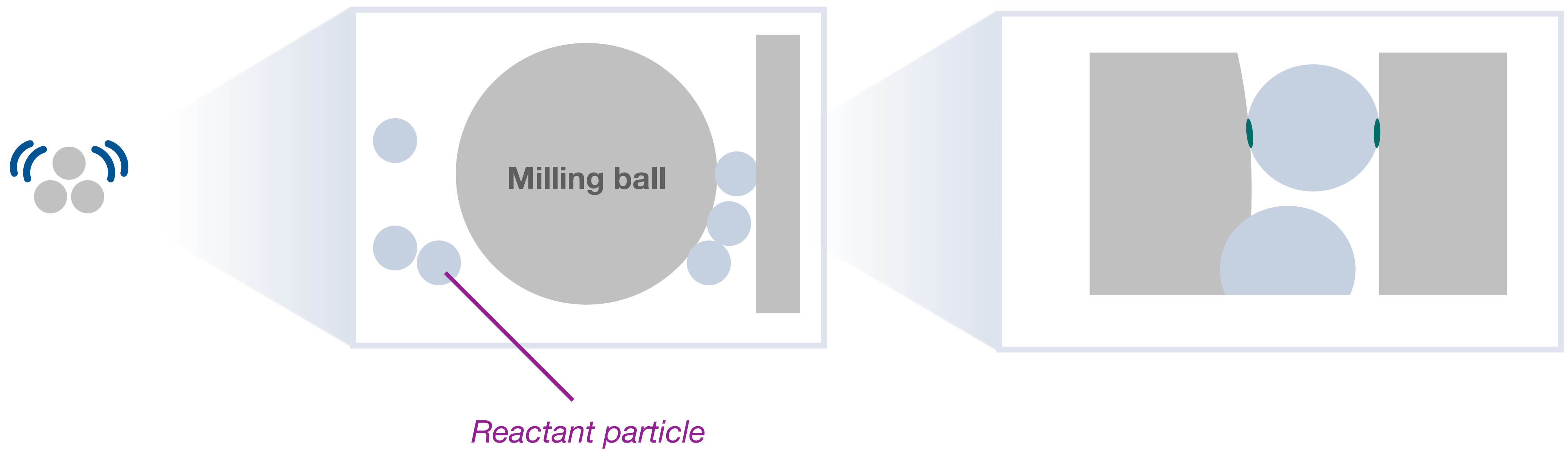
Efforts focus on unveiling the underlying physics of mechanochemistry



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Mechanochemistry in Organic Synthesis

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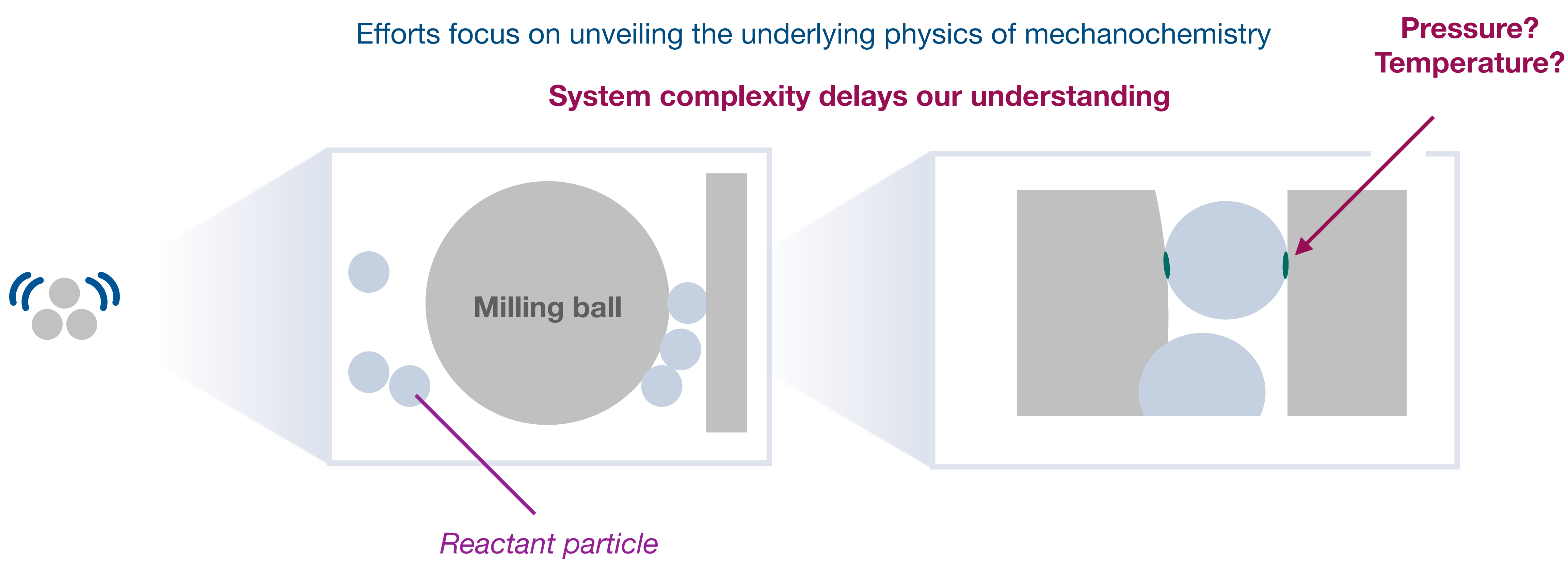
Efforts focus on unveiling the underlying physics of mechanochemistry

System complexity delays our understanding



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Mechanochemistry in Organic Synthesis

Mechanical Actions

Classification of Mechanical Actions

(i.e., the stimuli which induce mechanochemical reactions)

Adam A. L. Michalchuk et al., *Front. Chem.* **2012**, *9*, 685789.

Mechanochemistry in Organic Synthesis

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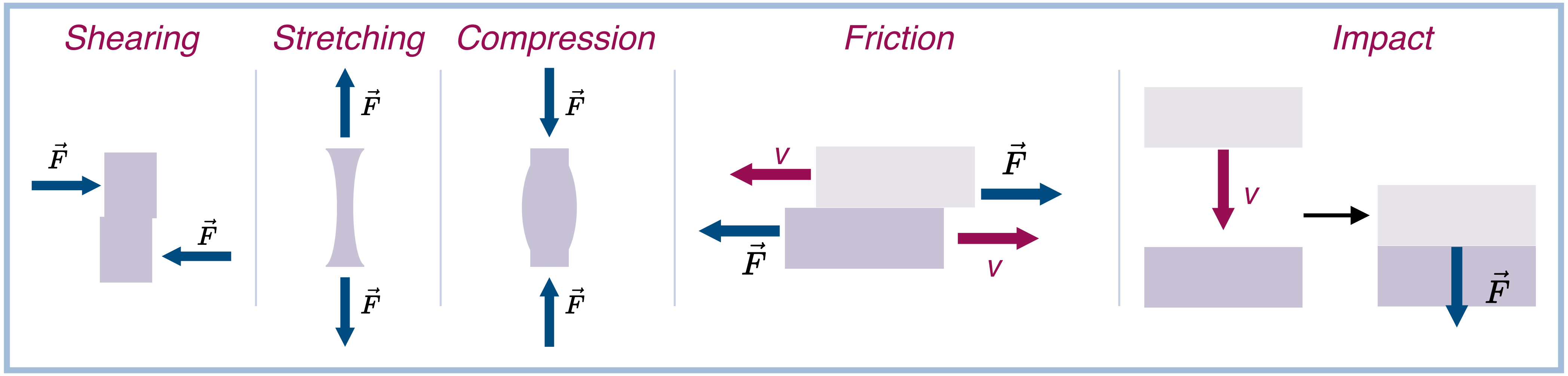

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Mechanochemistry in Organic Synthesis

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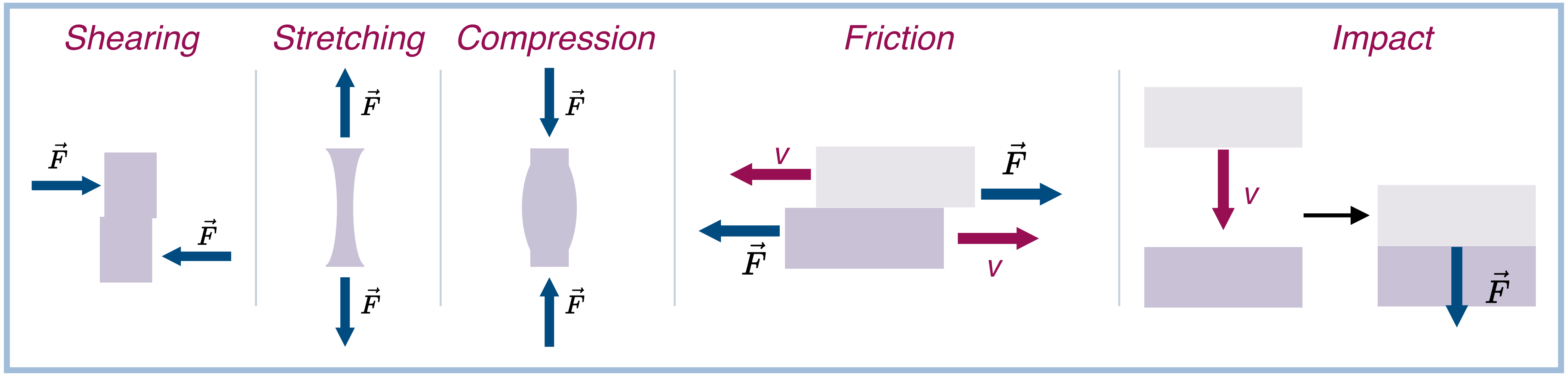
(i.e., the stimuli which induce mechanochemical reactions)

- **Instantaneous**

  e.g., shock wave



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Mechanochemistry in Organic Synthesis

Mechanical Actions

Classification of Mechanical Actions

(i.e., the stimuli which induce mechanochemical reactions)

- **Instantaneous**

  e.g., shock wave

- **Long duration**

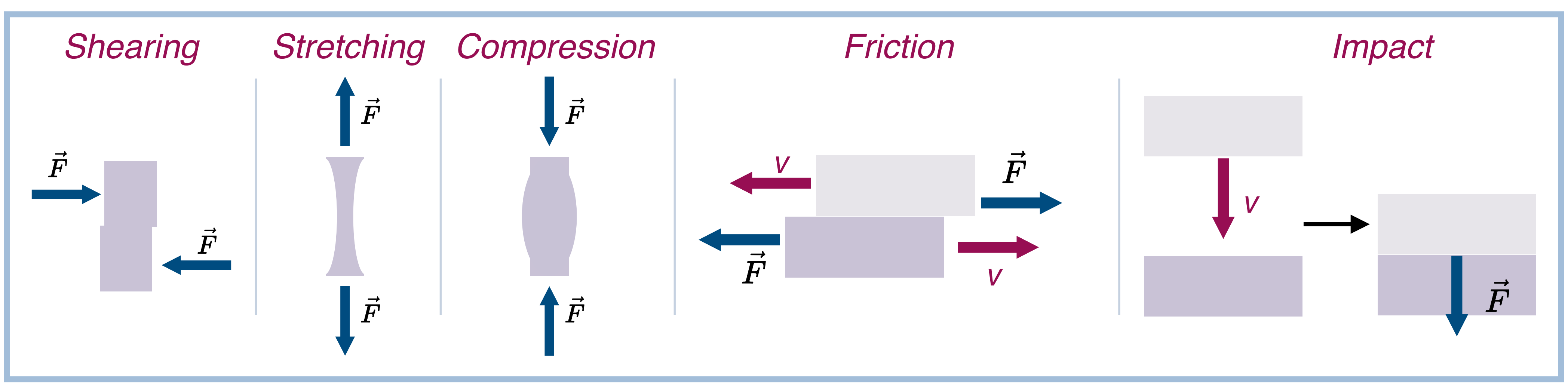
Continuous

Stretching, bending, twisting, compression, tableting

Pulsed

Rubbing, impact, shear

Ball milling



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Mechanochemistry in Organic Synthesis

Mechanoreactors

Pestle and mortar

Households/labs

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Mechanoreactors

Dynamic stressing control
(Challenging to predict/control)

Pestle and mortar

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Mechanochemistry in Organic Synthesis

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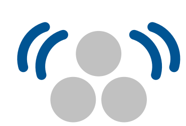
Well-defined parameters tackling the dynamic stressing

Pestle and mortar

Households/labs

Ball milling



Batch scales

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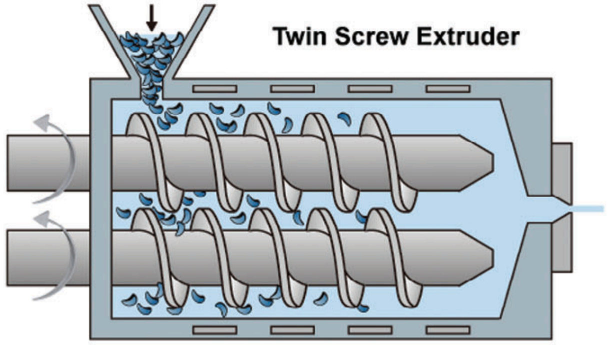
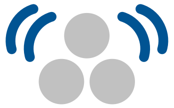
Mechanochemistry in Organic Synthesis

Mechanoreactors

Dynamic stressing control
(Challenging to predict/control)



Well-defined parameters tackling the dynamic stressing

Pestle and mortar	Ball milling	Twin-screw extruders
		***"Flow mechanochemistry"***
Households/labs	*Batch scales*	*Industrial scales*

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Ball milling

Ball milling categories

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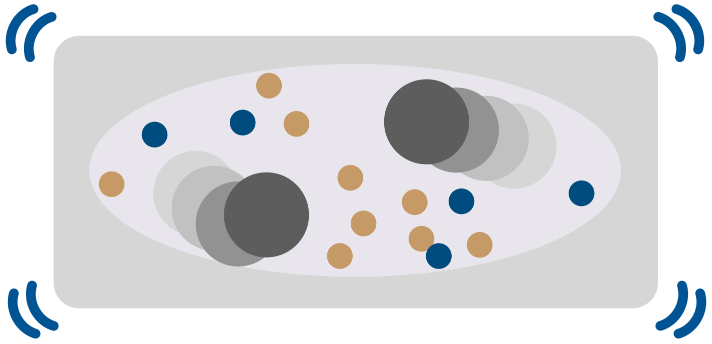

Mixer Mill
(most common)

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Mechanochemistry in Organic Synthesis

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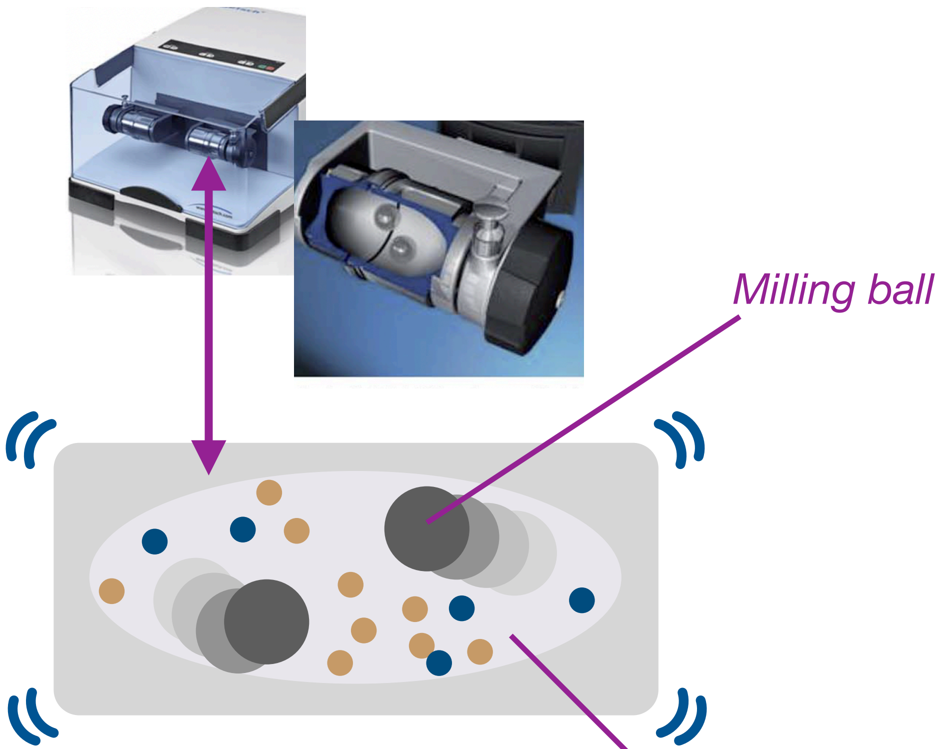

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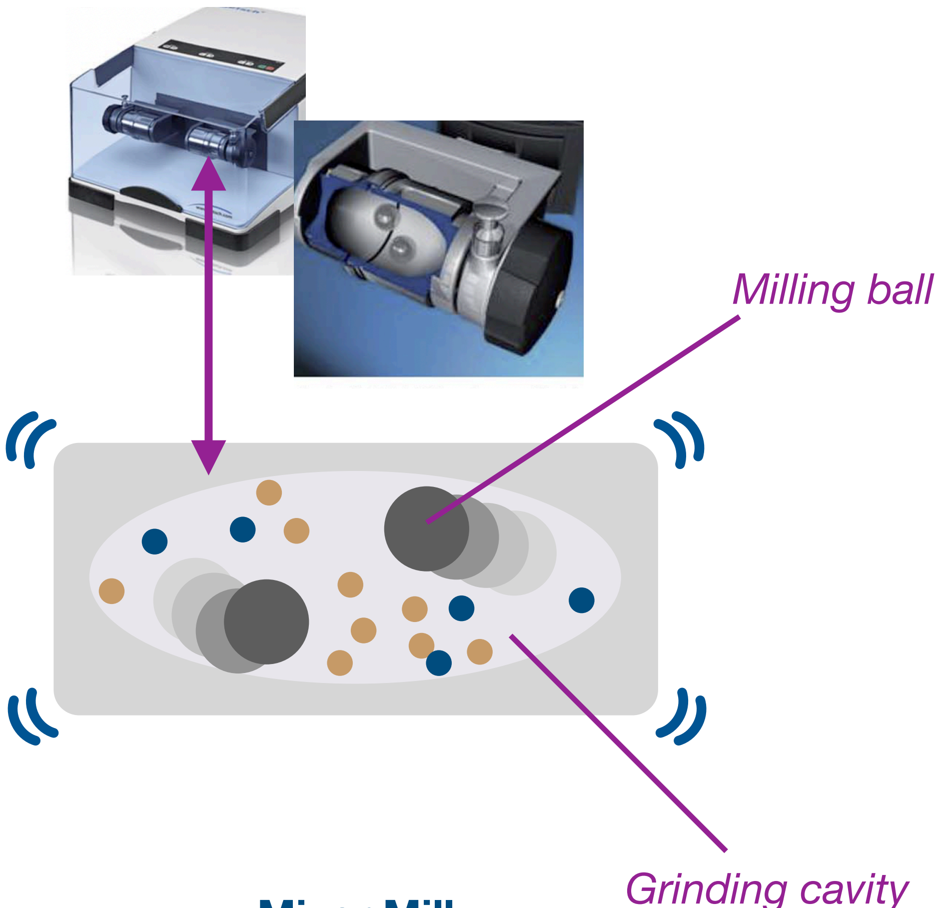

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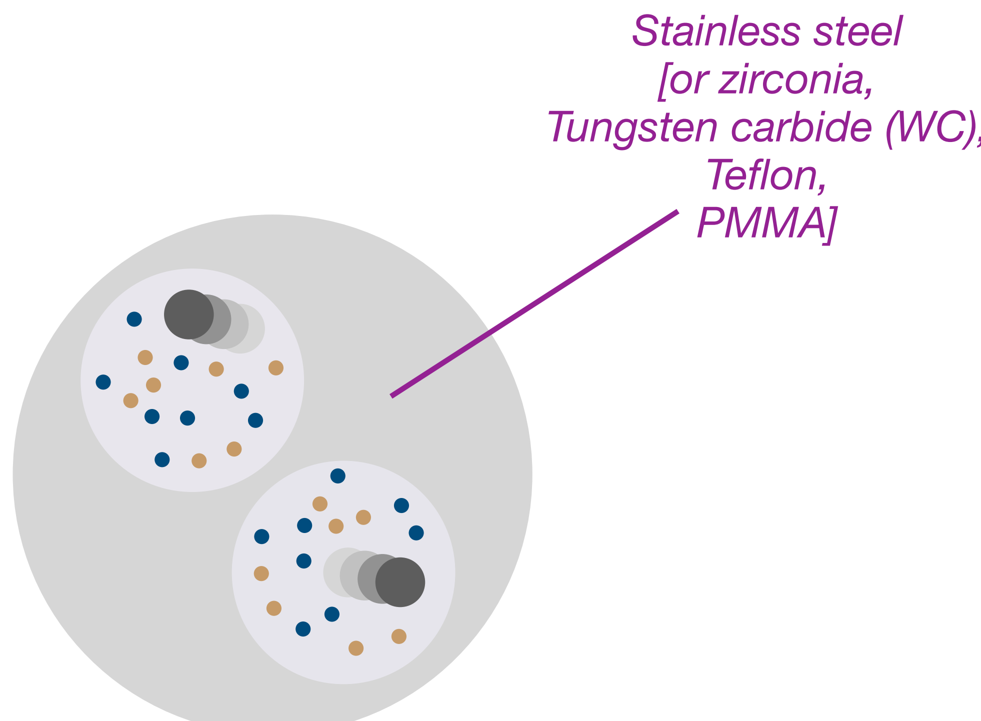
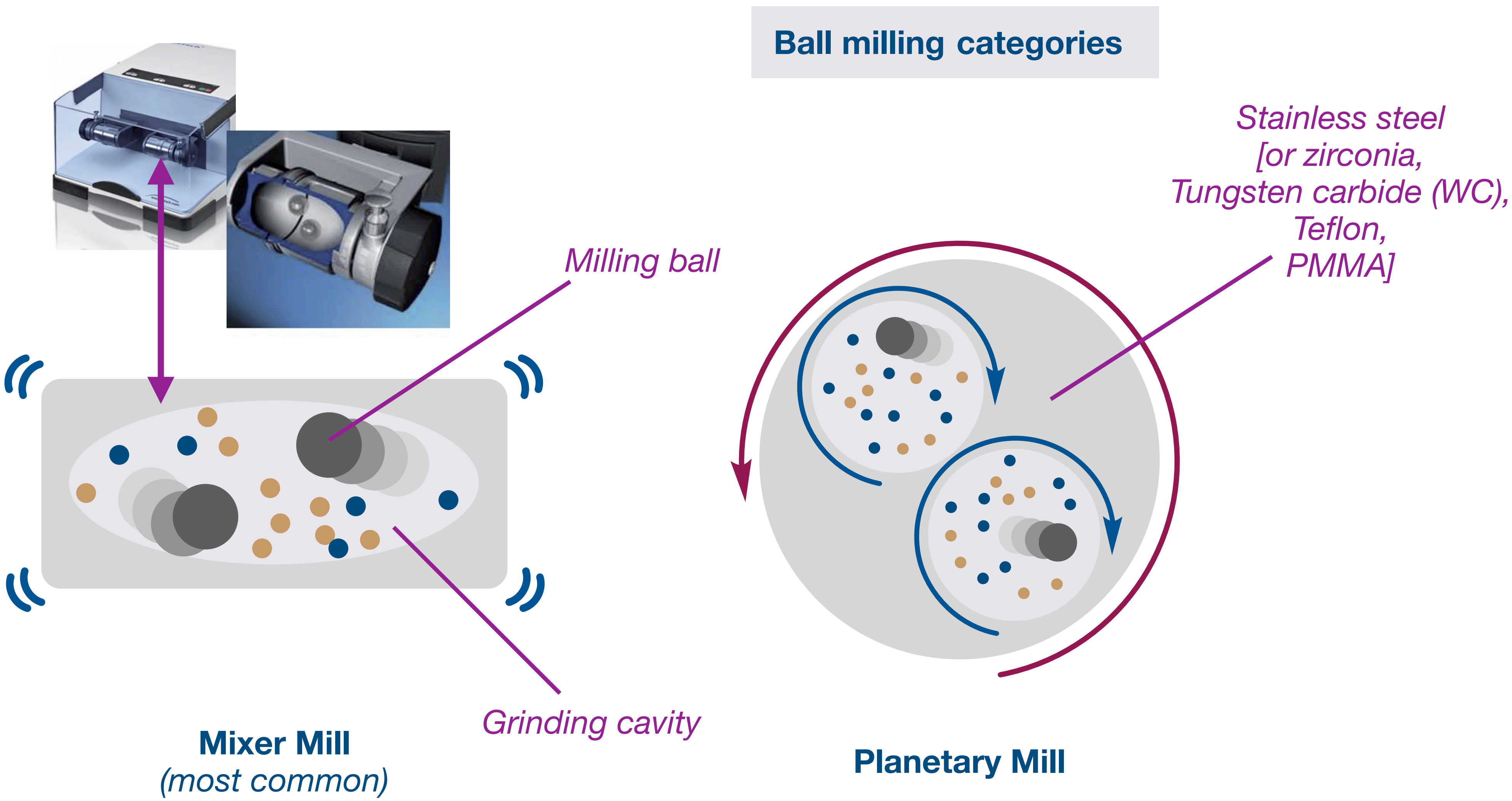


Planetary Mill

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Ball milling

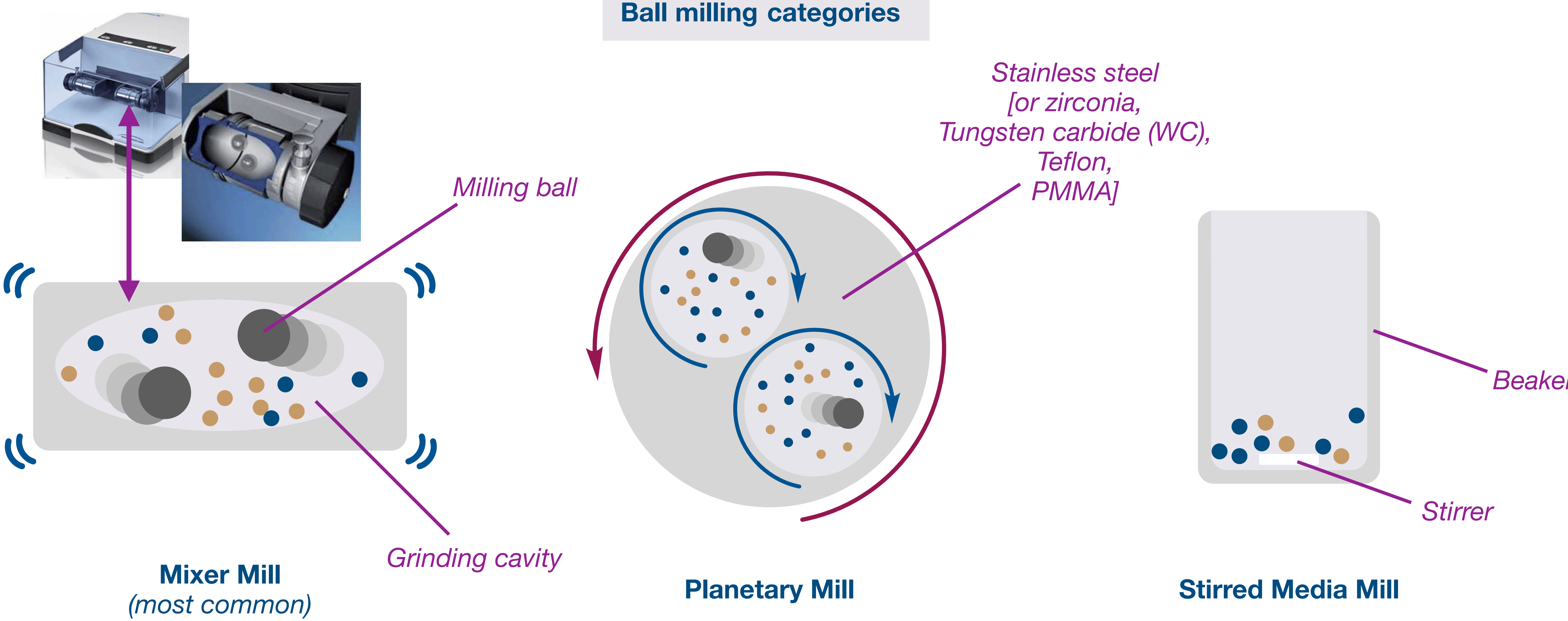


Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Ball milling

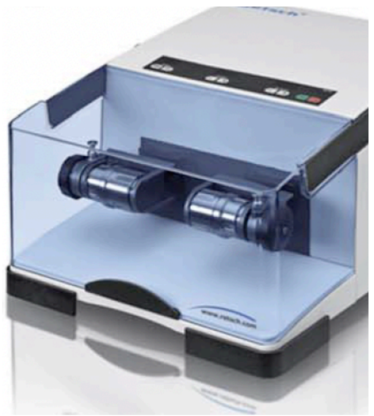
Ball milling categories

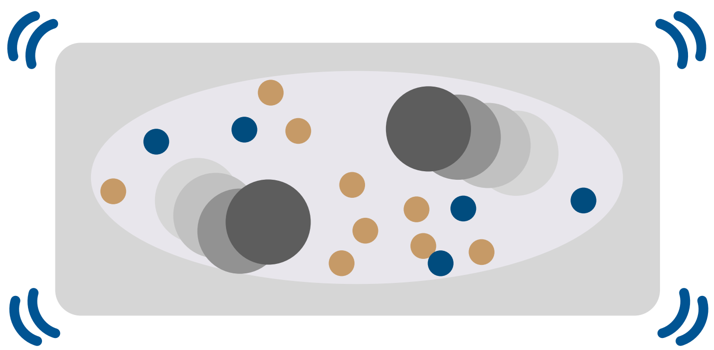


Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Setting up a mechanochem reaction 1.0



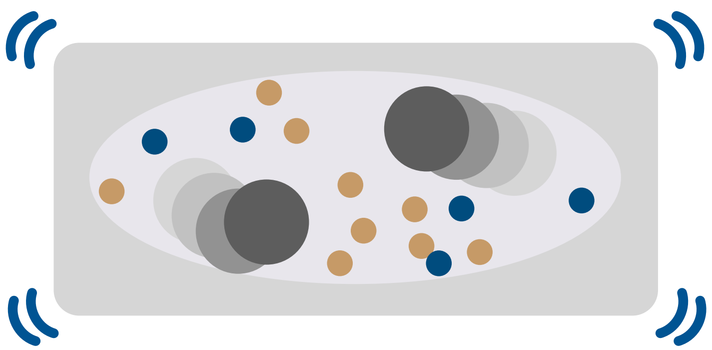


Mixer Mill

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Setting up a mechanochem reaction 1.0



Mixer Mill

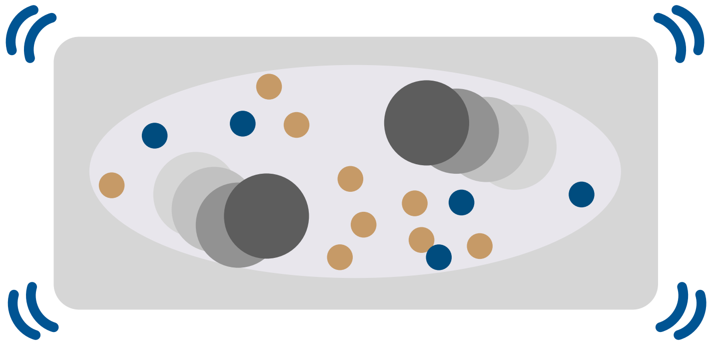
Key variables

- **Cavity/jar volume (V_J)**
- **Ball diameter (D_B)**
- **#balls**
- **Volume of reactants**
- **Milling/oscillating frequency (f)**
- **Time (t)**
- **Temperature (T)**

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Setting up a mechanochem reaction 1.0



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Additives

Grinding agents/auxiliaries

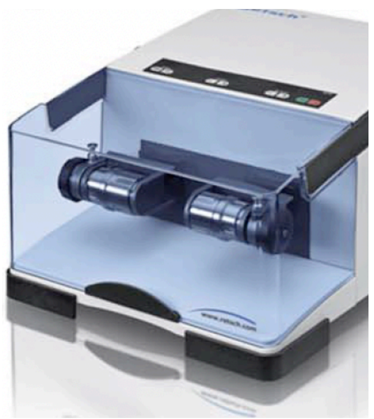
Ionic solids
(IAG)

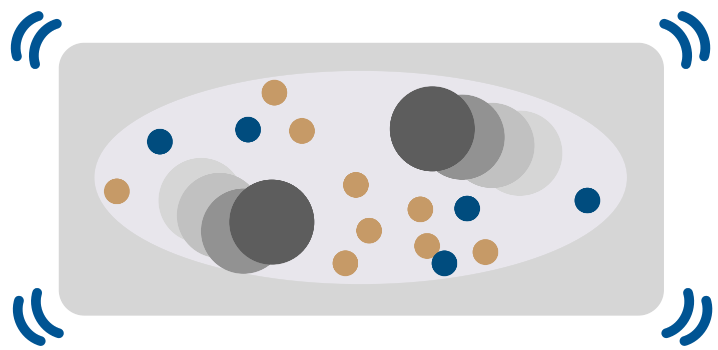
non-ionic additives
e.g., Polymer-assisted grinding (POLAG)

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Setting up a mechanochem reaction 1.0





Mixer Mill

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- **#balls**
- **Volume of reactants**
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- **Time (t)**
- **Temperature (T)**

Additives

Grinding agents/auxiliaries *and/or* **Liquid-assisted grinding (LAG)**

Ionic solids
(IAG)

non-ionic additives
e.g., Polymer-assisted grinding (POLAG)

Facilitate particle diffusion, stabilize solid forms,…

Duncan L. Browne et al., *Chem. Sci.* **2018**, *9*, 3080–3094.

Mechanochemistry in Organic Synthesis

Basic features

Is Mechanochemistry solvent-free?

Liquid-assisted grinding (LAG)

(Previously termed: “solvent drop grinding”)

Duncan L. Browne et al., *Green Chem.*, **2017**, *19*, 2798-2802; William Jones et al., *Chem. Commun.,* **2002**, 2372-2373.

Mechanochemistry in Organic Synthesis

Basic features

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η parameter

(μL "solvent"/mg of mixture)

Duncan L. Browne et al., *Green Chem.*, **2017**, *19*, 2798-2802; William Jones et al., *Chem. Commun.,* **2002**, 2372-2373.

Mechanochemistry in Organic Synthesis

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Duncan L. Browne et al., *Green Chem.*, **2017**, *19*, 2798-2802; William Jones et al., *Chem. Commun.*, **2002**, 2372-2373.

Mechanochemistry in Organic Synthesis

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Mechanochemistry in Organic Synthesis

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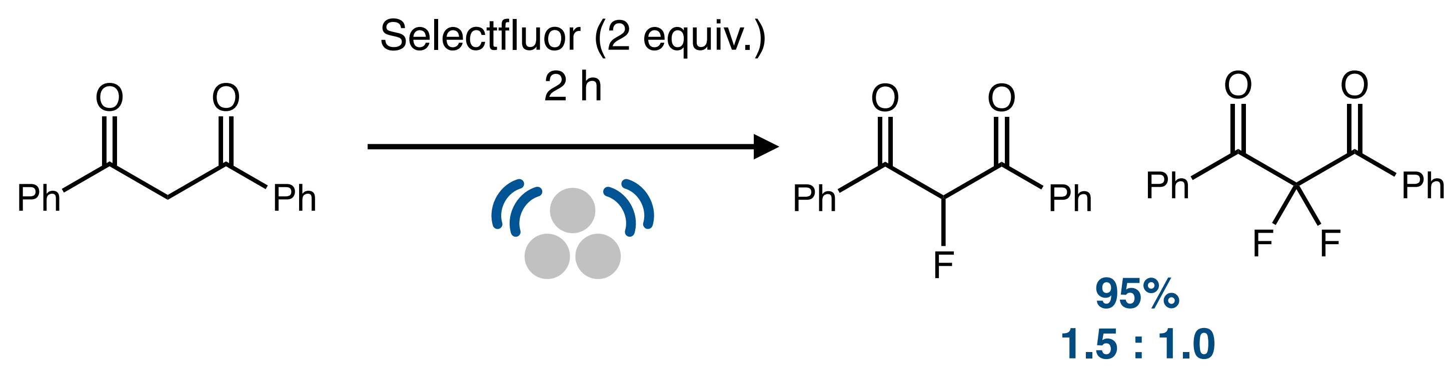

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Mechanochemistry in Organic Synthesis

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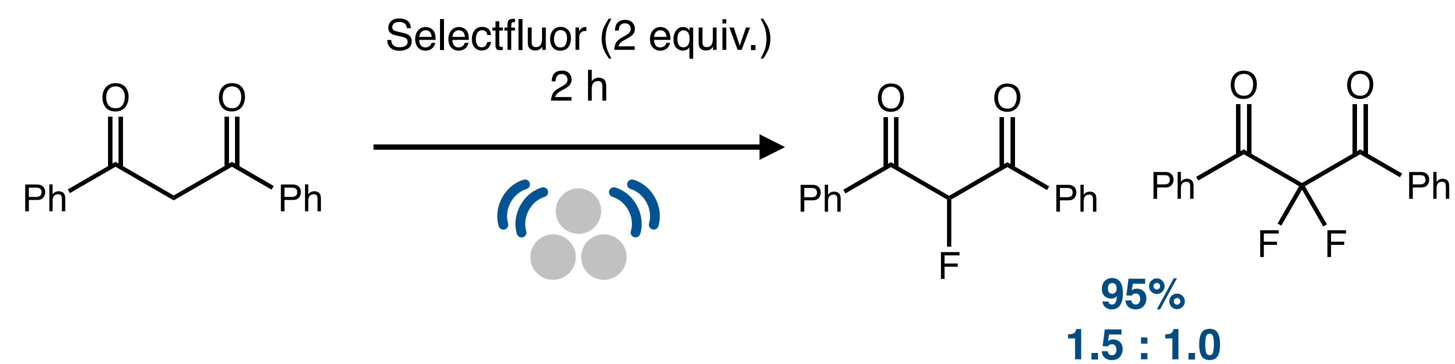

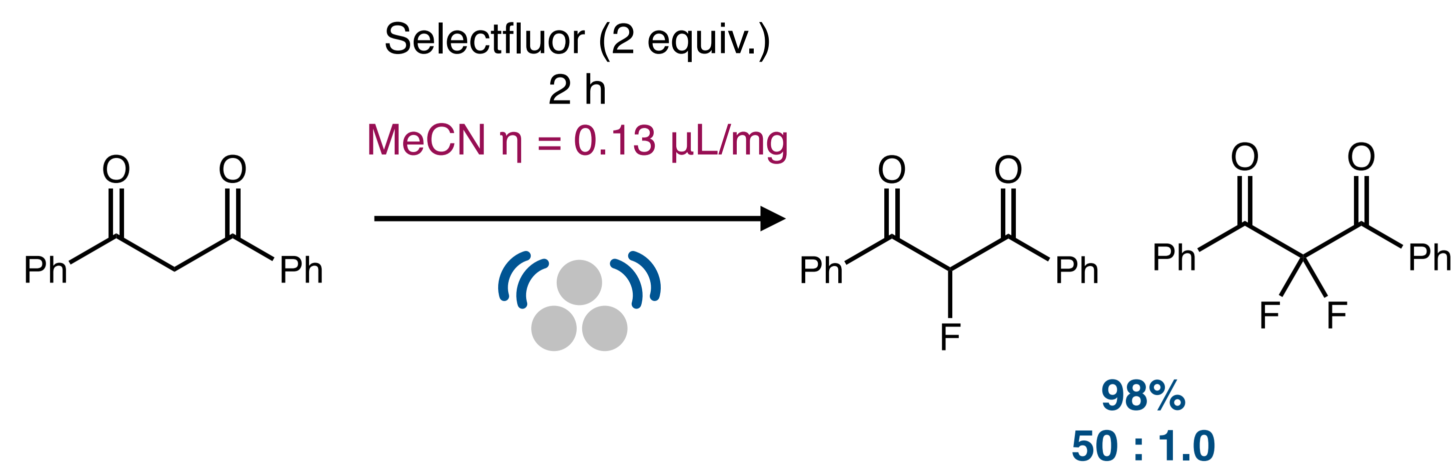

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Mechanochemistry in Organic Synthesis

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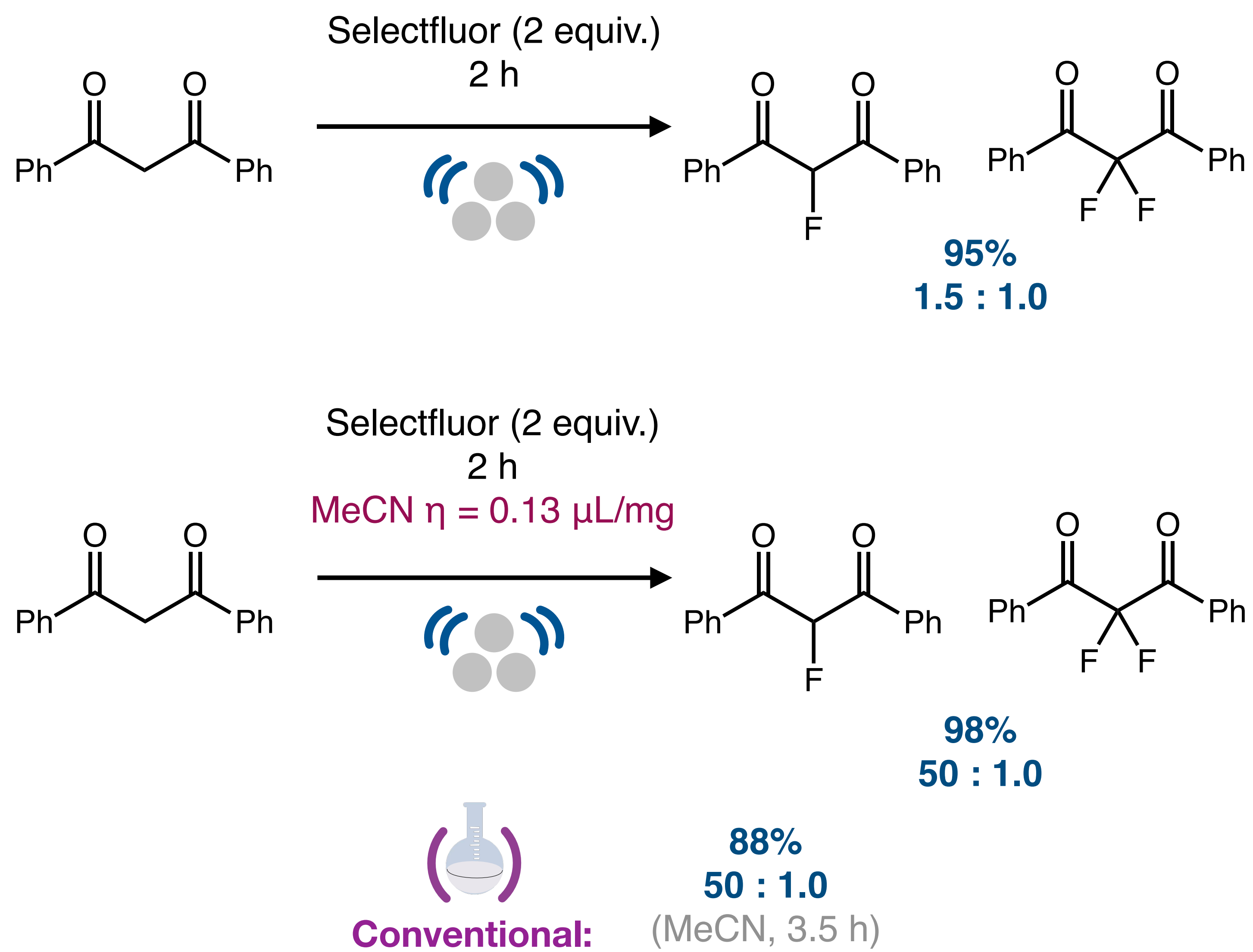

Duncan L. Browne et al., *Green Chem.*, **2017**, *19*, 2798-2802; William Jones et al., *Chem. Commun.*, **2002**, 2372-2373.

Mechanochemistry in Organic Synthesis

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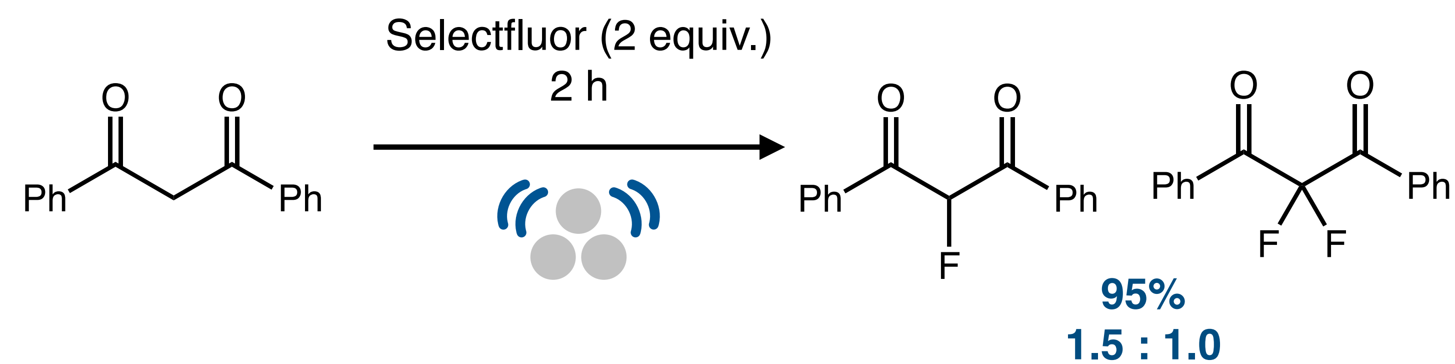
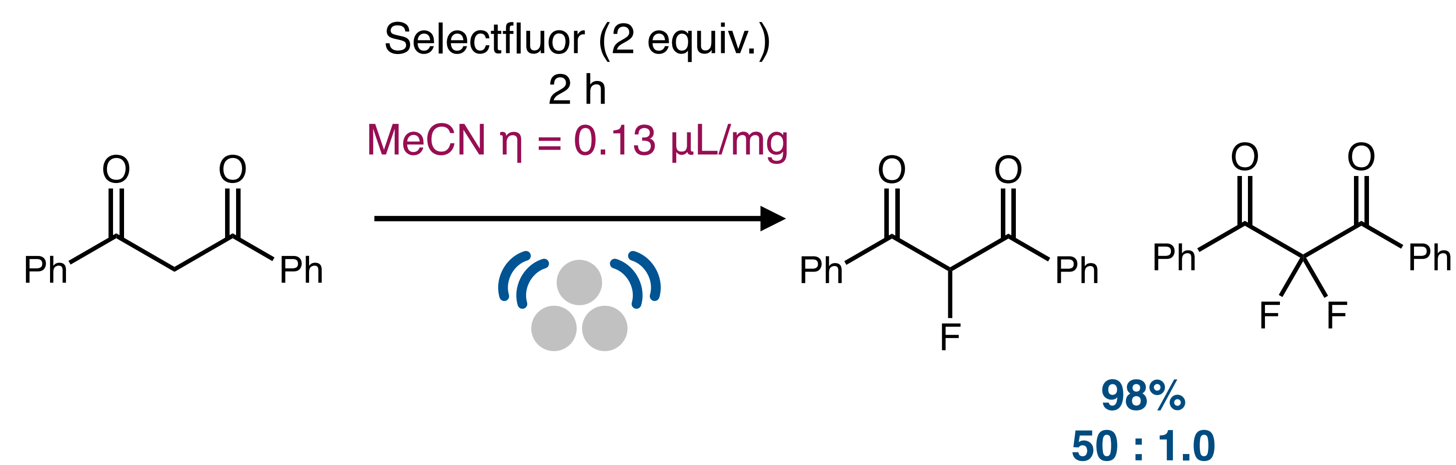
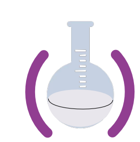




“The precise effects of LAG on organic reactions are poorly characterized and the exact rationale for the observed selectivity in this reaction remains unclear."



Conventional: **88%** **50 : 1.0** (MeCN, 3.5 h)

Duncan L. Browne et al., *Green Chem.*, **2017**, *19*, 2798-2802; William Jones et al., *Chem. Commun.*, **2002**, 2372-2373.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

How do we monitor a mechanochemical reaction?

Mechanochemistry in Organic Synthesis

Reaction Monitoring

How do we monitor a mechanochemical reaction?

In situ monitoring

X-Ray diffraction

Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.

Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Raman spectroscopy

Halasz I., Užarević, K. et al., *Angew. Chem. Int. Ed.* **2014**, *53*, 6193 –6197.

Halasz, I. *Nat. Protoc.* **2021***, 16*, 3492–3521.

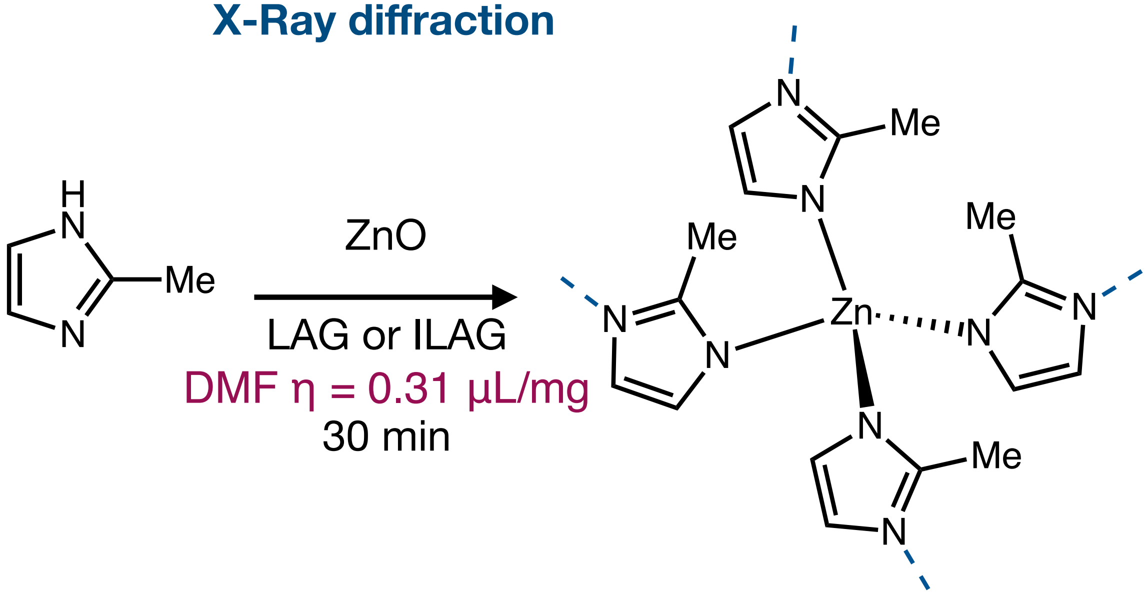
X-Ray absorption spectroscopy

Emmerling F. et al., *Chem. Commun.*, **2020**, *56*, 10329-10332.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

X-Ray diffraction

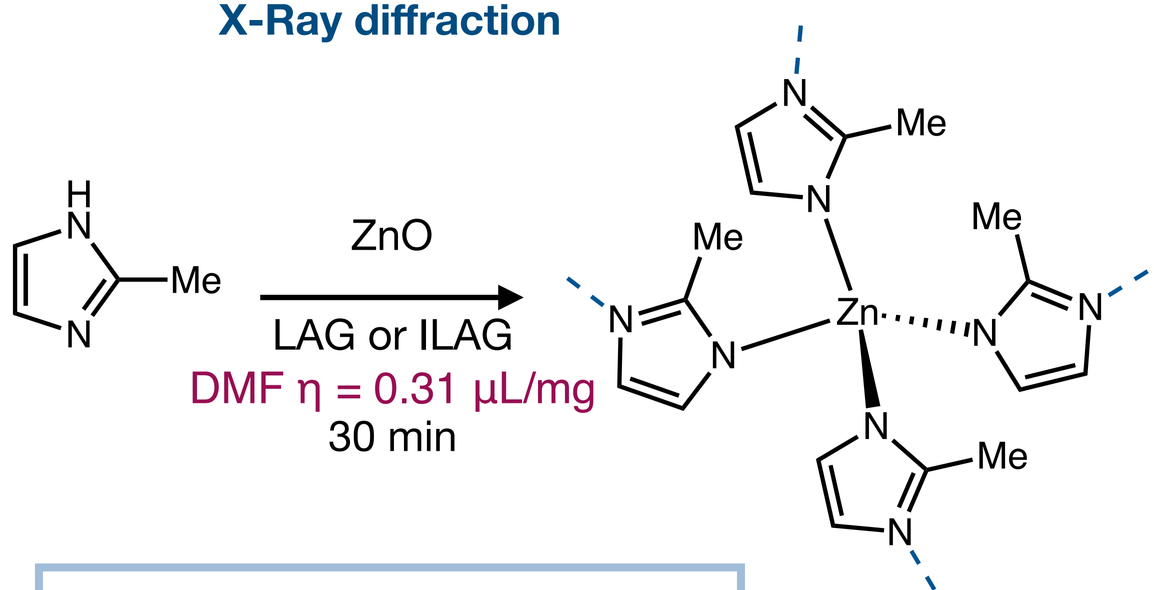


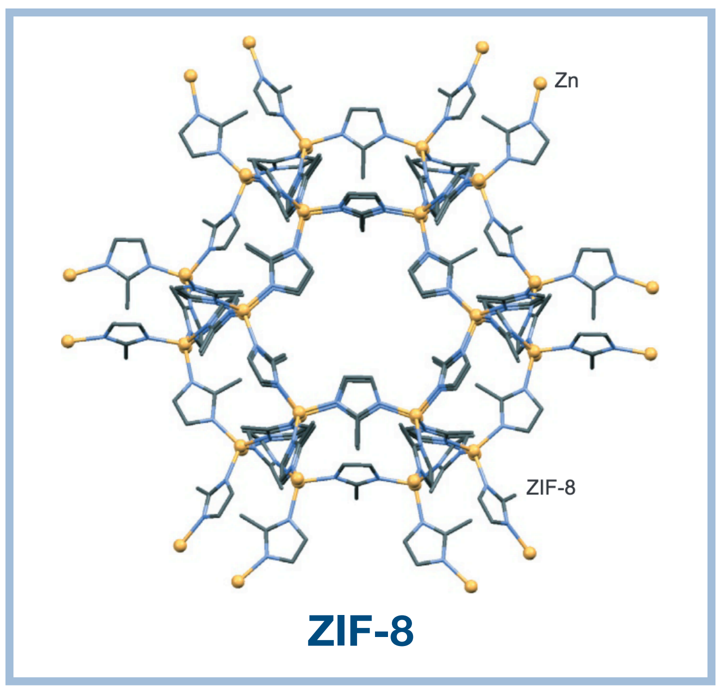
Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

X-Ray diffraction





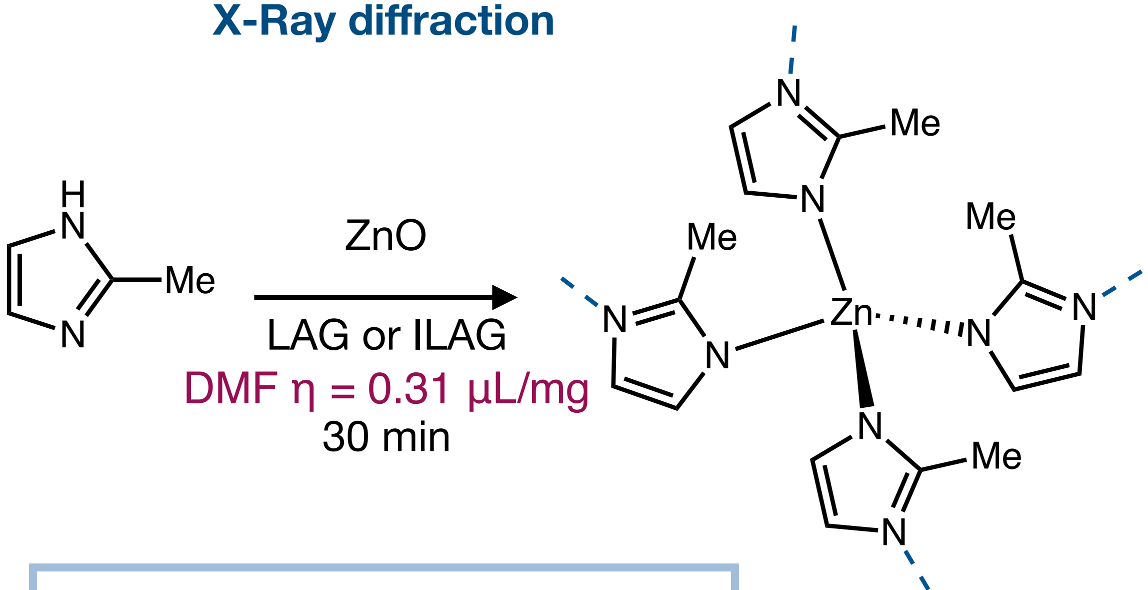
(Zeolite Imidazole Framework)

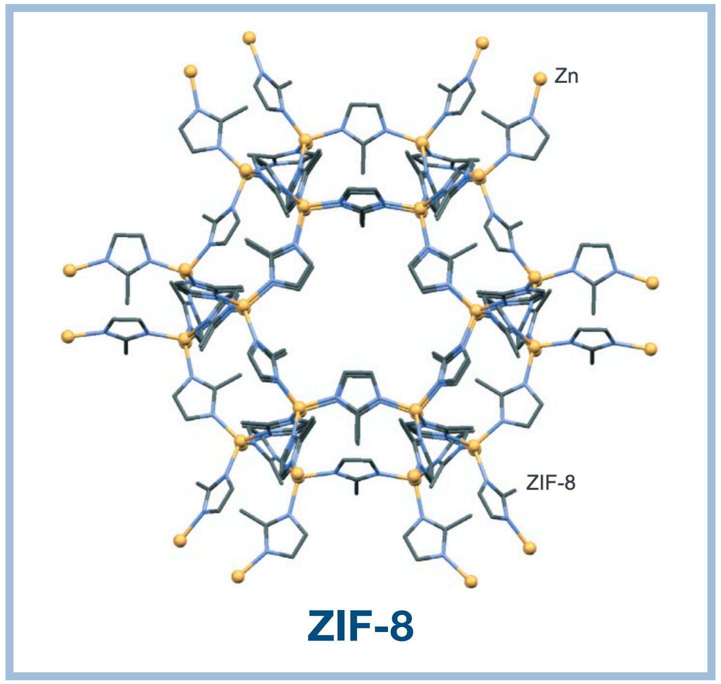
Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

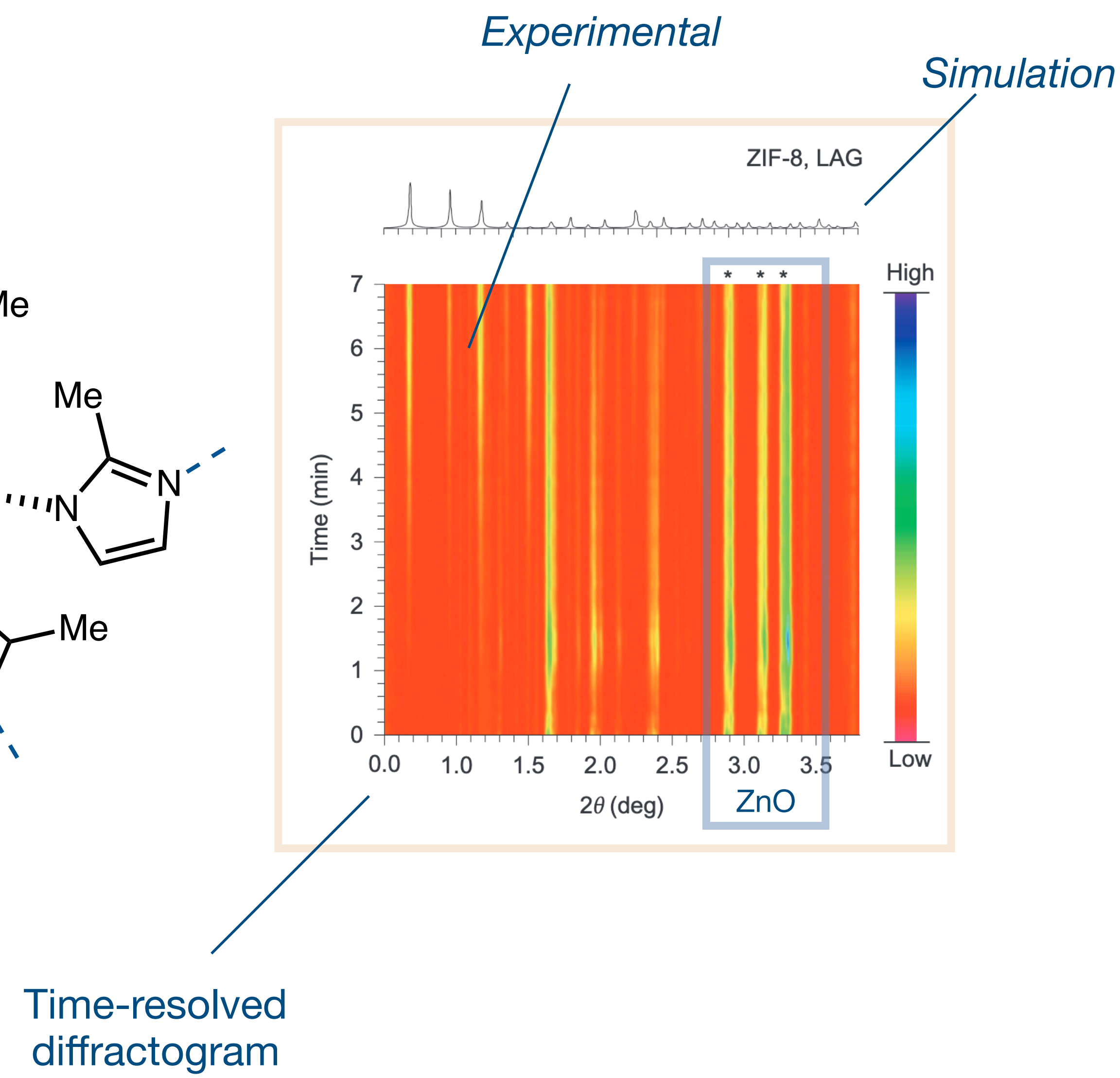
X-Ray diffraction





ZIF-8

(Zeolite Imidazole Framework)

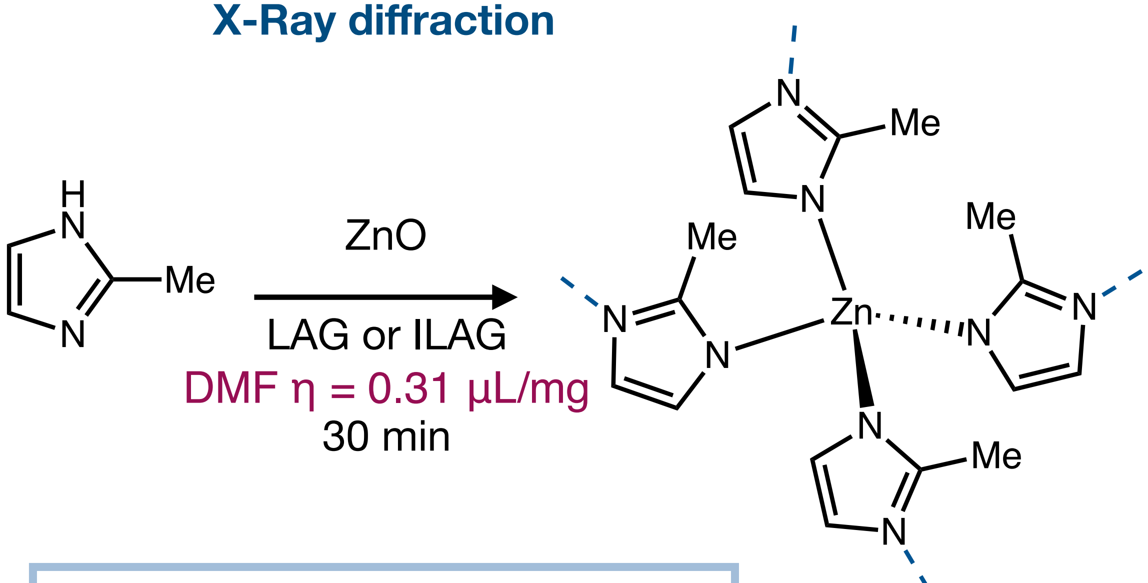


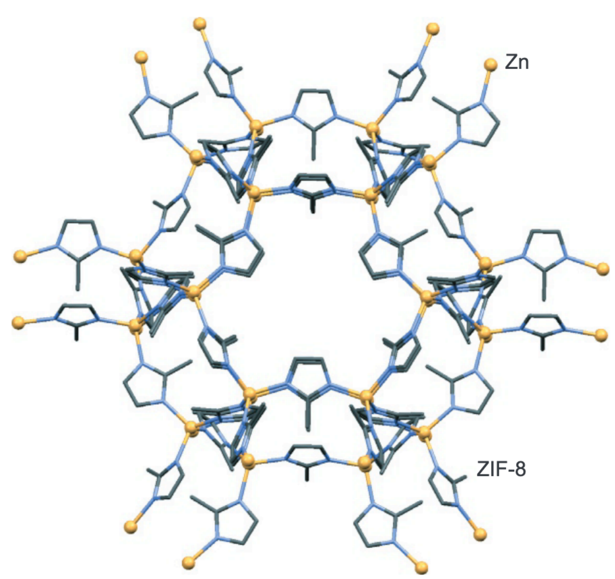
Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

X-Ray diffraction



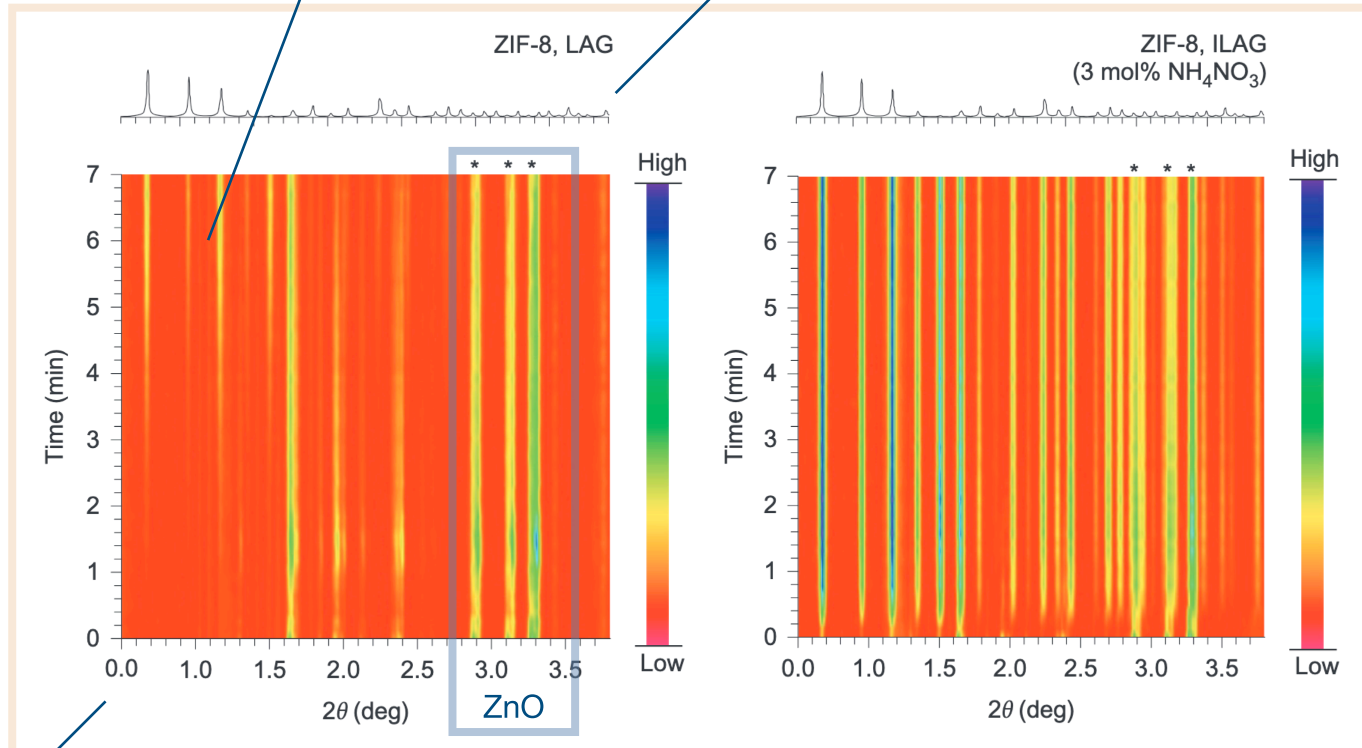


ZIF-8

(Zeolite Imidazole Framework)

Experimental

Simulation



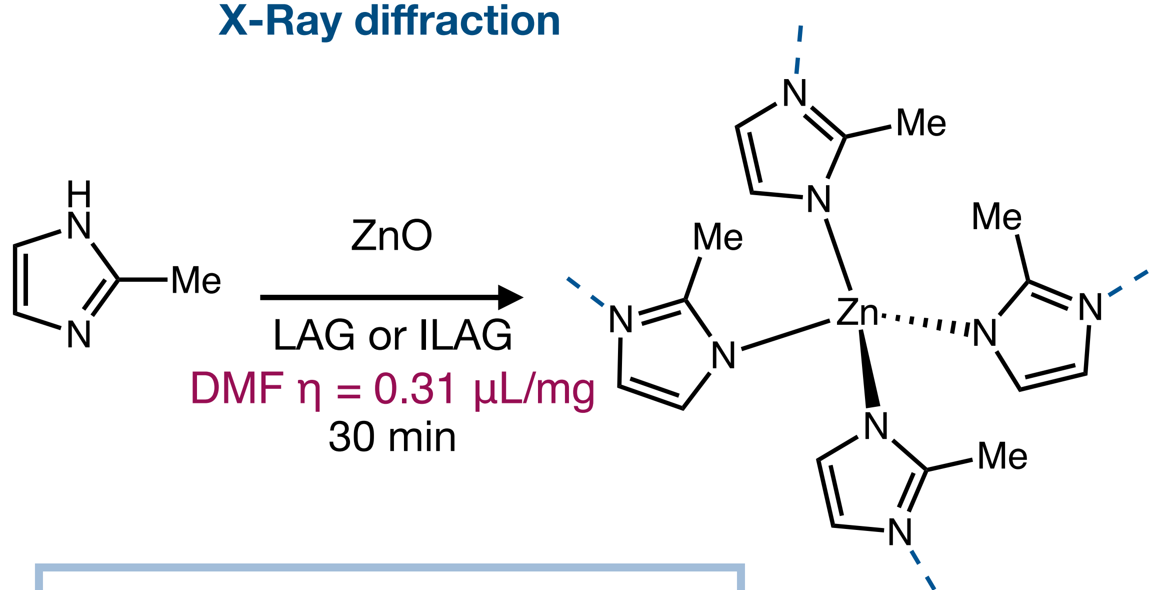
Time-resolved diffractogram

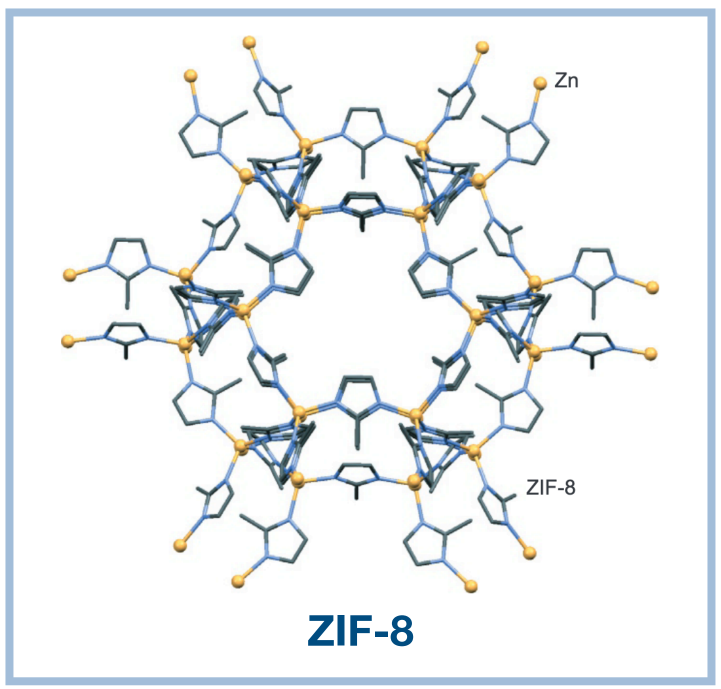
Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

X-Ray diffraction





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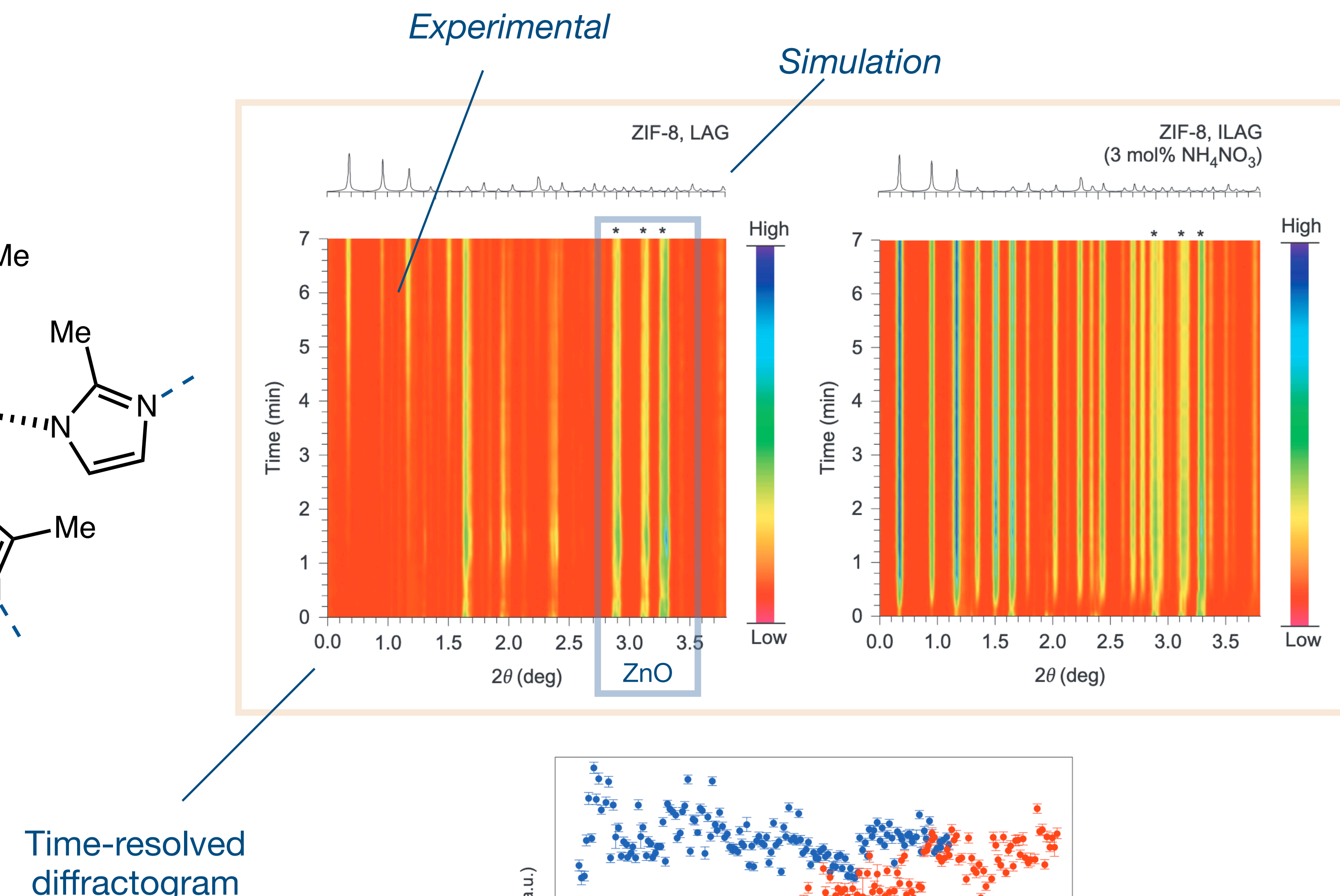
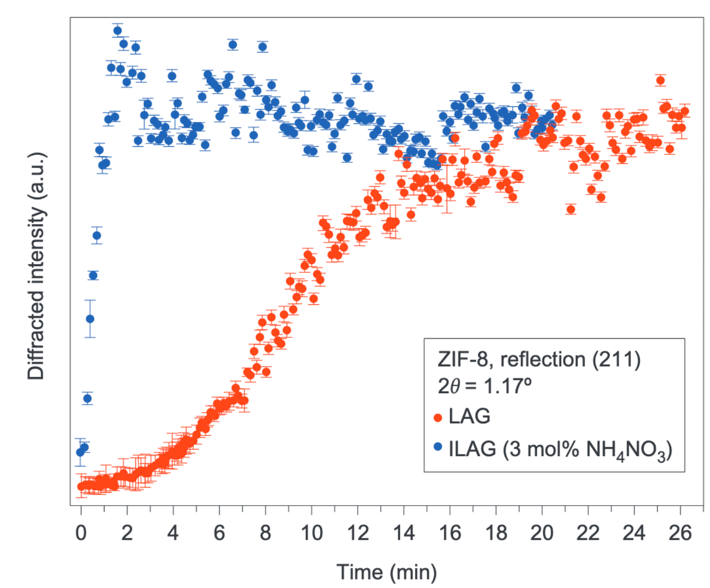


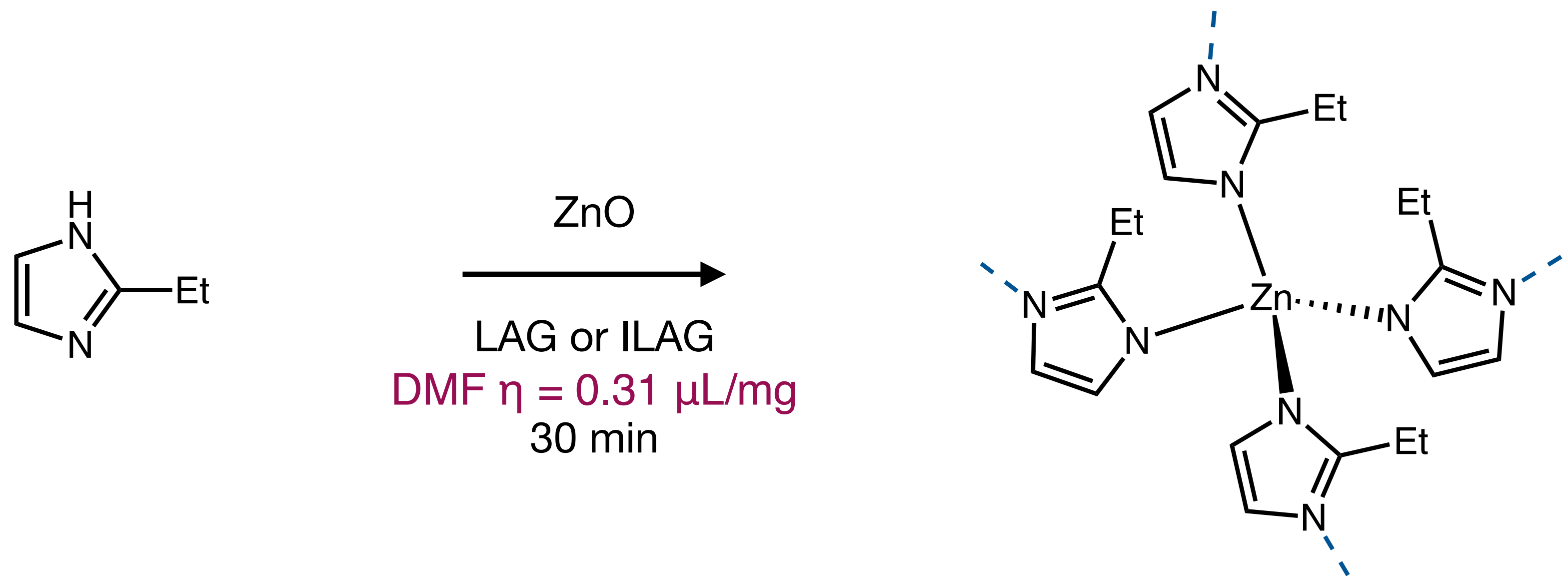


Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

X-Ray diffraction



Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring

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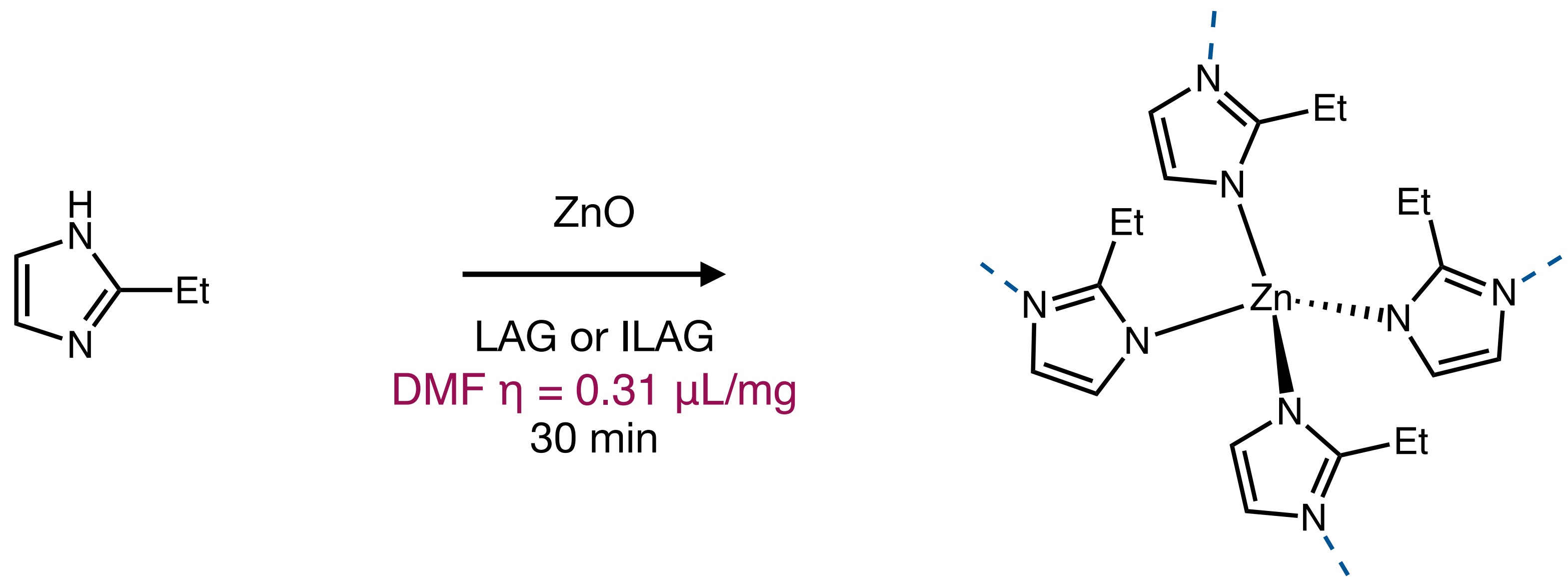
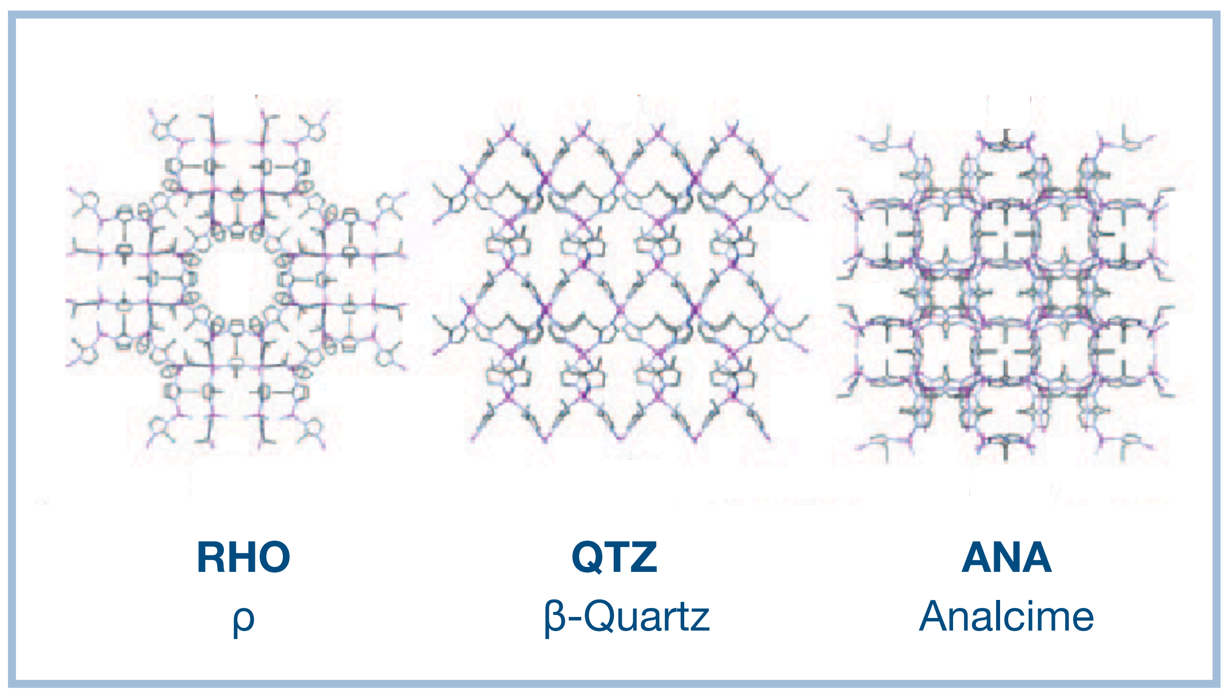


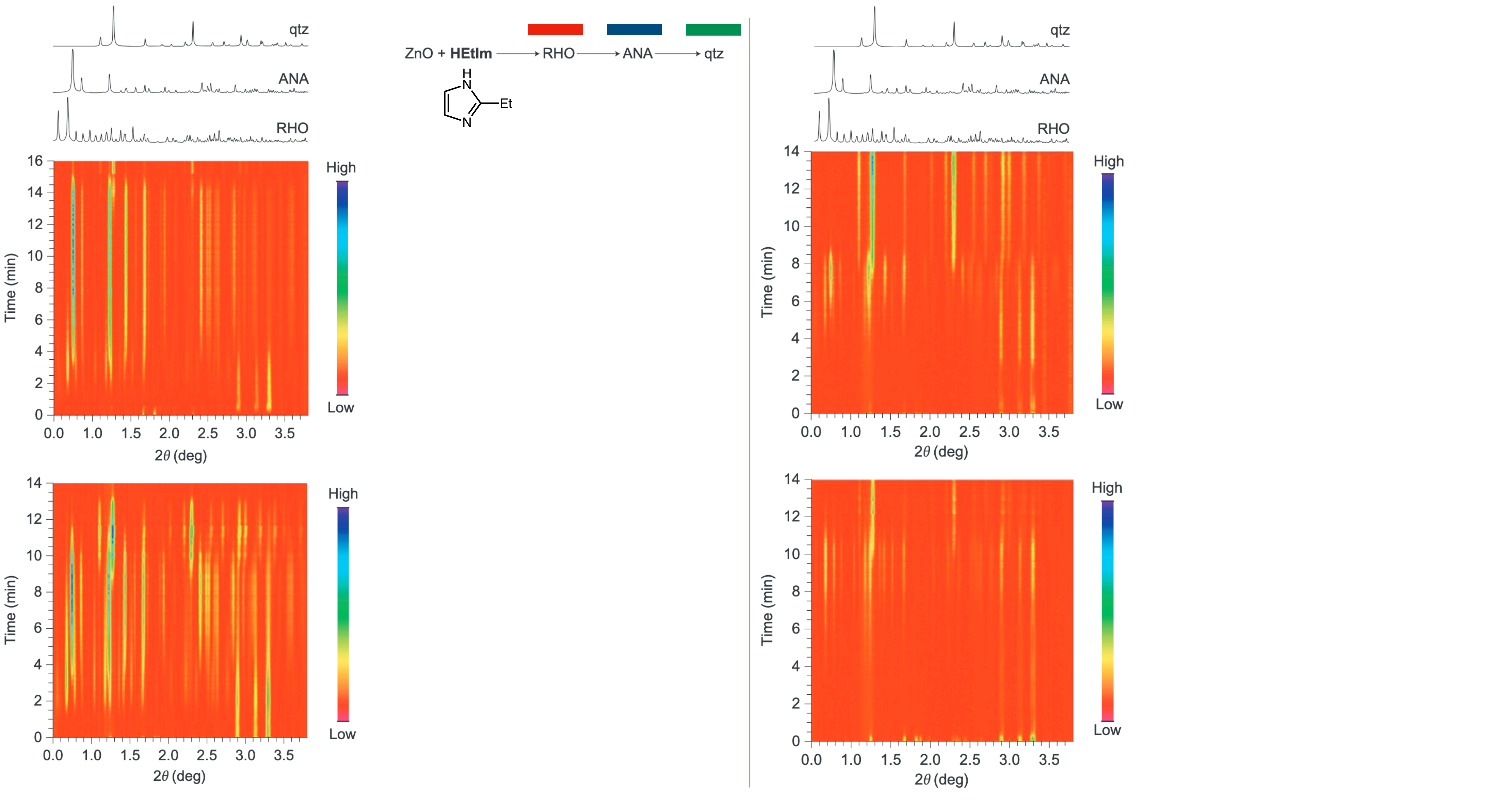


Sequential formation of three frameworks

Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

Reaction Monitoring



Friščić T. et al., *Nat. Chem.* **2013**, *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Mechanochemistry in Organic Synthesis

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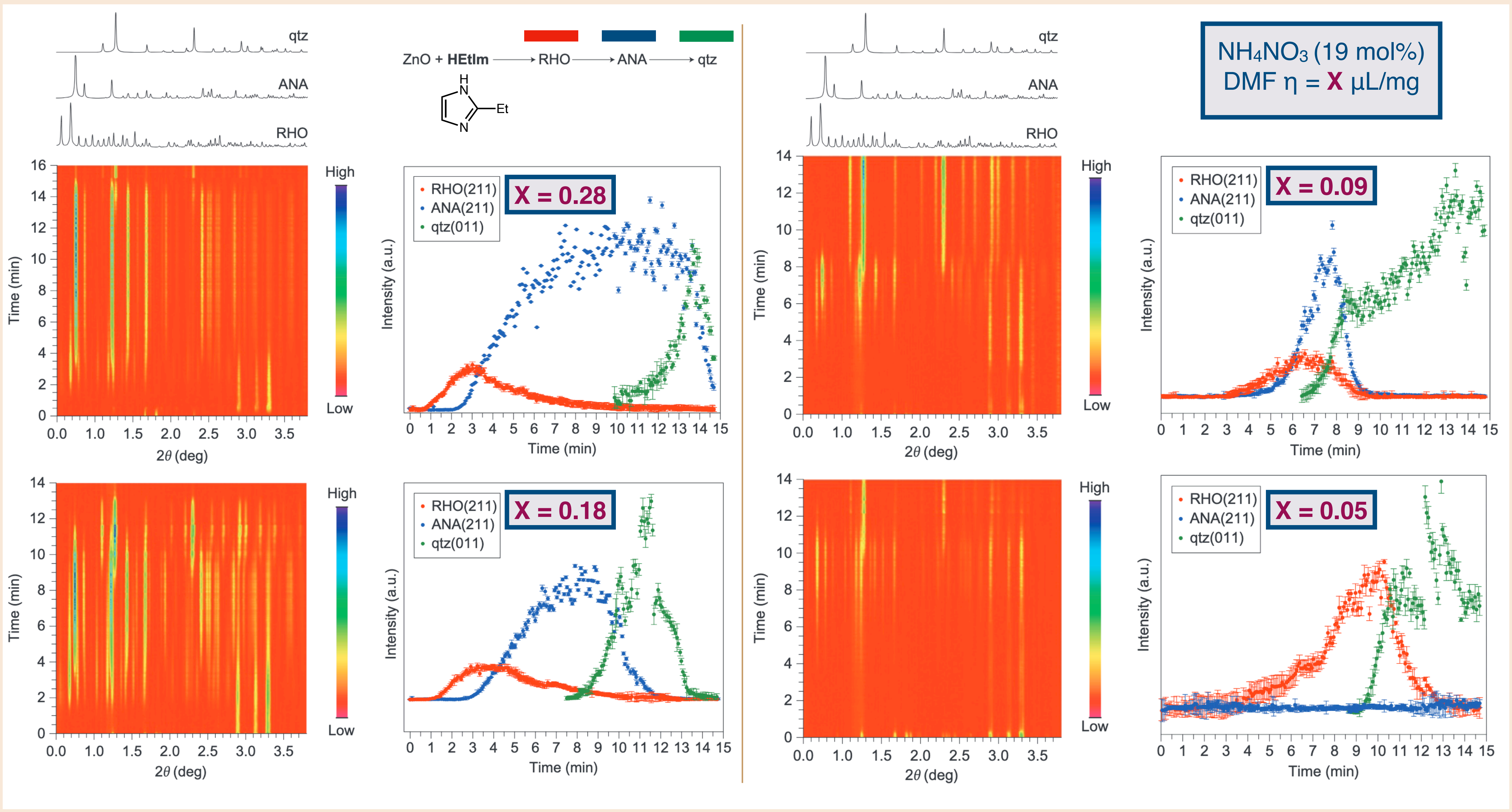


Friščić T. et al., *Nat. Chem.* **2013,** *5*, 66–73.; Friščić T. et al., *J. Phys. Chem. Lett.* **2015**, *6*, 4129–4140.

Brief tutorial introduction on Mechanochem (generally)

History

Mechanistic aspects

Mechanical actions and mechanoreactors

Reaction Monitoring

Why mechanochemistry?

Mechanochemical vs. solution-based reactions

Medicinal mechanochemistry

“Mechanochemistry 2.0”

Mechanoredox

Mechanochemistry in Organic Synthesis

Why mechanochemistry?

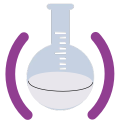
Sustainable synthesis

Realise "impossible" reactions
(i.e., not feasible in solution)

Complementary approach

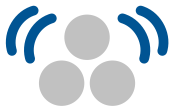
Mechanochemistry in Organic Synthesis

Environmental Impact



Solution chemistry

vs.



Mechanochemistry

Solvents

Production
Transportation
Storage
Heating/cooling
Degassing
Drying

Solvent-free or LAG

More sustainable
Energy-economical
Cost-effective
Cleaner
Safer

Felipe García, Evelina Colacino *Chem. Soc. Rev.*, **2023**, *52*, 6680; Evelina Colacino, Andrea Porcheddu et al., *ChemSusChem* **2022**, *15*, e202200362; Jean-Louis Do, Tomislav Friščić *ACS Cent. Sci.* **2017**, *3*, 13–19.

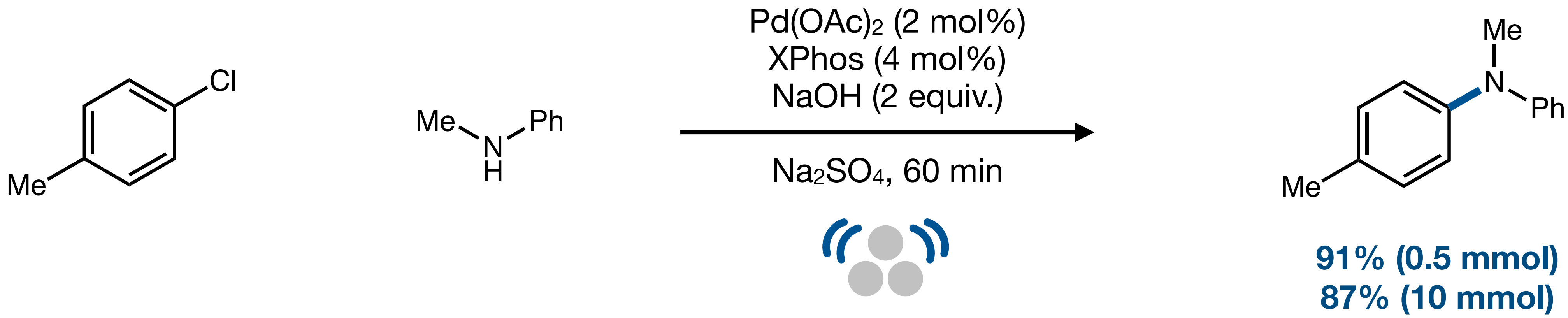
Mechanochemistry in Organic Synthesis

Solvent-free cross-couplings

Wei-Ke Su et al., *Tetrahedron Lett.* **2018**, *59*, 2277–2280.

Mechanochemistry in Organic Synthesis

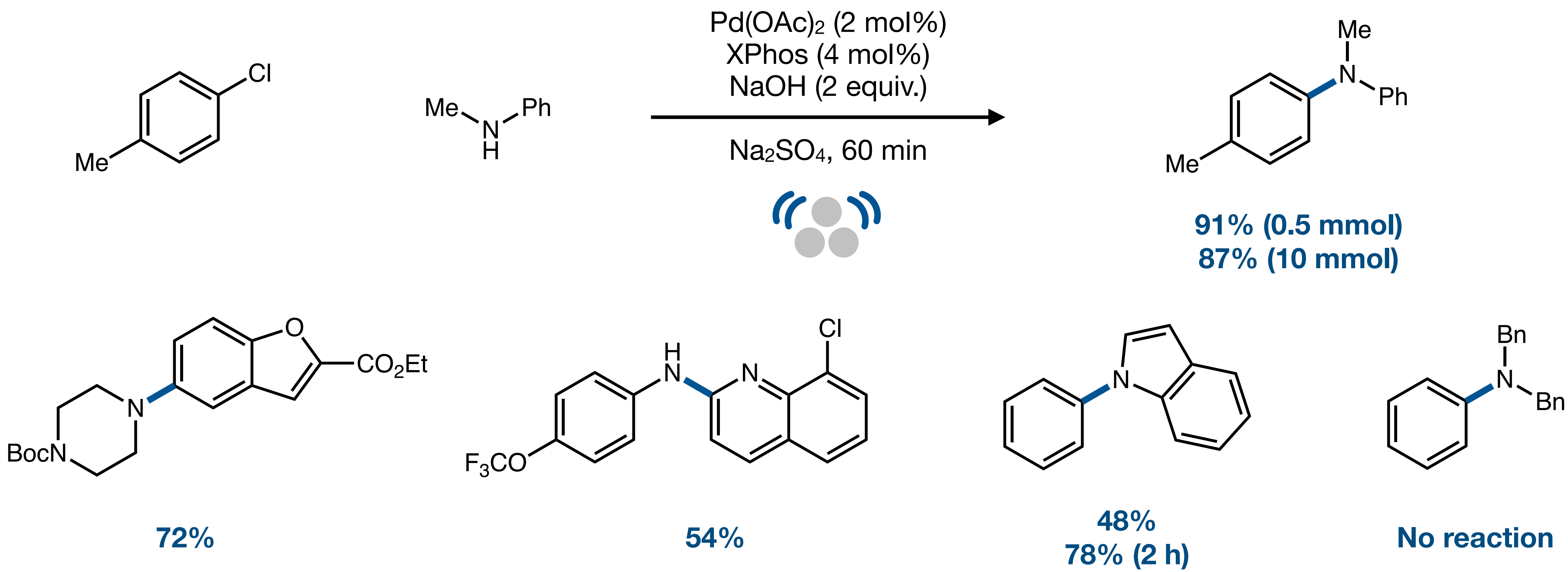
Solvent-free cross-couplings



Wei-Ke Su et al., *Tetrahedron Lett.* **2018**, *59*, 2277–2280.

Mechanochemistry in Organic Synthesis

Solvent-free cross-couplings



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Mechanochemistry in Organic Synthesis

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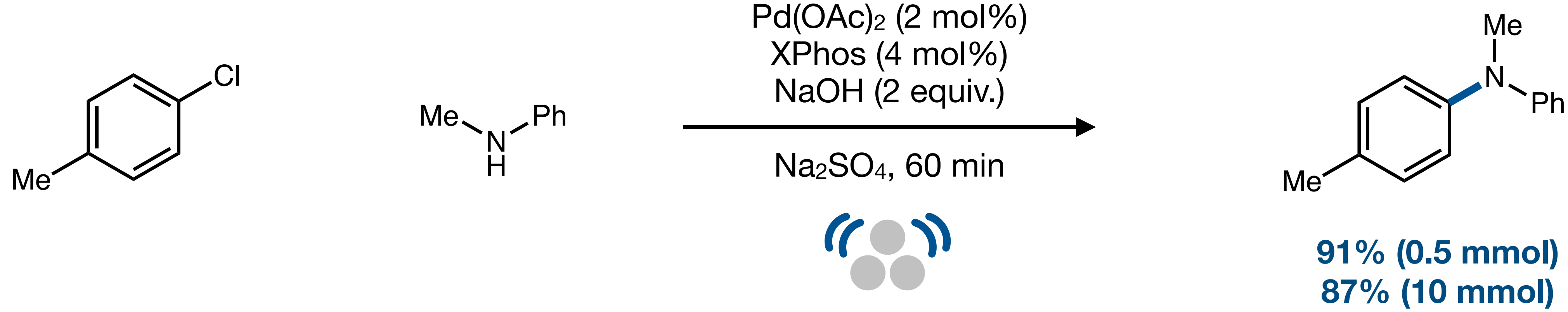
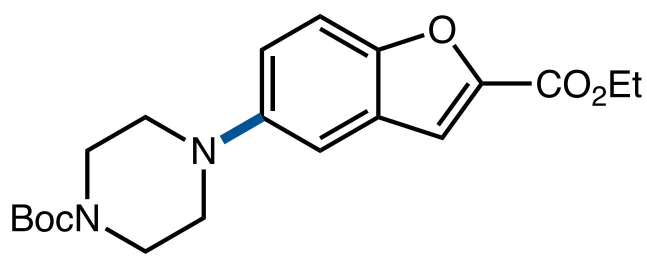
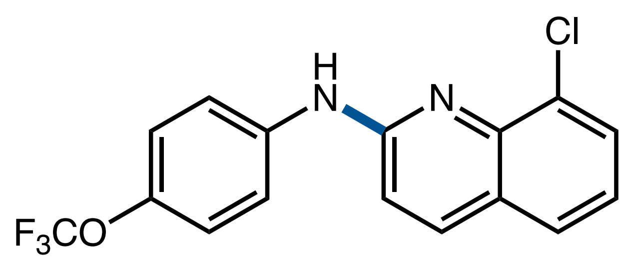
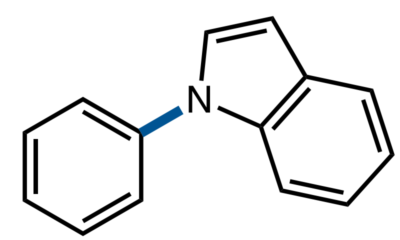




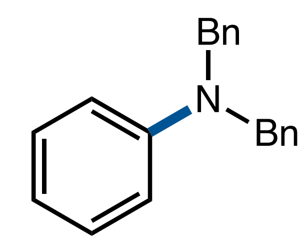
72%



54%

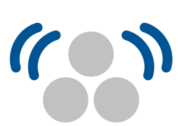


48%
78% (2 h)

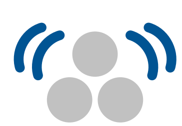


No reaction

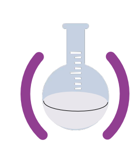
Under air



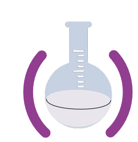
In glovebox: Negligible changes



91% Under Ar in dioxane



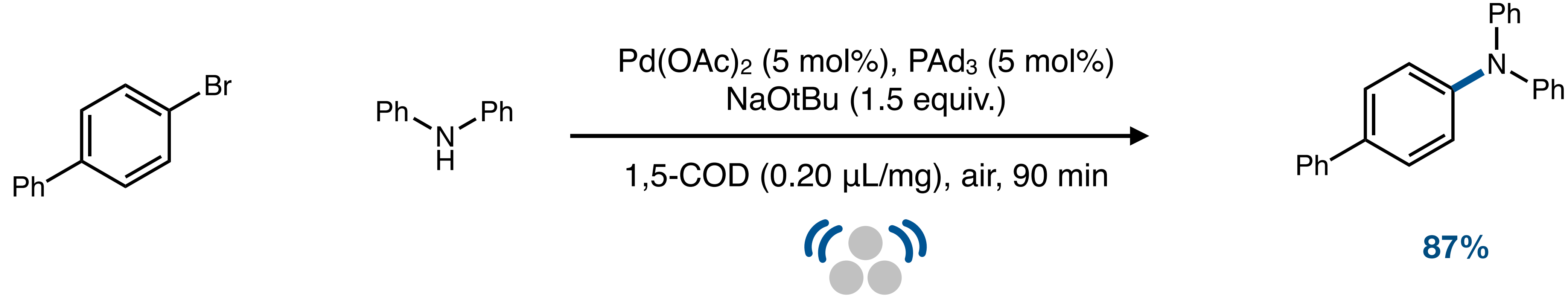
0% Under air in dioxane



Wei-Ke Su et al., *Tetrahedron Lett.* **2018**, *59*, 2277–2280.

Mechanochemistry in Organic Synthesis

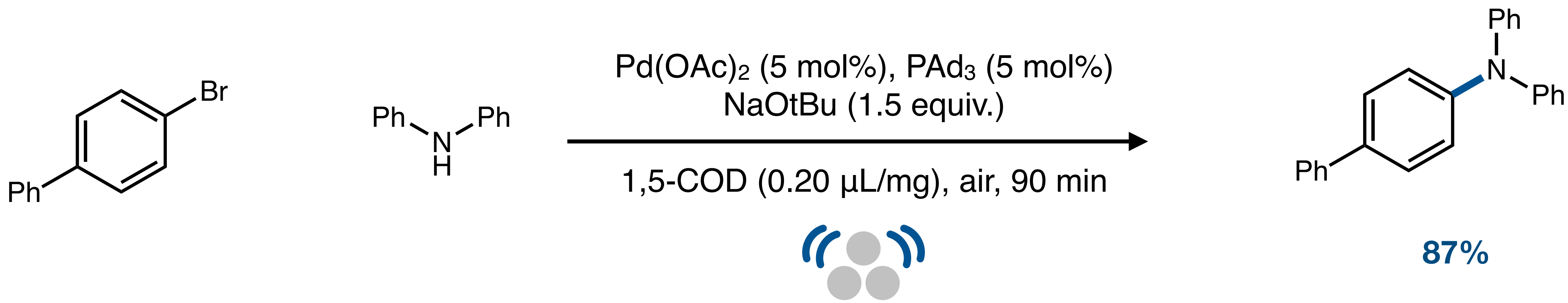
Solvent-free cross-couplings

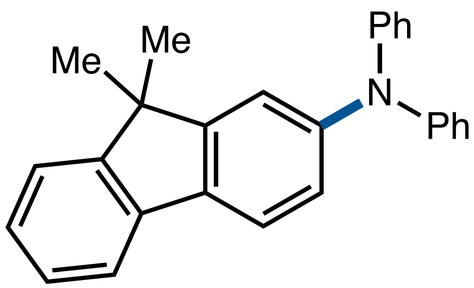


Koji Kubota, Hajime Ito et al., *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577–16582.

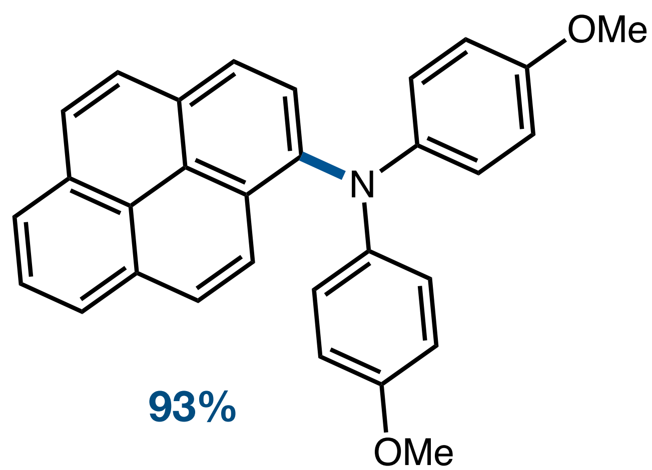
Mechanochemistry in Organic Synthesis

Solvent-free cross-couplings

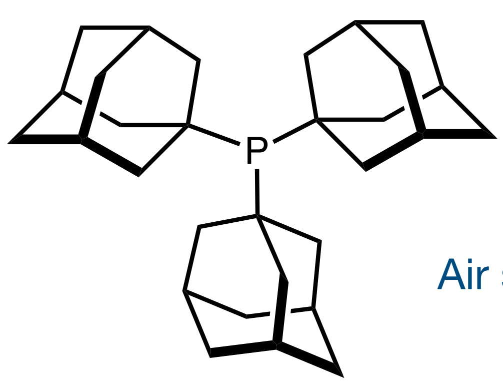




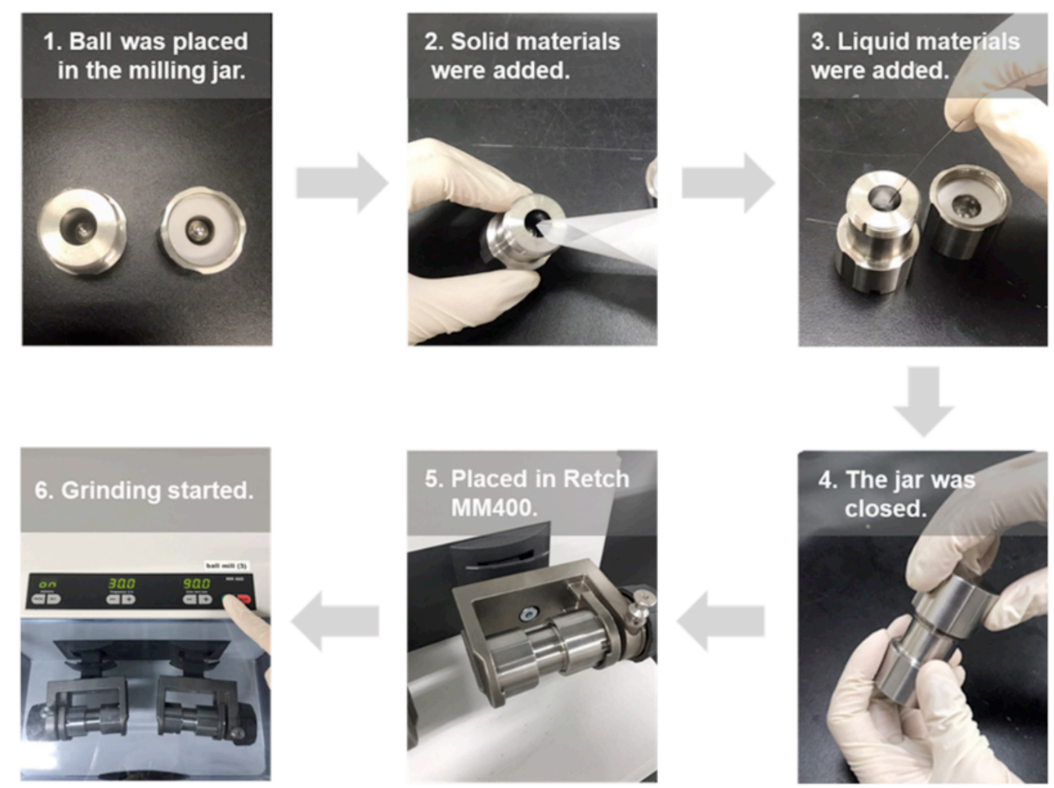
83%



93%



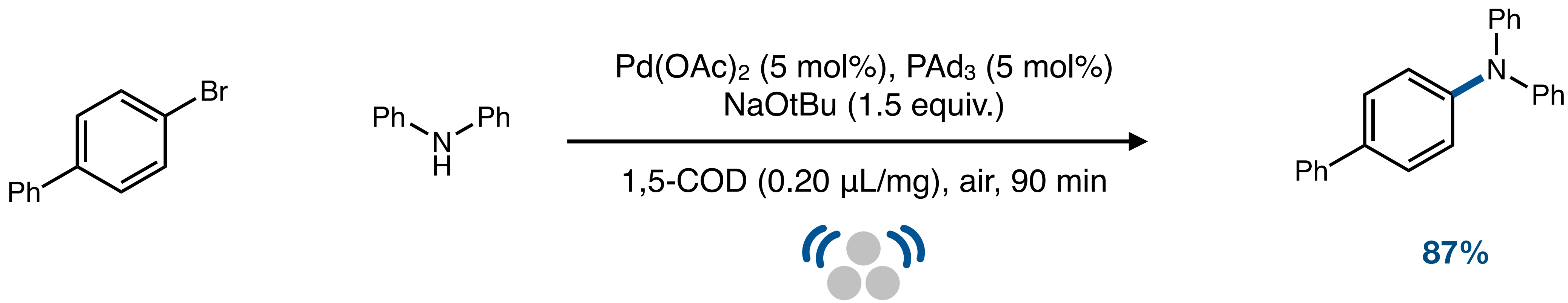
Air stable



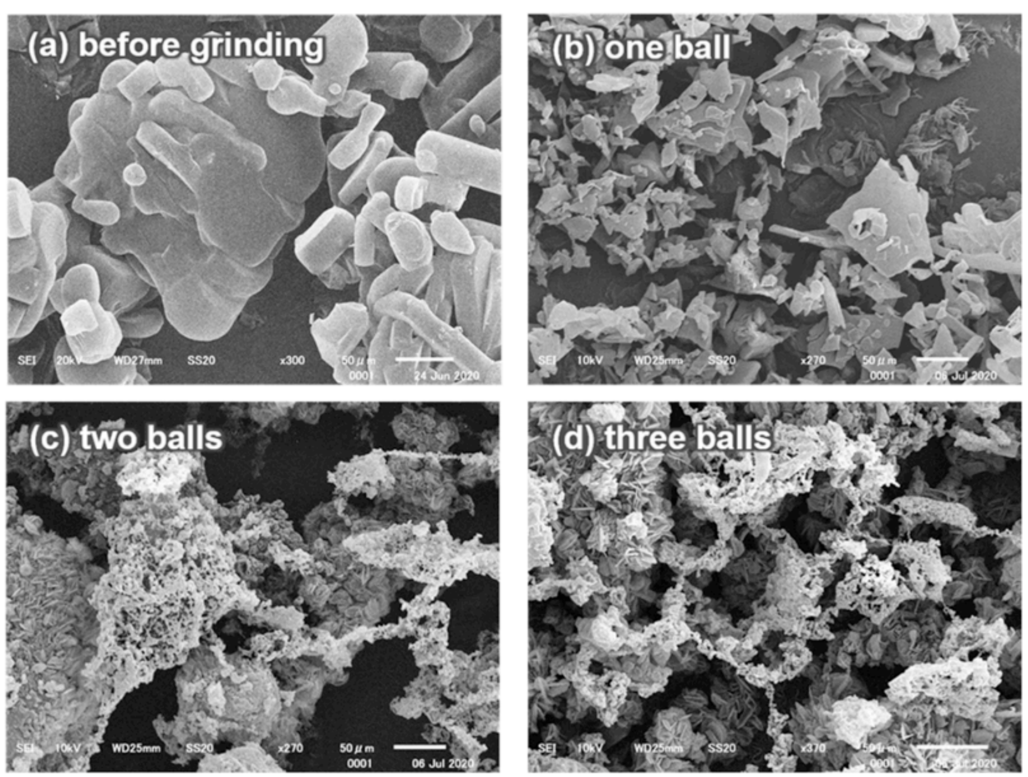
Koji Kubota, Hajime Ito et al., *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577–16582.

Mechanochemistry in Organic Synthesis

Solvent-free cross-couplings



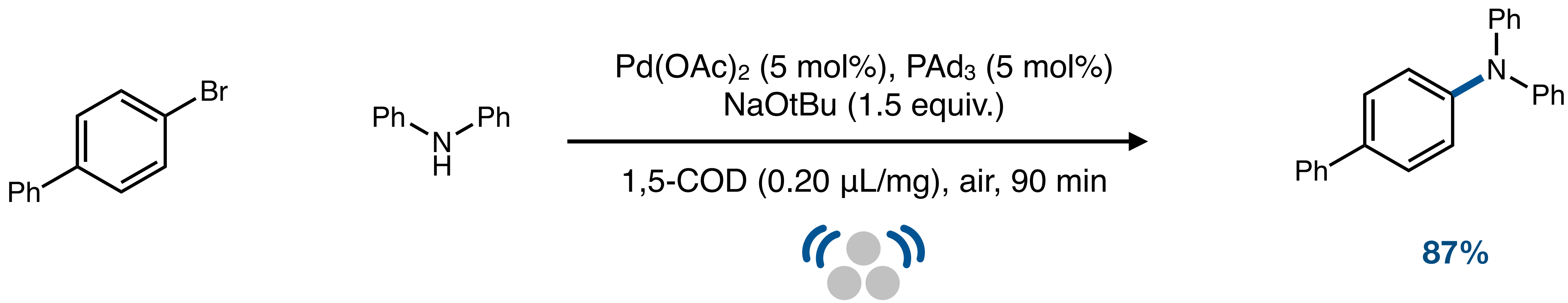
Scanning electron microscopy of $NHPh_2$



Koji Kubota, Hajime Ito et al., *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577−16582.

Mechanochemistry in Organic Synthesis

Solvent-free cross-couplings



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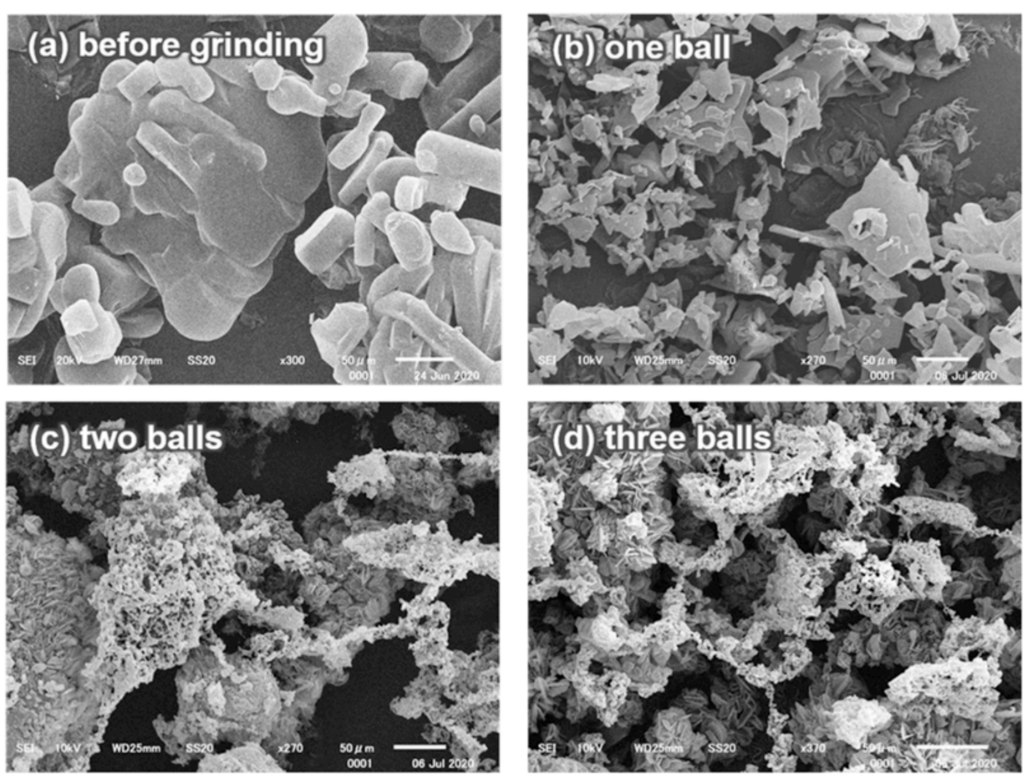
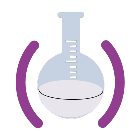
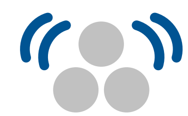


	Average AY		
Time (min)	1 ball	2 balls	**3 balls**
0	0	0	**0**
15	2	26	**4**
30	10	16	**5**
45	20	26	**25**
60	66	23	**52**
75	23	63	**66**
90	58	89	**90**

Koji Kubota, Hajime Ito et al., *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577–16582.

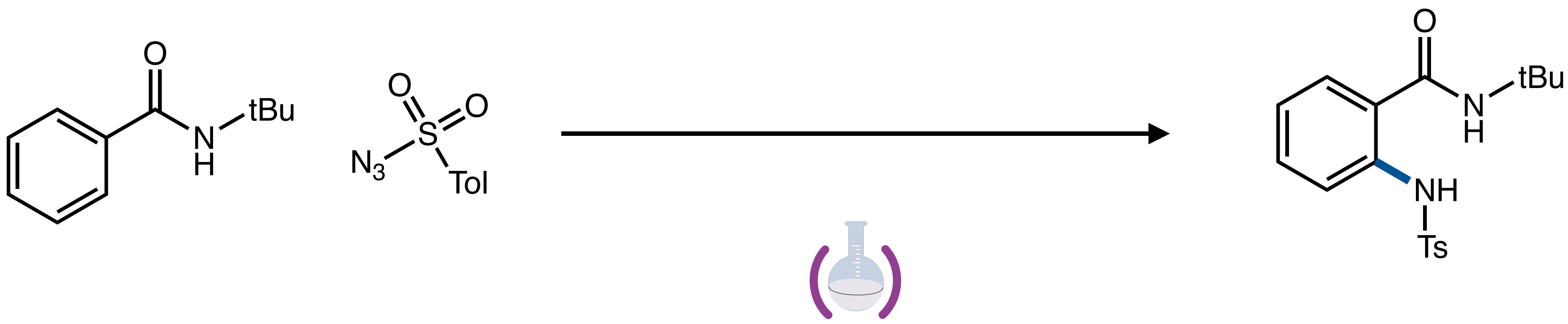


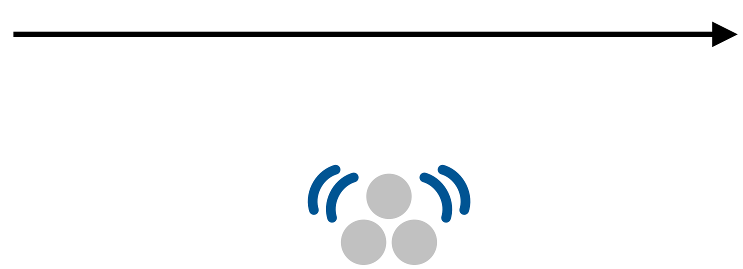
vs.



Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity





Duncan L. Browne Chem. Sci., **2018**, *9, 3080–3094.* Evelina Colacino, Andrea Porcheddu et al., *ChemSusChem* **2022**, *15*, e202200362.

Mechanochemistry in Organic Synthesis

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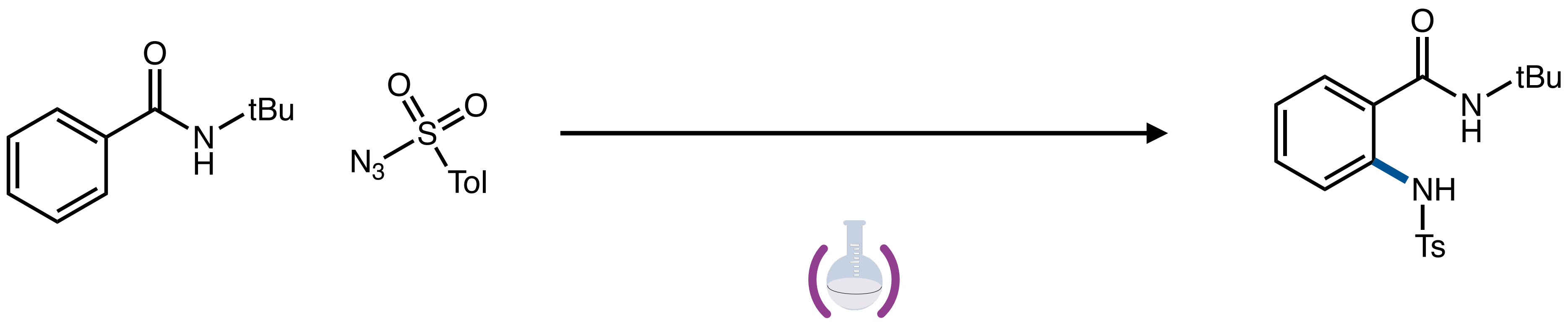
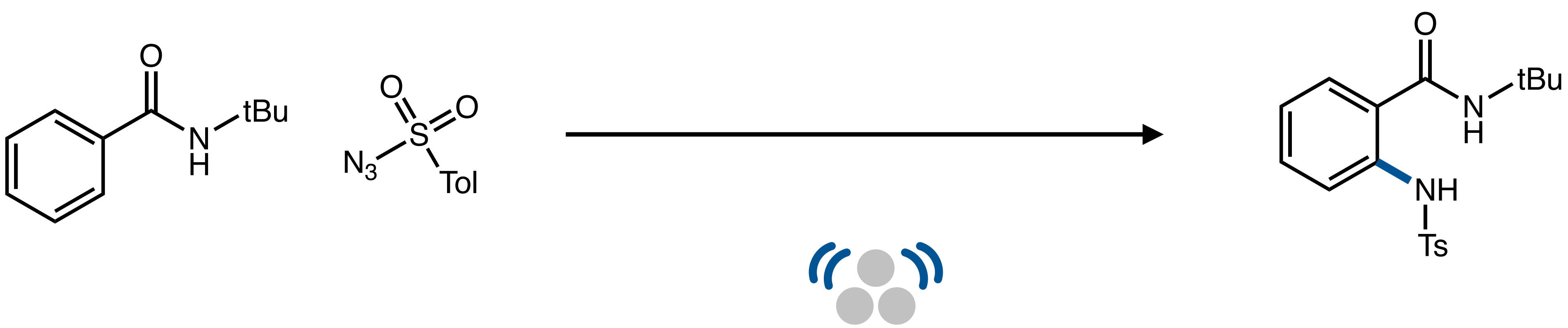


Sukbok Chang et al., *J. Org. Chem.* **2013**, *78*, 11102–11109.



Bolm et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 3781–3784.

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Mechanochemistry in Organic Synthesis

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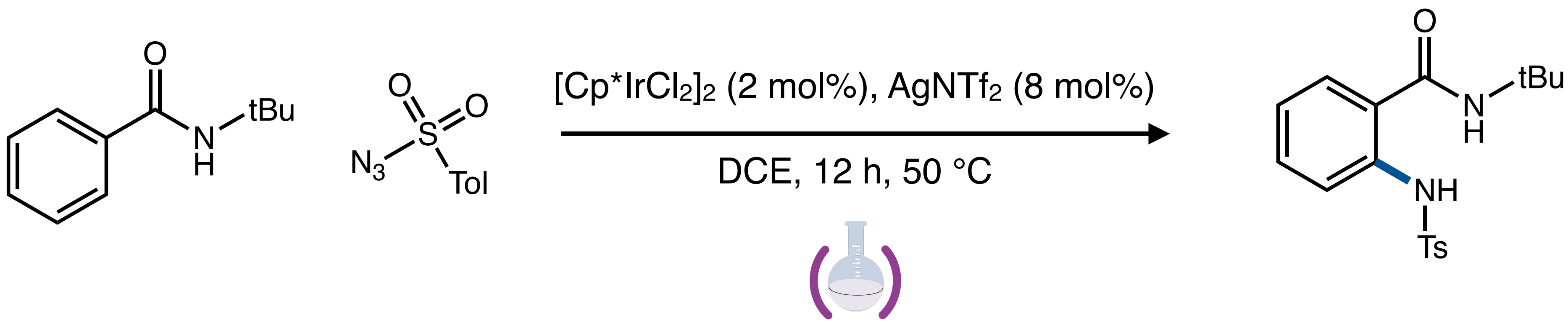
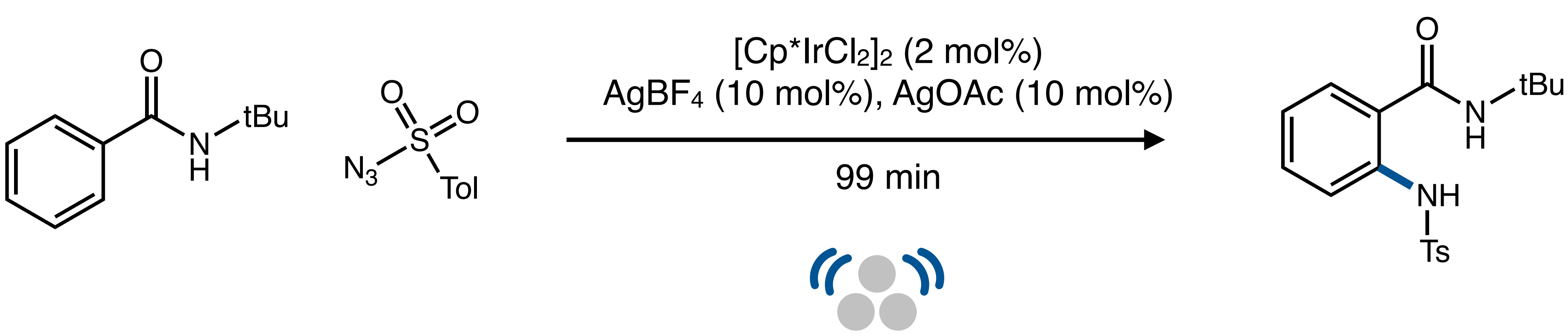


83%

Sukbok Chang et al., *J. Org. Chem.* **2013**, *78*, 11102–11109.



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Mechanochemistry in Organic Synthesis

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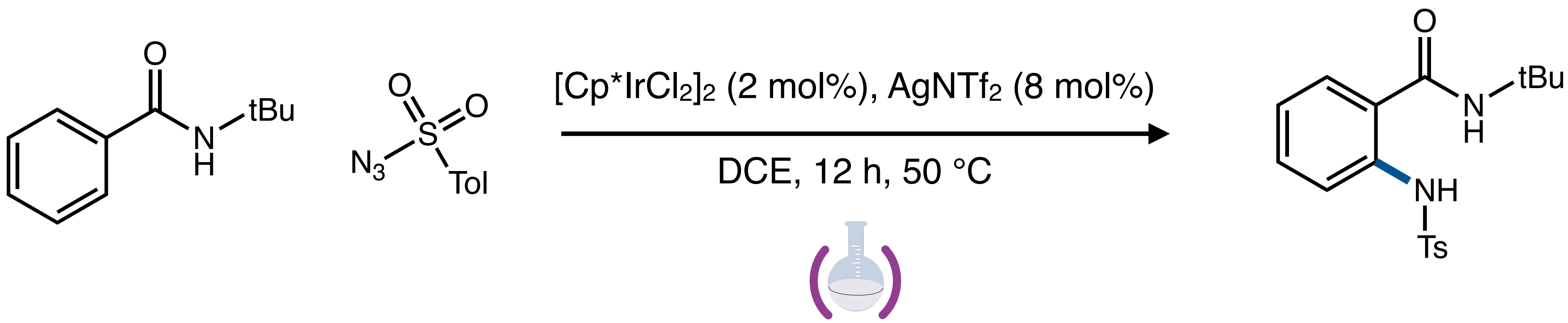

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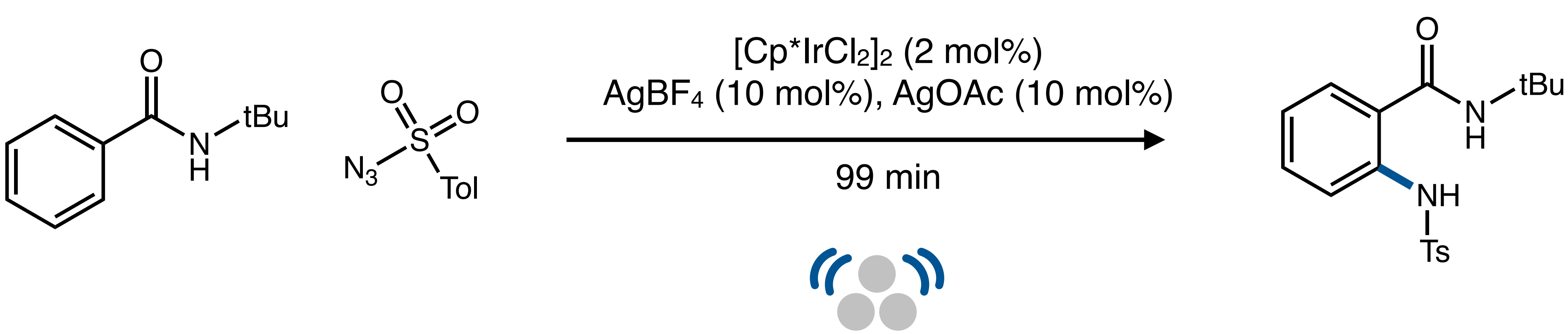


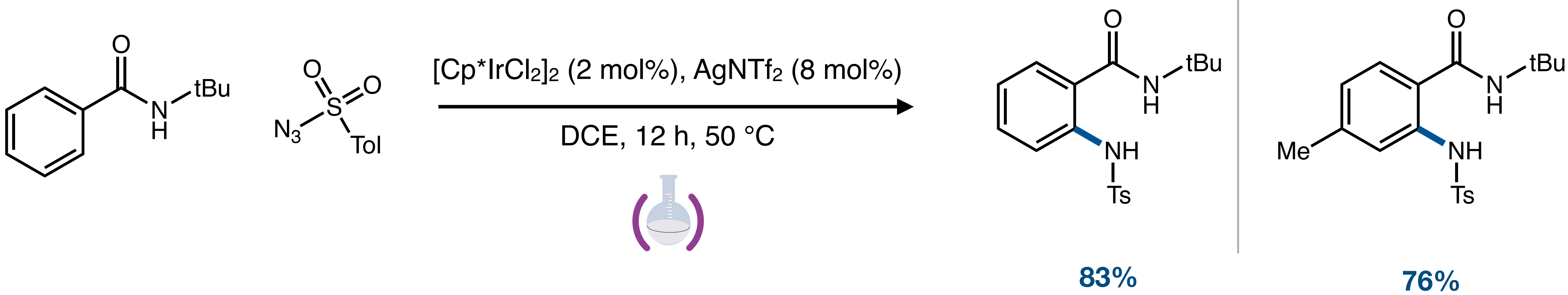
90%

Bolm et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 3781–3784.

Duncan L. Browne Chem. Sci., **2018**, *9, 3080–3094.* Evelina Colacino, Andrea Porcheddu et al., *ChemSusChem* **2022**, *15*, e202200362.

Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity



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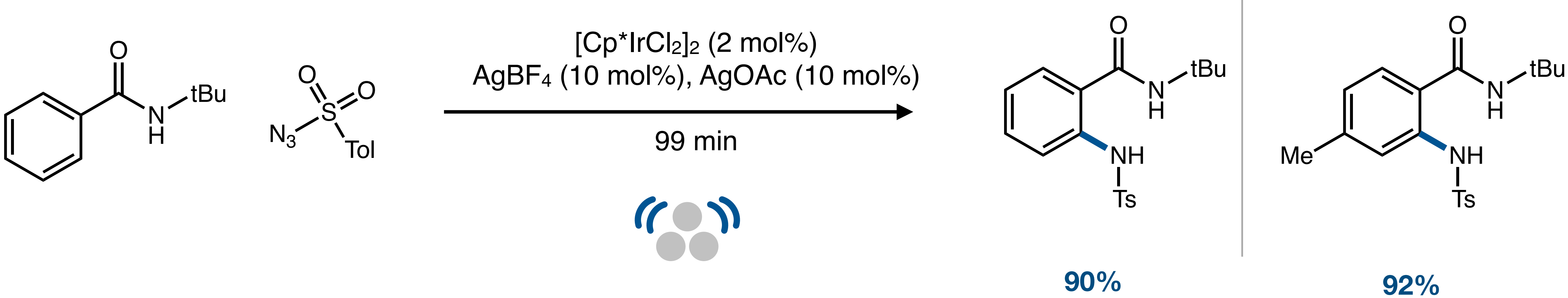

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Mechanochemistry in Organic Synthesis

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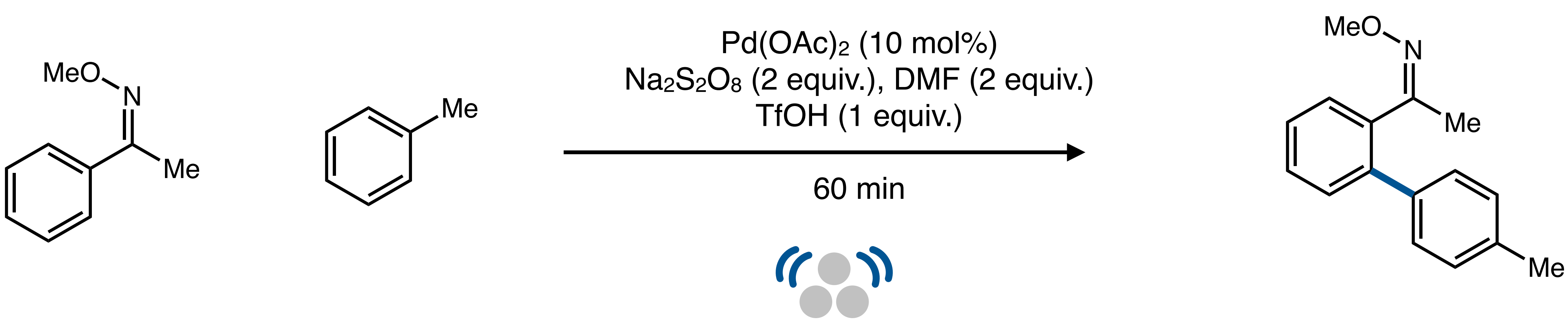

Zhen-Yuan Xu et al., *ACS Catal.* **2016**, *6*, 3890–3894.

Mechanochemistry in Organic Synthesis

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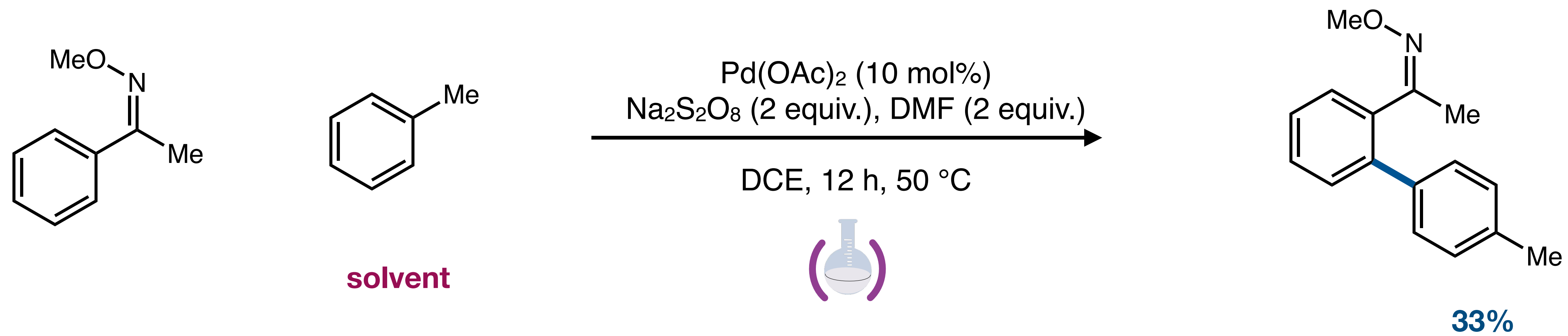

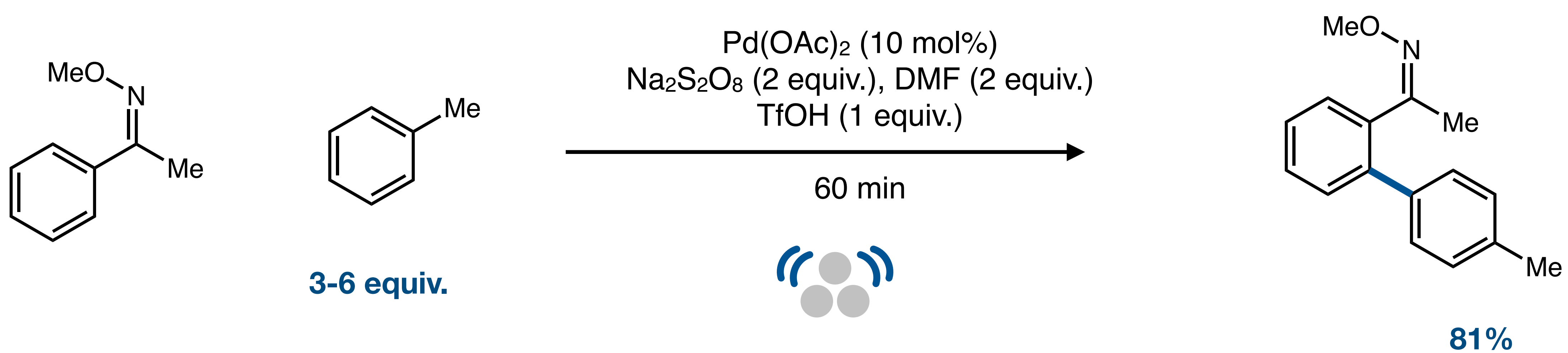

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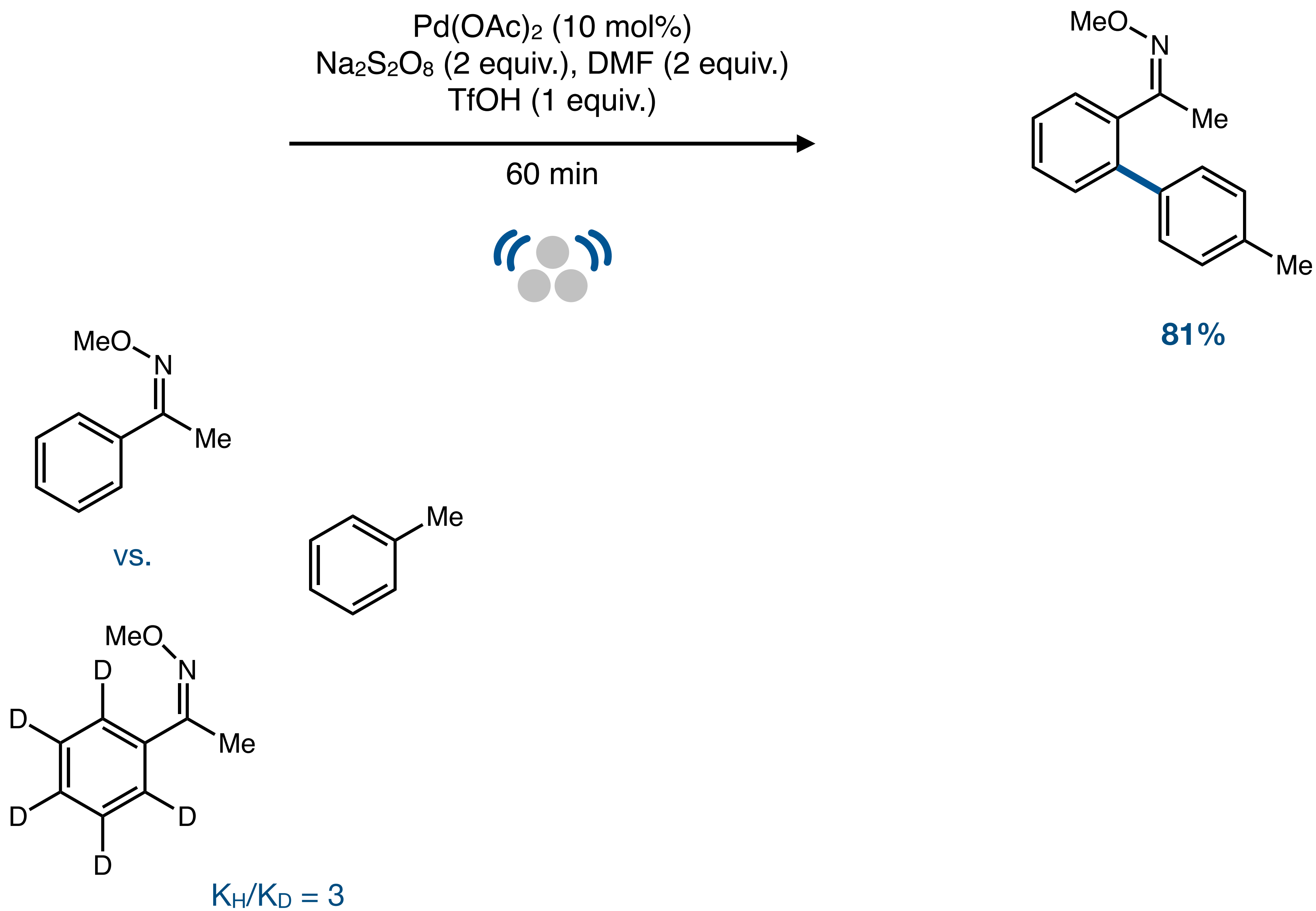
Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity



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Mechanochemistry in Organic Synthesis

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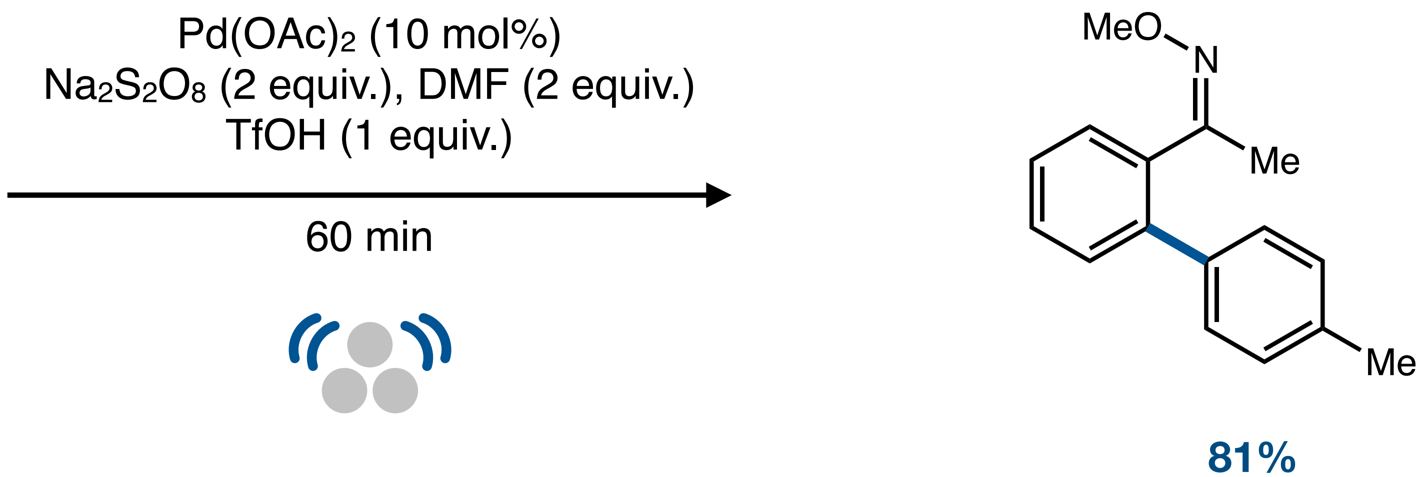
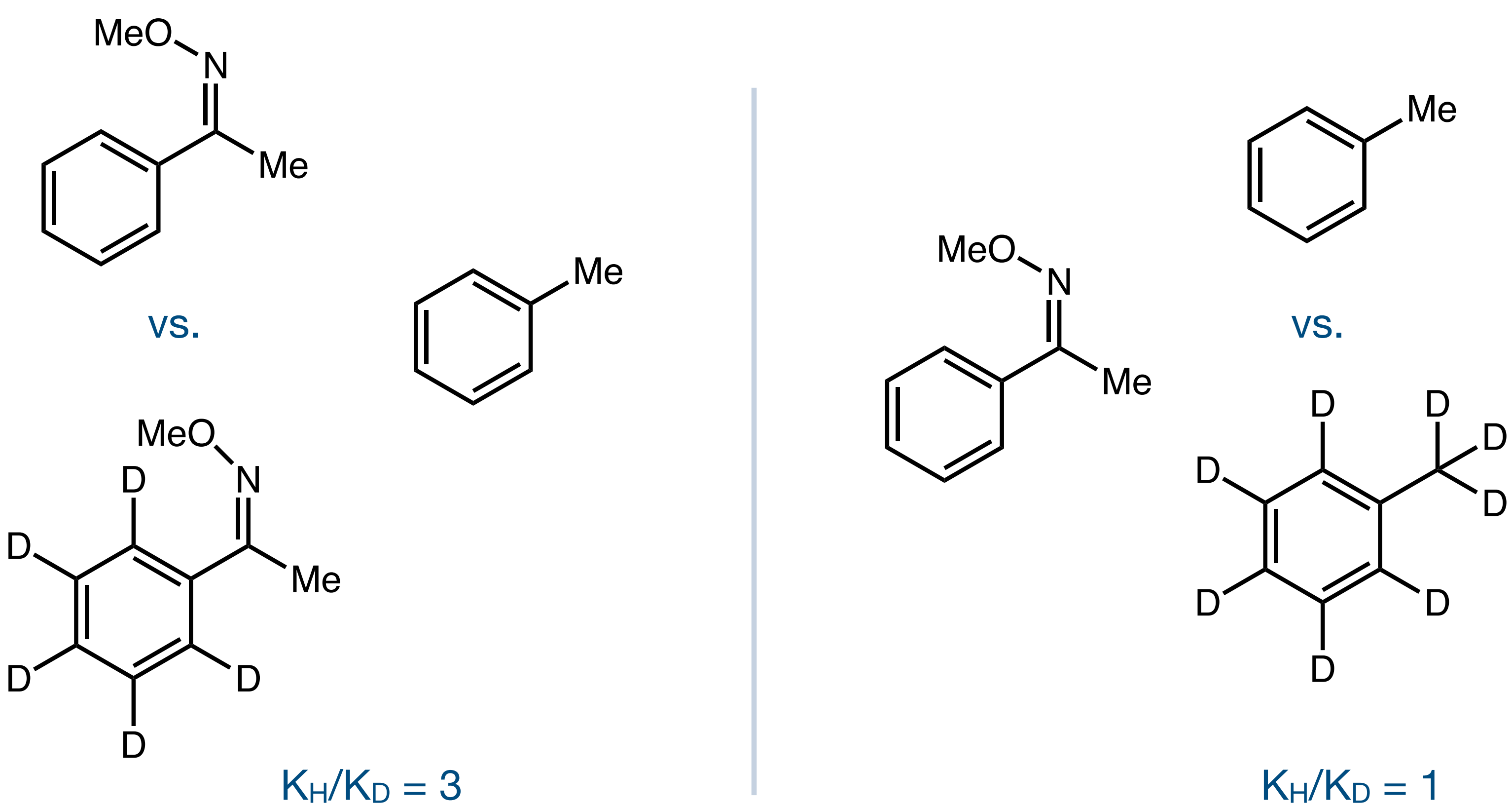




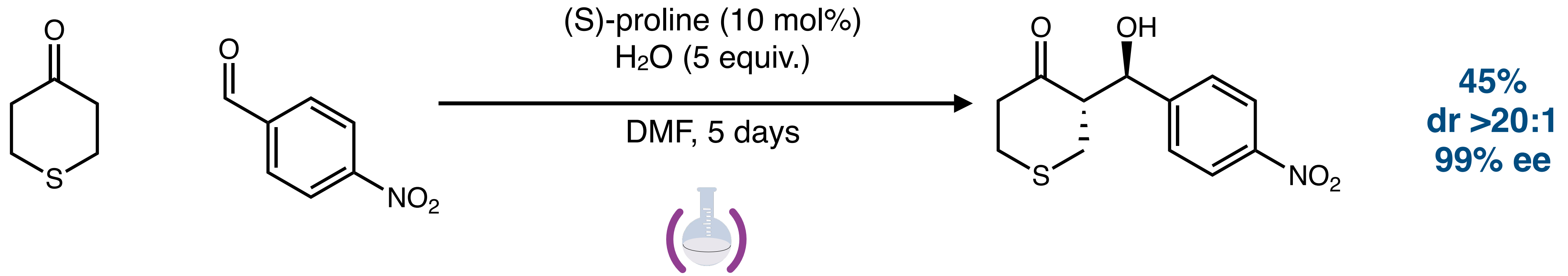
In accordance to solution-based protocol

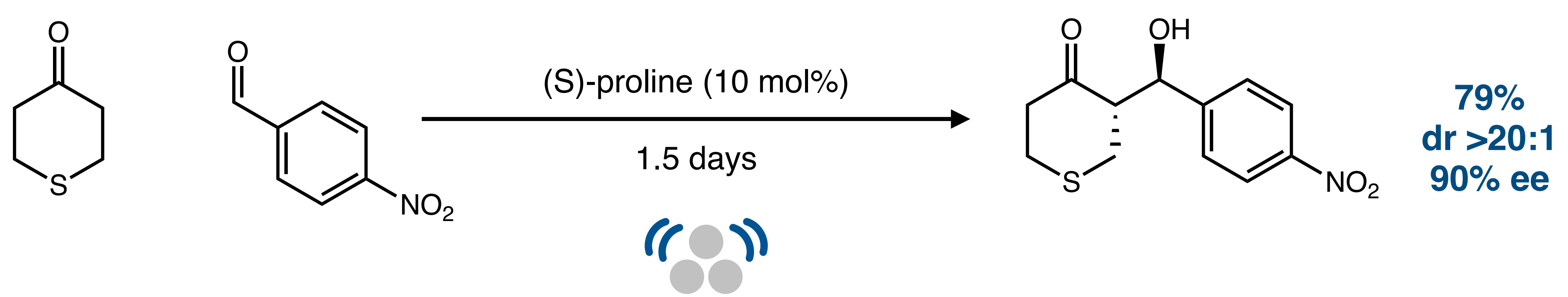
RDS = palladacycle formation

Zhen-Yuan Xu et al., *ACS Catal.* **2016**, *6*, 3890–3894.

Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity

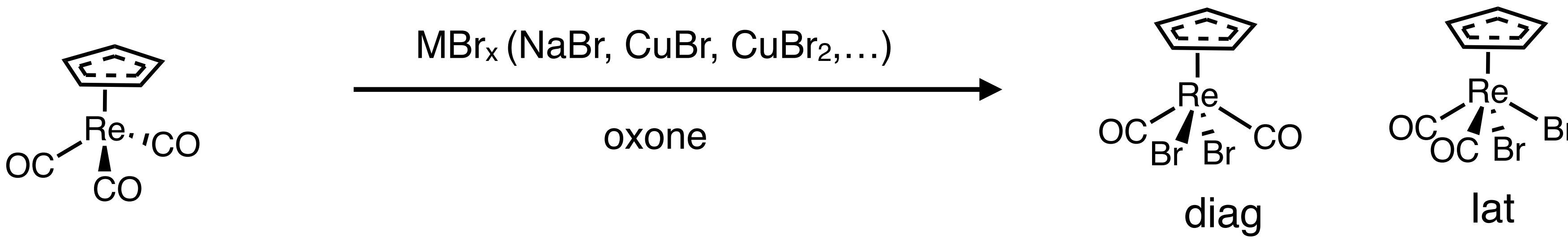




Bolm et al., *Chem. Eur. J.* **2007**, *13*, 4710 – 4722.

Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity

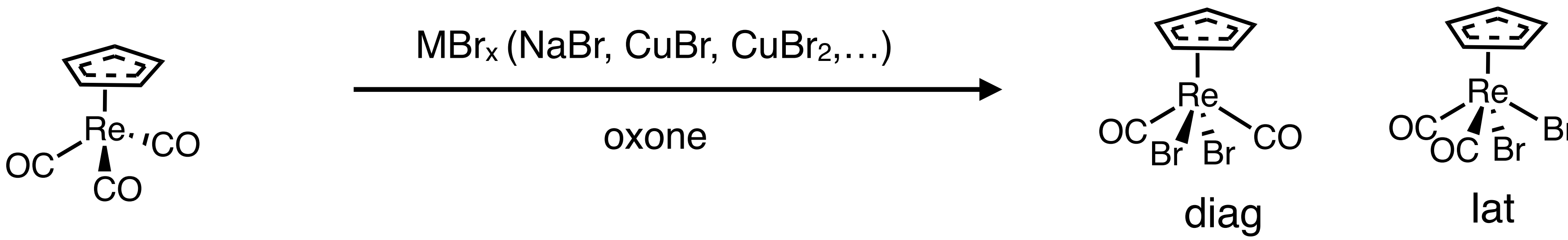


Poor selectivity

Tomislav Friščić et al., Green Chem., **2014,** *16*, 1087-1092.

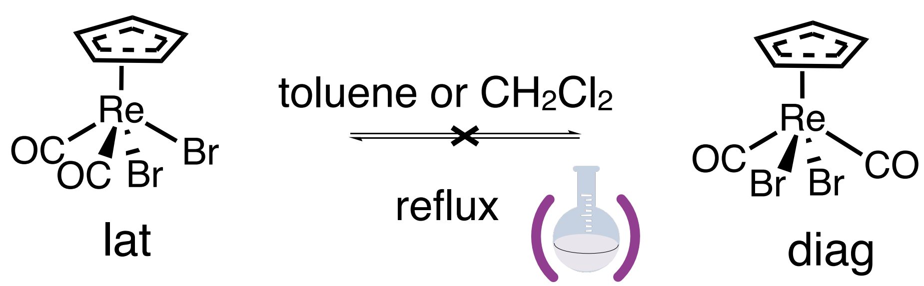
Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity



Poor selectivity

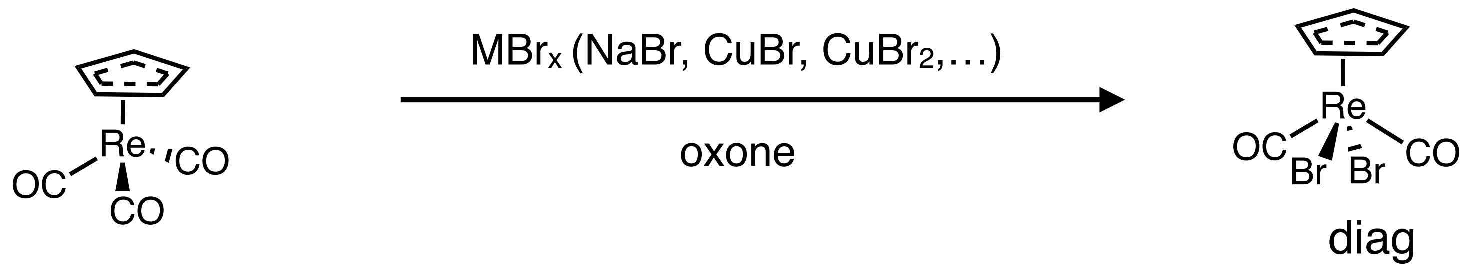
no isomerization in solution



Tomislav Friščić et al., *Green Chem.*, **2014,** *16*, 1087-1092.

Mechanochemistry in Organic Synthesis

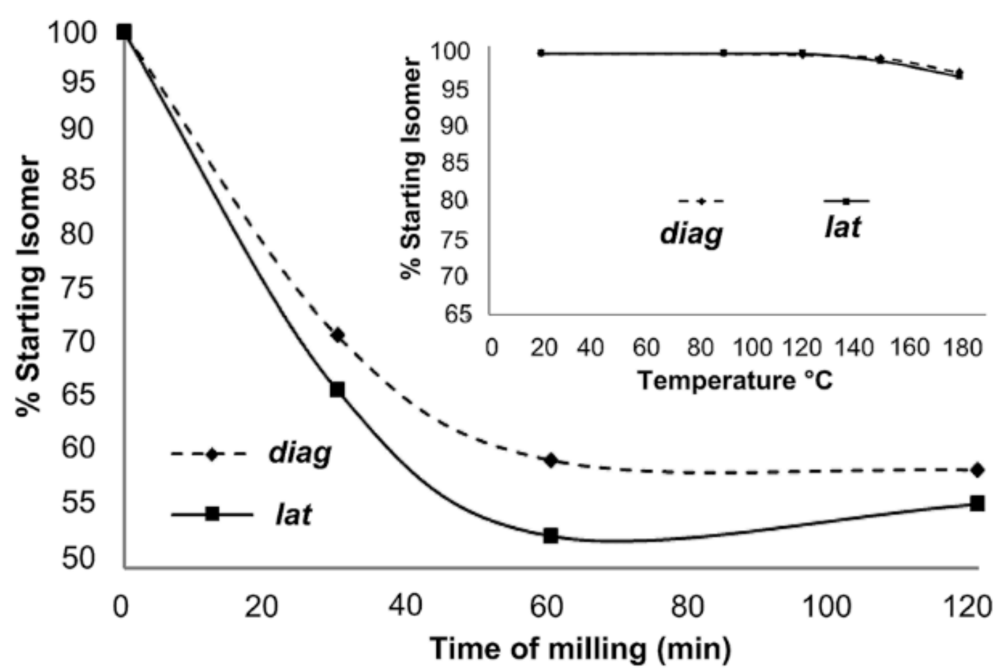
Mechanochemistry vs. solution-based reactivity



Poor selectivity

no isomerization in solution

isomerization possible with mechanochem



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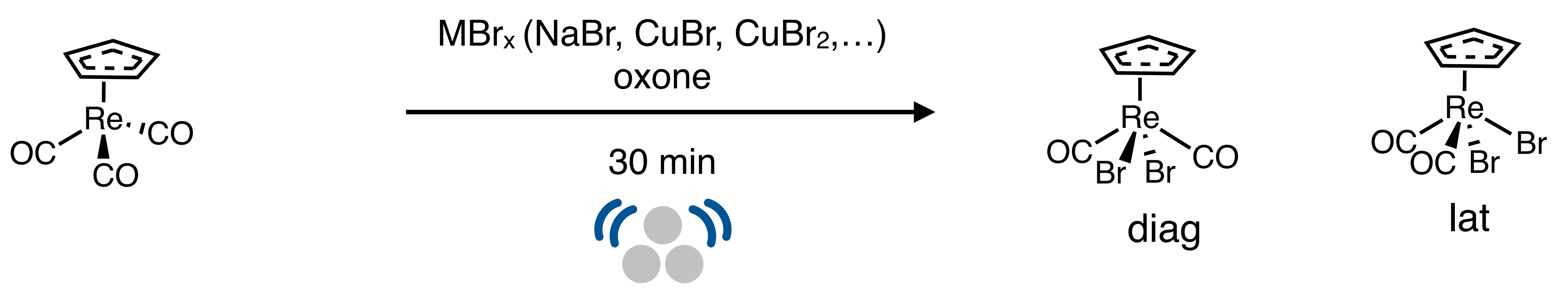
Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity

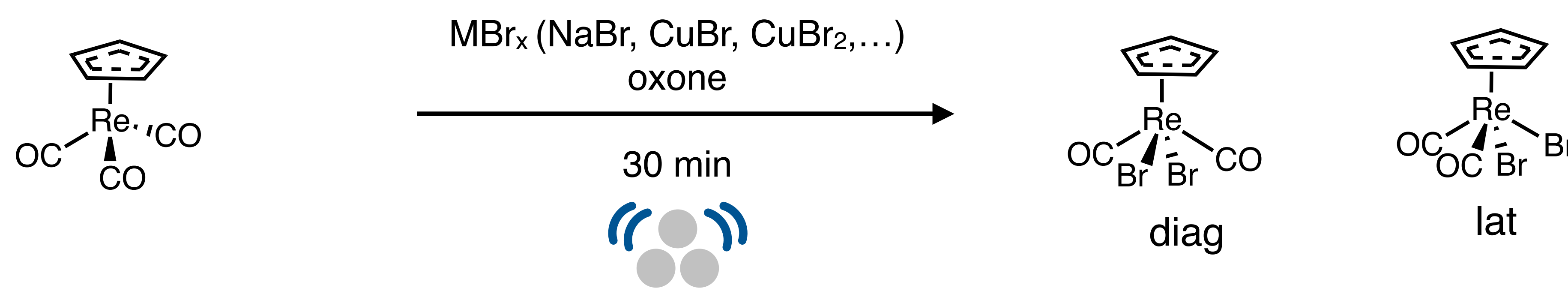


tunable ratio

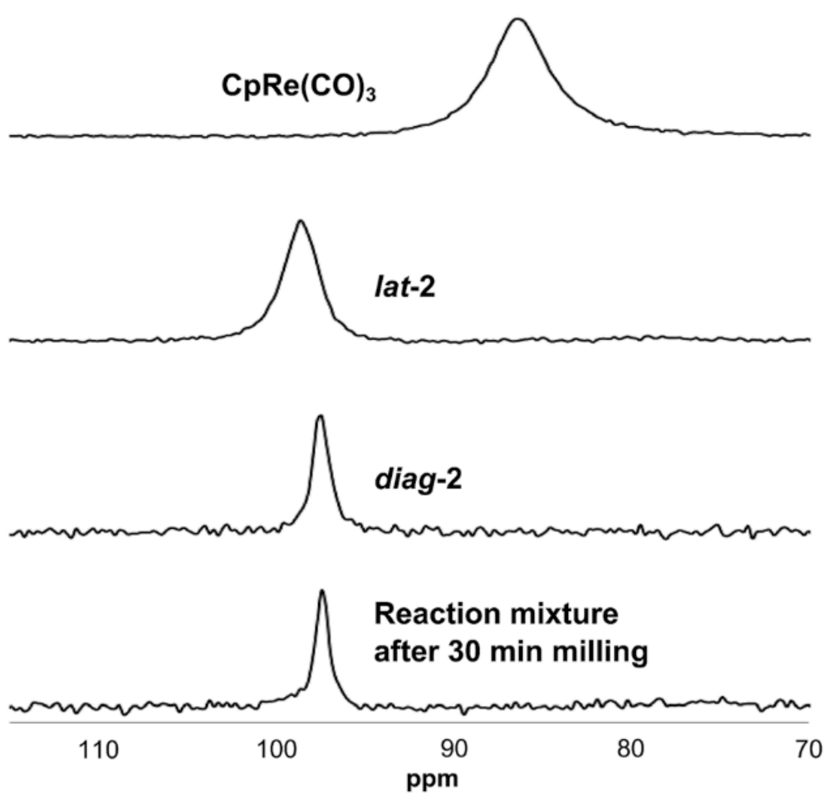
Tomislav Friščić et al., Green Chem., **2014,** *16*, 1087-1092.

Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity



tunable ratio



NaBr: **98**:2 (72% IY_{major})

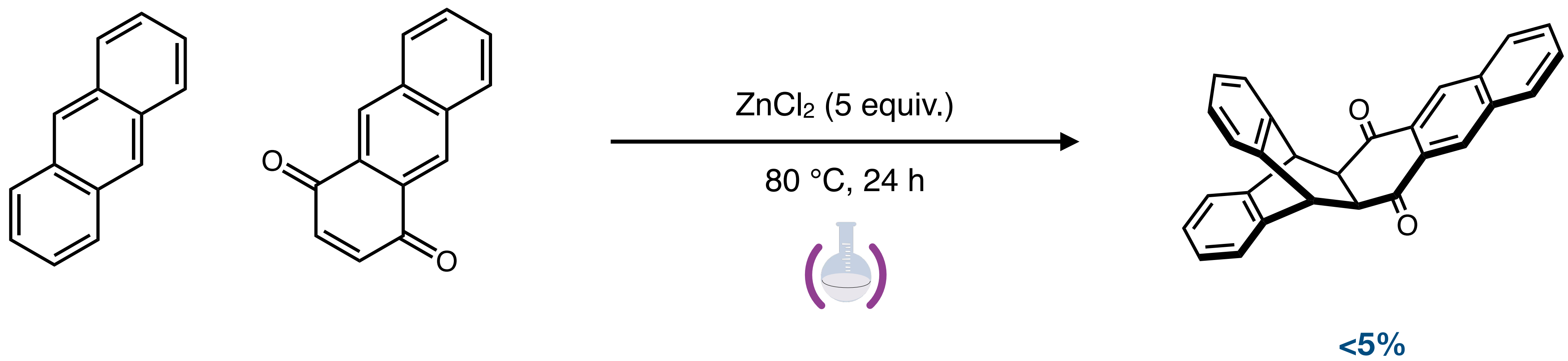
CuB$_2$: **72**:28 (55% IY_{major})

CuBr: 30:**70** (50% IY_{major})

Tomislav Friščić et al., Green Chem., **2014,** *16*, 1087-1092.

Mechanochemistry in Organic Synthesis

Mechanochemistry vs. solution-based reactivity



Swager et al., *J. Am. Chem. Soc.* **2016**, *138*, 13834–13837.

Mechanochemistry in Organic Synthesis

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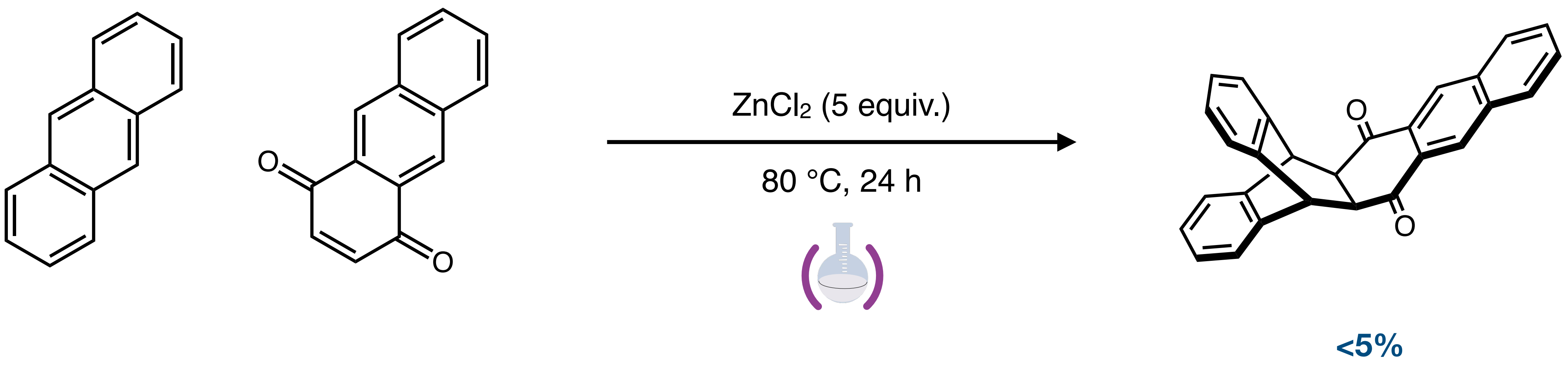
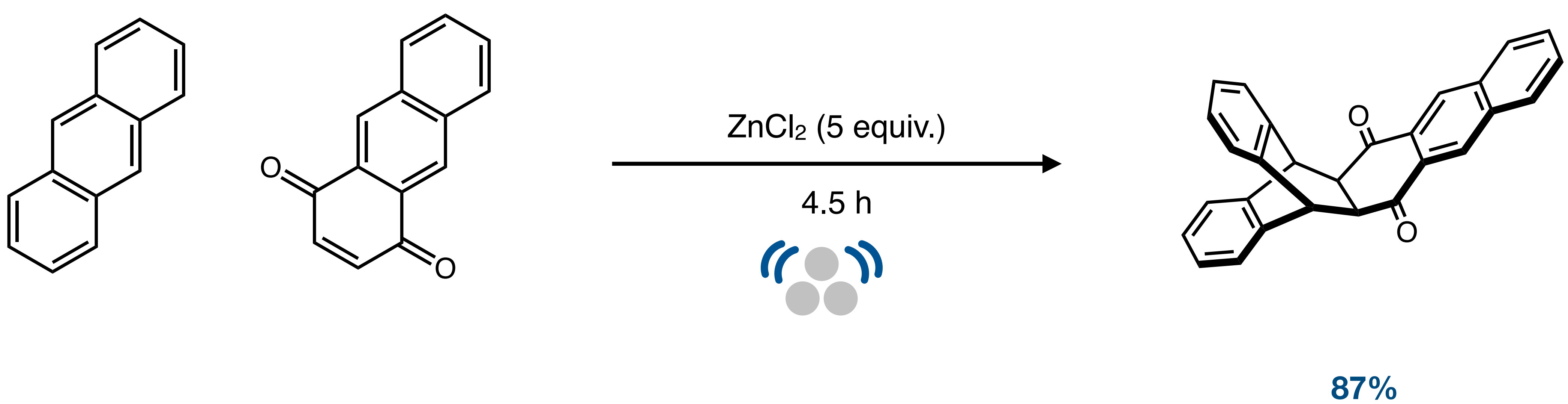
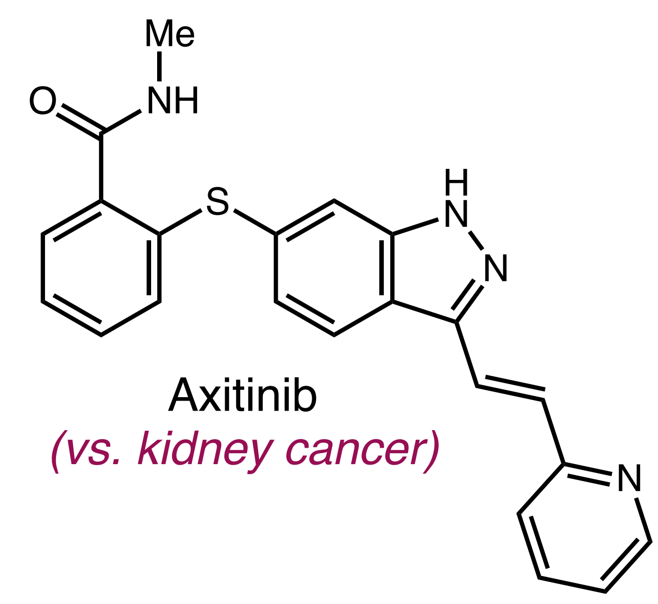




Swager et al., *J. Am. Chem. Soc.* **2016**, *138*, 13834–13837.

Medicinal Mechanochemistry



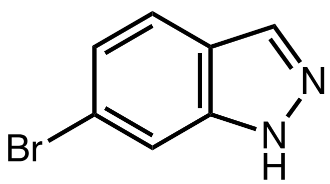
Axitinib

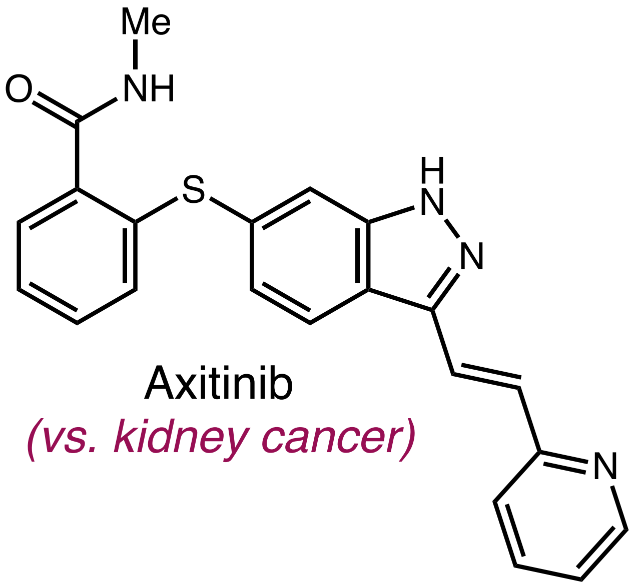
(vs. kidney cancer)

Weike Su et al., *Beilstein J. Org. Chem.* **2018**, *14*, 786–795.

Mechanochemistry in Organic Synthesis

Medicinal Mechanochemistry





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Mechanochemistry in Organic Synthesis

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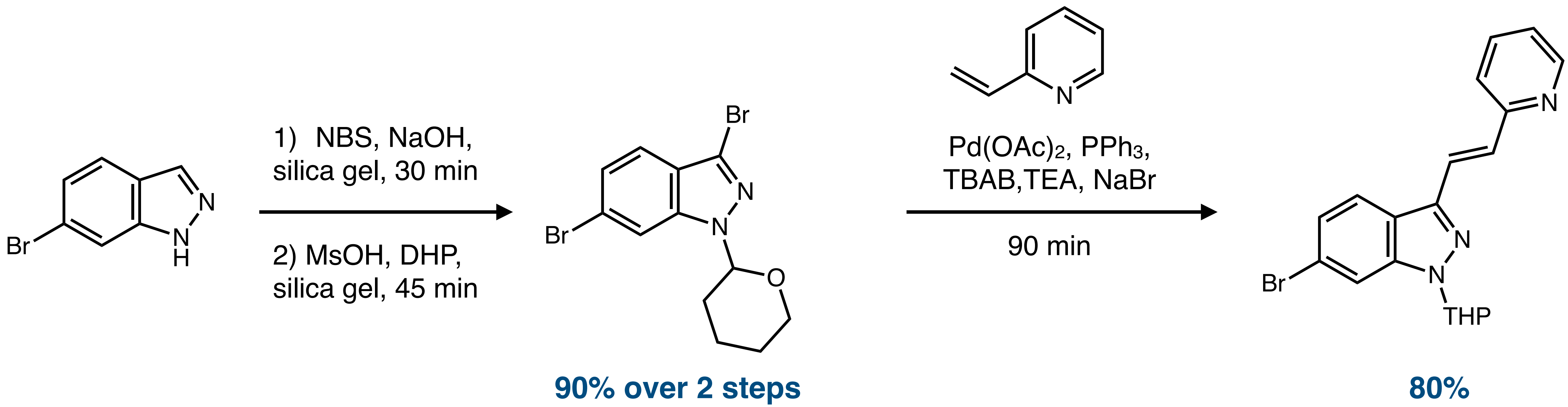

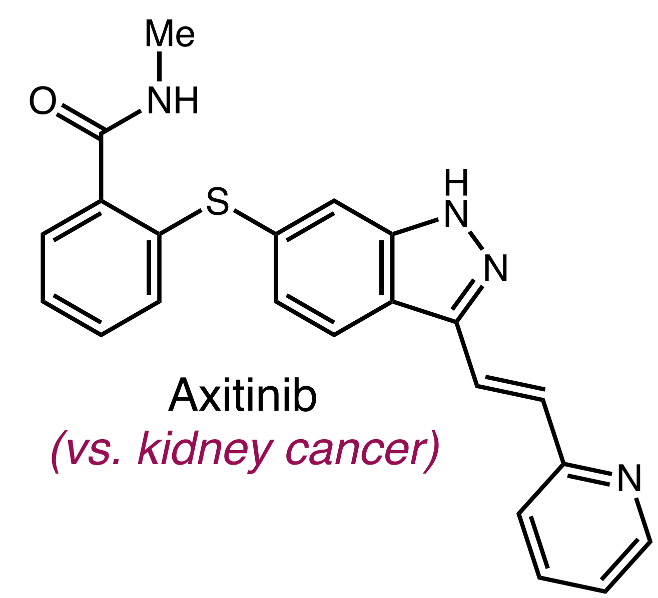

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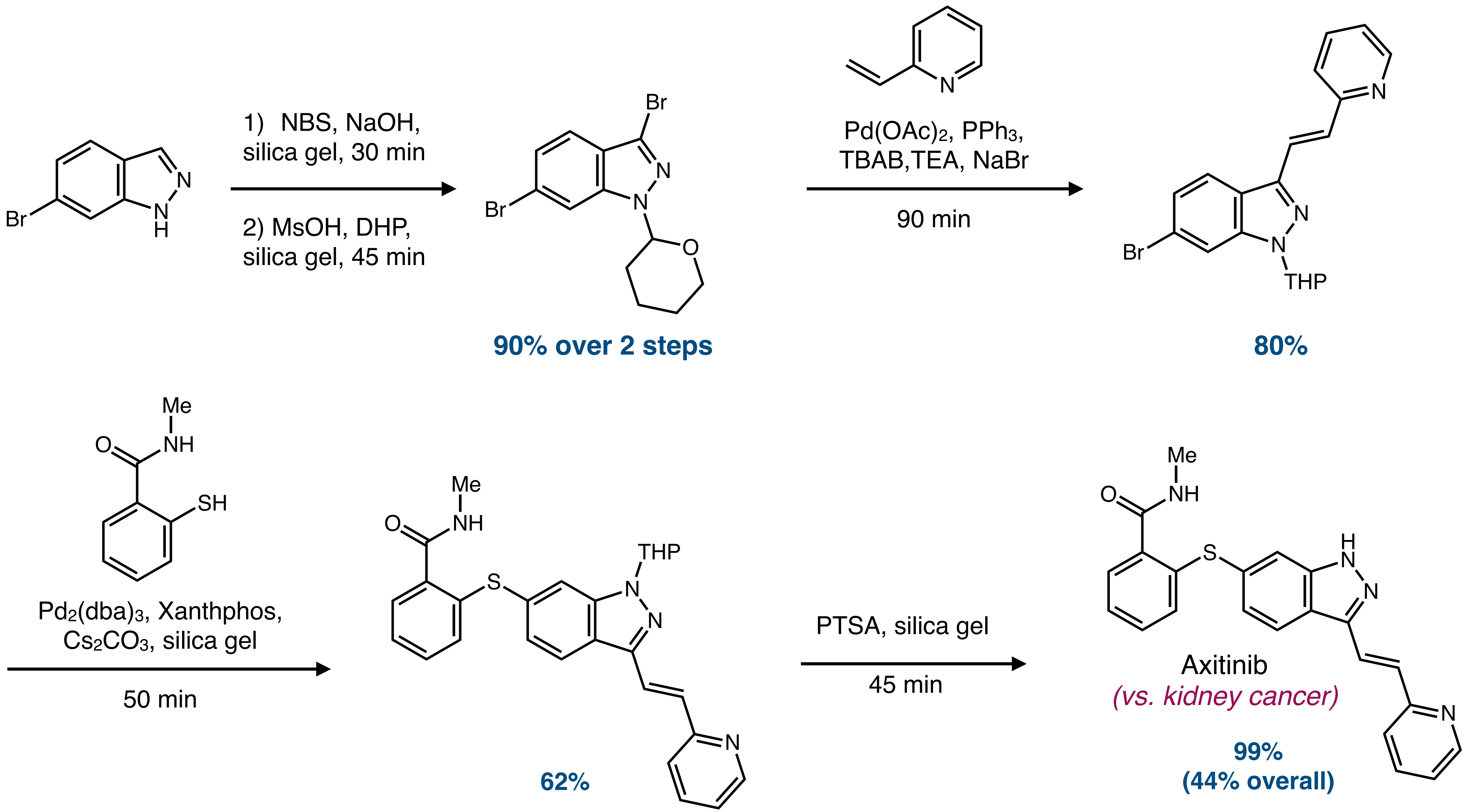

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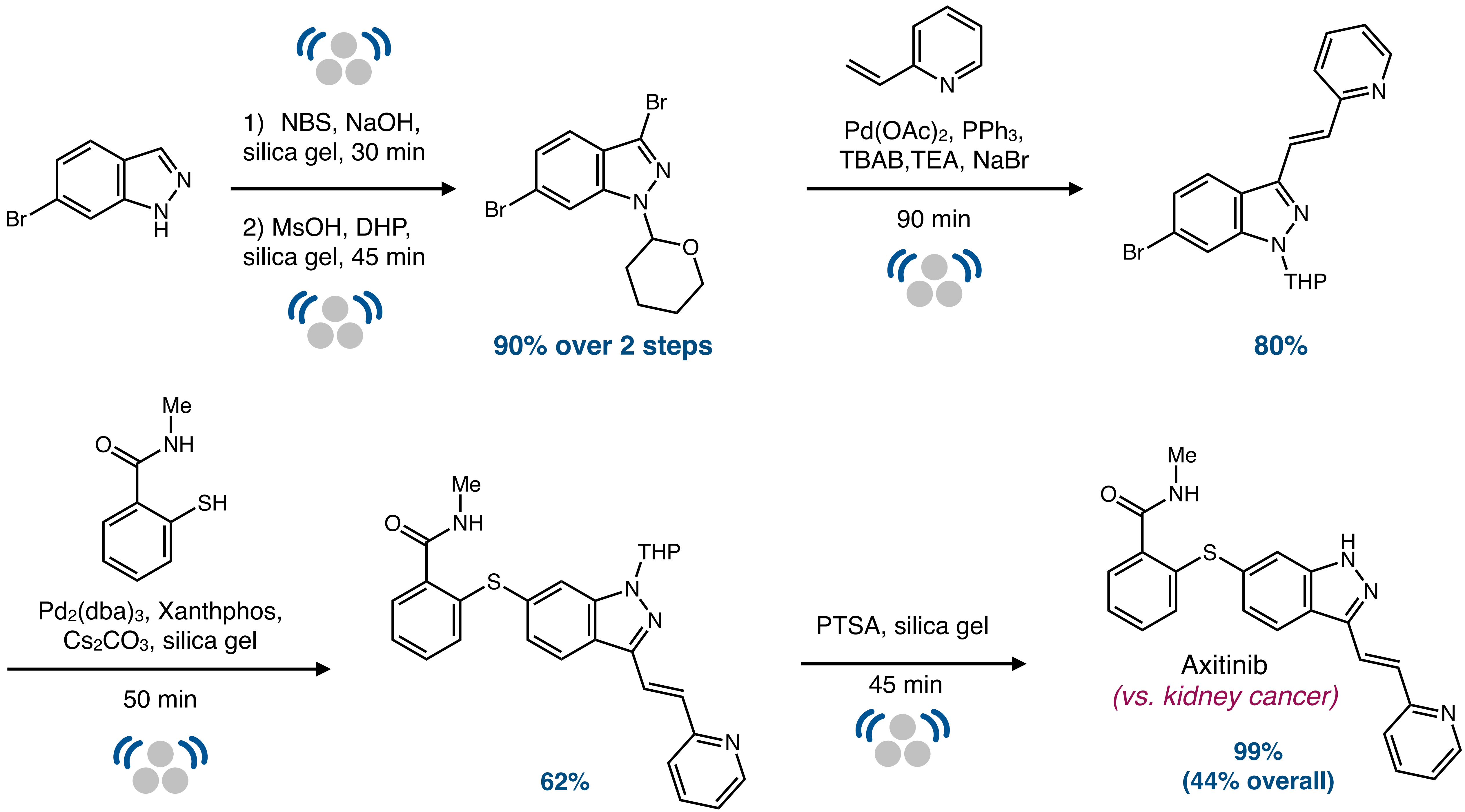

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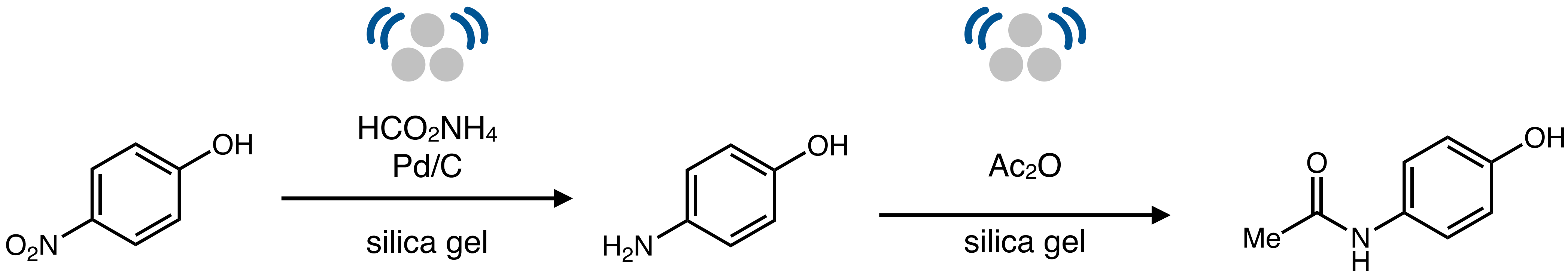


Paracetamol

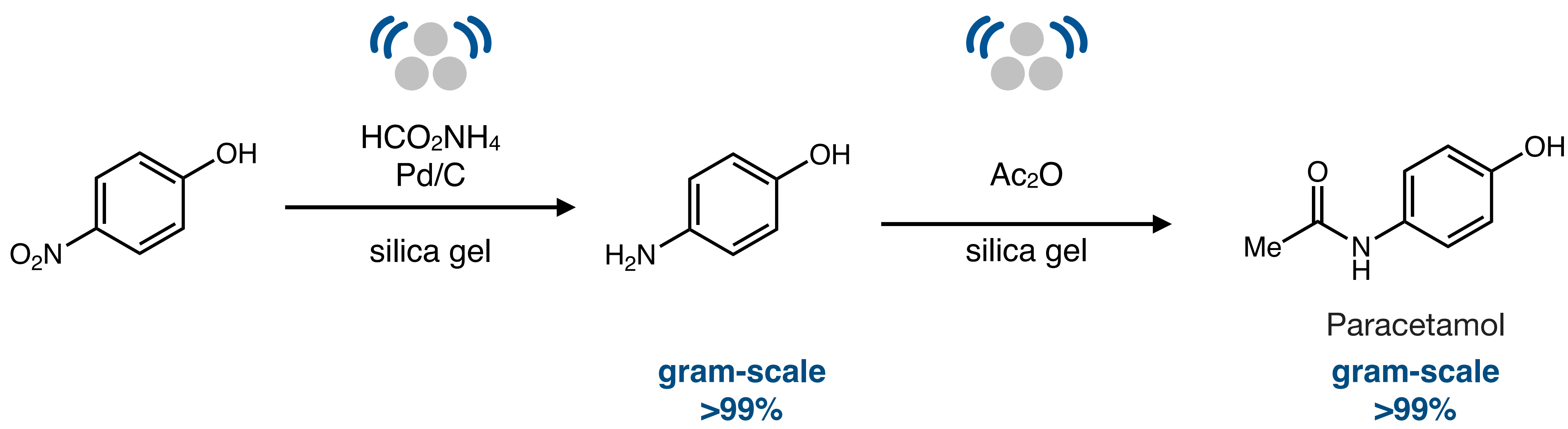
gram-scale
>99%

gram-scale
>99%

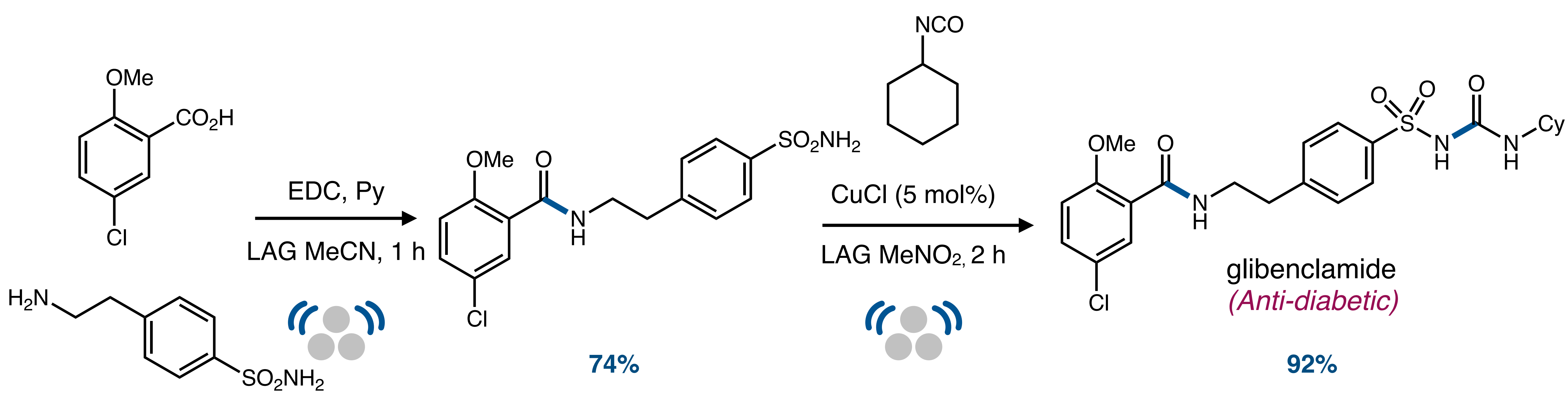
Vjekoslav Štrukil et al., *Molecules* **2018**, *23*, 3163.

Mechanochemistry in Organic Synthesis

Medicinal Mechanochemistry



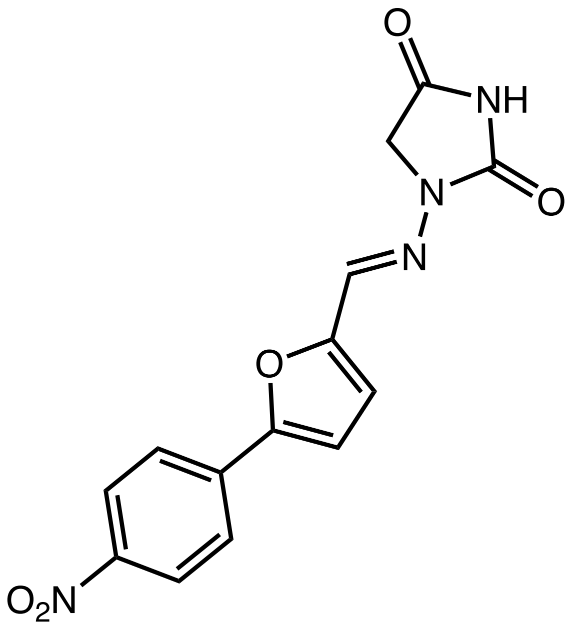
Vjekoslav Štrukil et al., *Molecules* **2018**, *23*, 3163.



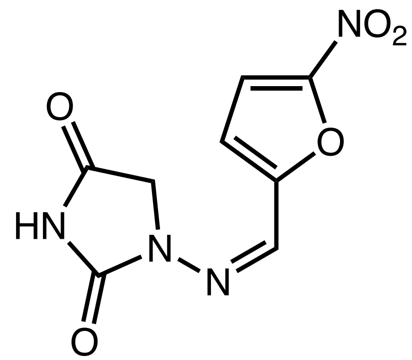
Tomislav Friščić et al., *Chem. Commun.* **2014**, *50*, 5248-5250.

Mechanochemistry in Organic Synthesis

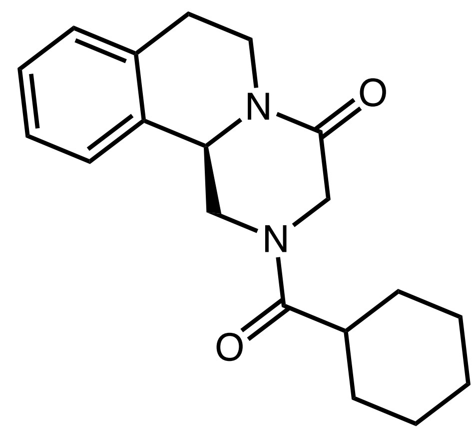
Medicinal Mechanochemistry



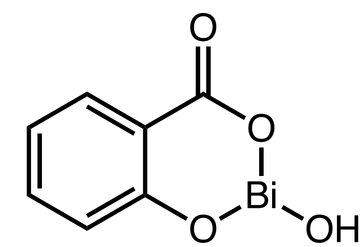
dantrolene



nitrofurantoin



Praziquantel



bismuth salicylate

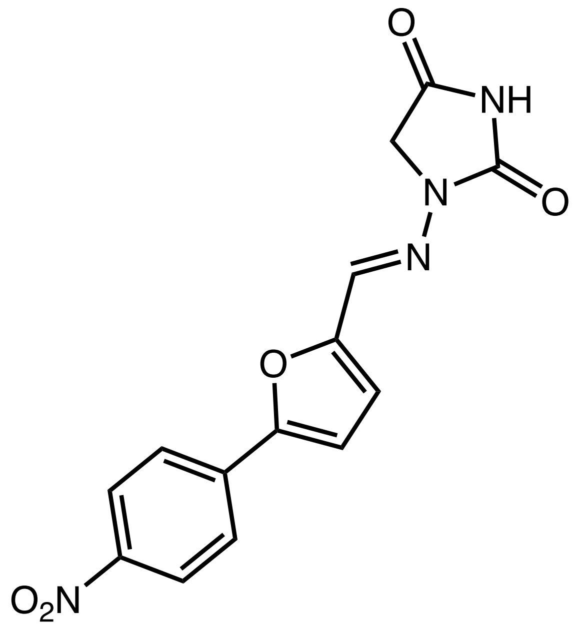
Weike Su et al., *Adv. Synth. Catal.* **2021**, *363*, 1246.

K. Su et al., CN111171027A

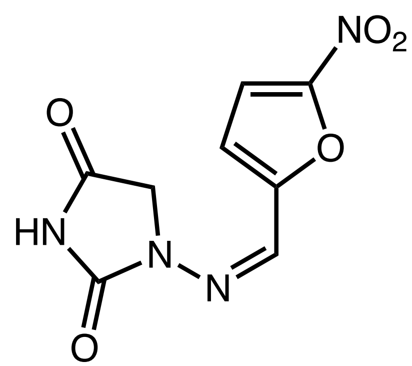
M. D. Levitt et al., *Dig. Dis. Sci.* **2000**, *45*, 1444–1446.

Mechanochemistry in Organic Synthesis

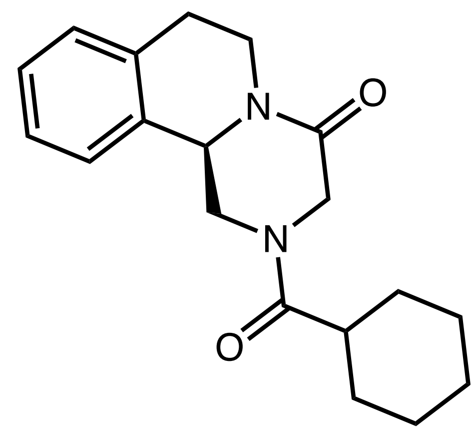
Medicinal Mechanochemistry



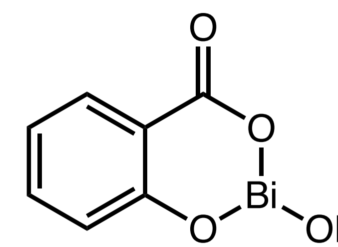
dantrolene



nitrofurantoin



Praziquantel



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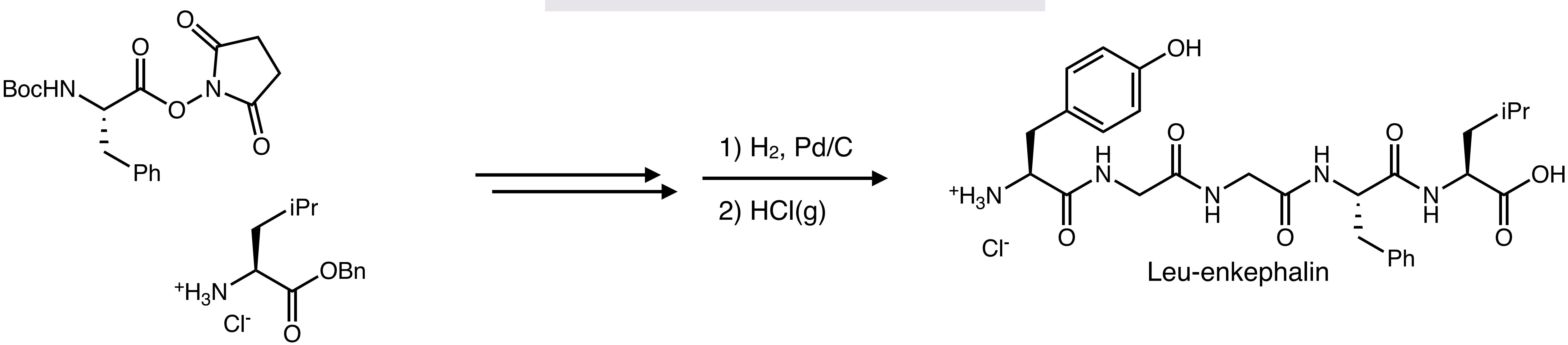
M. D. Levitt et al., *Dig. Dis. Sci.* **2000**, *45*, 1444–1446.

mechanochemical peptide synthesis

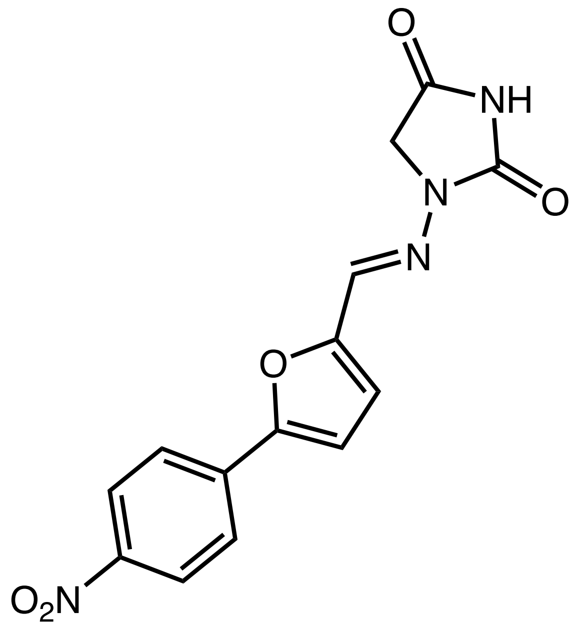


Leu-enkephalin

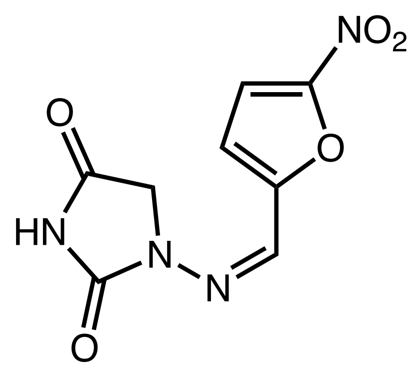
Weike Su et al., *Adv. Synth. Catal.* **2021**, *363*, 1246.

Mechanochemistry in Organic Synthesis

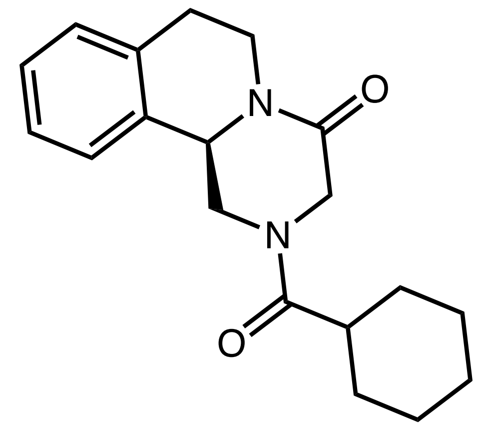
Medicinal Mechanochemistry



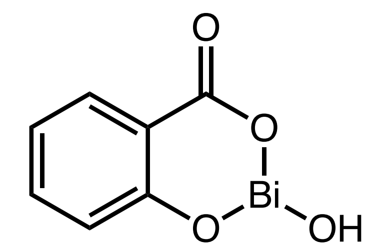
dantrolene



nitrofurantoin



Praziquantel



bismuth salicylate

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K. Su et al., CN111171027A

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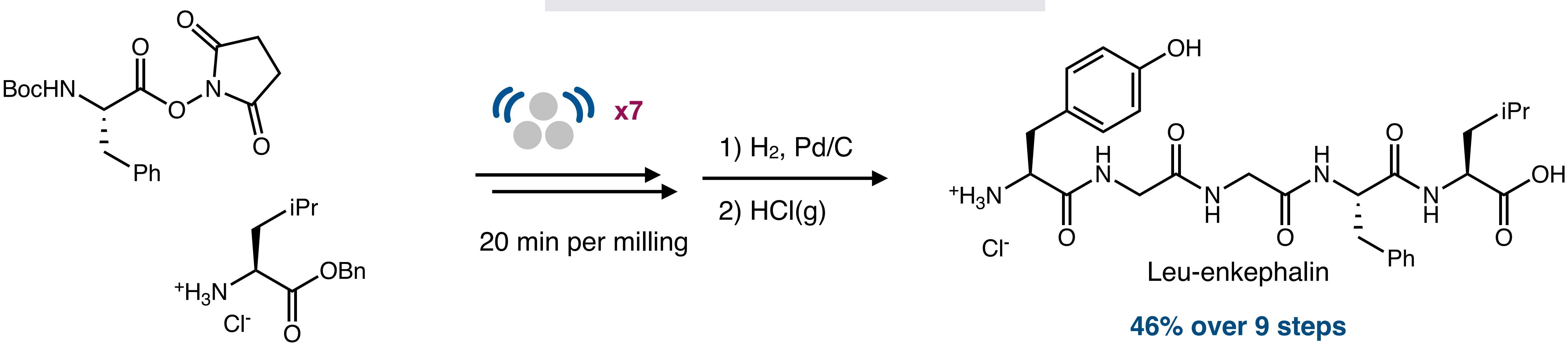
mechanochemical peptide synthesis

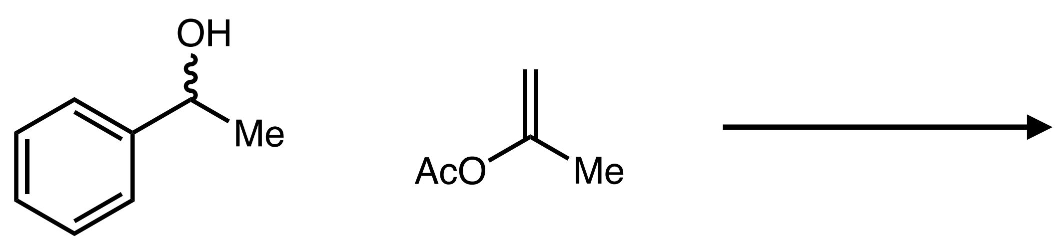


Weike Su et al., *Adv. Synth. Catal.* **2021**, *363*, 1246.

Mechanochemistry in Organic Synthesis

***Enzymatic**-Medicinal Mechanochemistry*

Mechanochemical Enzymatic Kinetic Resolution



(Rac)-1

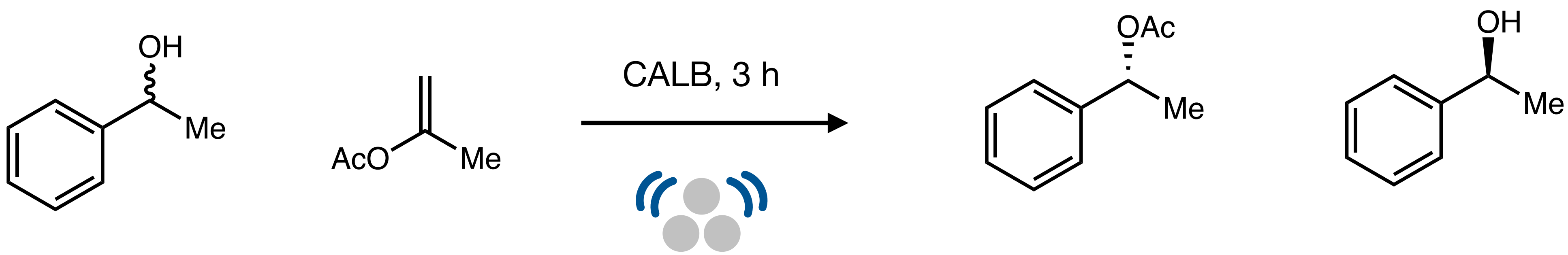
2

Carsten Bolm et al., *ChemCatChem* **2016**, *8*, 1769–1772.

Mechanochemistry in Organic Synthesis

***Enzymatic**-Medicinal Mechanochemistry*

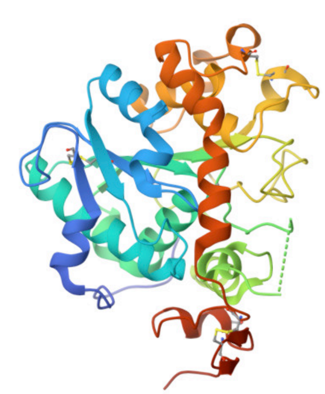
Mechanochemical Enzymatic Kinetic Resolution



c = 47%
E>200

(Rac)-1 | 2 | (R)-3 99% *ee* | (S)-1 90% *ee*

candida antarctica lipase B
(CALB)



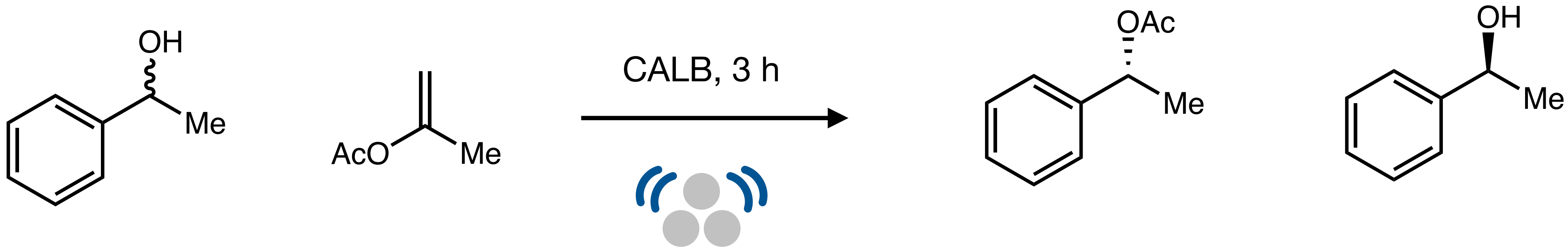
RCSB PDB
(4K6G)

Carsten Bolm et al., *ChemCatChem* **2016**, *8*, 1769–1772.

Mechanochemistry in Organic Synthesis

***Enzymatic**-Medicinal Mechanochemistry*

Mechanochemical Enzymatic Kinetic Resolution



c = 47%
E>200

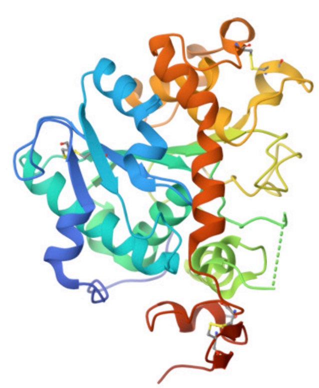
(Rac)-1

2

(R)-3
99% *ee*

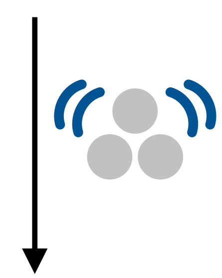
(S)-1
90% *ee*

candida antarctica lipase B
(CALB)



RCSB PDB
(4K6G)

Pre-milled CALB

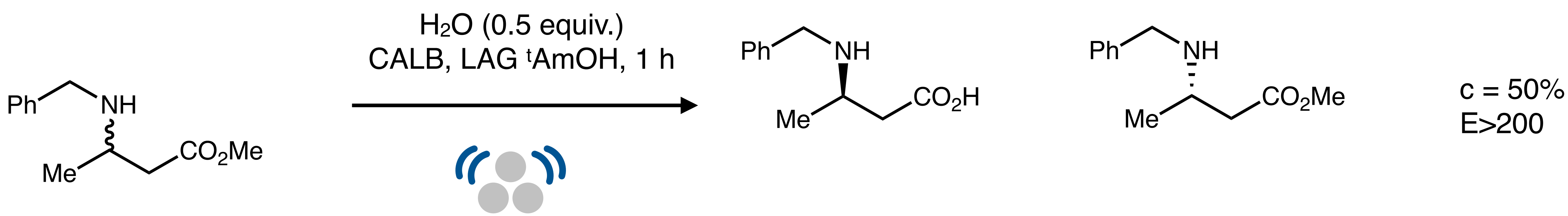


No reaction
(Protein denaturation)

Carsten Bolm et al., *ChemCatChem* **2016**, *8*, 1769–1772.

Mechanochemistry in Organic Synthesis

Enzymatic-Medicinal Mechanochemistry



(Rac)-1

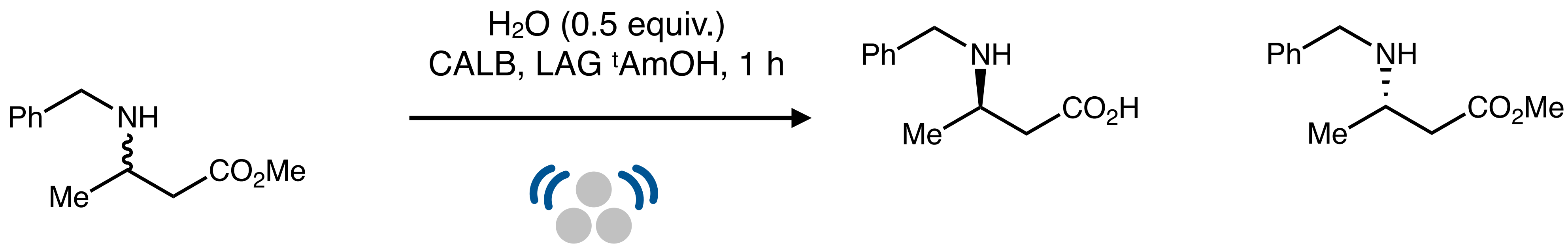
(R)-2
99% *ee*

(S)-1
95% *ee*

Jaime Escalante, Eusebio Juaristi et al., *Beilstein J. Org. Chem.* **2017**, *13*, 1728–1734.

Mechanochemistry in Organic Synthesis

***Enzymatic**-Medicinal Mechanochemistry*



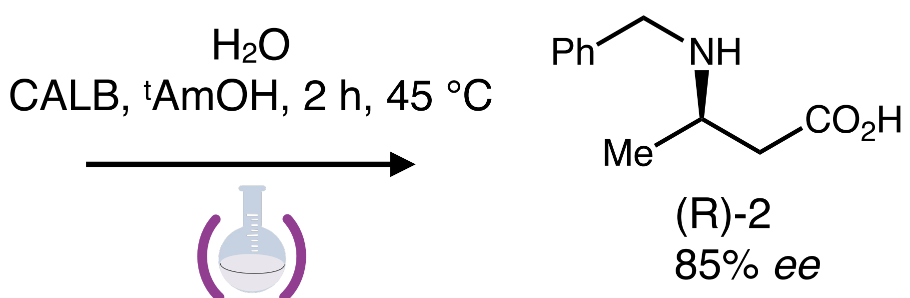
(Rac)-1

(R)-2
99% *ee*

(S)-1
95% *ee*

c = 50%
E>200

vs. Solution-based approach

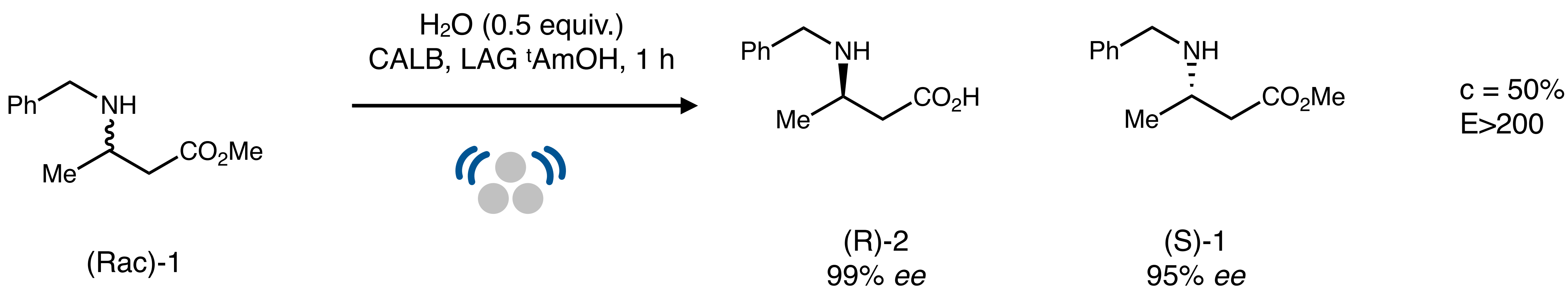


(R)-2
85% *ee*
c = 45%

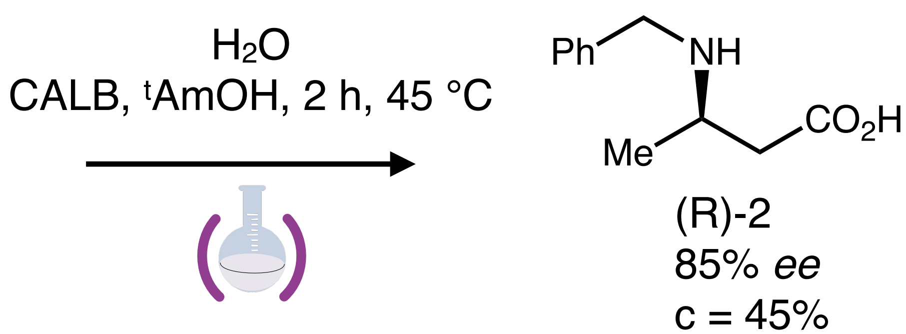
Jaime Escalante, Eusebio Juaristi et al., *Beilstein J. Org. Chem.* **2017**, *13*, 1728–1734.

Mechanochemistry in Organic Synthesis

***Enzymatic**-Medicinal Mechanochemistry*



vs. Solution-based approach



Effect of LAG

LAG	AY (S)-1/(R)-2	*ee* (S)-1	*ee* (R)-2
tAmOH	51/49	99	95
IPA	80/20	48	95
MeCN	65/29	65	95
Hexane	40/60	97	86

Jaime Escalante, Eusebio Juaristi et al., *Beilstein J. Org. Chem.* **2017**, *13*, 1728–1734.

Brief tutorial introduction on Mechanochem (generally)

History

Mechanistic aspects

Mechanical actions and mechanoreactors

Reaction Monitoring

Why mechanochemistry?

Mechanochemical vs. solution-based reactions

Medicinal mechanochemistry

“Mechanochemistry 2.0”

Mechanoredox

Mechanochemistry in Organic Synthesis

“Mechanochemistry 2.0”

Electrochemistry

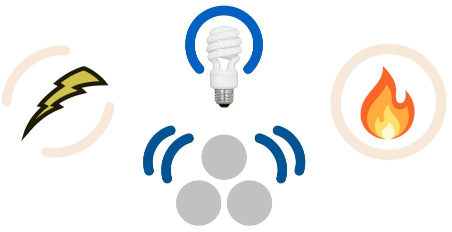
Photochemistry

Thermal chemistry

Mechanochemistry

Mechanochemistry in Organic Synthesis

"Mechanochemistry 2.0"



Mechanochemistry "2.0"

Martinez, V. et al., *Nat. Rev. Chem.* **2023**, *7*, 51–65.

Mechanochemistry in Organic Synthesis

Thermo-mechanochemistry

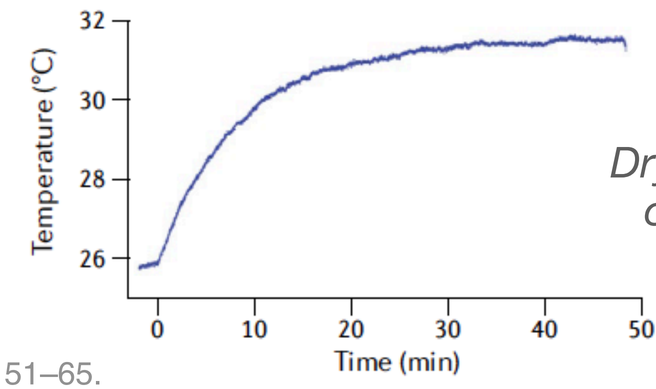
Milling alone causes
increase of T until
equilibrium

Krunoslav Užarević et al., *ACS Sustainable Chem. Eng.* **2019**, *7*, 16301–16309.

Mechanochemistry in Organic Synthesis

Thermo-mechanochemistry

Milling alone causes increase of T until equilibrium



Dry milling of ZnO

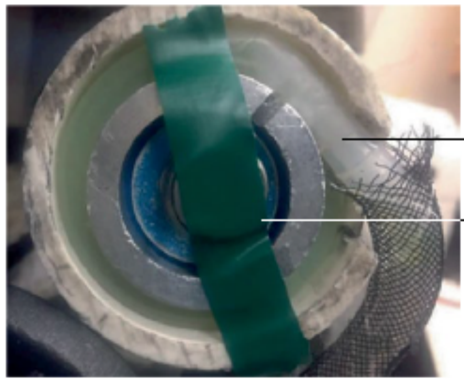
Martinez, V. et al., *Nat. Rev. Chem.* **2023**, *7*, 51–65.

Krunoslav Užarević et al., *ACS Sustainable Chem. Eng.* **2019**, *7*, 16301–16309.

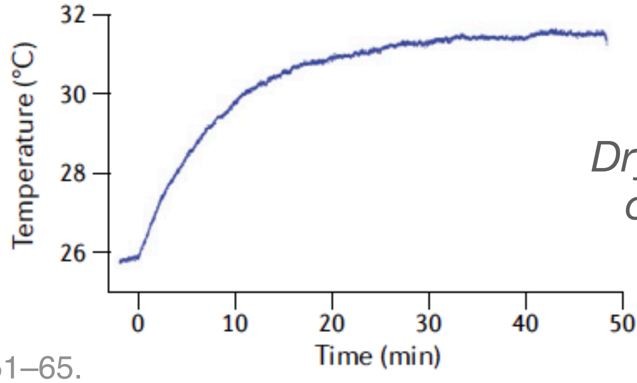
Mechanochemistry in Organic Synthesis

Thermo-mechanochemistry

Tube cooling & Cryo-milling



Milling alone causes increase of T until equilibrium



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Mechanochemistry in Organic Synthesis

Thermo-mechanochemistry

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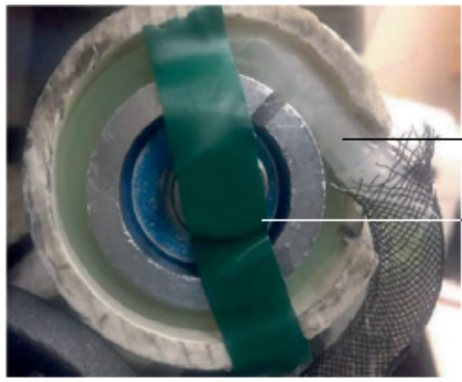
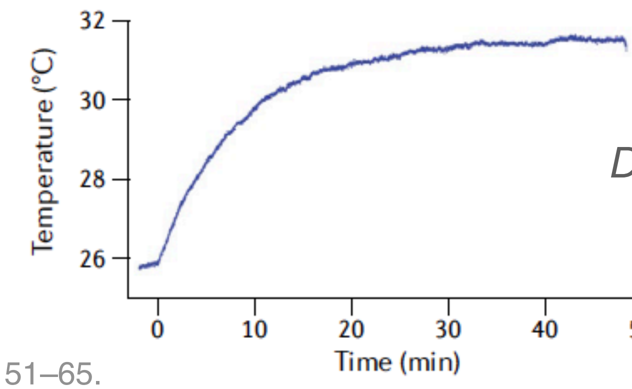


Cooling coil

Thermal sensor

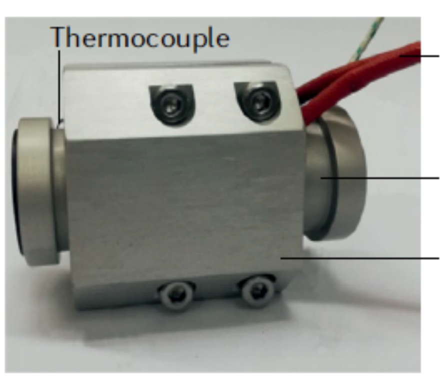
Milling alone causes increase of T until equilibrium



Dry milling of ZnO

Martinez, V. et al., *Nat. Rev. Chem.* **2023**, *7*, 51–65.

PID devices Up to 250 °C



Wiring

Milling vessel

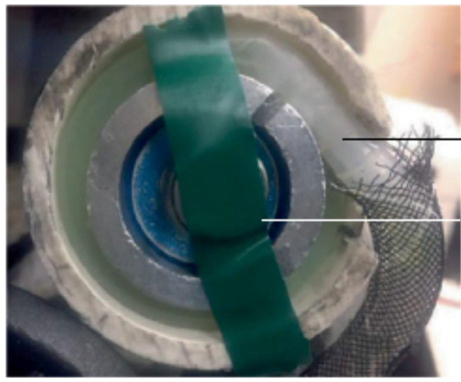
Heating mantle

Krunoslav Užarević et al., *ACS Sustainable Chem. Eng.* **2019**, *7*, 16301–16309.

Mechanochemistry in Organic Synthesis

Thermo-mechanochemistry

Tube cooling & Cryo-milling



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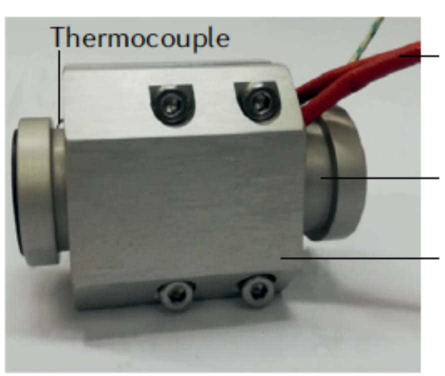

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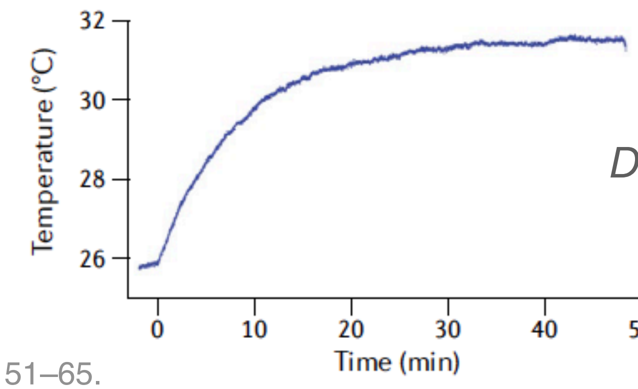
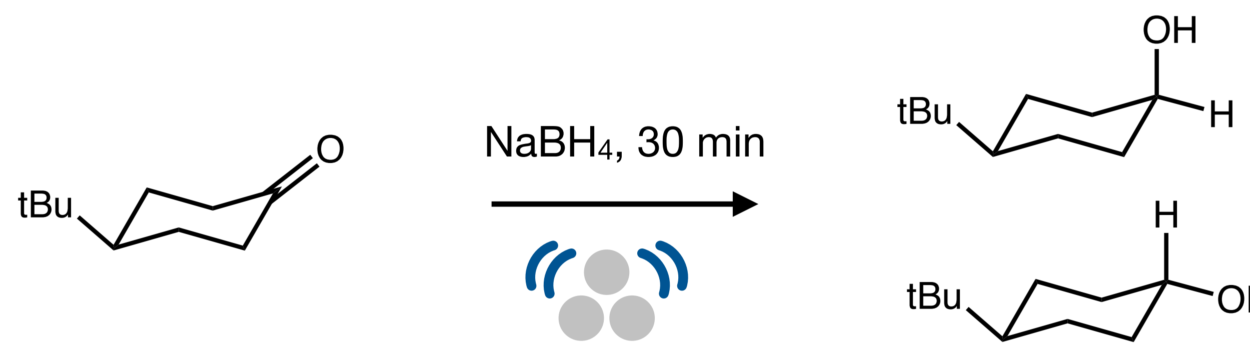
Heating mantle

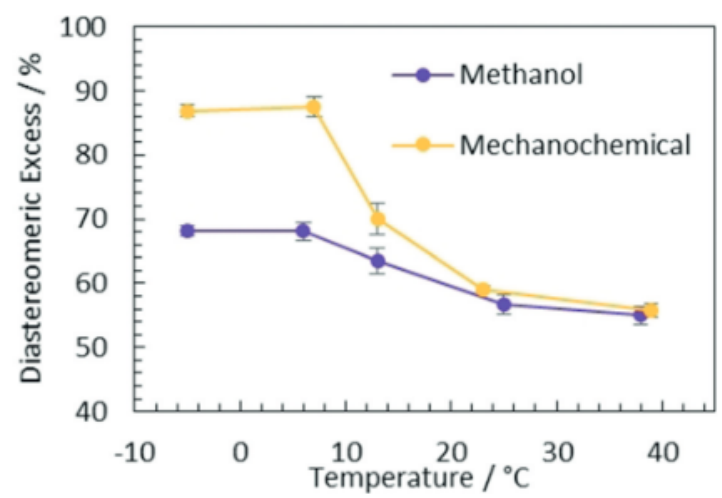
Milling alone causes increase of T until equilibrium

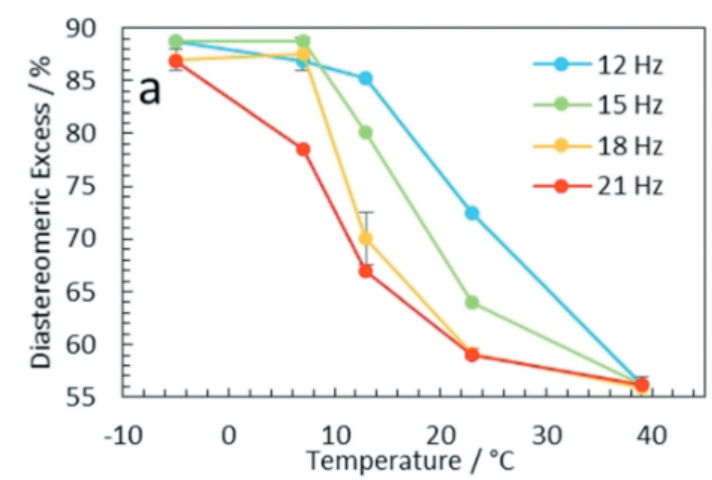


Dry milling of ZnO

Martinez, V. et al., *Nat. Rev. Chem.* **2023**, *7*, 51–65.







James Mack et al., *Angew. Chem. Int. Ed.* **2018**, *57*, 13062–13065.

Krunoslav Užarević et al., *ACS Sustainable Chem. Eng.* **2019**, *7*, 16301–16309.

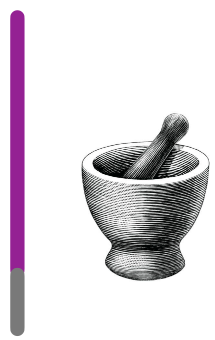
Mechanochemistry in Organic Synthesis

Photo-mechanochemistry

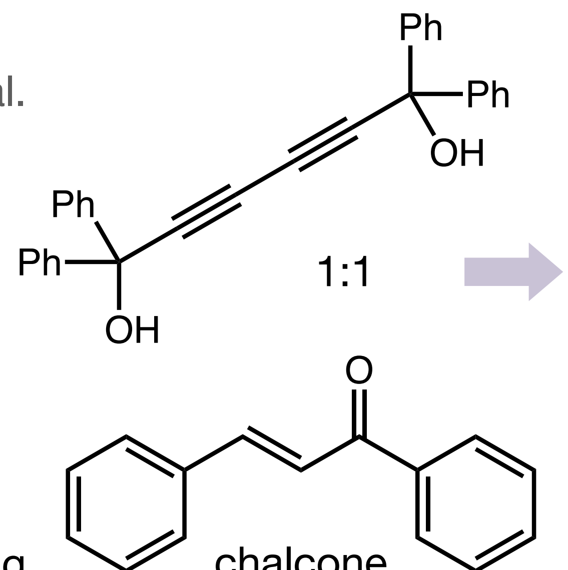
Mechanochemistry in Organic Synthesis

Photo-mechanochemistry

1987, Toda et al.



Irradiation with Hg lamp at rt

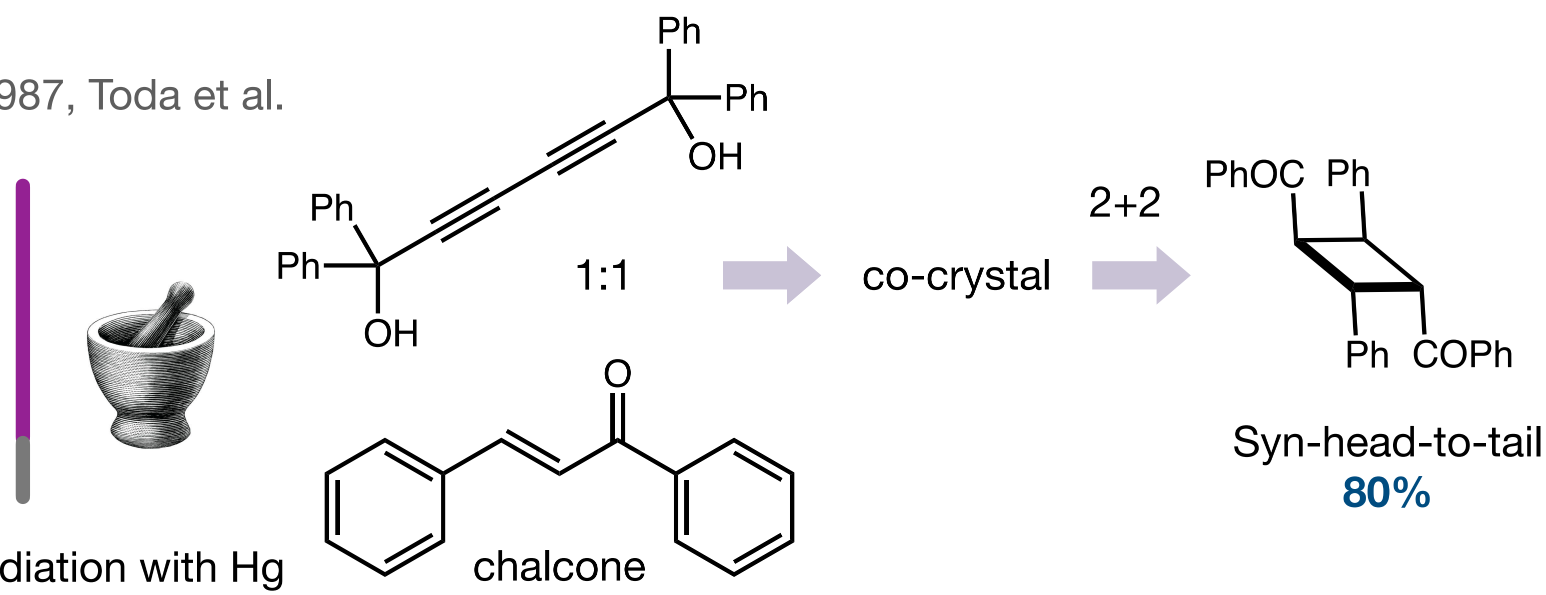


Fumio Toda et al., *J. Chem. Soc., Chem. Commun.*, **1987**, 279-280.

Mechanochemistry in Organic Synthesis

Photo-mechanochemistry

1987, Toda et al.



Irradiation with Hg lamp at rt

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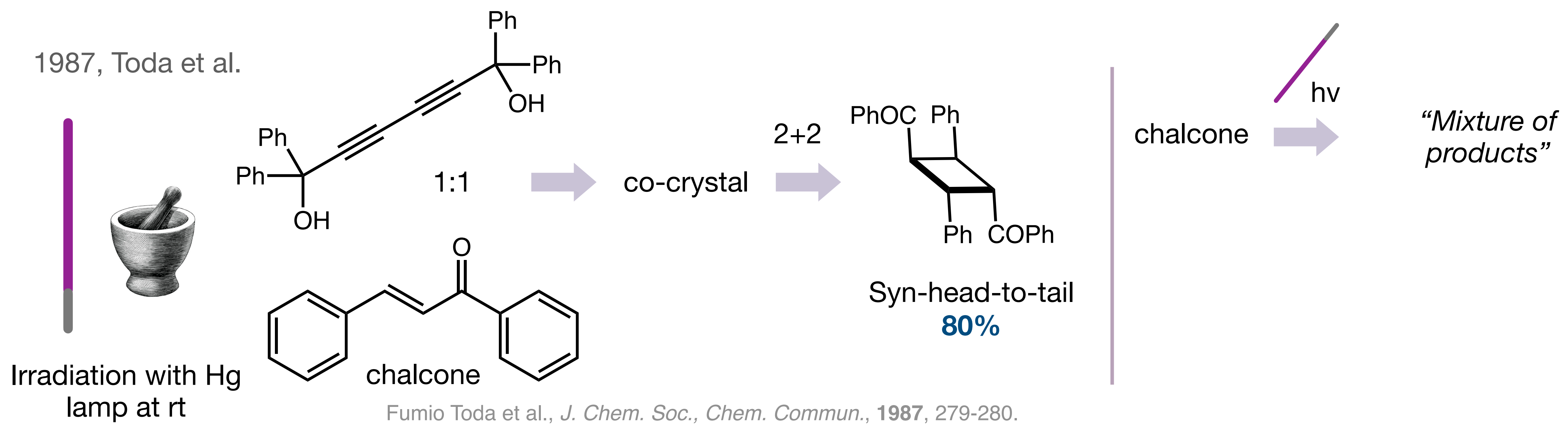
Mechanochemistry in Organic Synthesis

Photo-mechanochemistry



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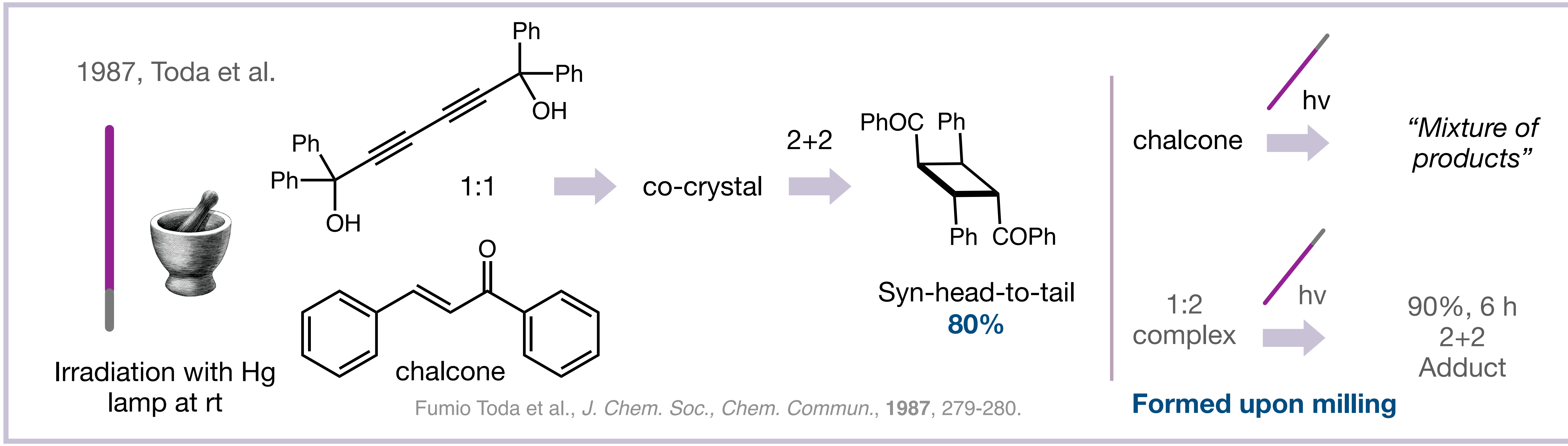
Mechanochemistry in Organic Synthesis

Photo-mechanochemistry



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Mechanochemistry in Organic Synthesis

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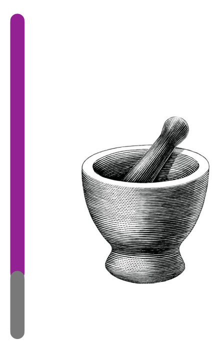

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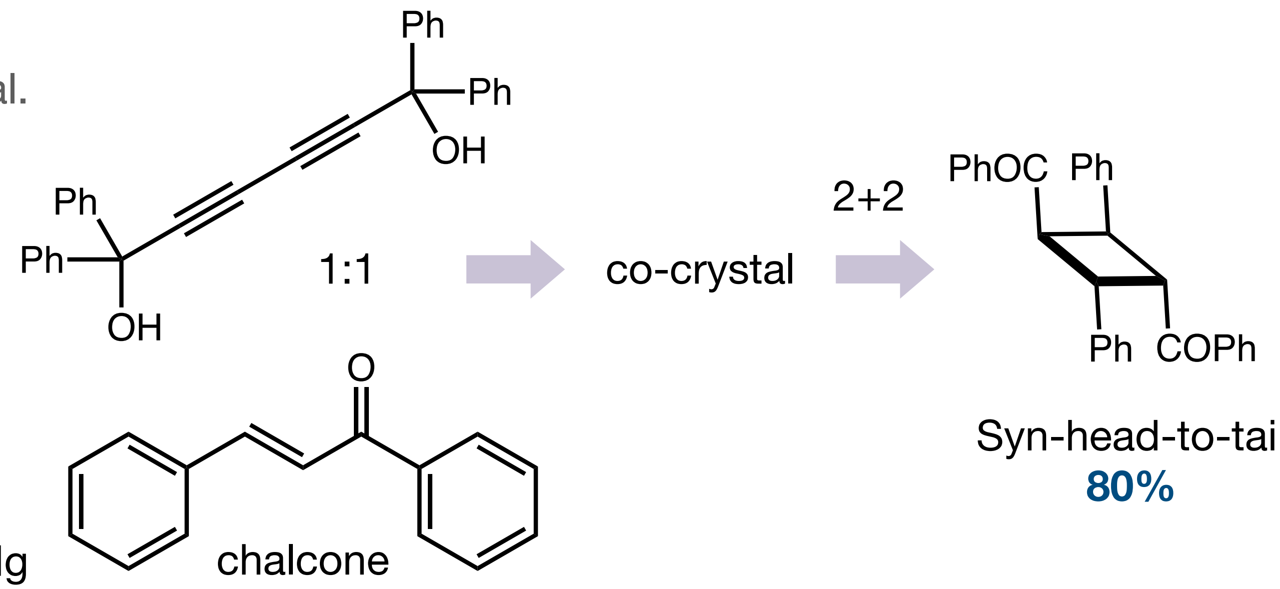
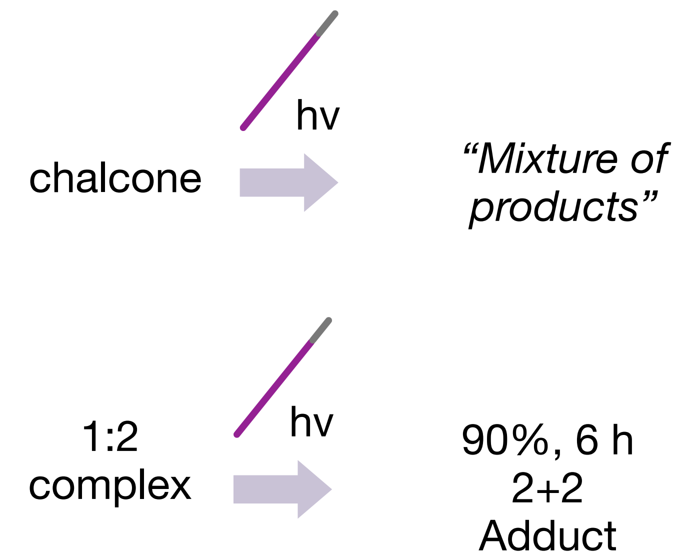
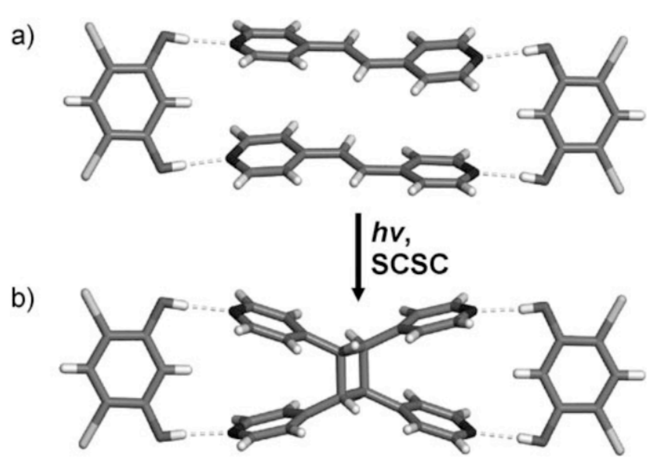


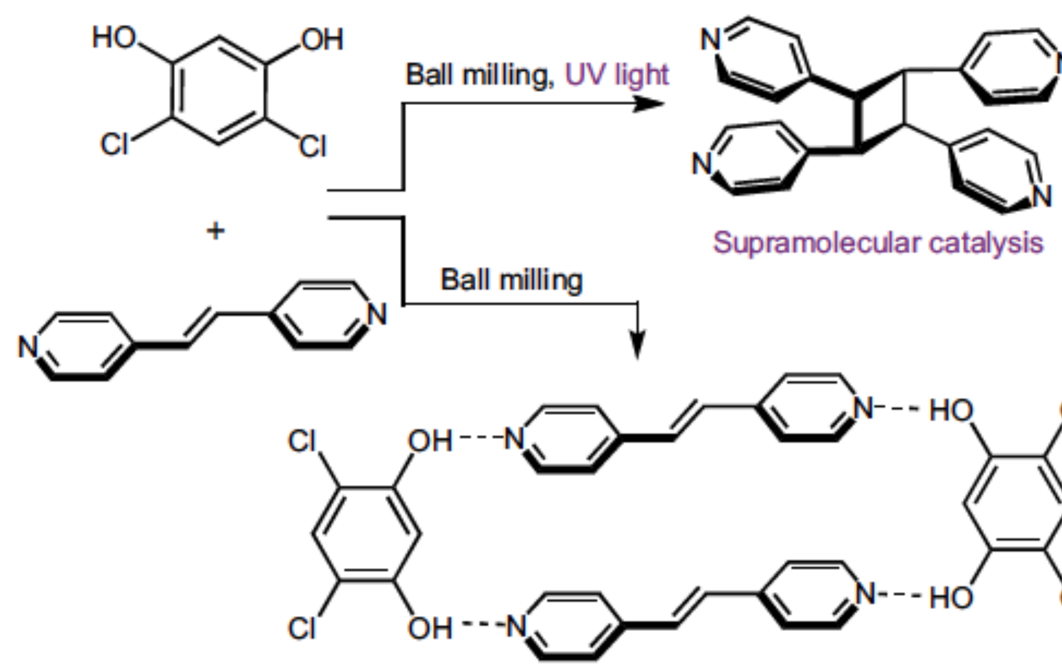
Syn-head-to-tail
80%

Fumio Toda et al., *J. Chem. Soc., Chem. Commun.*, **1987**, 279-280.



Formed upon milling





Cocrystal formation

Leonard R. MacGillivray et al., *Angew. Chem. Int. Ed.* **2010**, *49*, 4273–4277.

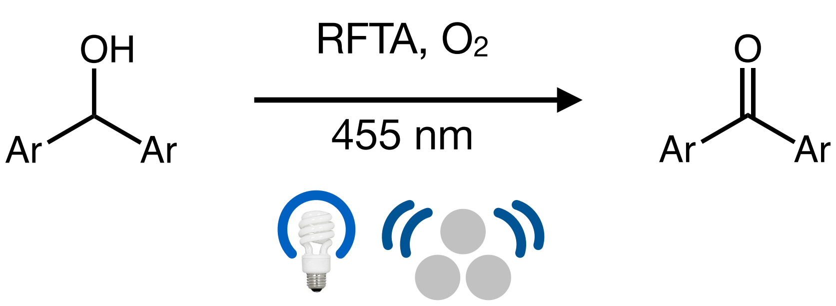
Leonard R. MacGillivray et al., *Chem. Sci.*, **2020**, *11*, 3569-3573.

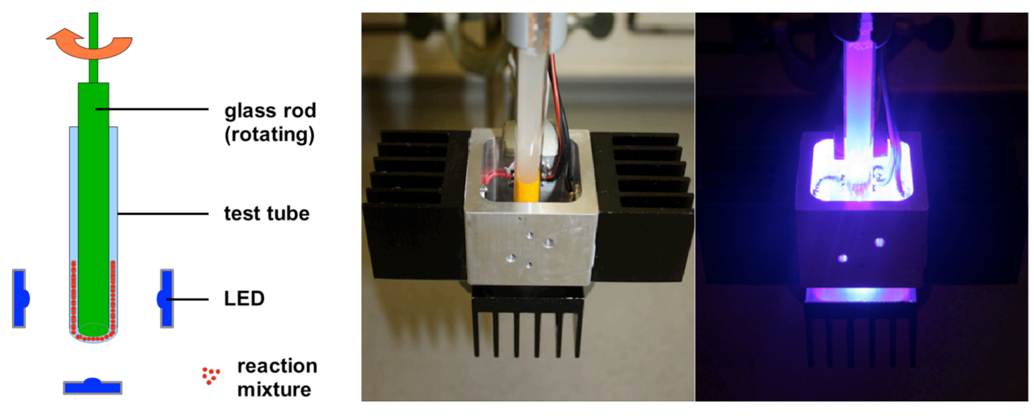
Mechanochemistry in Organic Synthesis

Photo-mechanochemistry

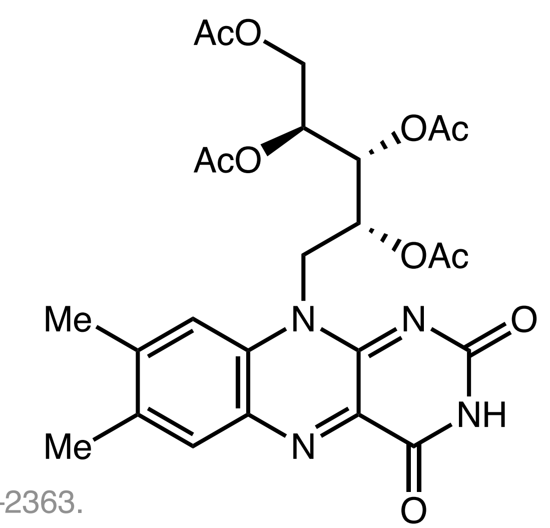
Visible-light photo-mechanochemistry

First report, König, 2016





riboflavin tetraacetate (RFTA)



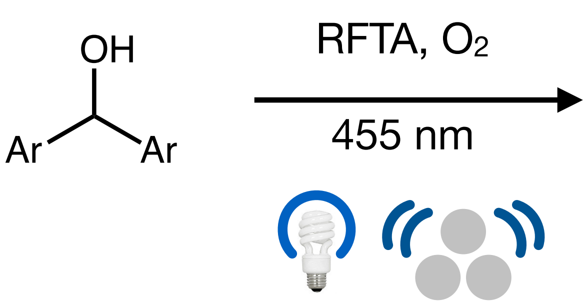
Martin Obst, Burkhard König, *Beilstein J. Org. Chem.* **2016,** *12,* 2358–2363.

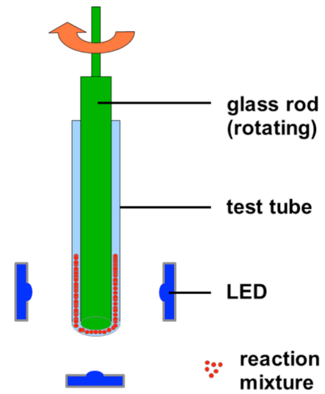
Mechanochemistry in Organic Synthesis

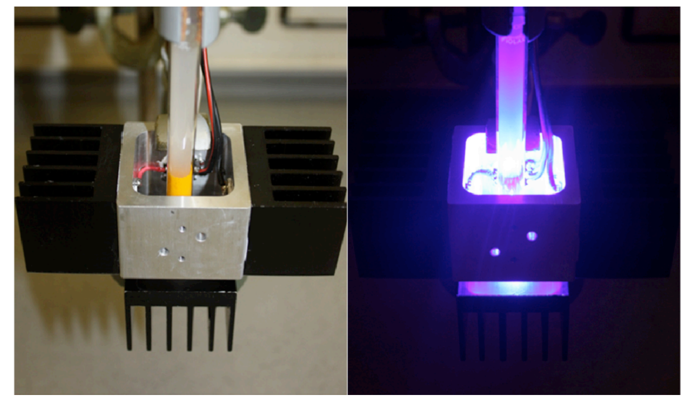
Photo-mechanochemistry

Visible-light photo-mechanochemistry

First report, König, 2016







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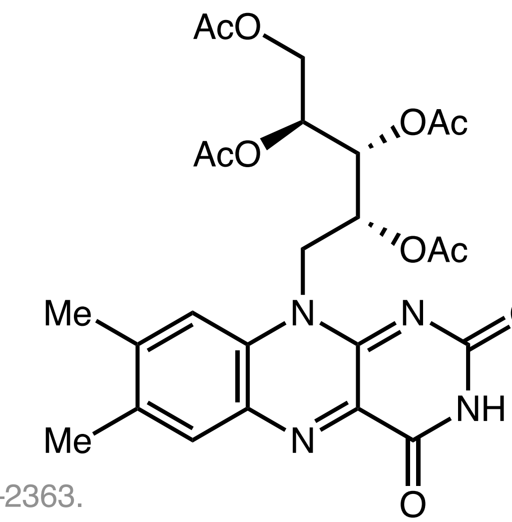
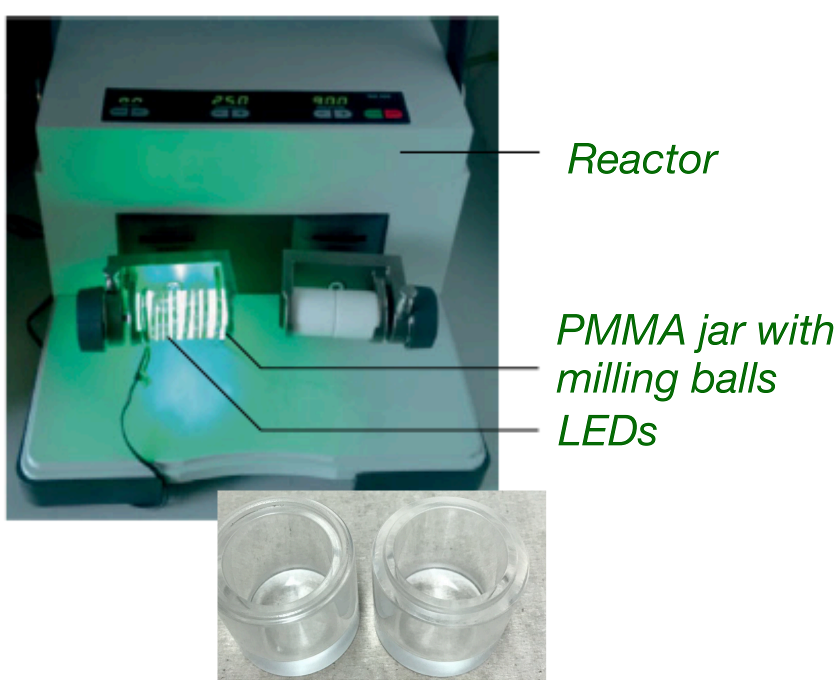
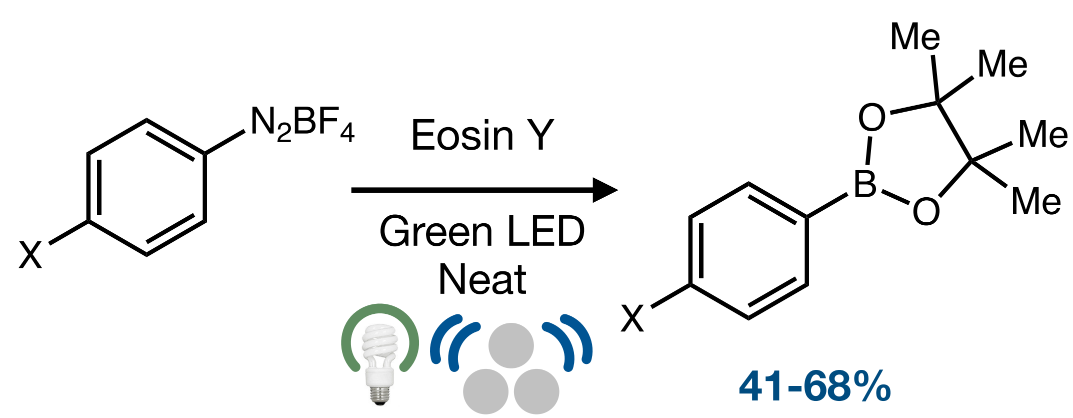


Martin Obst, Burkhard König, *Beilstein J. Org. Chem.* **2016,** *12,* 2358–2363.





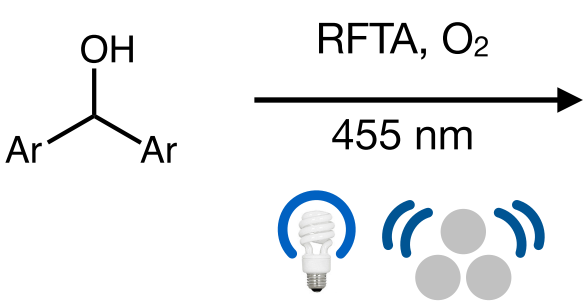
José G. Hernández, *Beilstein J. Org. Chem.* **2017**, *13*, 1463–1469.

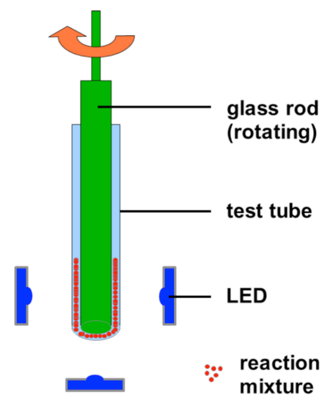
Mechanochemistry in Organic Synthesis

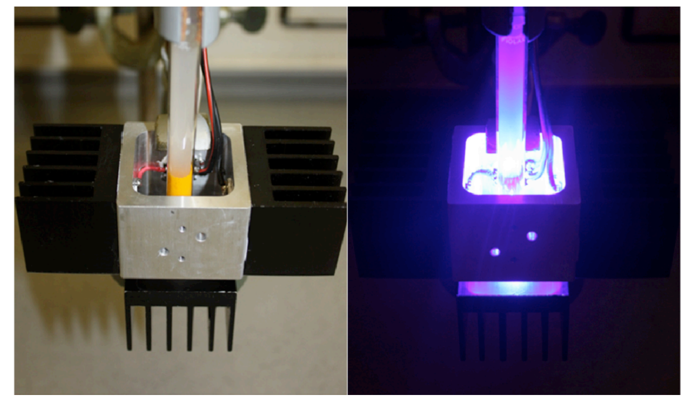
Photo-mechanochemistry

Visible-light photo-mechanochemistry

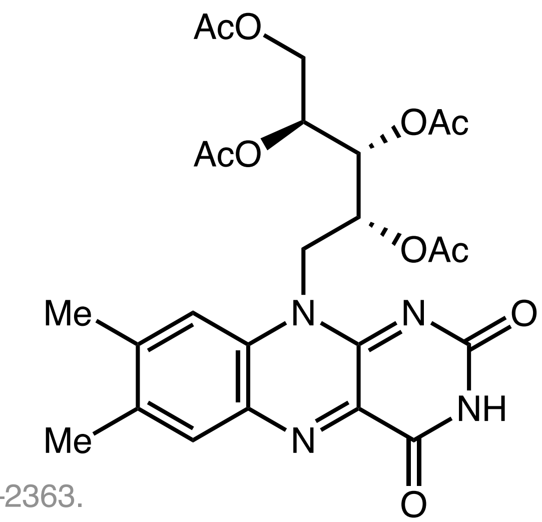
First report, König, 2016



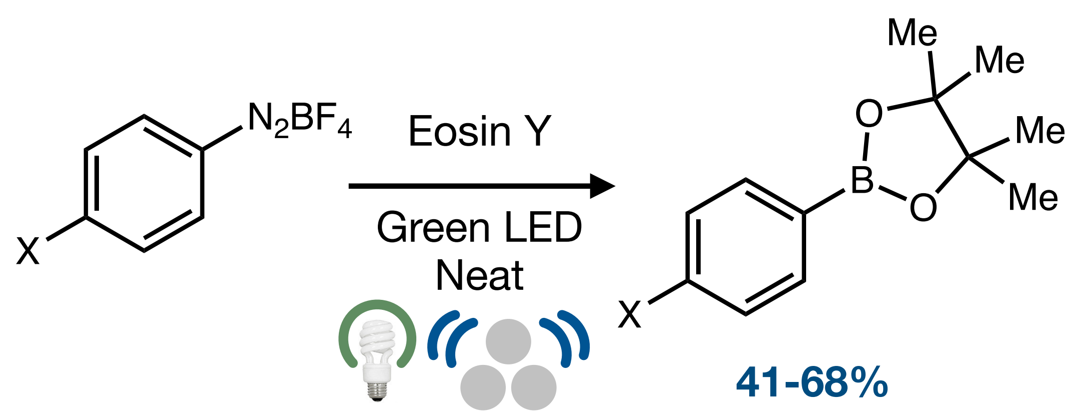




riboflavin tetraacetate (RFTA)



Martin Obst, Burkhard König, *Beilstein J. Org. Chem.* **2016,** *12,* 2358–2363.



Controls:

Teflon jar
w/ or w/o PC
0%

PPMA jar
Ambient light
0%

No PC
0%

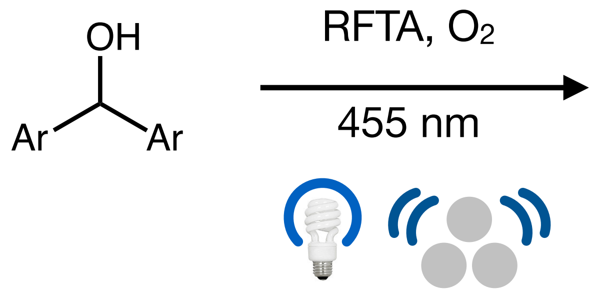
José G. Hernández, *Beilstein J. Org. Chem.* **2017**, *13*, 1463–1469.

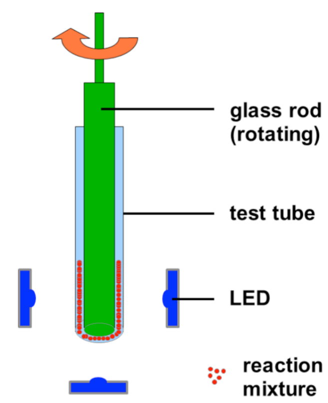
Mechanochemistry in Organic Synthesis

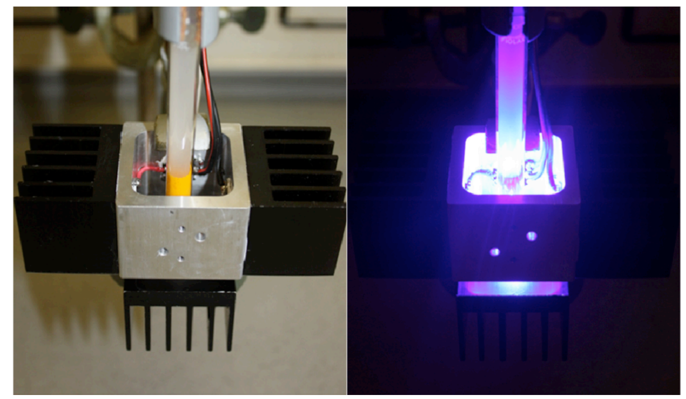
Photo-mechanochemistry

Visible-light photo-mechanochemistry

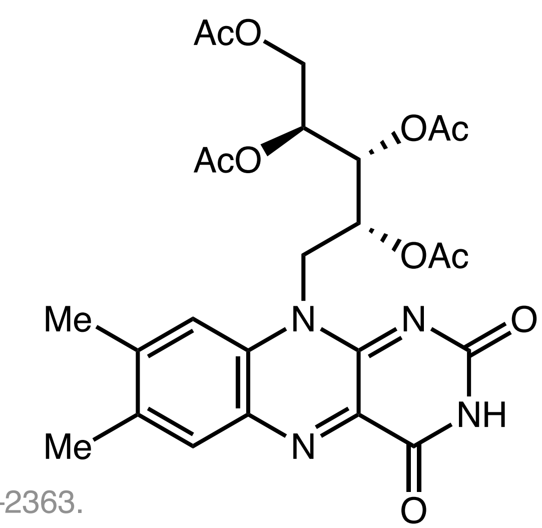
First report, König, 2016





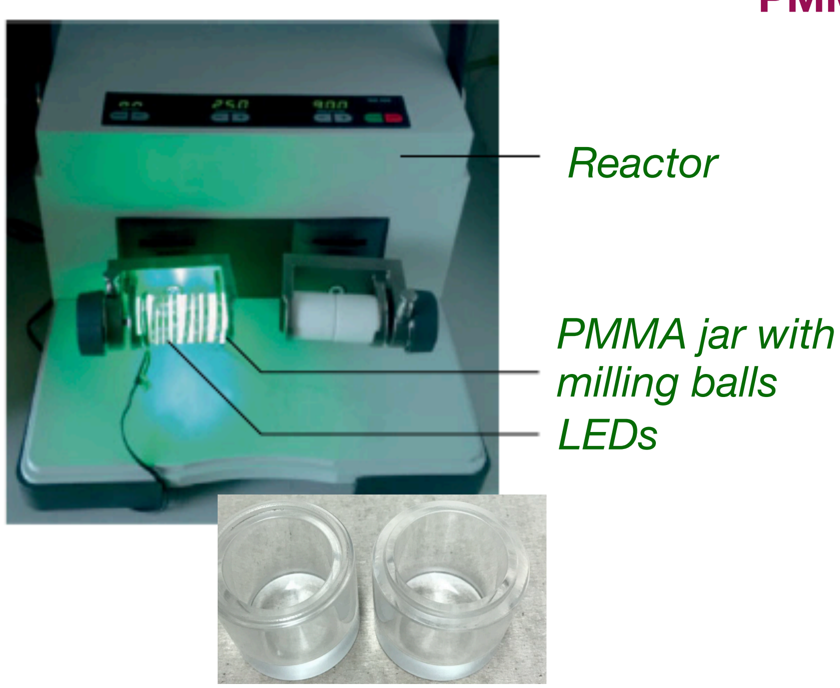


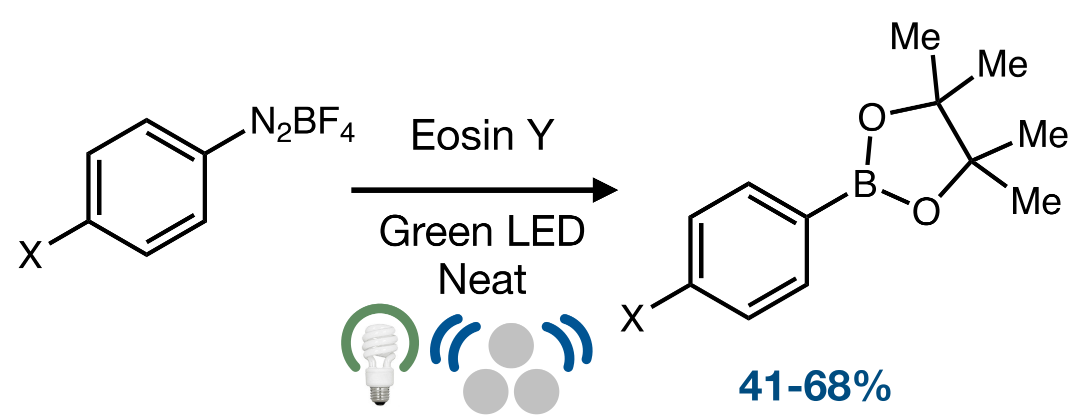
riboflavin tetraacetate (RFTA)



Martin Obst, Burkhard König, *Beilstein J. Org. Chem.* **2016,** *12,* 2358–2363.

PMMA causes opacity **Lower light penetration**





Controls:

Teflon jar
w/ or w/o PC
0%

PPMA jar
Ambient light
0%

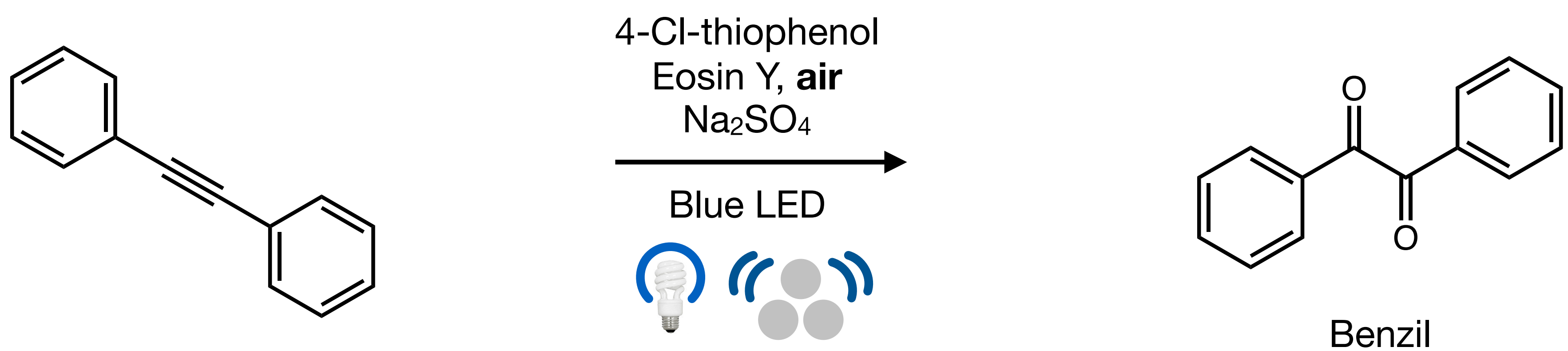
No PC
0%

José G. Hernández, *Beilstein J. Org. Chem.* **2017**, *13*, 1463–1469.

Mechanochemistry in Organic Synthesis

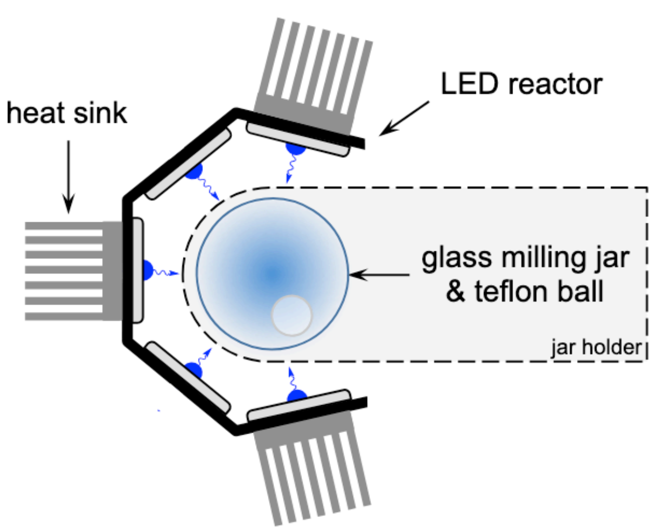
Photo-mechanochemistry

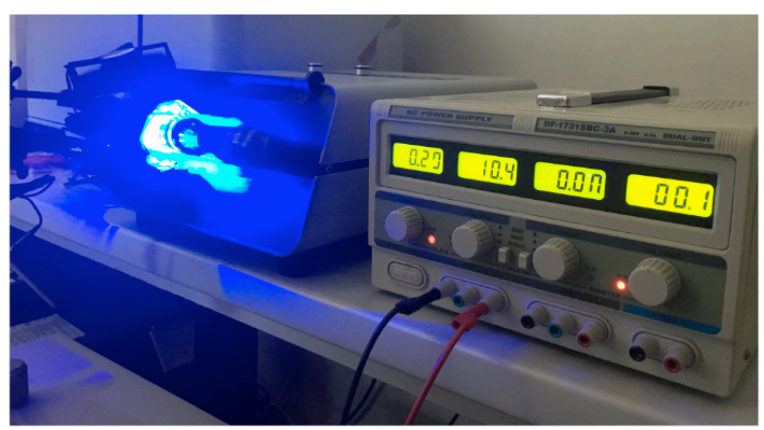
Visible-light photo-mechanochemistry

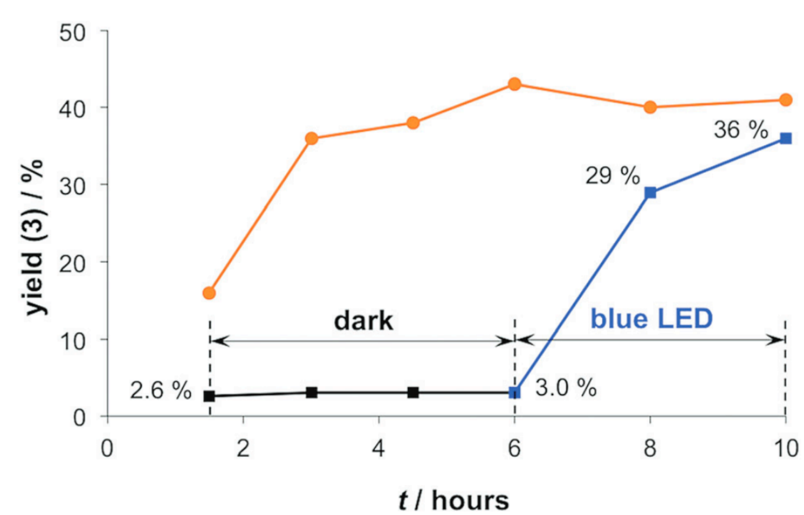


Benzil
43%

(via $^3O_2$ sensitisation)







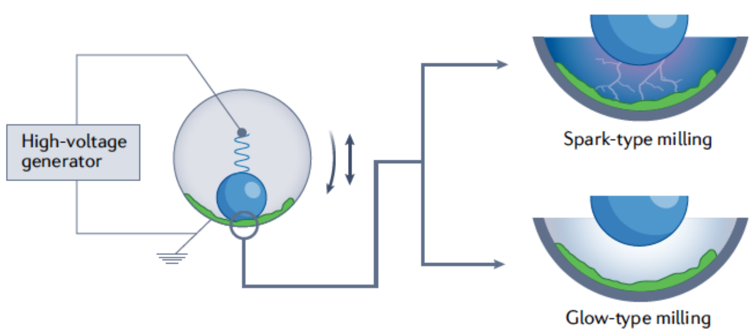
Vjekoslav Štrukil , Igor Sajko, *Chem. Commun.*, **2017**, *53*, 9101-9104.

Mechanochemistry in Organic Synthesis

Electro-mechanochemistry

How to induce electric discharge?

electrical-discharge-assisted mechanical milling (EDAMM)

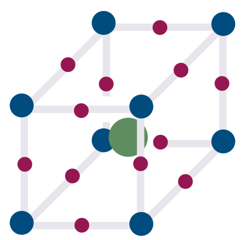


Spark-type milling

Glow-type milling

Calka, A., Wexler, D. *Nature* **2002**, *419*, 147–151.

Piezoelectric materials

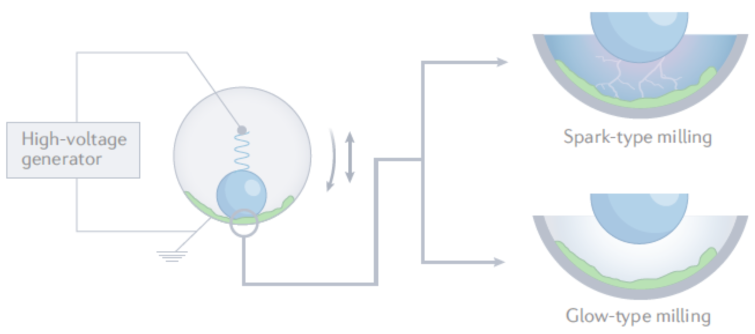


e.g., $BaTiO_3$

Mechanochemistry in Organic Synthesis

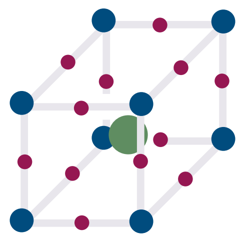
Electro-mechanochemistry

How to induce electric discharge?



Calka, A., Wexler, D. *Nature* **2002**, *419*, 147–151.

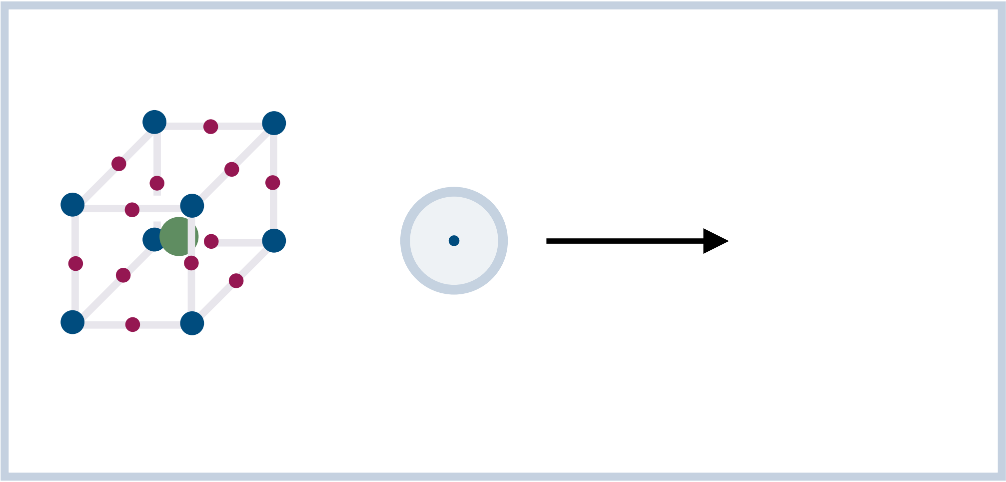
Piezoelectric materials



e.g., $BaTiO_3$

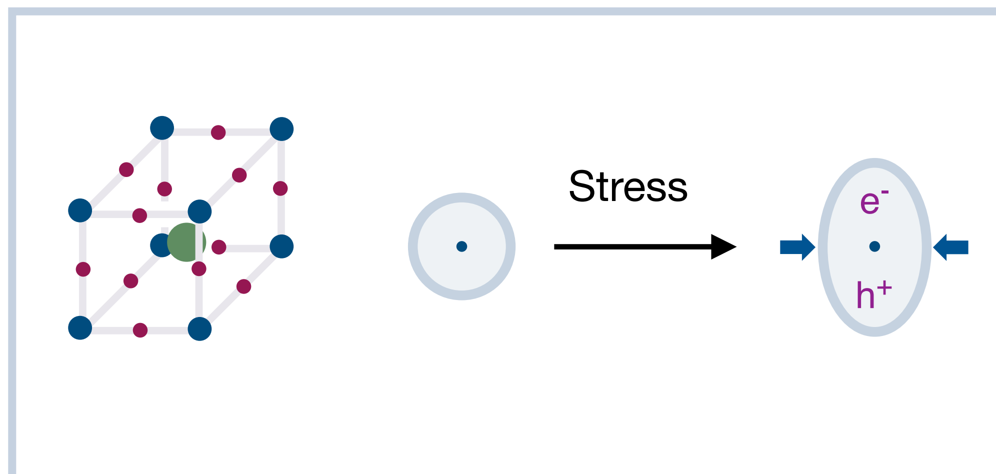
Mechanochemistry in Organic Synthesis

Piezoelectric Materials

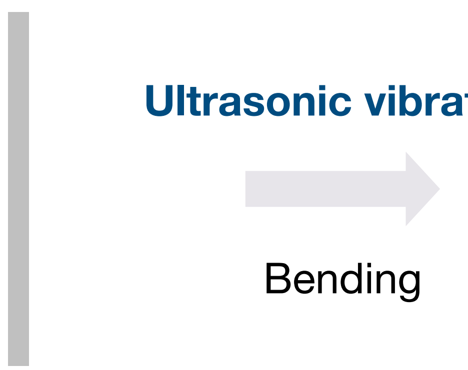


Mechanochemistry in Organic Synthesis

Piezoelectric Materials



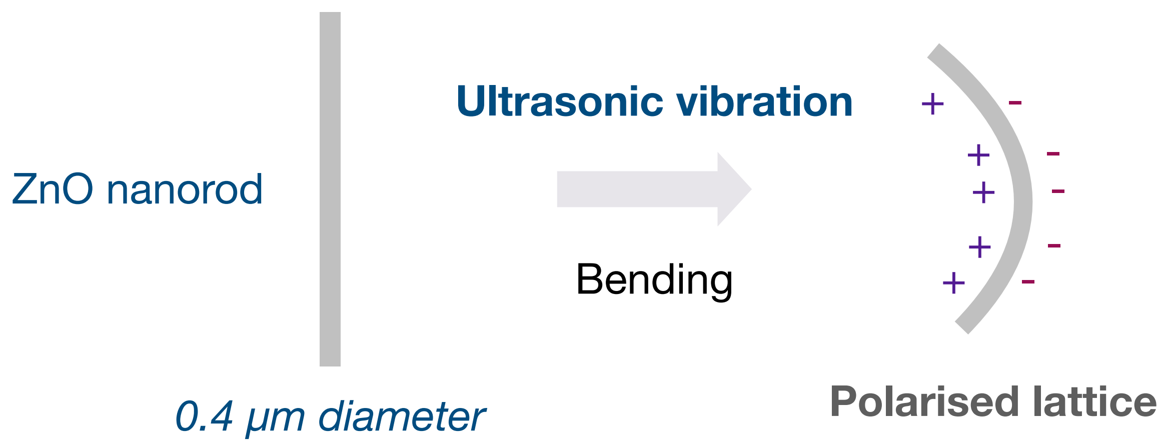
Piezoelectric Materials



Kuang-Sheng Hong, Huifang Xu, Hiromi Konishi, Xiaochun Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997–1002.

Mechanochemistry in Organic Synthesis

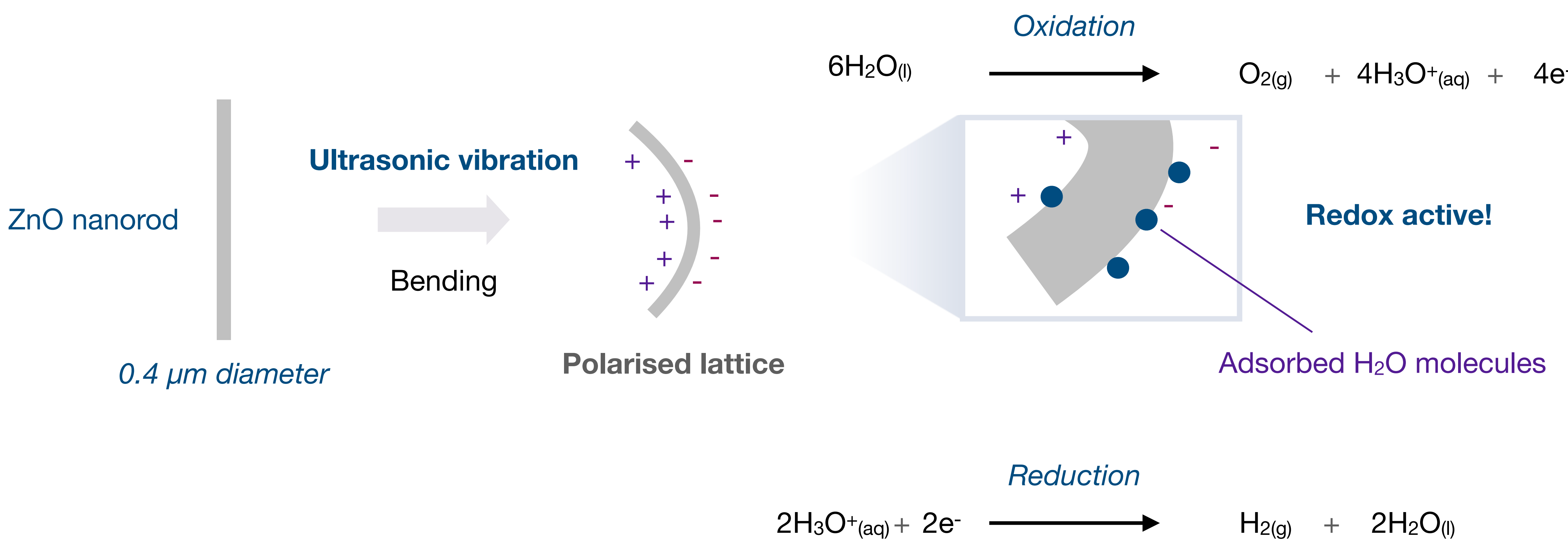
Piezoelectric Materials



Kuang-Sheng Hong, Huifang Xu, Hiromi Konishi, Xiaochun Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997–1002.

Mechanochemistry in Organic Synthesis

Piezoelectric Materials



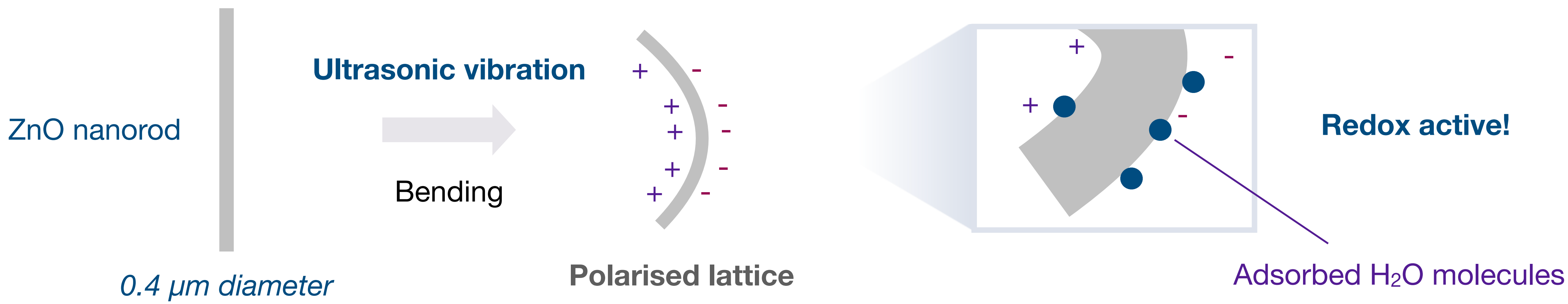
Kuang-Sheng Hong, Huifang Xu, Hiromi Konishi, Xiaochun Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997–1002.

Mechanochemistry in Organic Synthesis

Piezoelectric Materials

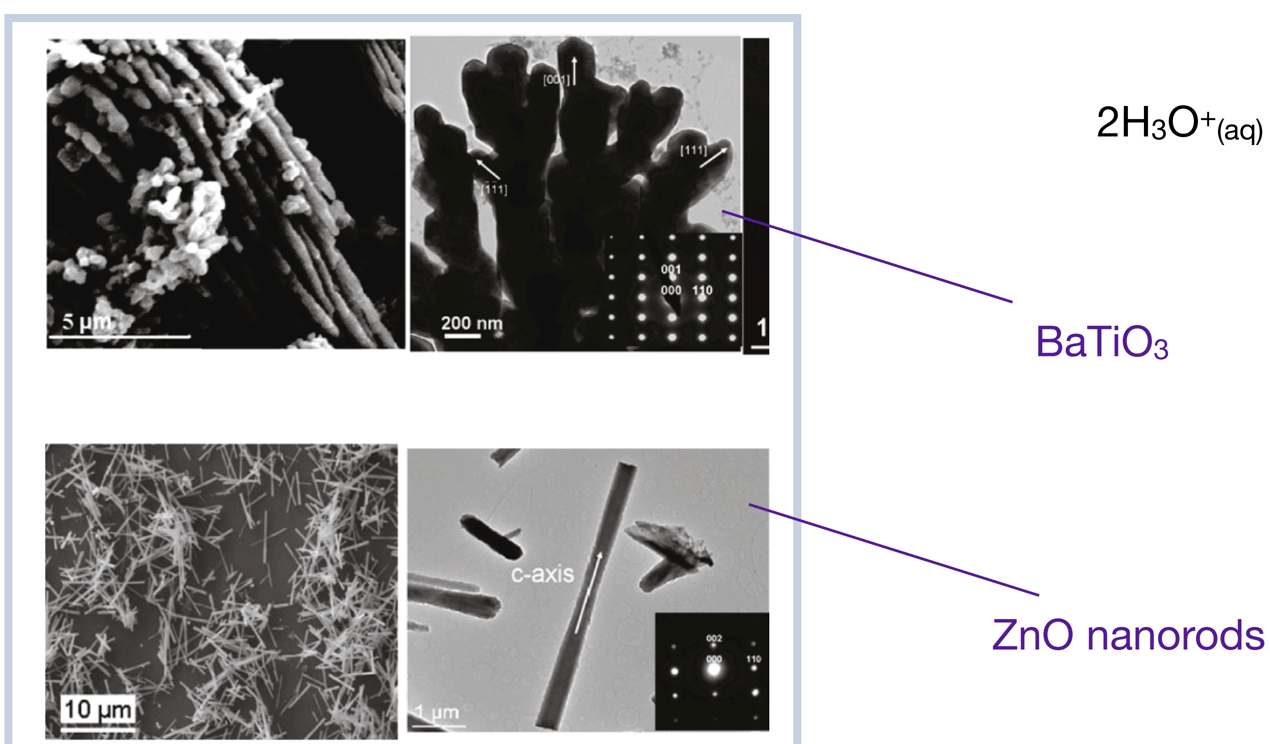
Oxidation

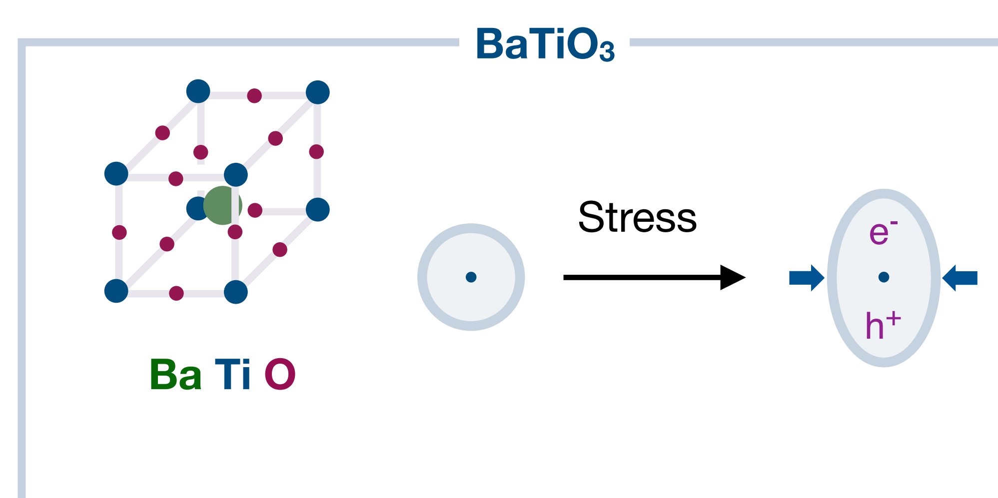
$$6H_2O_{(l)} \longrightarrow O_{2(g)} + 4H_3O^+_{(aq)} + 4e^-$$



Reduction

$$2H_3O^+_{(aq)} + 2e^- \longrightarrow H_{2(g)} + 2H_2O_{(l)}$$

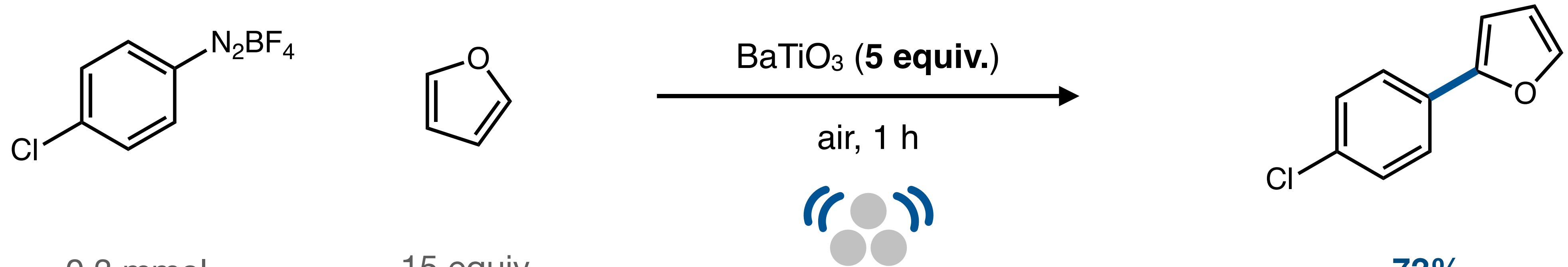




Kuang-Sheng Hong, Huifang Xu, Hiromi Konishi, Xiaochun Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997–1002.

Mechanochemistry in Organic Synthesis

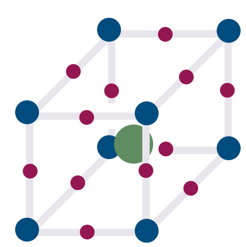
Mechanoredox Chemistry



0.3 mmol

15 equiv.

73%

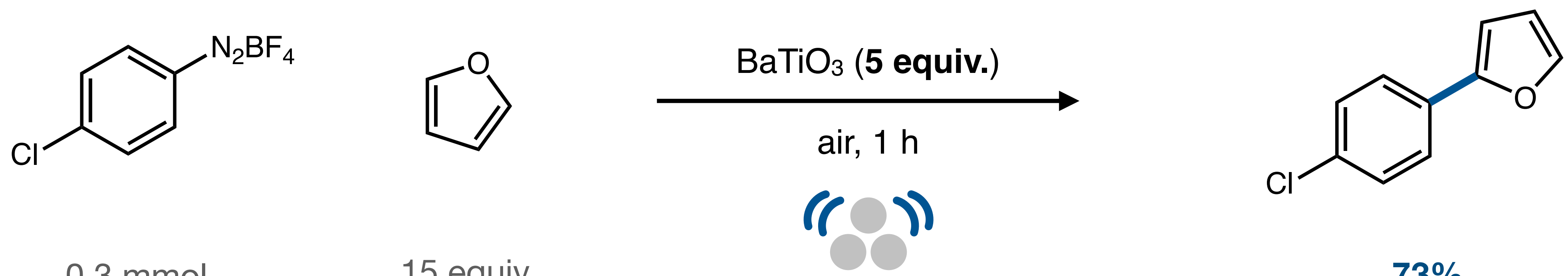


BaTiO₃

Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry



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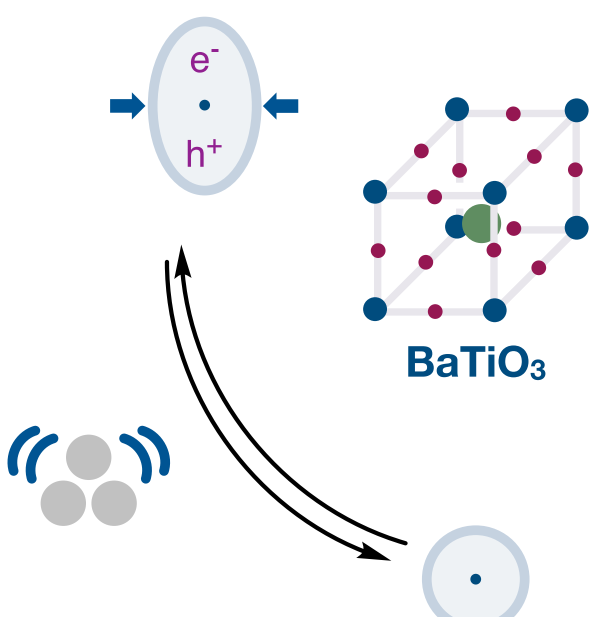
15 equiv.

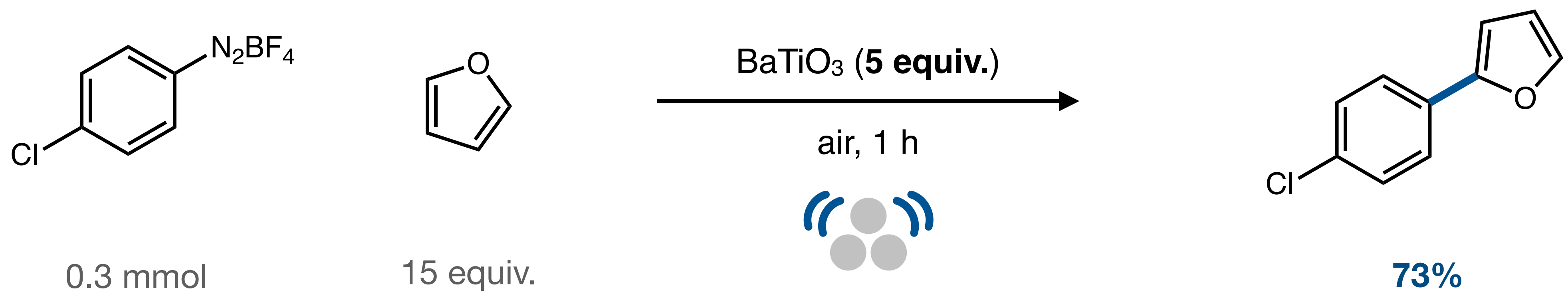
73%

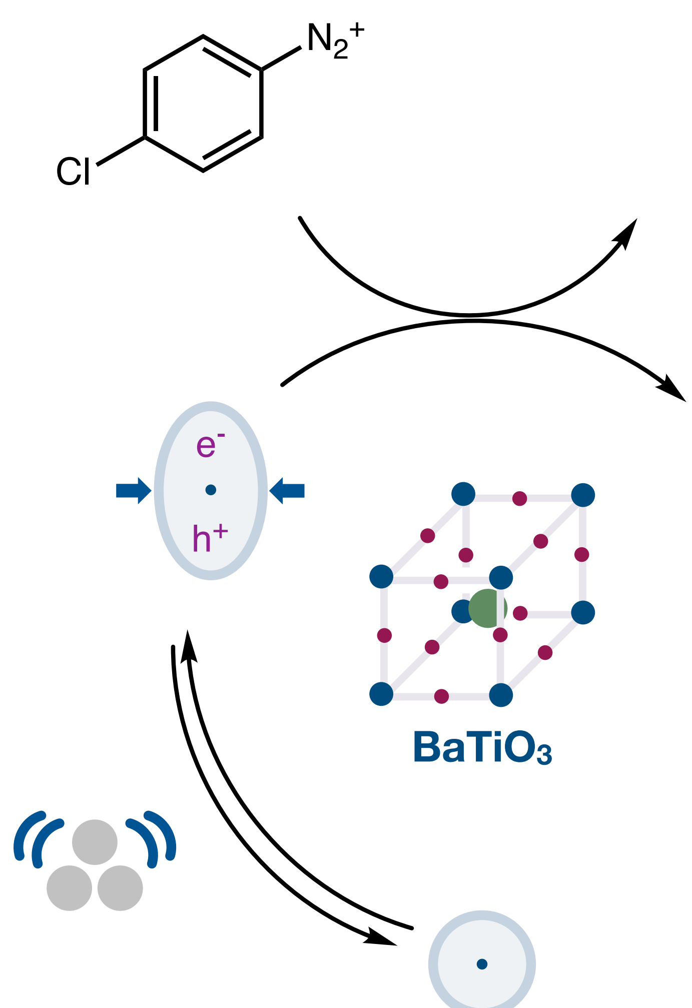


Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry





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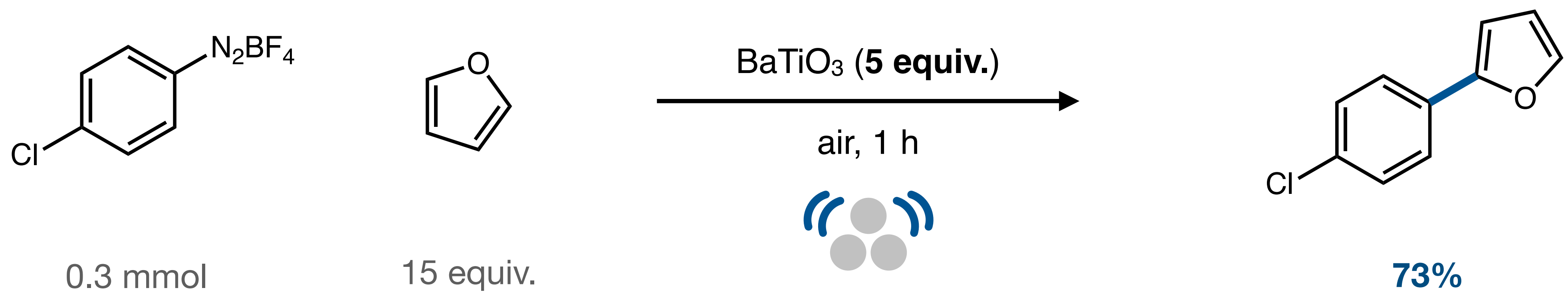
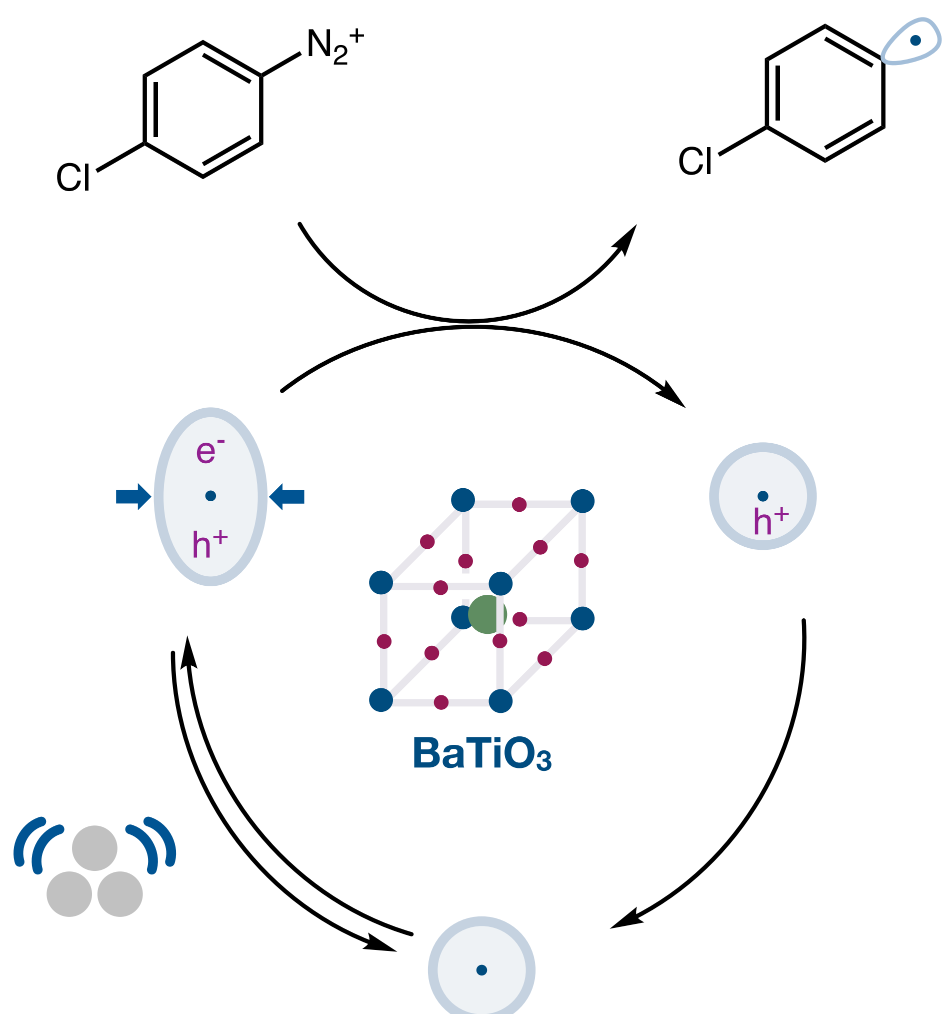
Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry





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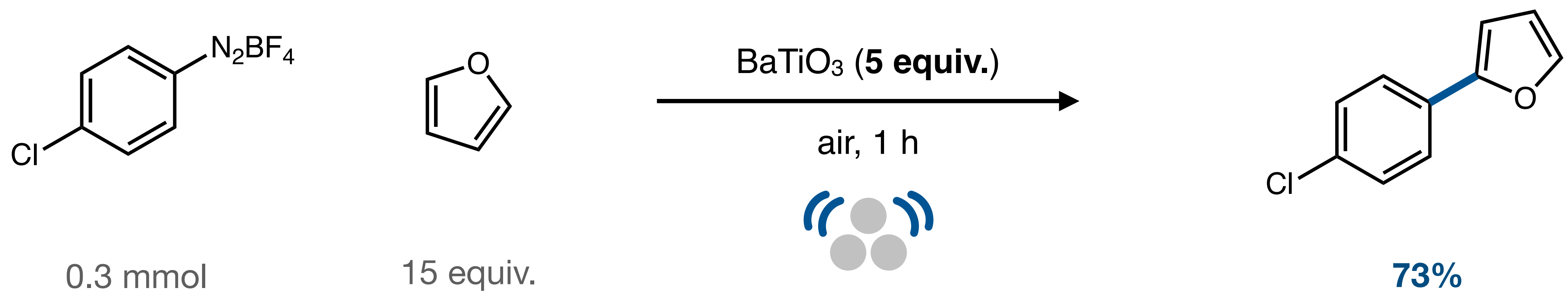
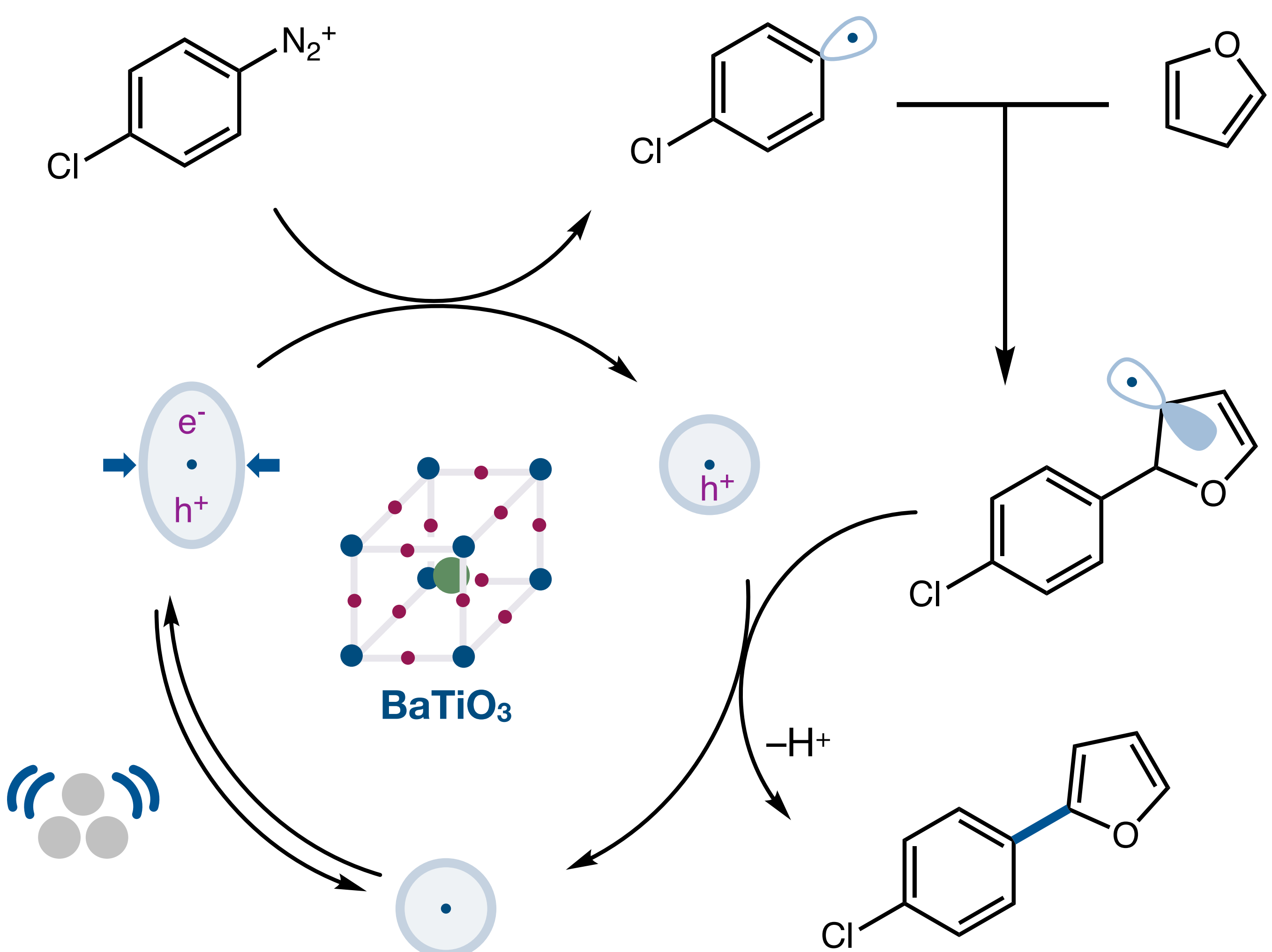
Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry





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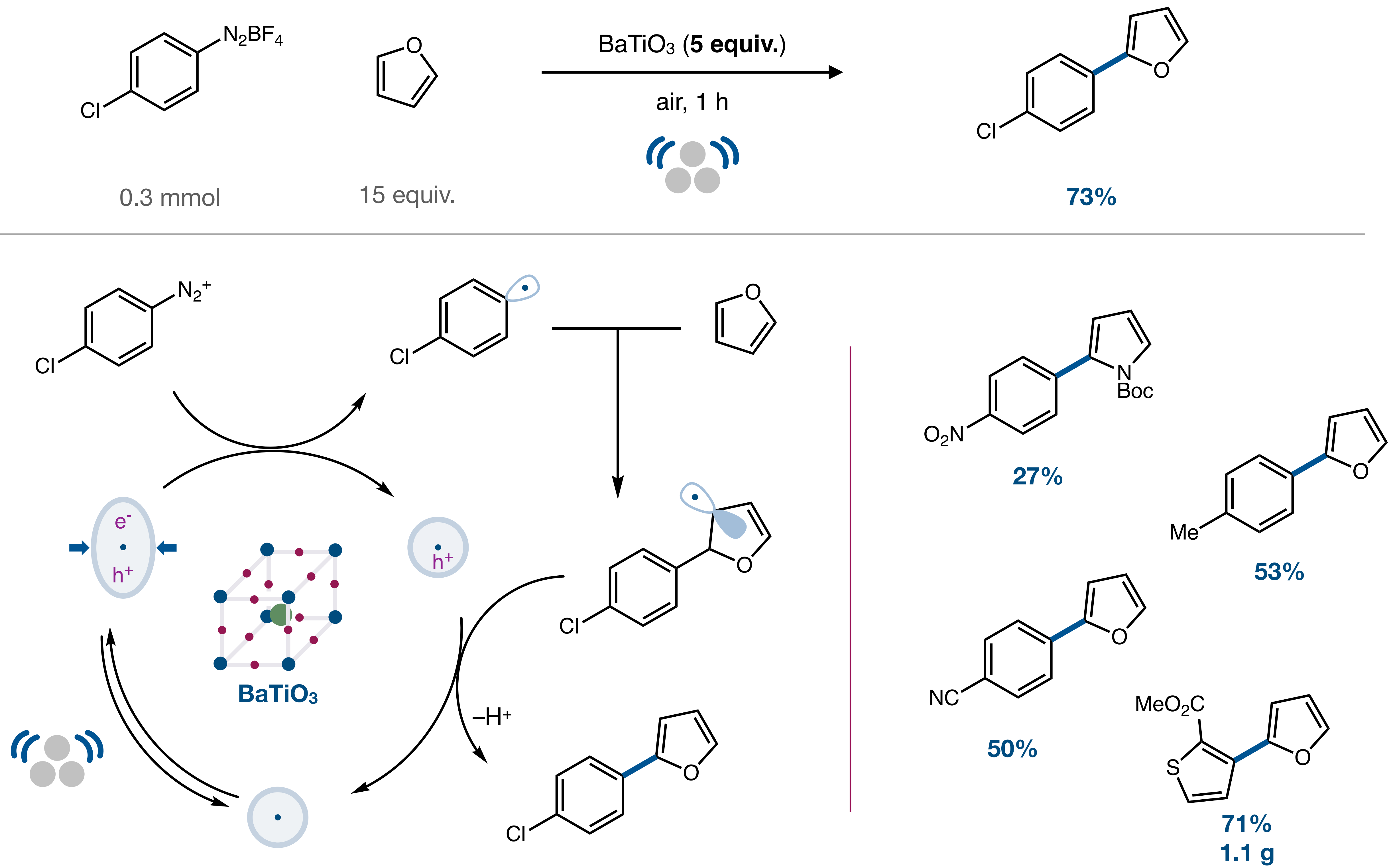
Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry

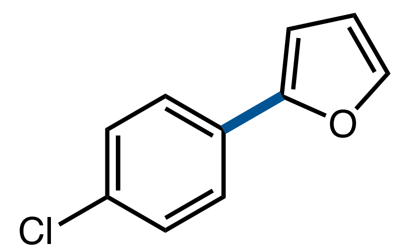


Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

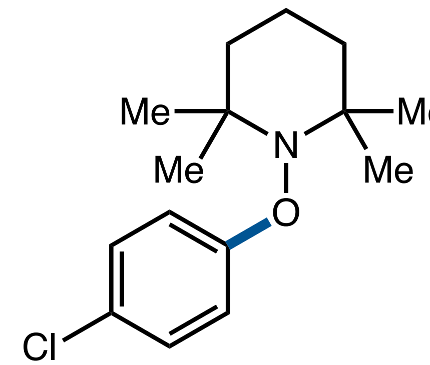
Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry

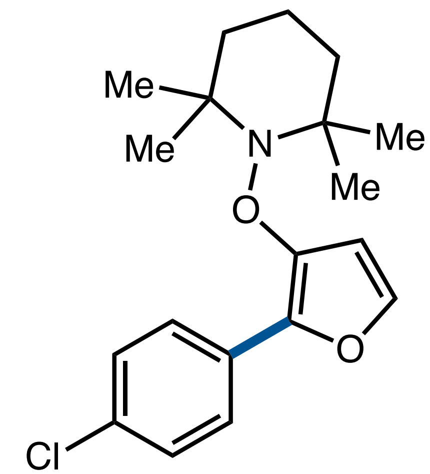
TEMPO trap studies



7%
(NMR)



28%
(NMR)



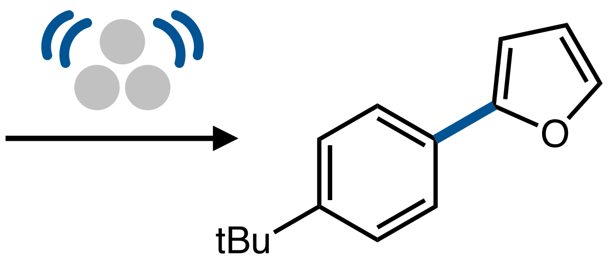
Mass detected
(GCMS)

Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

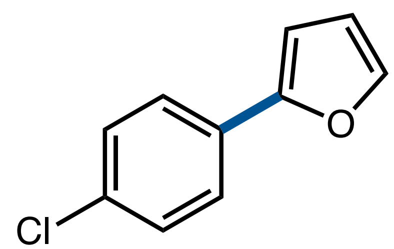
Mechanoredox Chemistry

$BaTiO_3$ recovery

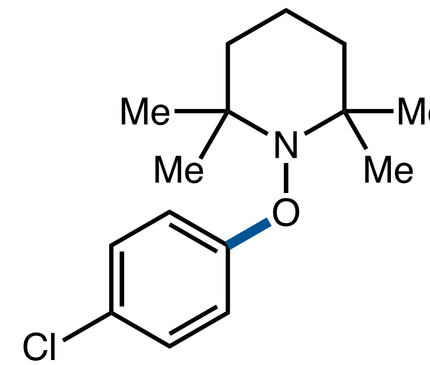


	AY	Recovery
1st run	73%	95%
2nd run	71%	96%
3rd run	66%	96%
4th run	52%	98%
5th run	43%	-

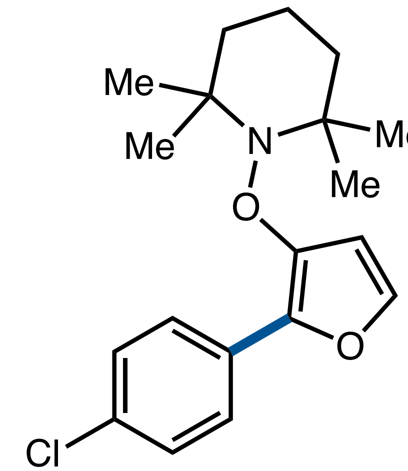
TEMPO trap studies



7%
(NMR)



28%
(NMR)



Mass detected
(GCMS)

Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry

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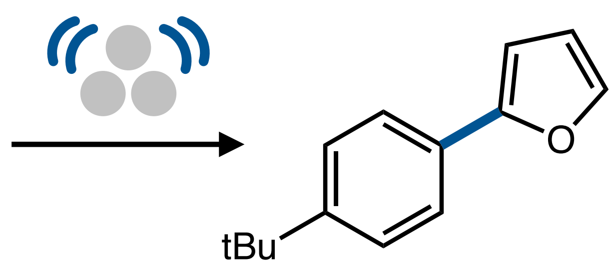

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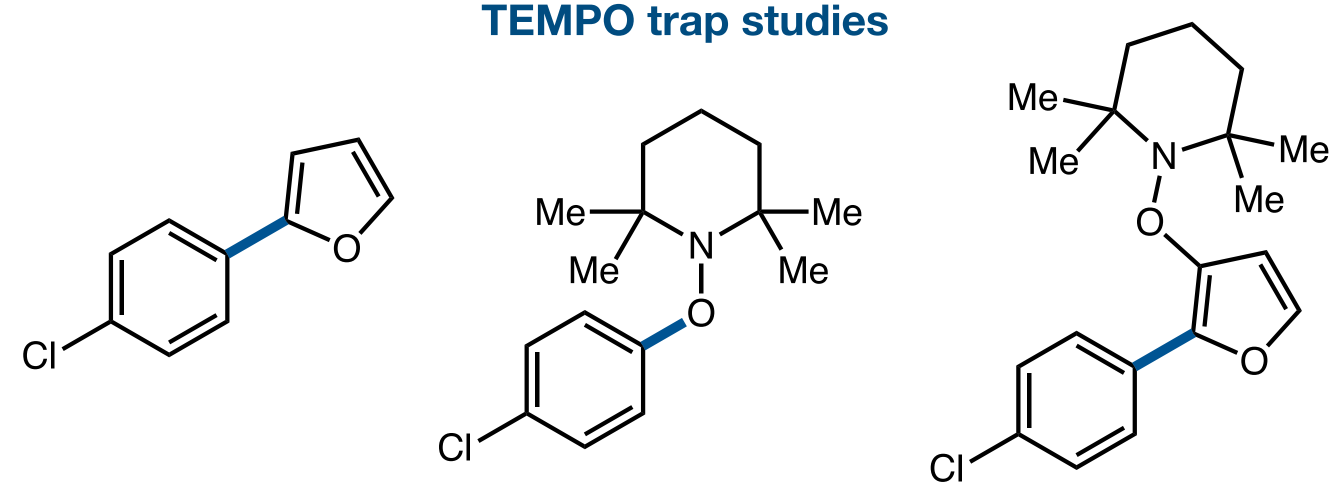
TEMPO trap studies



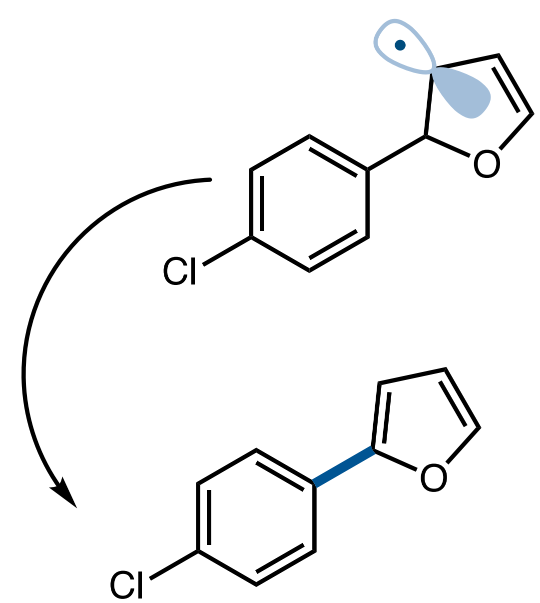
7% (NMR)

28% (NMR)

Mass detected (GCMS)

Oxidation by O$_2$?

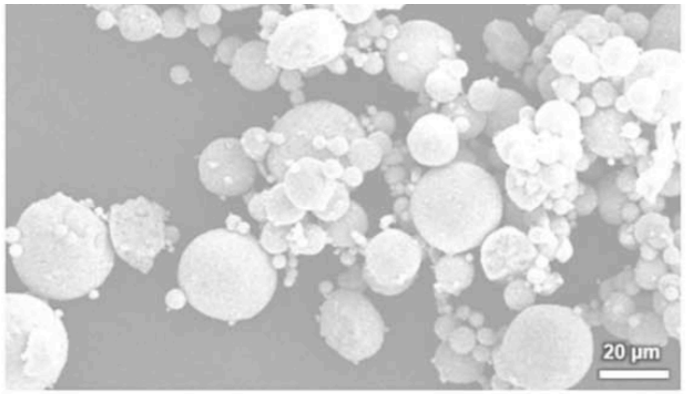
Under air	81%
Under Ar	78%



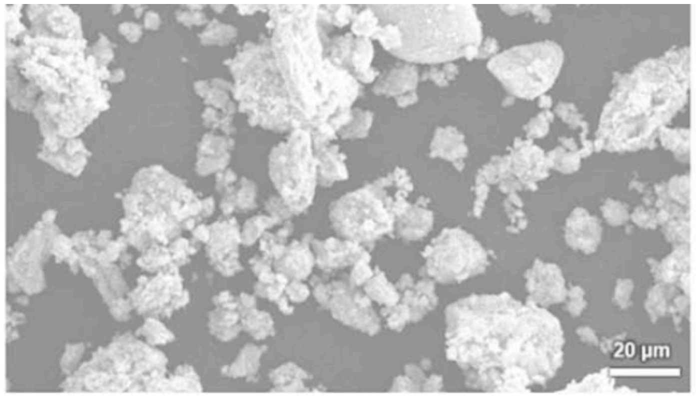
Hajime Ito et al., *Science*, **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry



$BaTiO_3$
Intact

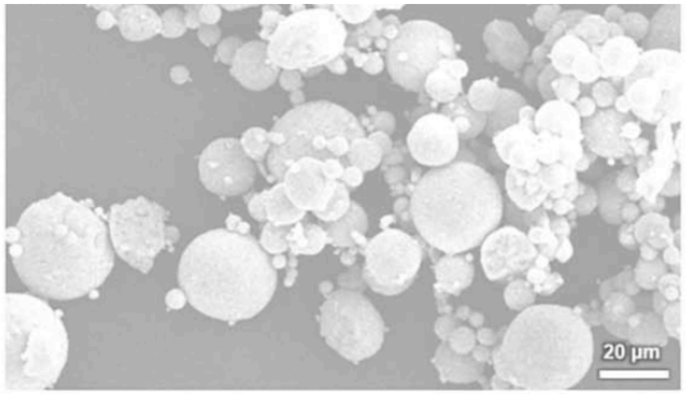


$BaTiO_3$
60 min, 30 Hz

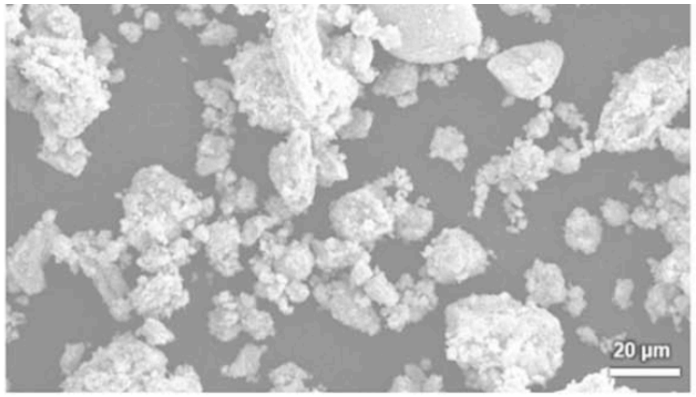
Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

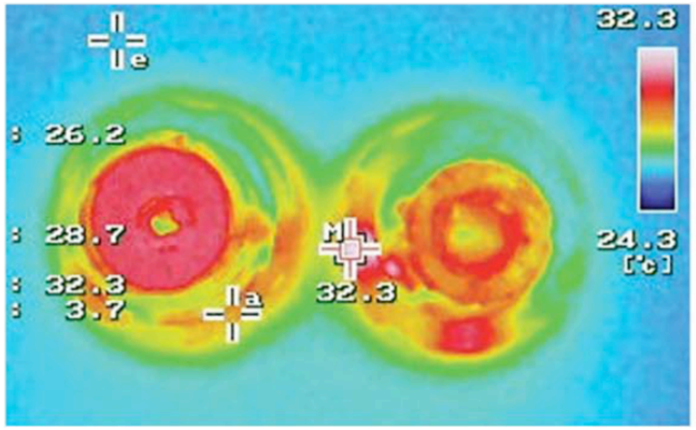
Mechanoredox Chemistry



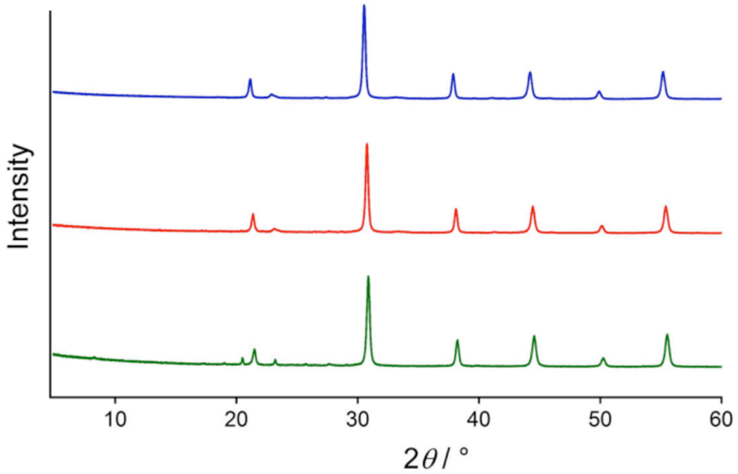
$BaTiO_3$
Intact



$BaTiO_3$
60 min, 30 Hz



Standard conditions
Ball temperature 30 °C

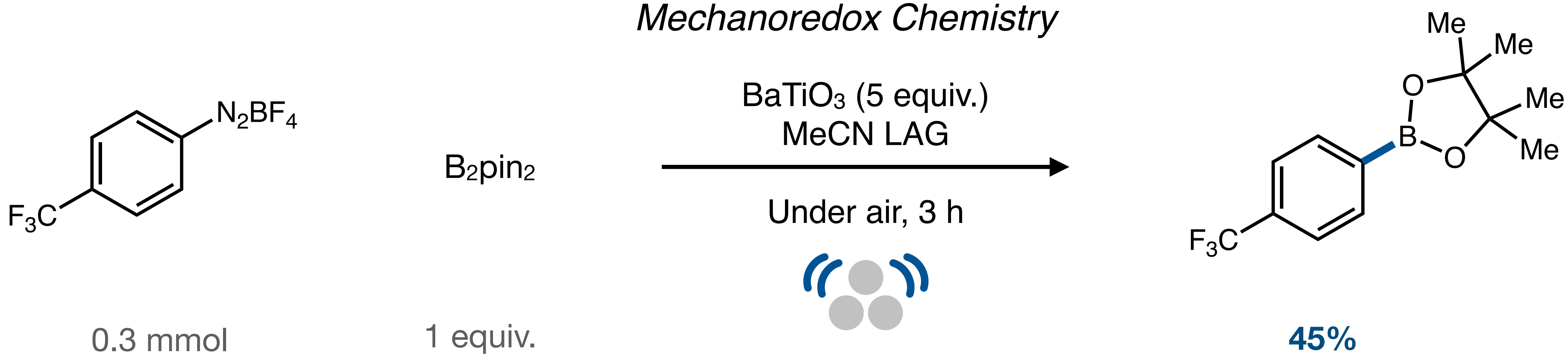


PXRD

Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

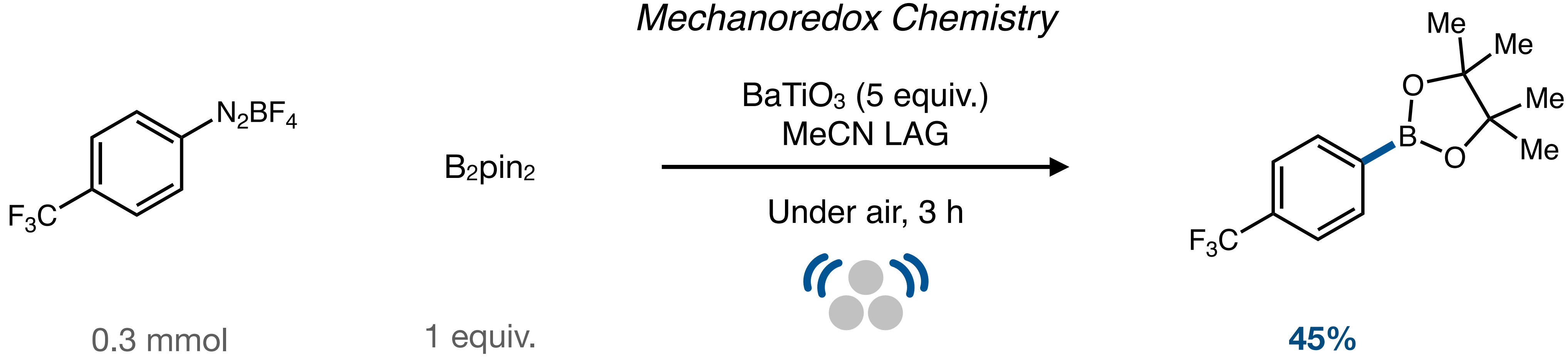
Mechanoredox Chemistry

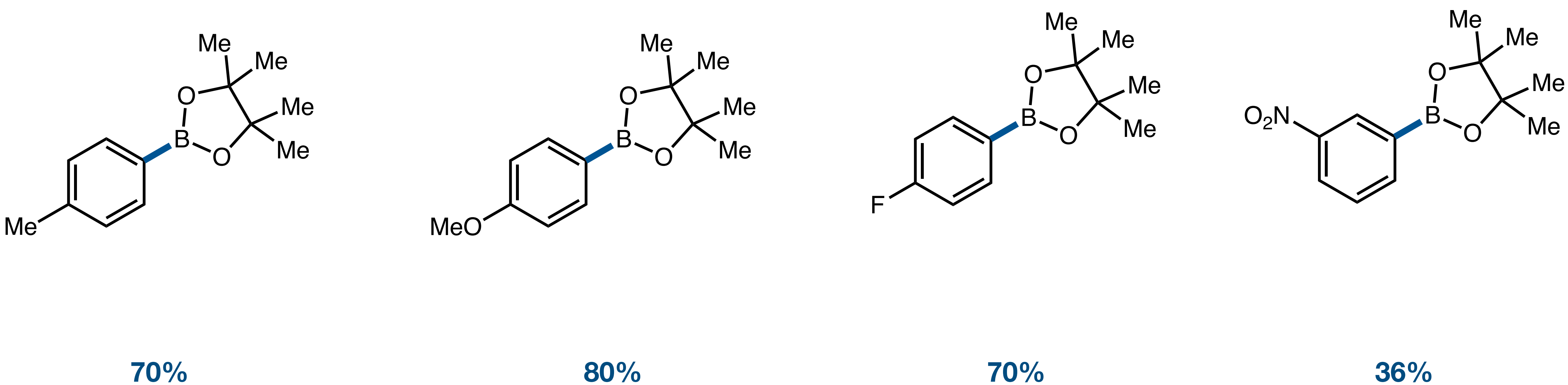


Hajime Ito et al., *Science,* **2019**, *366*, 1500–1504.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry





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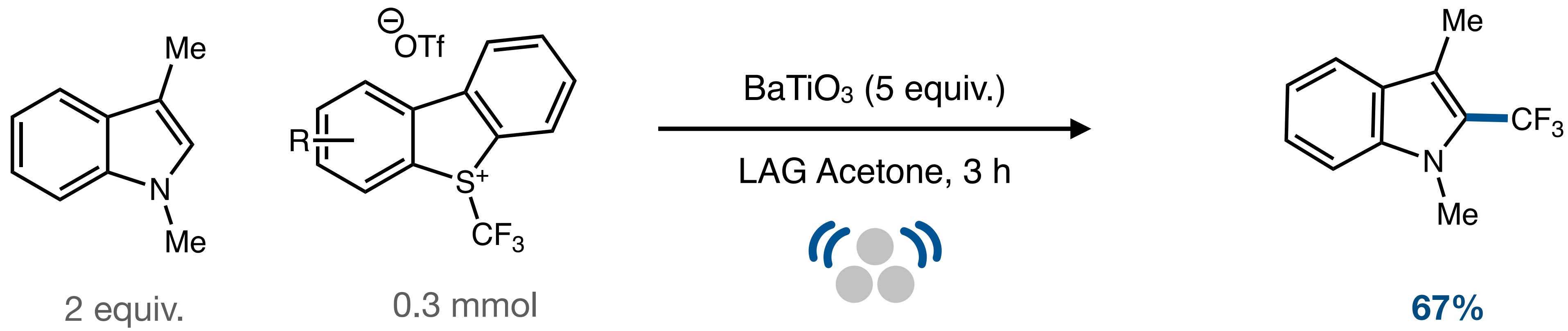
Mechanochemistry in Organic Synthesis

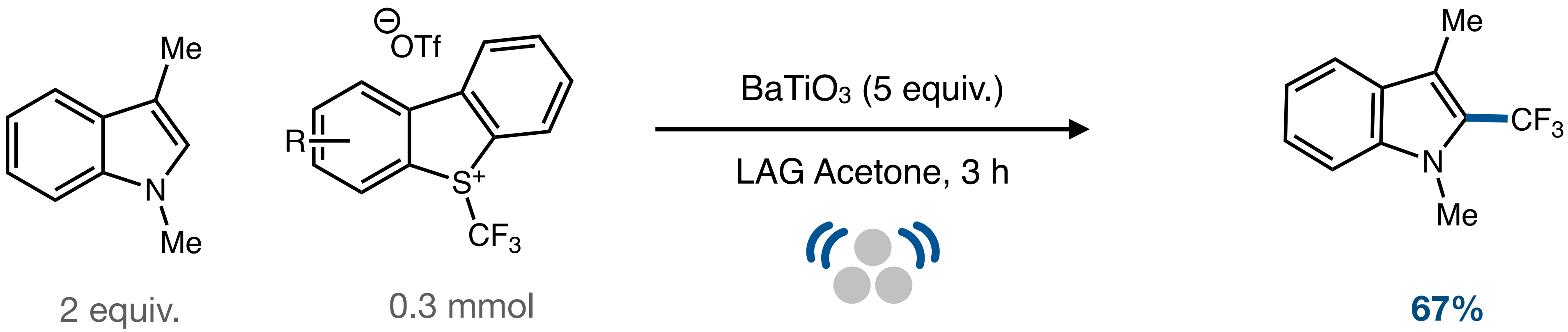
Mechanoredox Chemistry

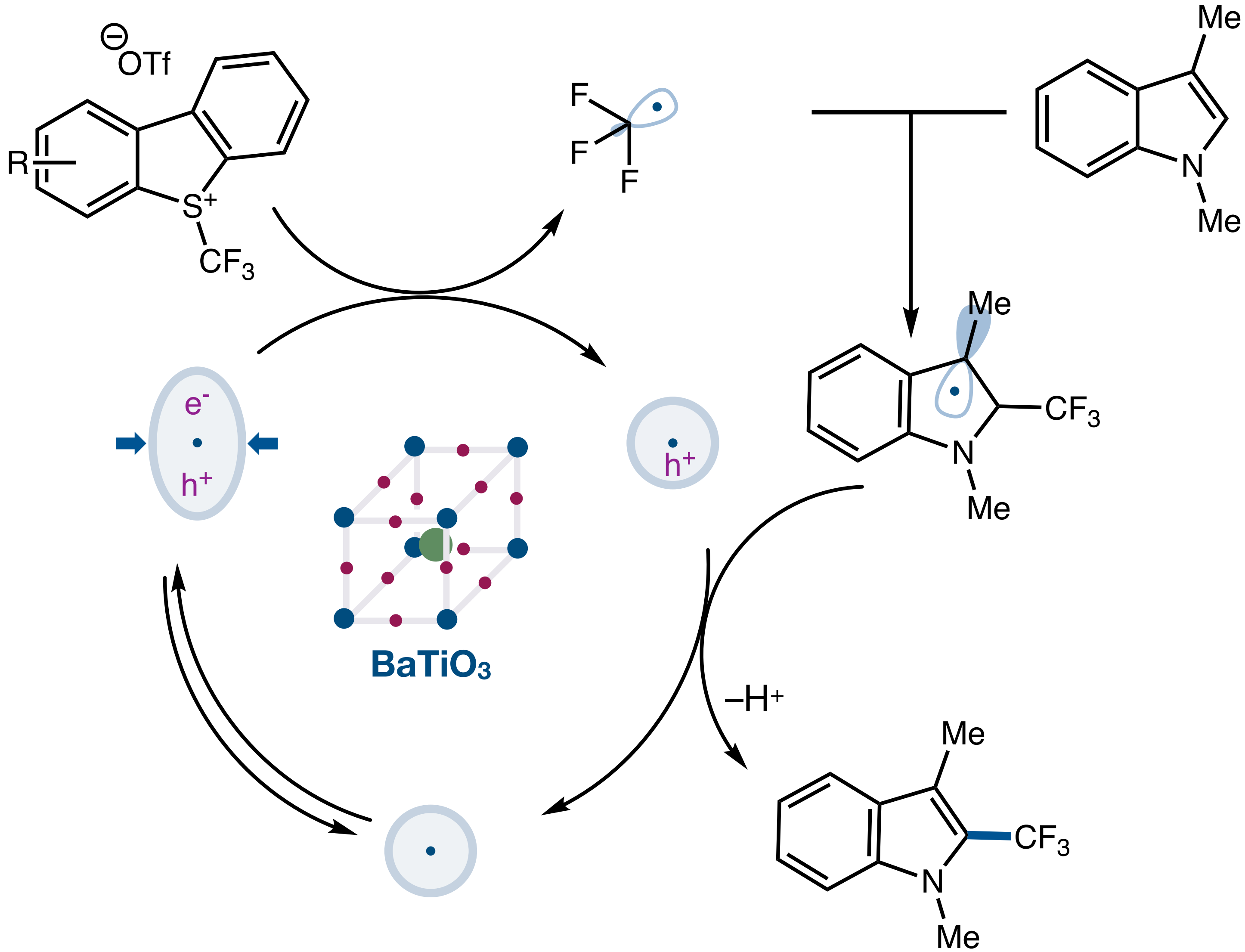


Hajime Ito et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 22570–22576.

Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry





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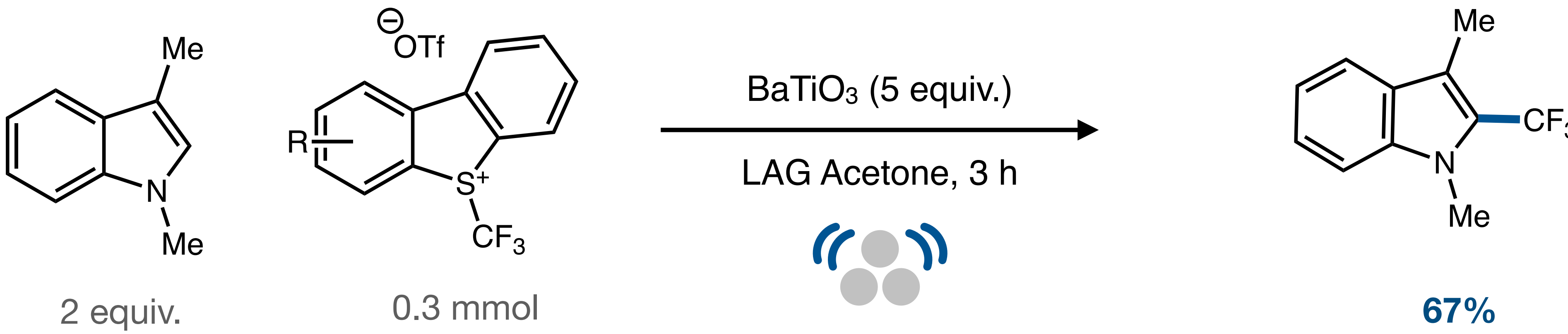
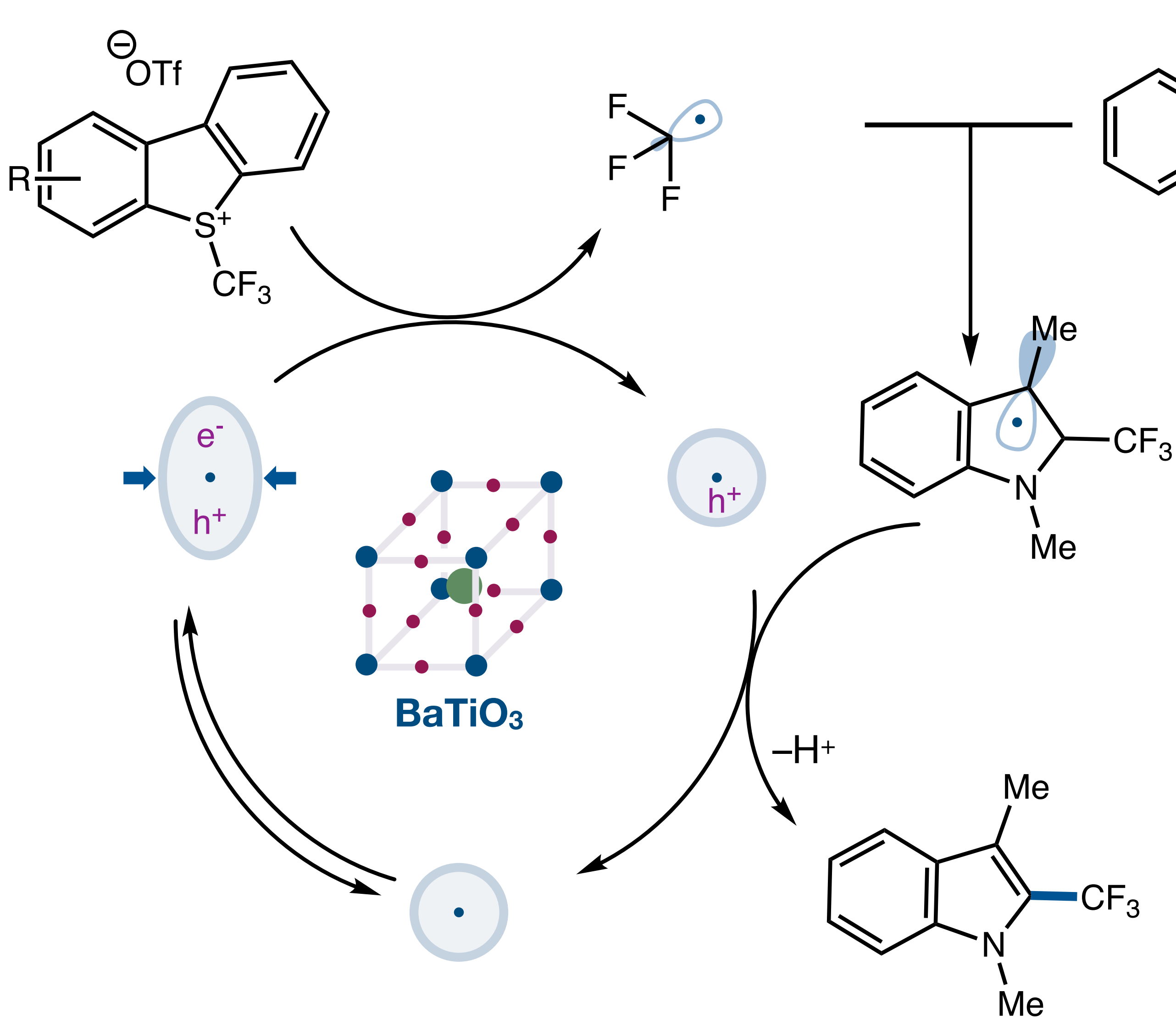
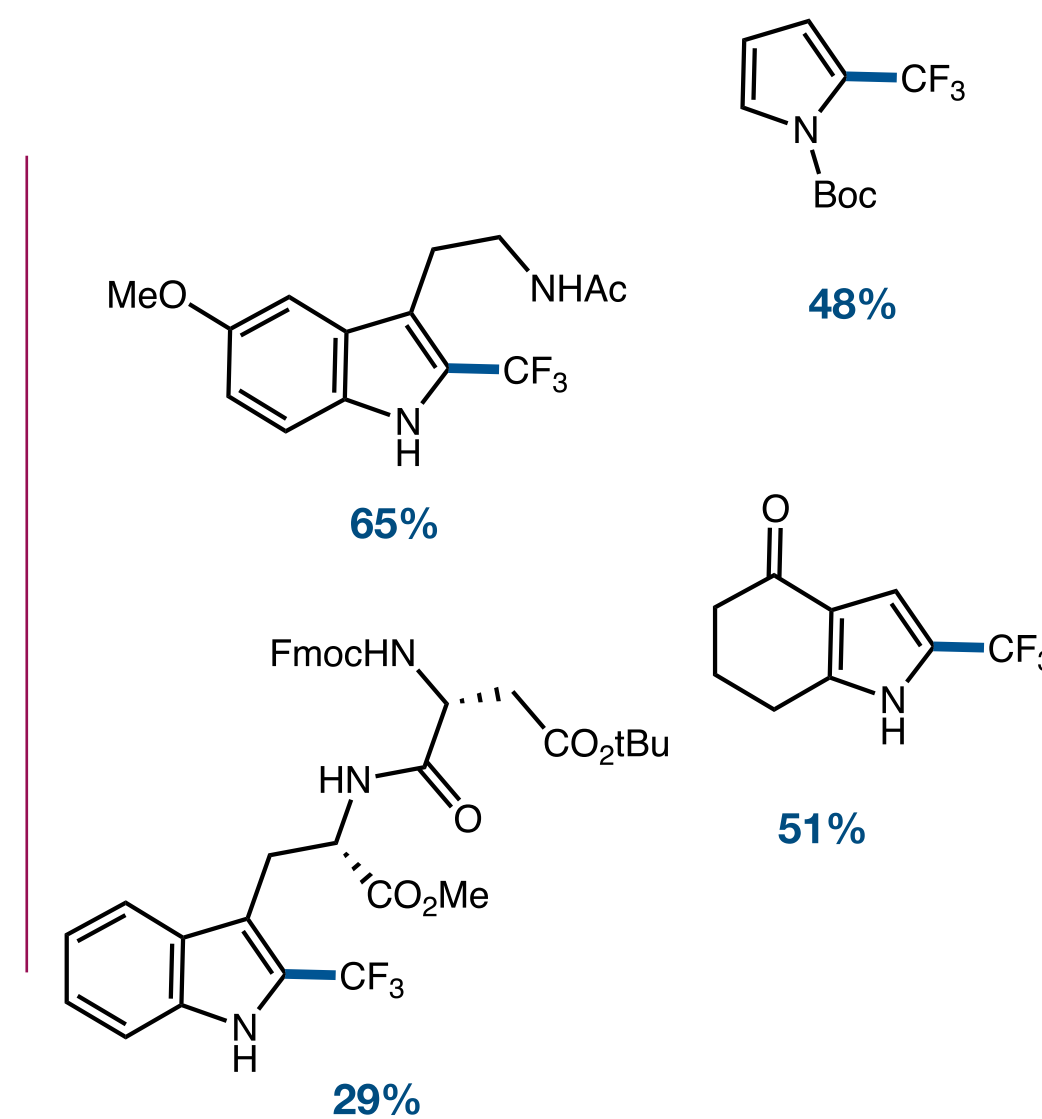
Mechanochemistry in Organic Synthesis

Mechanoredox Chemistry







Hajime Ito et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 22570–22576.

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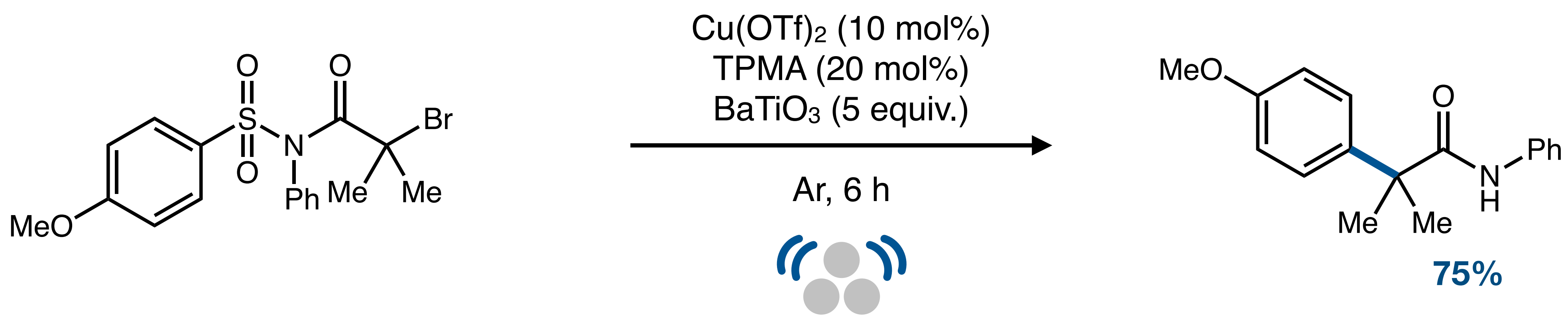

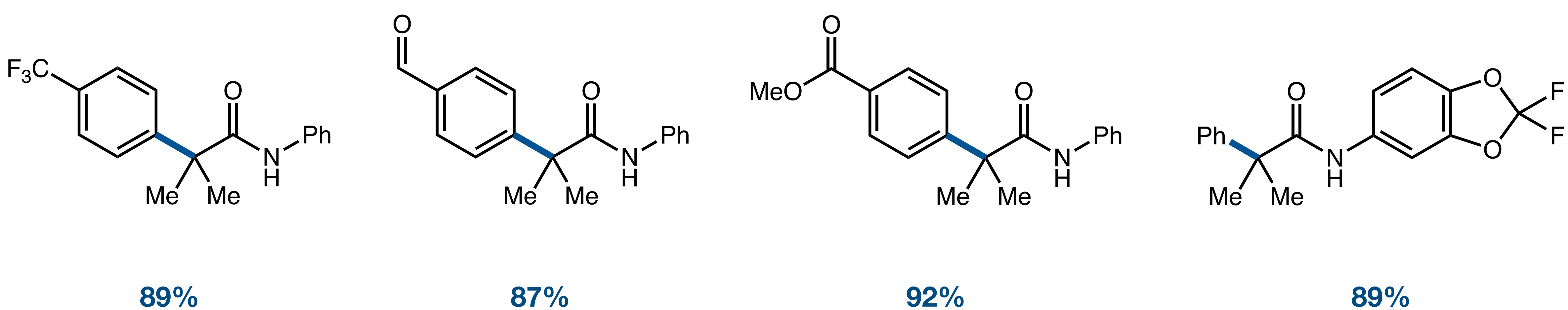

Honggui Lv, Guoyong Fang et al., *Angew. Chem. Int. Ed.* **2022**, *61*, e202206420.

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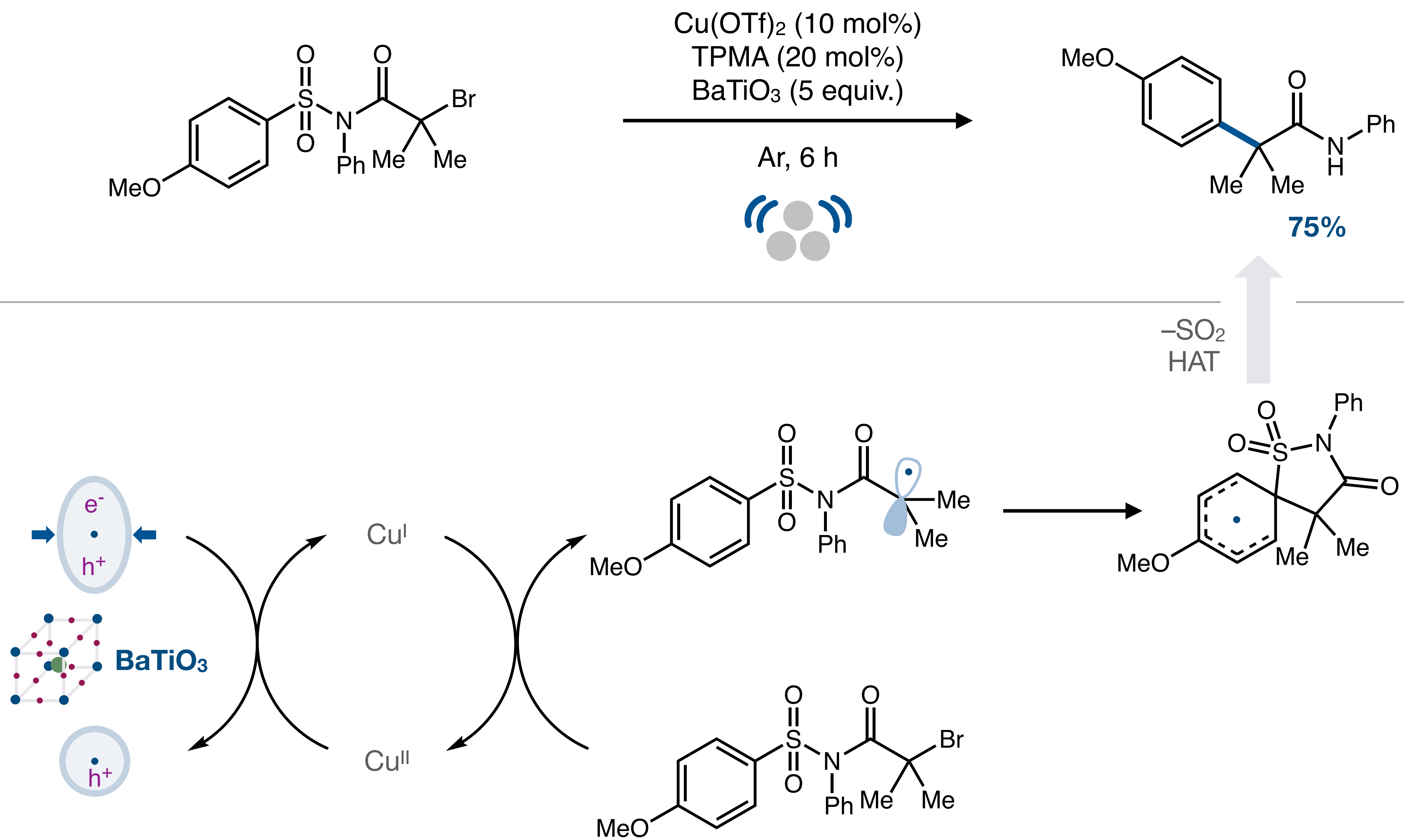

Honggui Lv, Guoyong Fang et al., *Angew. Chem. Int. Ed.* **2022**, *61*, e202206420.

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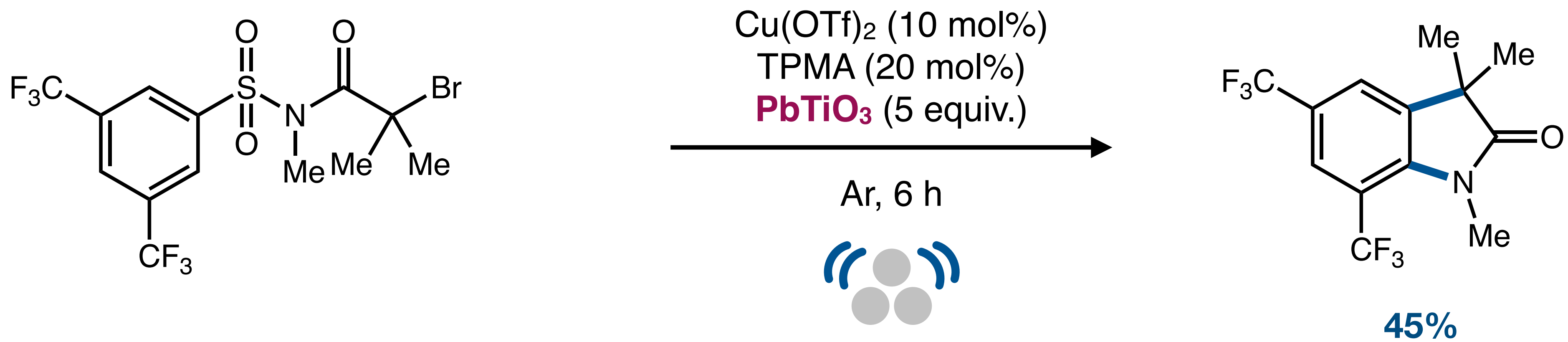

Honggui Lv, Guoyong Fang et al., *Angew. Chem. Int. Ed.* **2022**, *61*, e202206420.

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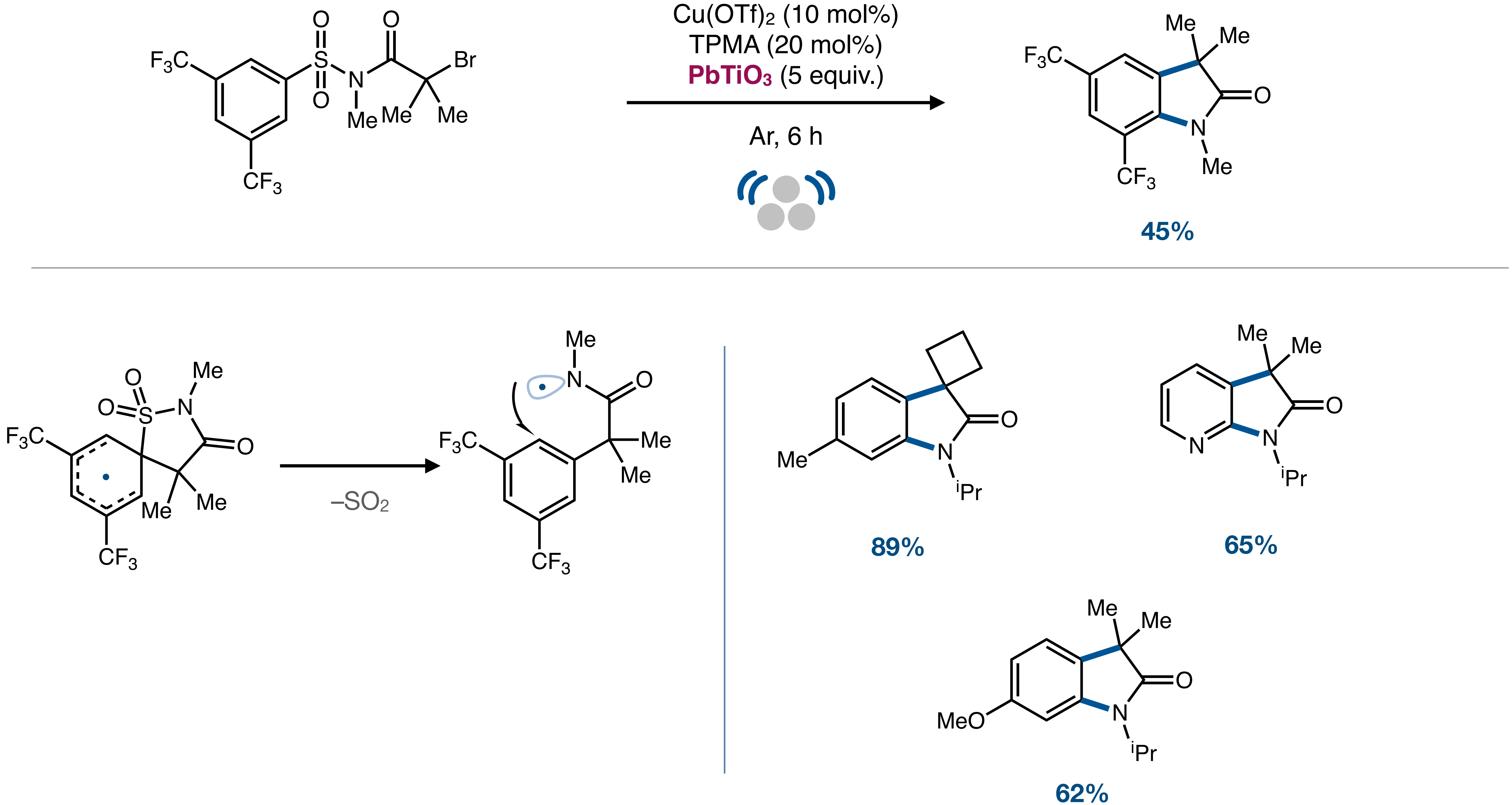

Honggui Lv, Guoyong Fang et al., *Angew. Chem. Int. Ed.* **2022**, *61*, e202206420.

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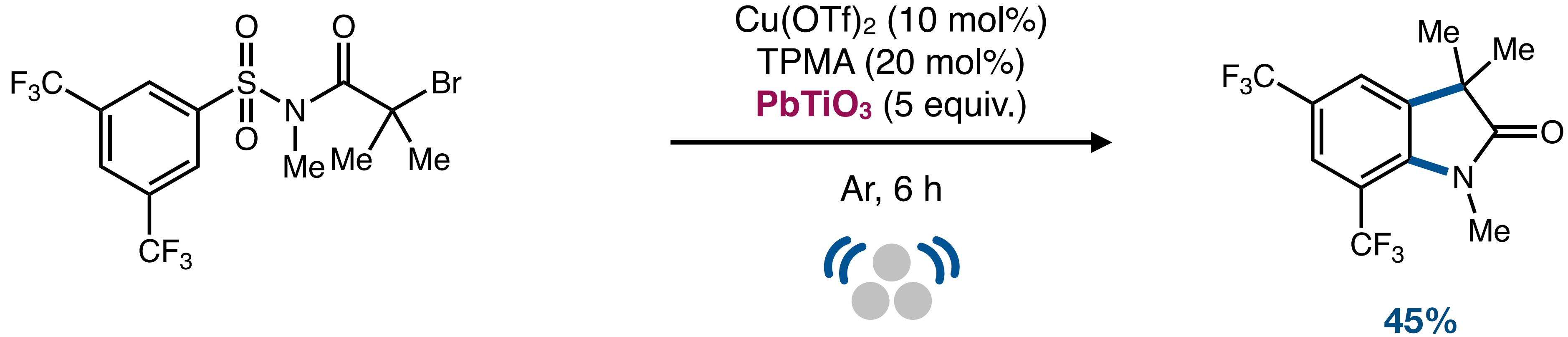

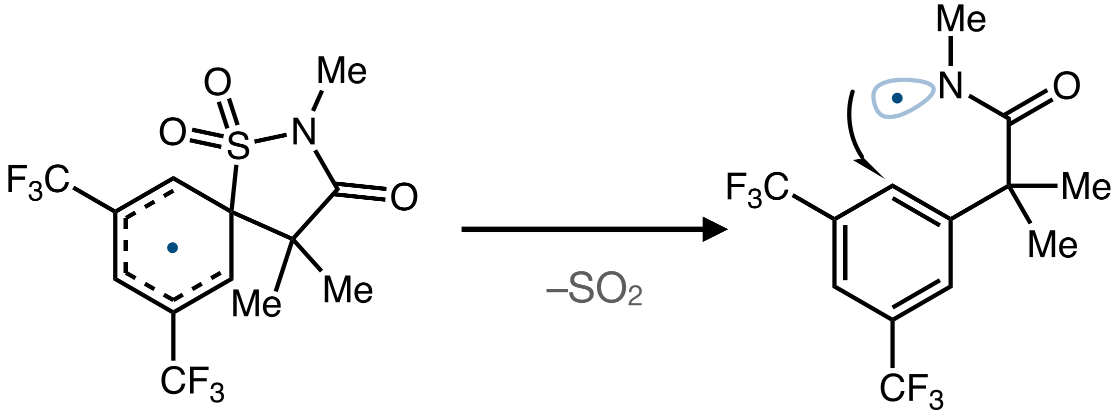

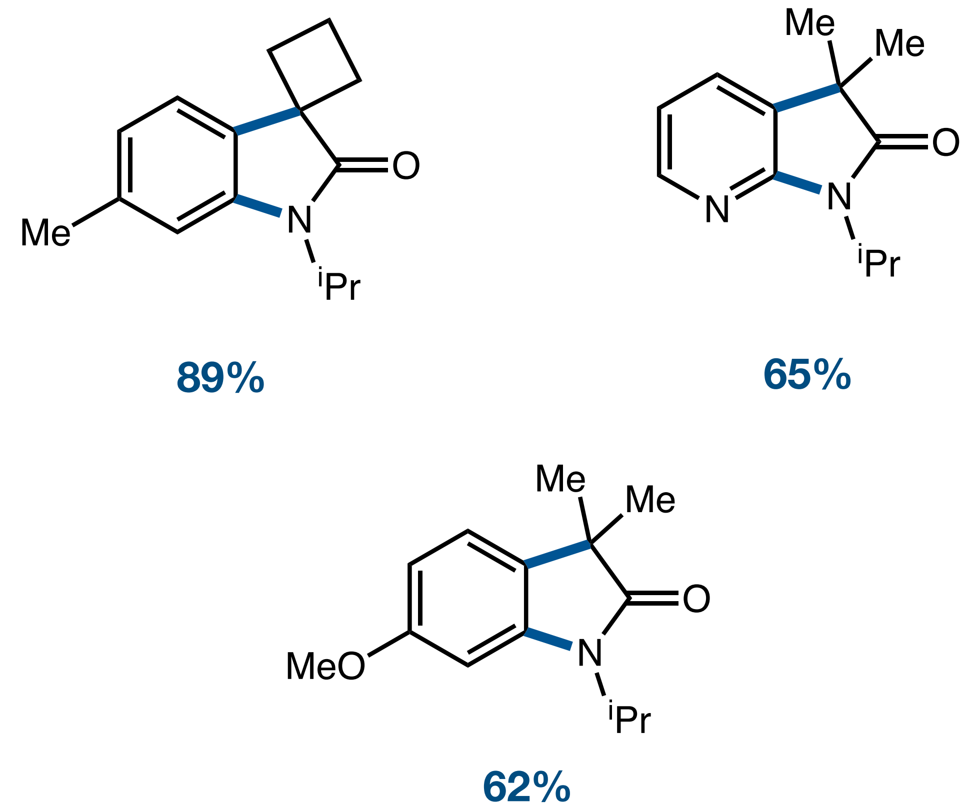

No studies took place to understand the divergent reactivity between $BaTiO_3$ and $PbTiO_3$

Honggui Lv, Guoyong Fang et al., *Angew. Chem. Int. Ed.* **2022**, *61*, e202206420.

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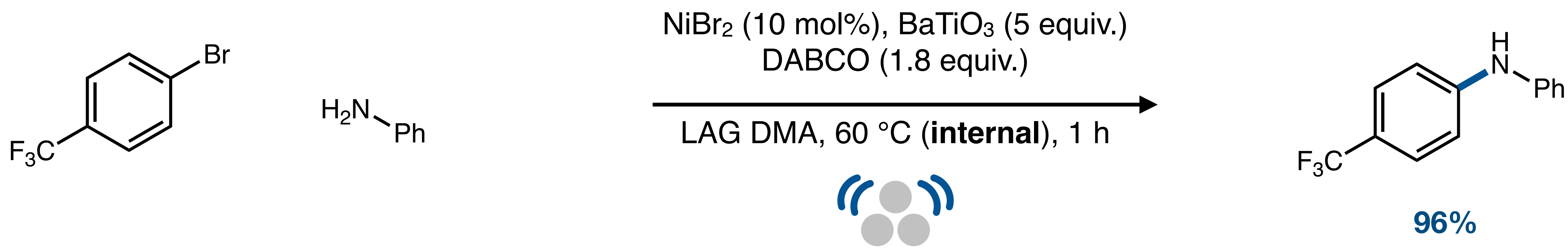

Koji Kubota, Hajime Ito et al., *Angew. Chem. Int. Ed.* **2023**, *62*, e202311531.

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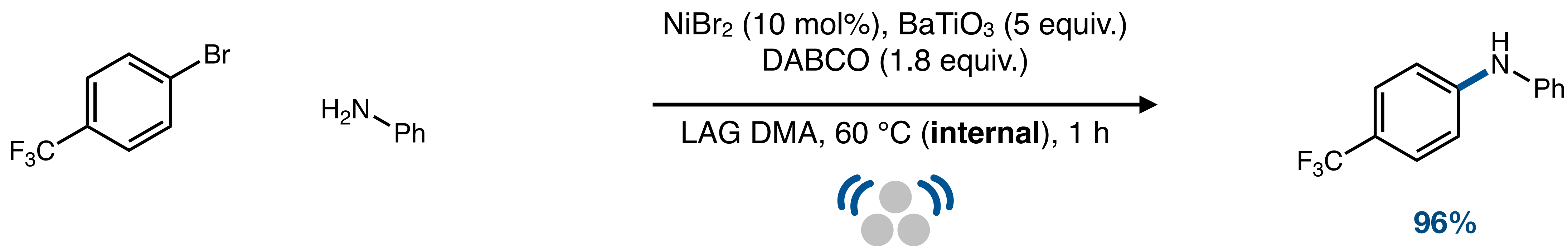

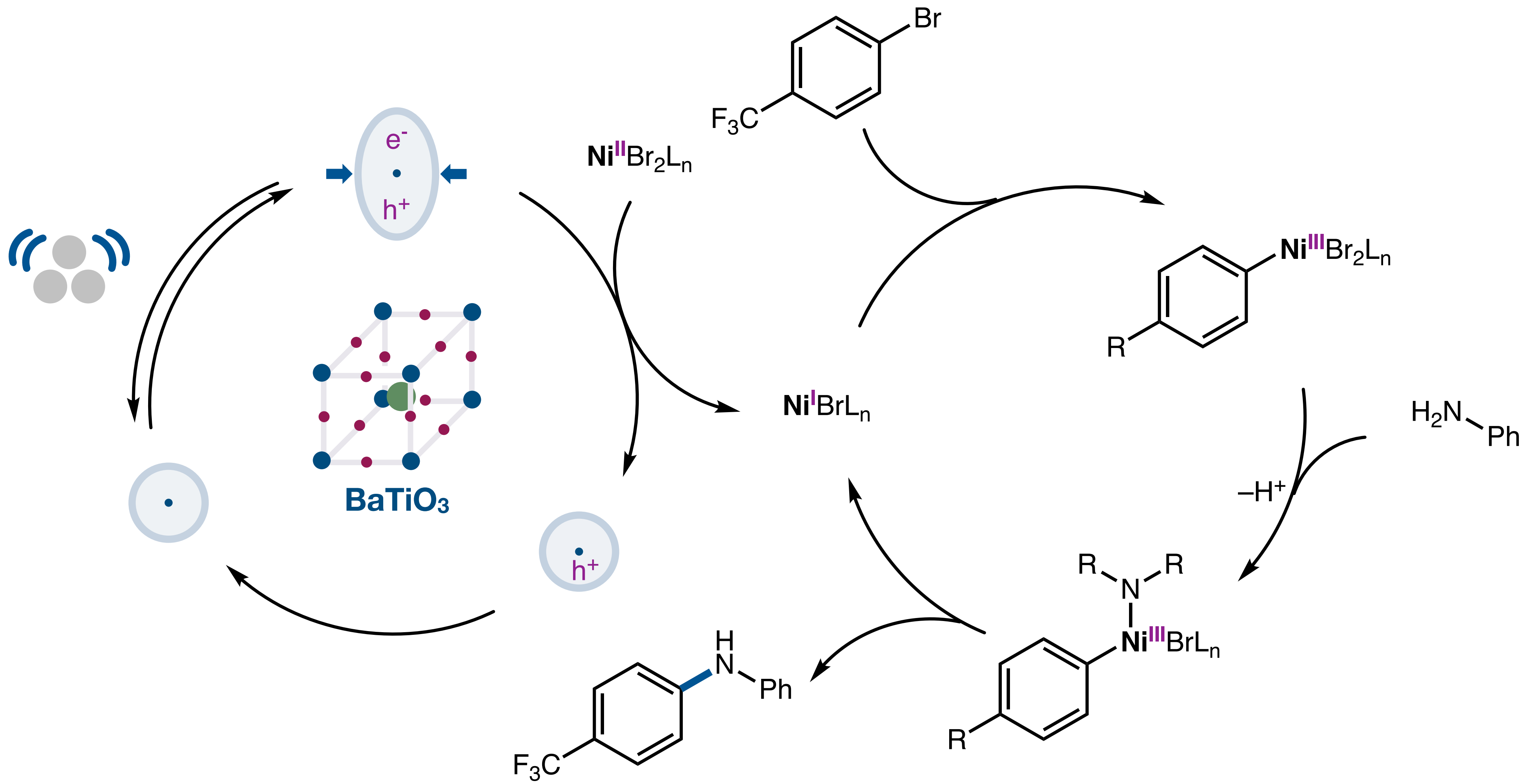

Koji Kubota, Hajime Ito et al., *Angew. Chem. Int. Ed.* **2023**, *62*, e202311531.

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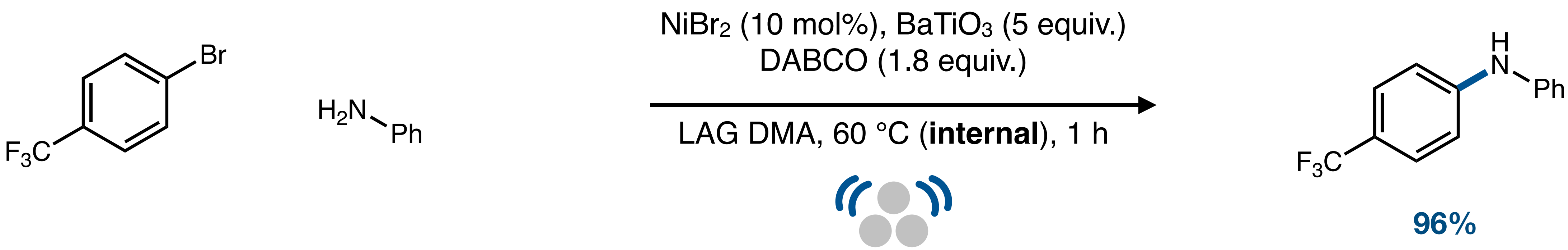

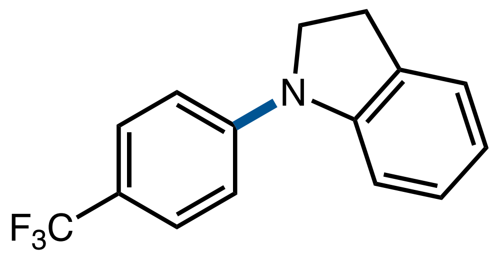

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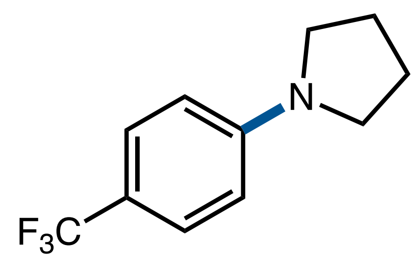
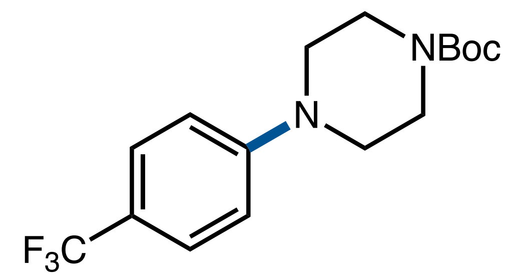
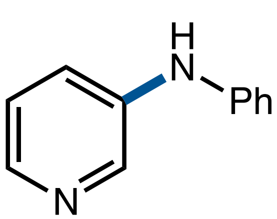


92%



63%



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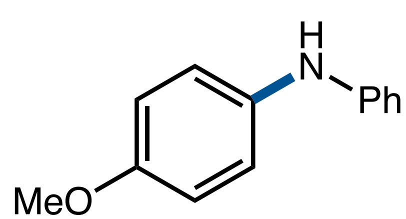
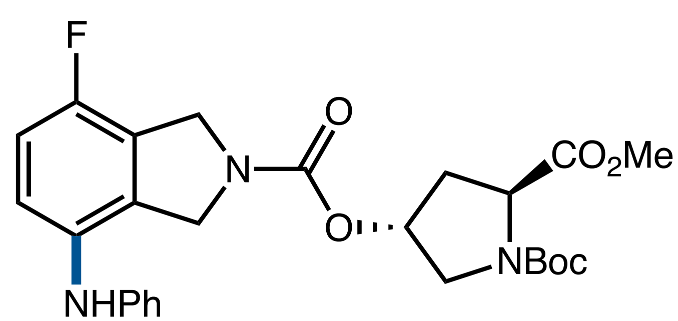


48%



98%

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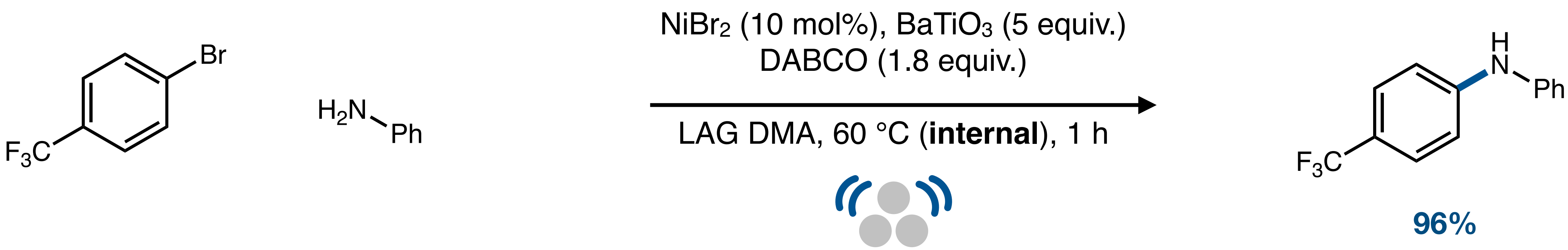

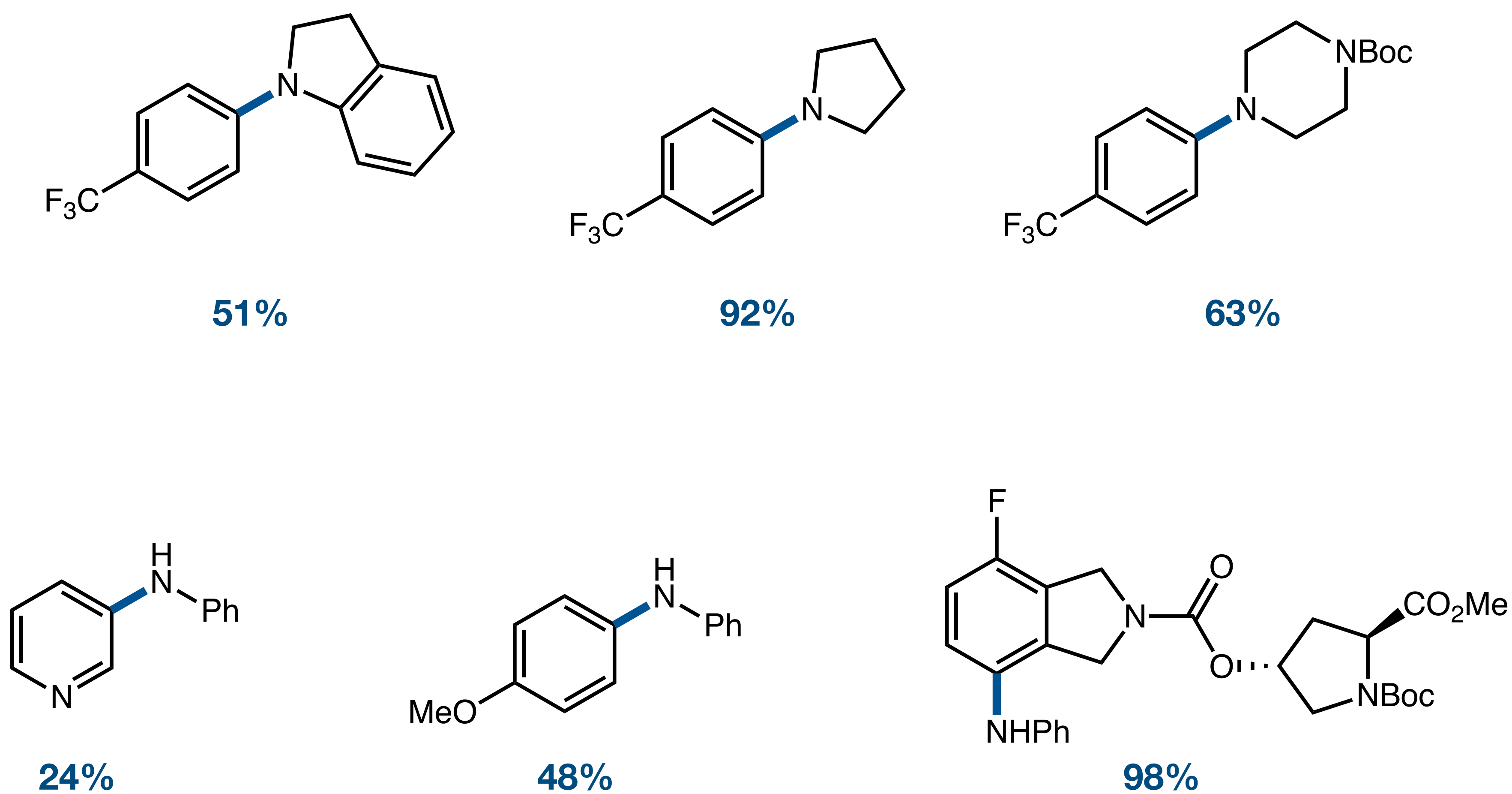

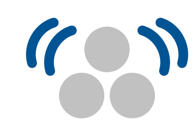

Scale-up:
11 g (93%)

In planetary ball mill

Koji Kubota, Hajime Ito et al., *Angew. Chem. Int. Ed.* **2023**, *62*, e202311531.

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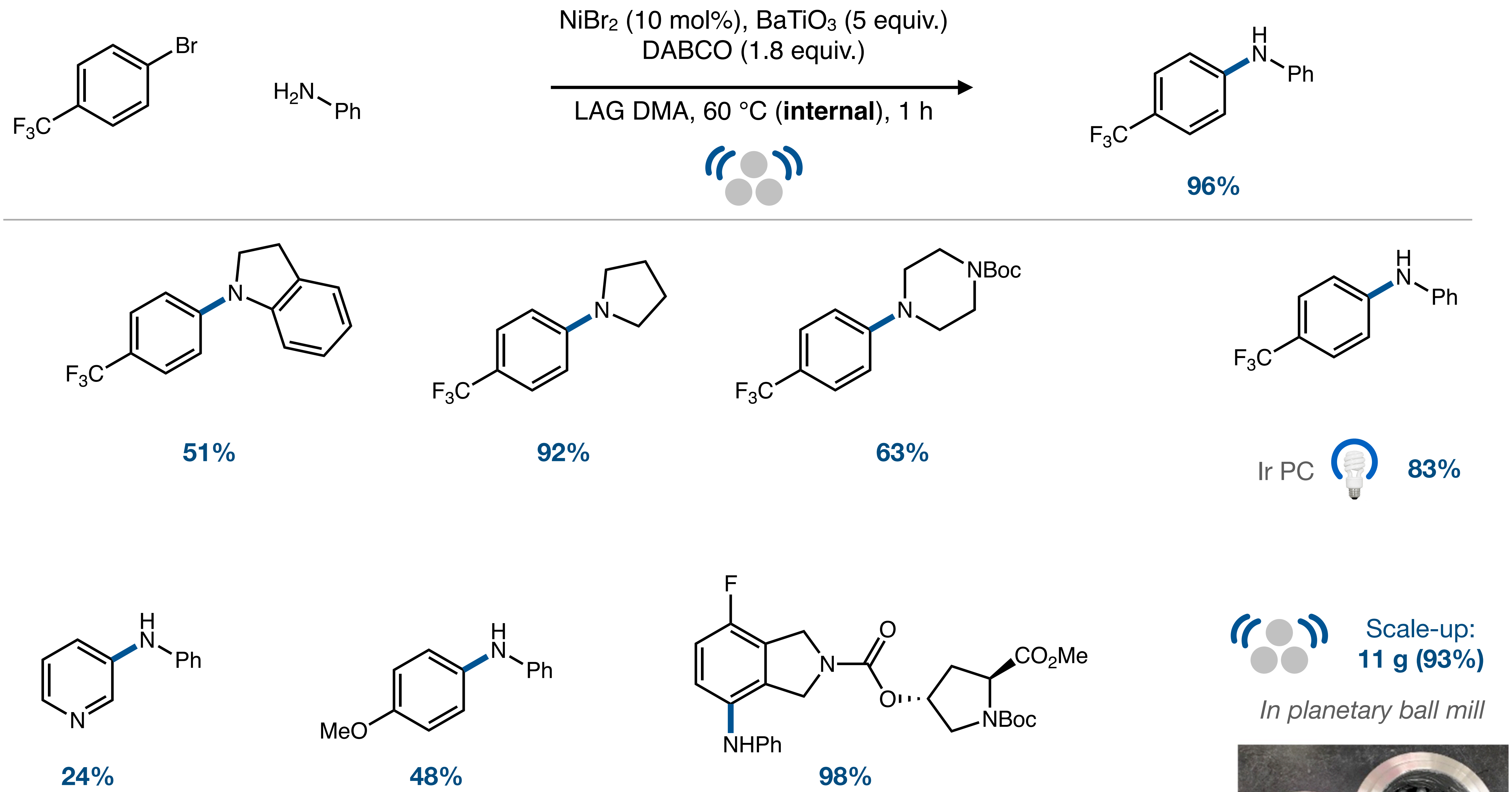

Koji Kubota, Hajime Ito et al., *Angew. Chem. Int. Ed.* **2023**, *62*, e202311531.

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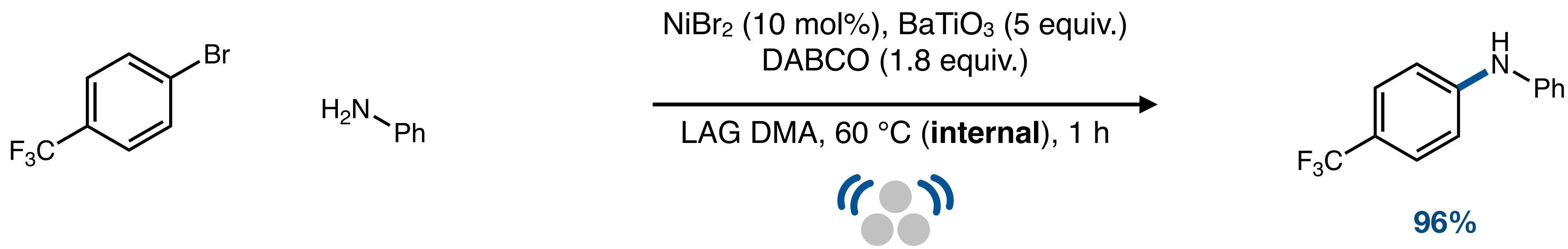
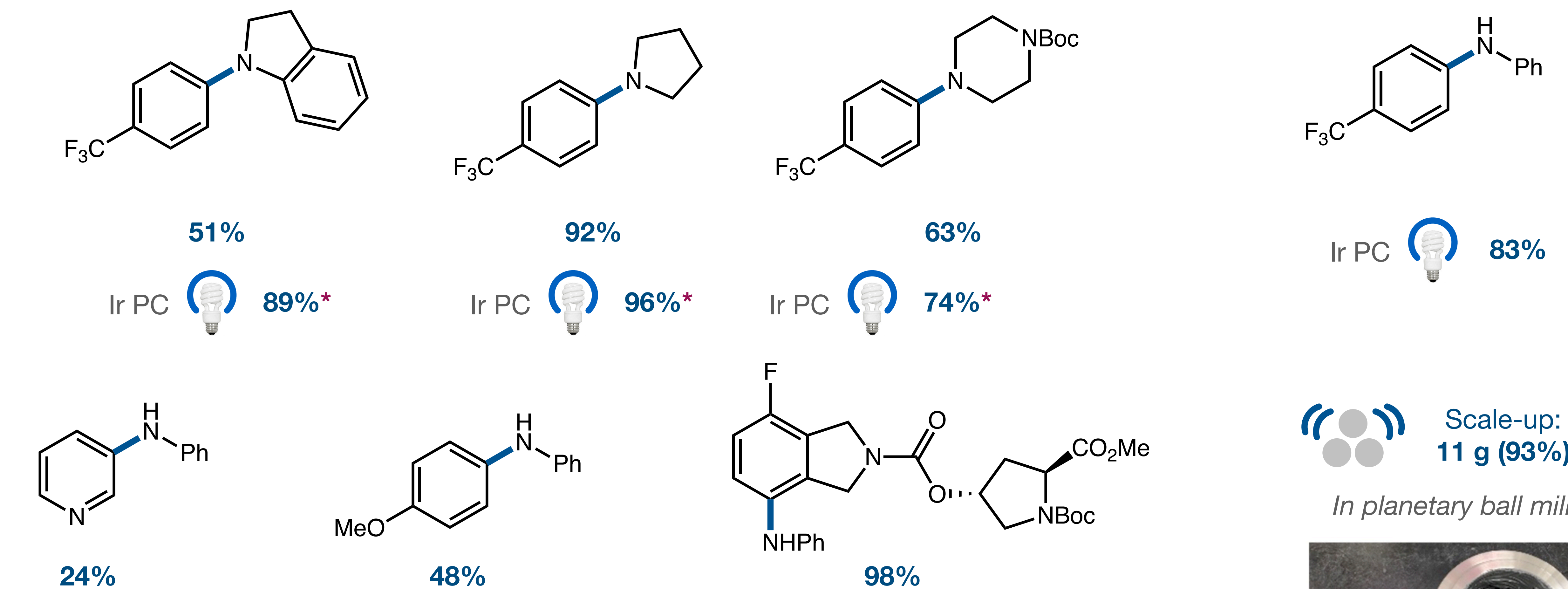




*Stephen L. Buchwald, David W. C. MacMillan et al., *Science* **2017**, *353*, 279-283.

Koji Kubota, Hajime Ito et al., *Angew. Chem. Int. Ed.* **2023**, *62*, e202311531.

Brief tutorial introduction on Mechanochem (generally)

History

Mechanistic aspects

Mechanical actions and mechanoreactors

Reaction Monitoring

Why mechanochemistry?

Mechanochemical vs. solution-based reactions

Medicinal mechanochemistry

“Mechanochemistry 2.0”

Mechanoredox

Mechanochemistry in Organic Synthesis

Further Reading

In situ monitoring

Raman spectroscopy

Angew. Chem. Int. Ed. **2014**, *53*, 6193 –6197.

Nat. Protoc. **2021***, 16*, 3492–3521.

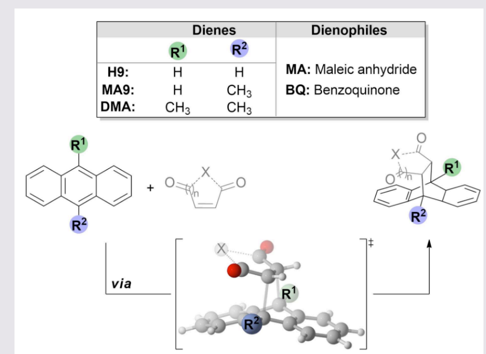
X-Ray absorption spectroscopy

Chem. Commun., **2020**, *56*, 10329-10332.

Computational Studies

DFT

ChemSusChem **2021**, *14*, 2763–2768.

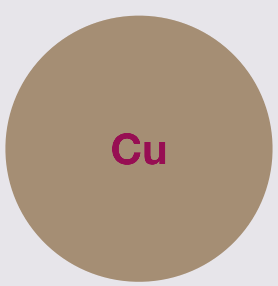


MD

J. Phys. Chem. Lett. **2019**, *10*, 6455–6461.

Chem. Sci., **2019**, *10*, 2924-2929.

Ball "Catalysis"



Milling ball

ACS Sustainable Chem. Eng. **2016**, *4*, 5, 2464–2469

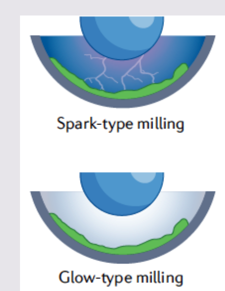
Chem. Eur. J. **2020**, *26*, 12903 – 12911

Angew. Chem. Int. Ed. **2019**, *58*, 18942 –18947

Green Chem. **2009**, *11*, 1821-182

Electro-mechanochemistry

electrical-discharge-assisted mechanical milling (EDAMM)



Spark-type milling

Glow-type milling

Calka, A., Wexler, D. *Nature* **2002***, 419*, 147–151.

Questions?