Mechanochemistry in Organic Synthesis

2019/3/28

M2 Kentaro Sakai

Today's Topics

1. Introduction

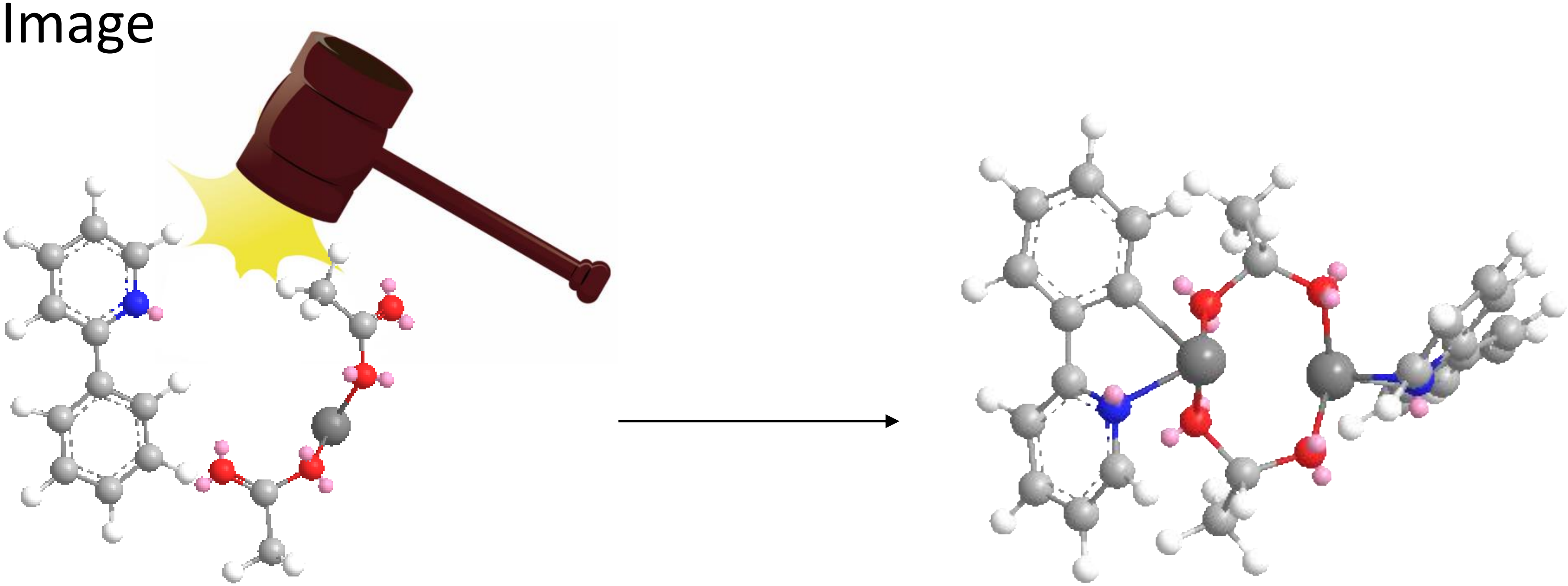
What is Mechanochemistry?

Definition (IUPAC)

"a chemical reaction that is induced by the direct absorption of mechanical energy"

IUPAC Compendium of Chemical Terminology, ed. M. Nič, J. Jirát, B. Košata, A. Jenkins and A. McNaught, IUPAC, 2009.

Image



History of Mechanochemistry

S. L. James *et al. Chem. Soc. Rev.* **2012**, *41*, 413.

1820 (M. Faraday)
$AgCl \rightarrow Ag$ (with some metals such as Zn, Cu, Sn, Fe)

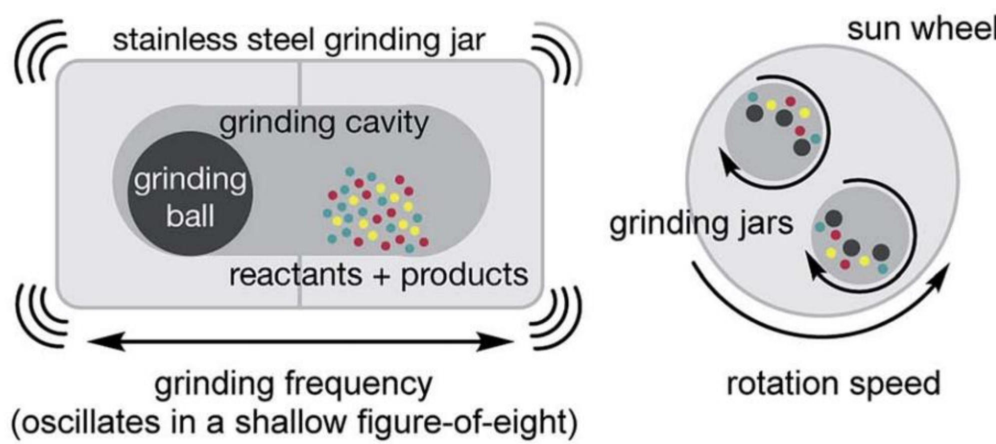
1890s (C. Lea)
mechanochemical reactions could give different products

1893~1920s
cocrystalization, organic polymers

1980s~1990s
solvent-free organic reactions with additional heating

Around 2000
organic, metal-organic, supramolecular synthesis

Equipment



Key Parameters

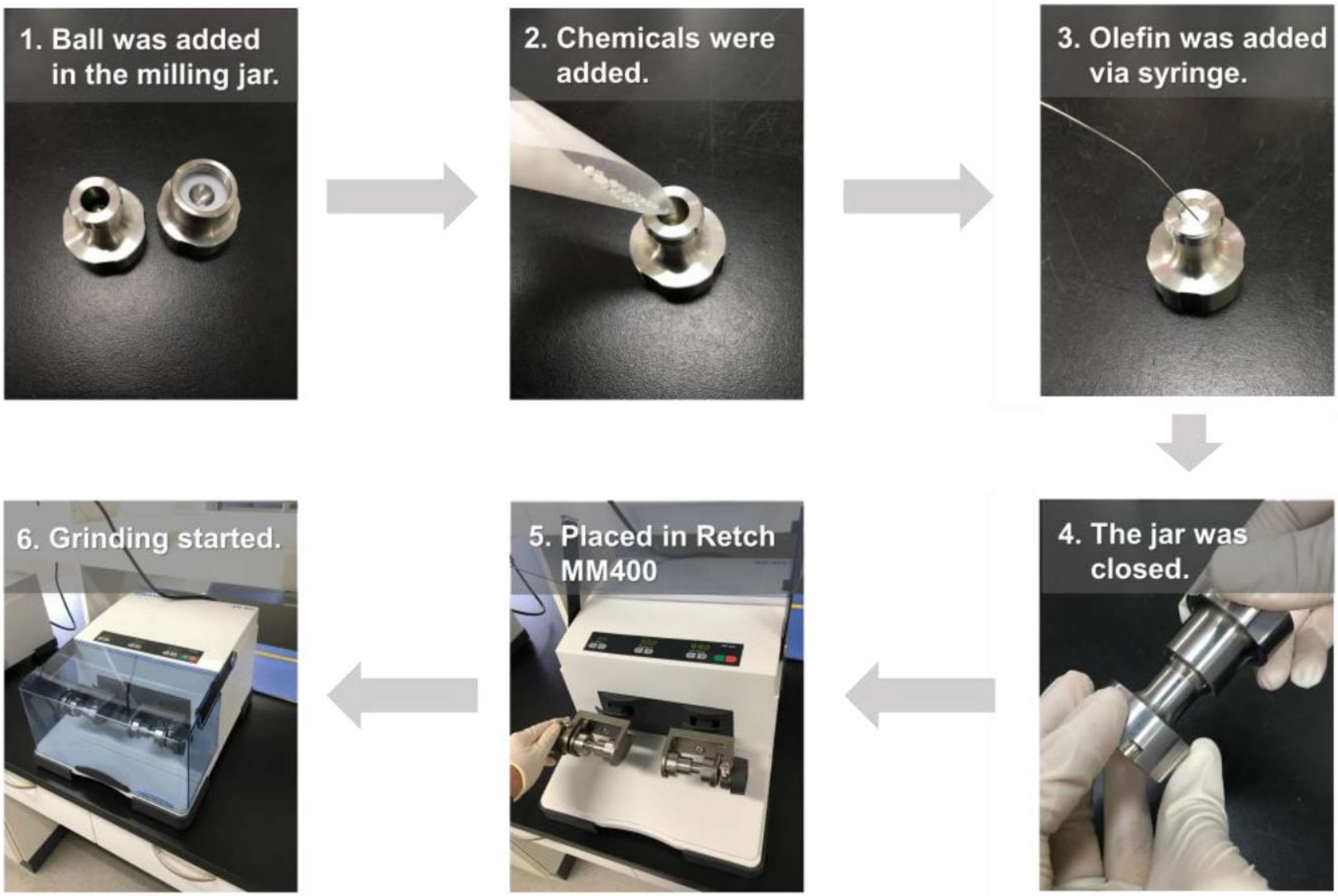
- **cavity or jar volume* = V_J**
- **ball diameter = D_B** (proportional to V and m)
- **number of balls**
- **volume of reactants = V_R** (dependent on sample *D*)
- **Volume ratio** of balls : sample : free space
- **milling/oscillating frequency = f**
- **milling time = t**

*for mixer mills, length of the jar is constant, volume varies with bore

D. L. Browne *et al. Chem. Sci.* **2018**, *9*, 3080.

✓ ***Ball mill is usually used for organic synthesis.***

Example of Reaction Setup (Mixer Mill)



H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

LAG (Liquid Assisted Grinding)

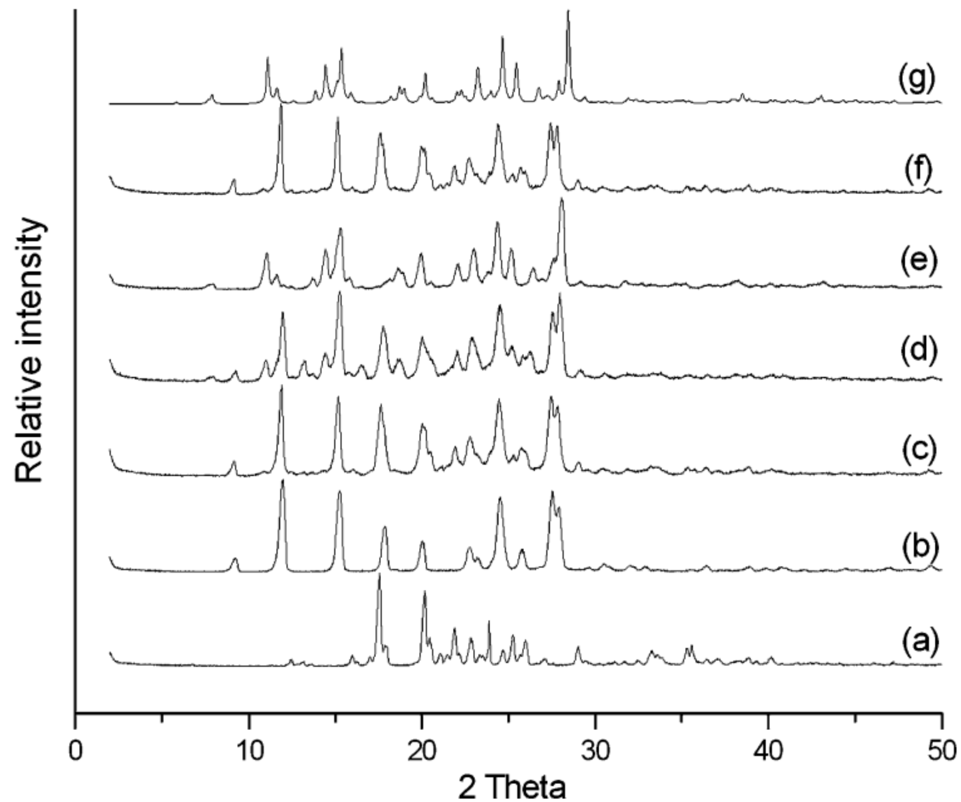
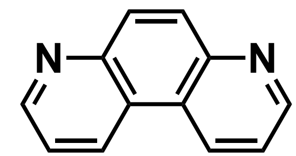
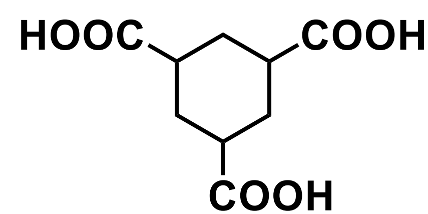


Fig. 2 Powder X-ray diffraction pattern of (a) **CTA**, (b) **fPh**, (c) ground dry mixture of **CTA** + 2**fPh** (1 h), (d) ground mixture of **CTA** + 2**fPh** with MeOH (5 min), (e) ground mixture of **CTA** + 2**fPh** with MeOH (10 min), (f) ground mixture of **CTA** + 2**fPh** with cyclohexane (1.5 h), (g) simulated pattern from single-crystal structure of **CTA.2fPh**.



fPh



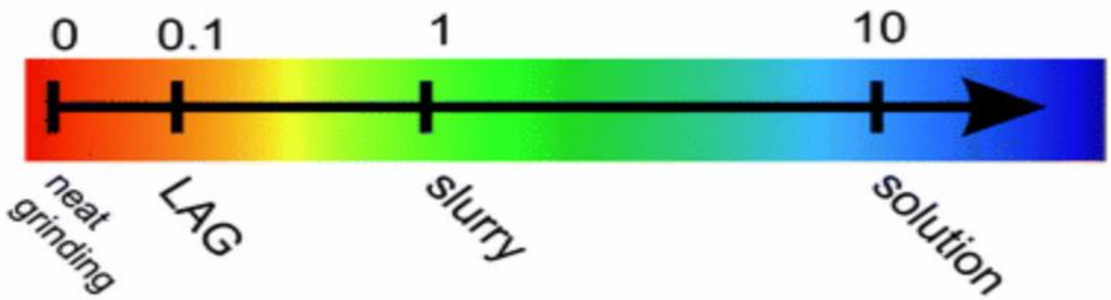
CTA

W. Jones *et al. Chem. Commun.* **2002**, 2372.

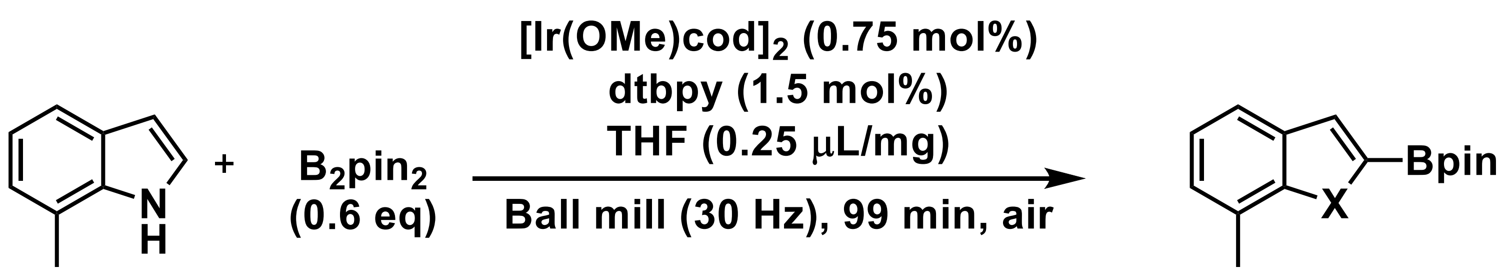
✓ ***Addition of MeOH enhanced the co-crystal fromation.***

LAG (Liquid Assisted Grinding) (2)

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



T. Friščić *et al. CrystEngComm*, **2009**, *11*, 418.



with LAG: 88%
w/o LAG : 0%

H. Ito *et al. Chem. Eur. J.* **2019**, *25*, 4654.

✓ ***LAG has been also used in organic synthesis.***

Analysis Methodology in Real Time

ex situ analysis

- FTIR (within seconds)
- powder X-ray diffraction (several minutes)
- solid-state NMR (~several hours)

In situ analysis

- synchrotron PXRD
- Raman spectroscopy
- tandem analysis (PXRD + Raman)

D. Tan, T. Friščić, *Eur. J. Org. Chem.* **2018**, *18*.

Summary of Section 1

- Ball mills are usually used for mechanochemistry.
- LAG accelerates the mechanochemical reactions.
- The analysis method is limited and the reaction mechanism is often unclear.

2. Mechanochemistry in Organic Synthesis

Mechanochemistry in Organic Synthesis

Carbon-Carbon Bond-Forming Reactions
Carbon-Nitrogen Bond-Forming Reactions
Carbon-Oxygen and Other Bond-Formation Reactions
Cycloaddition Reactions
Oxidations and Reductions

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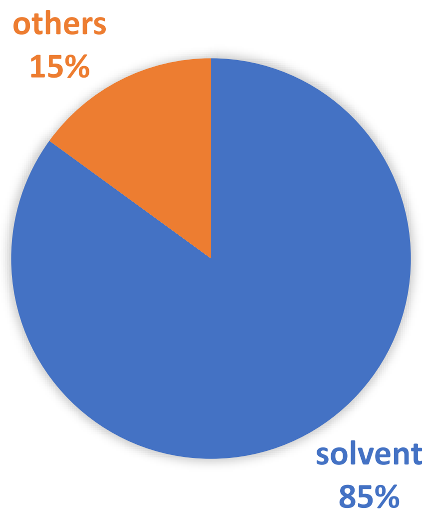
•

•

D. Margetić, V. Štrukil. (2016). *Mechanochemical organic synthesis*. Elsevier.

Some Merit of Mechanochemical Reactions

✓ ***Solvent-free mechanochemical reactions are cleaner and sustainable.***

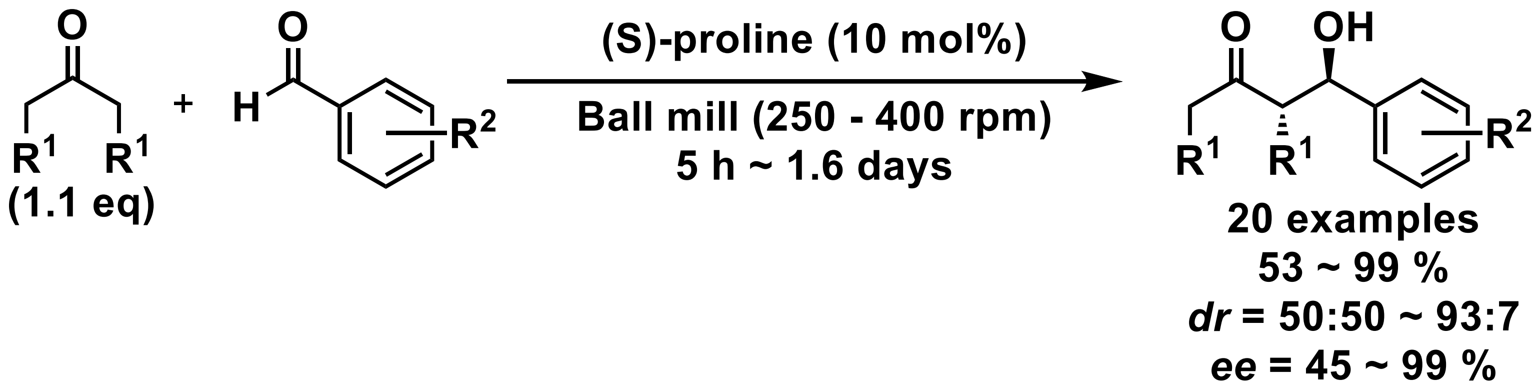


D. J. C. Constable *et al. Org. Process Res. Dev.* **2007**, *11,* 133.

✓ ***There are also some advantages in terms of reactivity.***

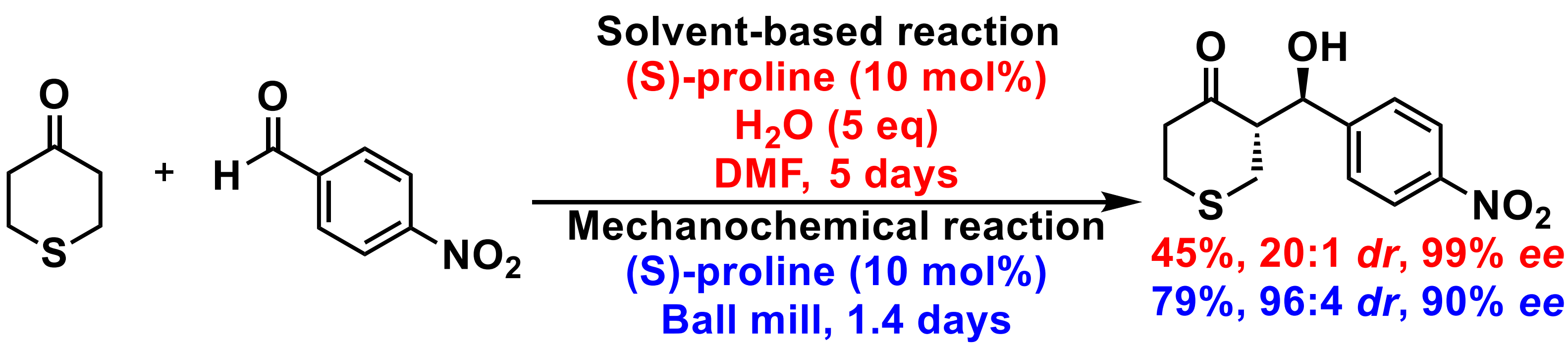
1. ***Time saving***
2. ***Selectivity enhancement***
3. ***Different products from solution-based reactions***

1. Time Saving



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

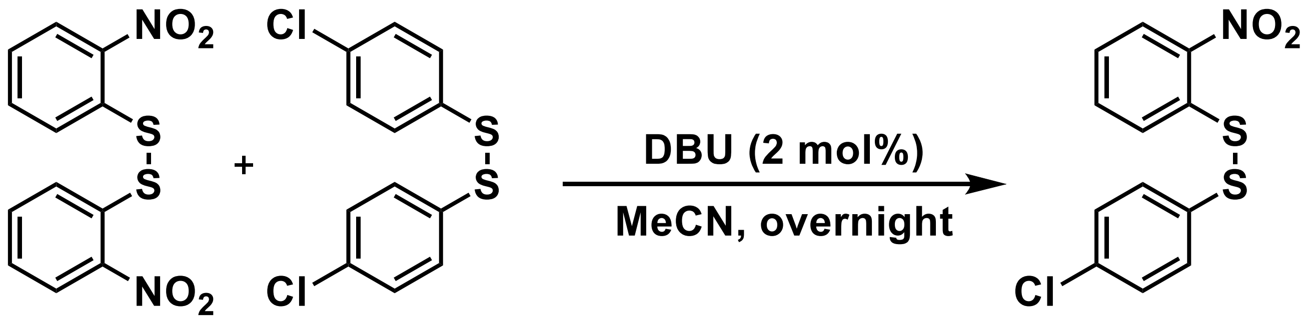
Comparison with Solution-based reaction



P. M. Pihko *et al. Synlett*, **2004**, 1891.

2. Selectivity Enhancement

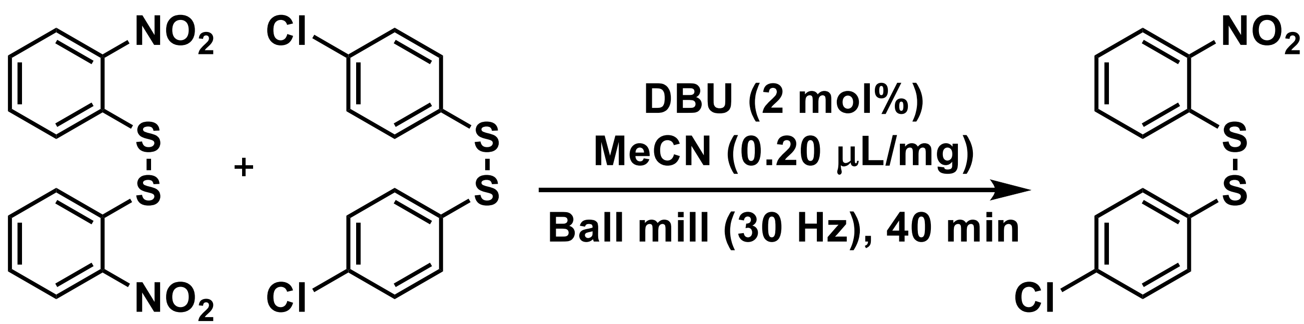
Solution-based reaction



A (1 eq) B (1 eq) C

result A:B:C = 1:1:2

Mechanochemical reaction



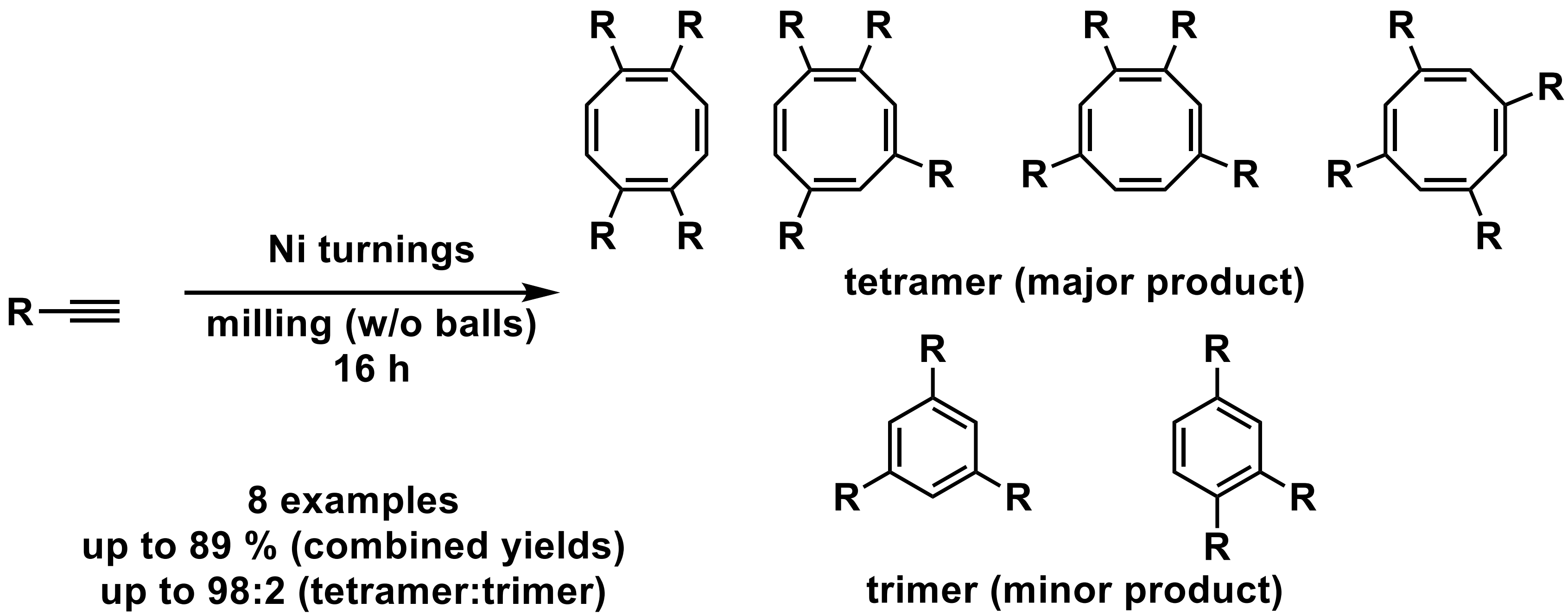
A (1 eq) B (1 eq) C

result A:B:C = 1:1:98

A. M. Belenguer, T. Friščić *et al. Chem. Sci.* **2011**, *2*, 696.

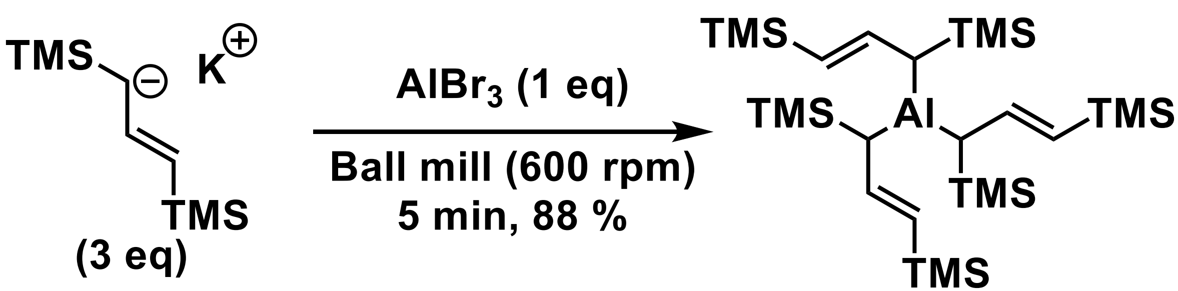
3. Different Products from Solution-based Reaction

✓ *Different reactivity*



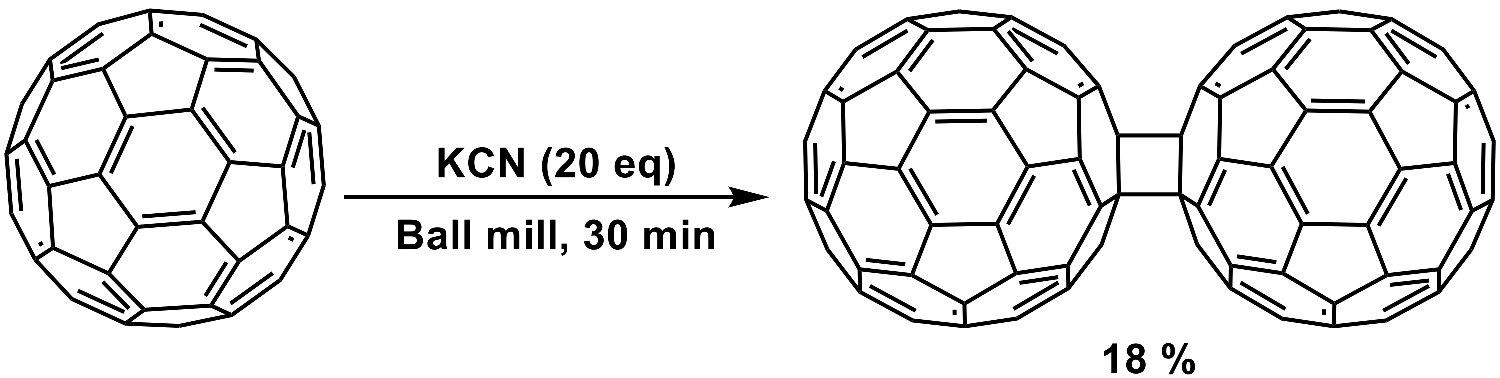
H. Guan, J. Mack *et al. ACS Sustainable Chem. Eng*. **2016**, *4*, 2464.

✓ *Solvent-sensitive products*

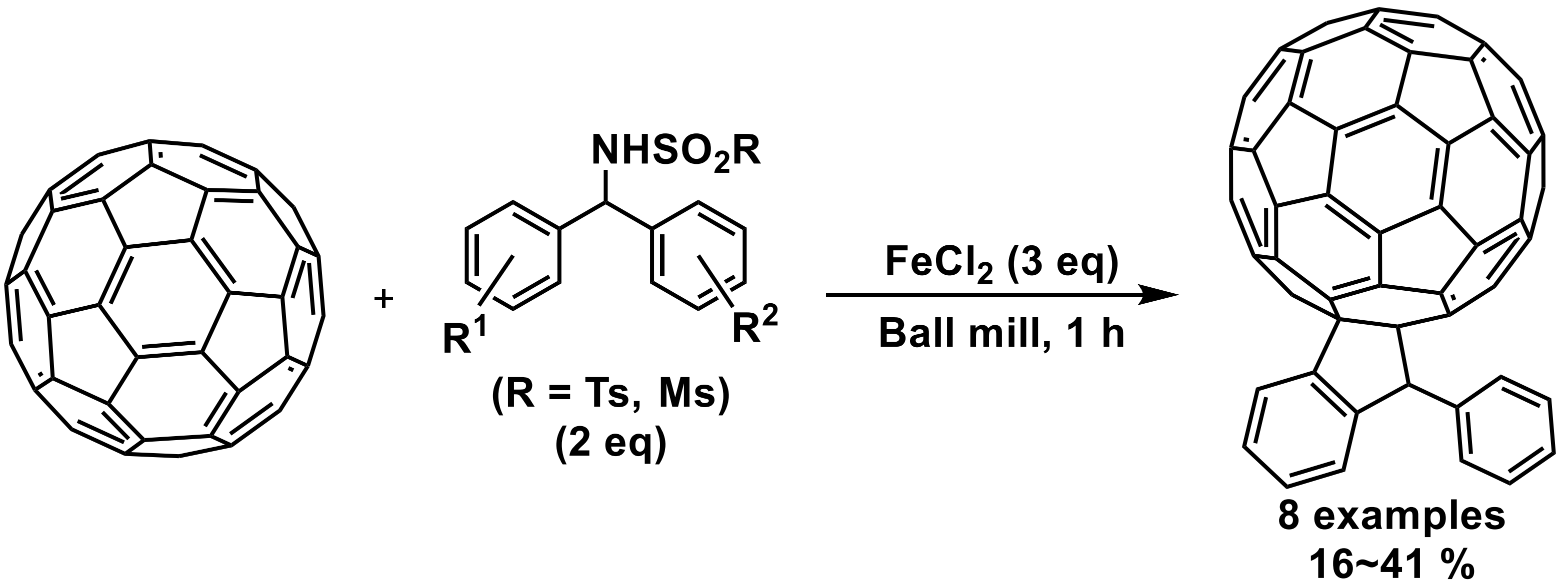


T. P. Hanusa *et al. Organometallics*, **2014**, *33*, 5952.

Application: Functionalization of Low Solubility Materials



K. Komatsu *et al. Nature*, **1997**, *387*, 583.



Y.-T. Su, G.-W. Wang, Org. *Lett.* **2013**, *15*, 3408.

Summary of Section 2

・Various kinds of organic reactions are performed using a ball mill.

・Improve and change the reactivity

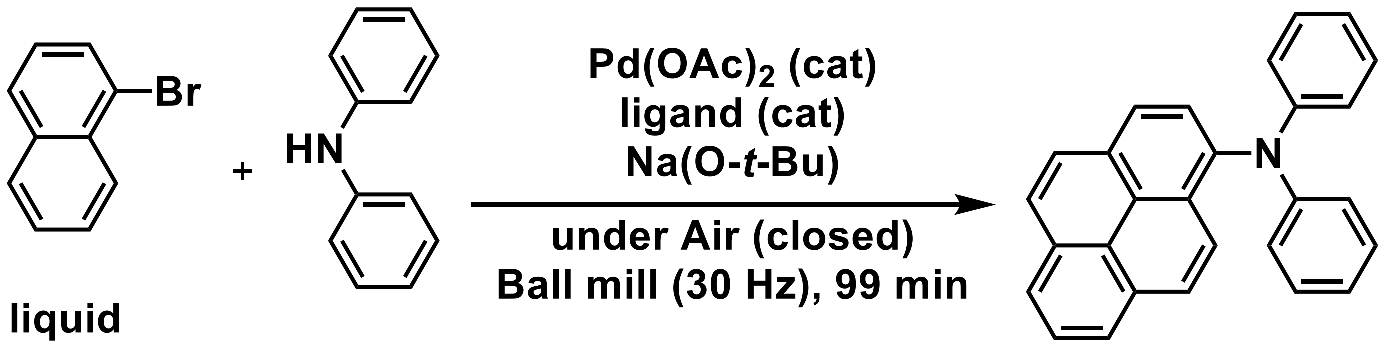
1. *Time saving*
2. *Selectivity enhancement*
3. *Different products from solution-based reactions*

3. Recent Examples

Cross-Coupling Reaction

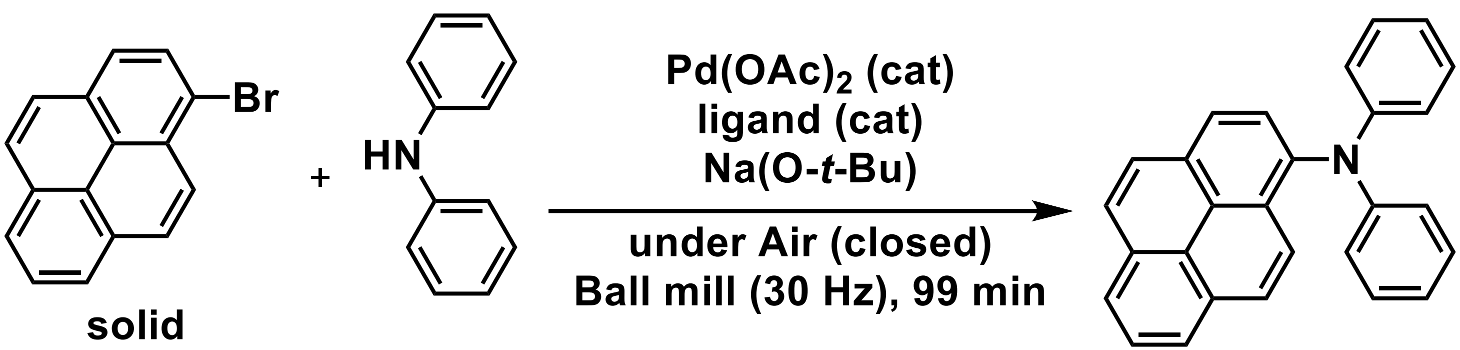
Buchwald-Hartwig Cross-Coupling in Solid-State

cross-coupling in the neat liquid



ligand: yields
XPhos: 41 %
***t*-Bu$_3$P: 95 %**

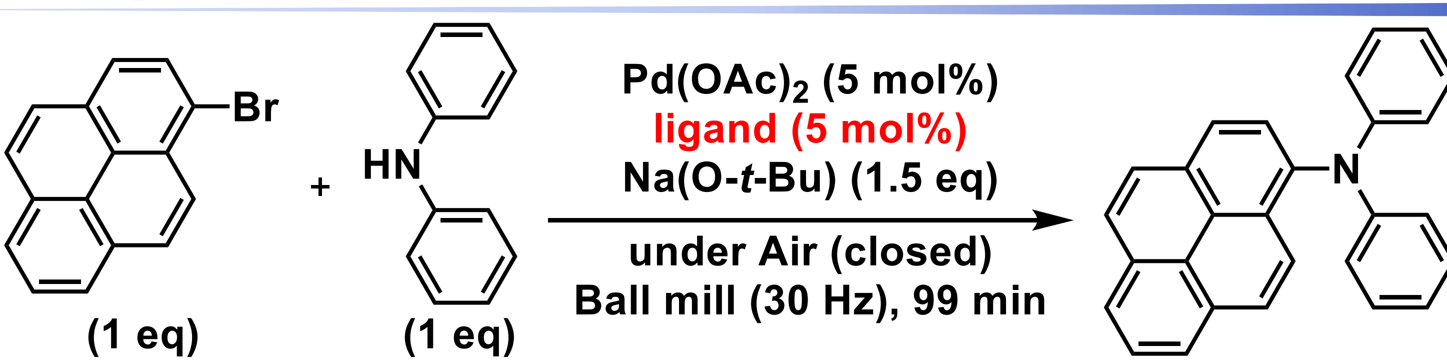
cross-coupling in the solid state



ligand: yields
XPhos: 3 %
***t*-Bu$_3$P: 28 %**

H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

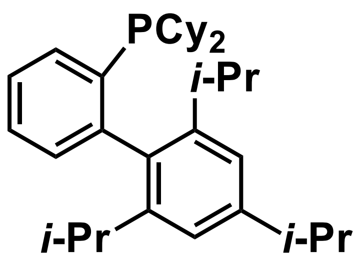
Screening of Ligand



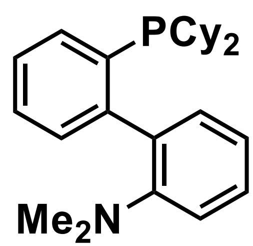
t-Bu$_3$P
28 %
(33 %)[a]

Ad$_3$P
18 %

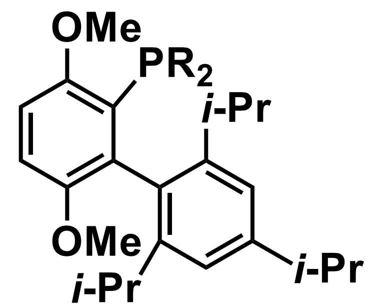
Cy$_3$P
0 %



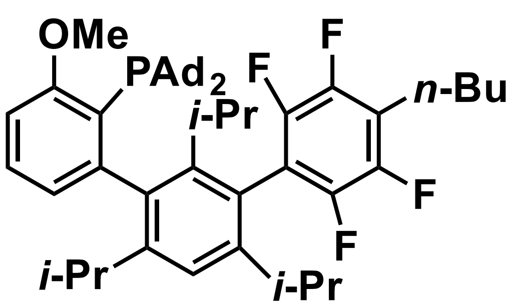
XPhos
3 %



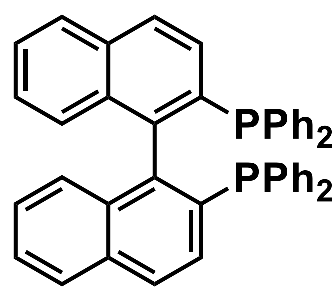
DavePhos
0 %



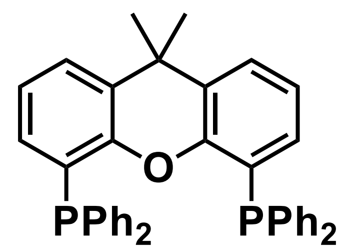
BrettPhos (R = Cy) : 0 %
t-BuBrettPhos (R = *t*-Bu) : 0 %
AdBrettPhos (R = Ad) : 0 %



AlPhos
0 %



rac-Binap
0 %

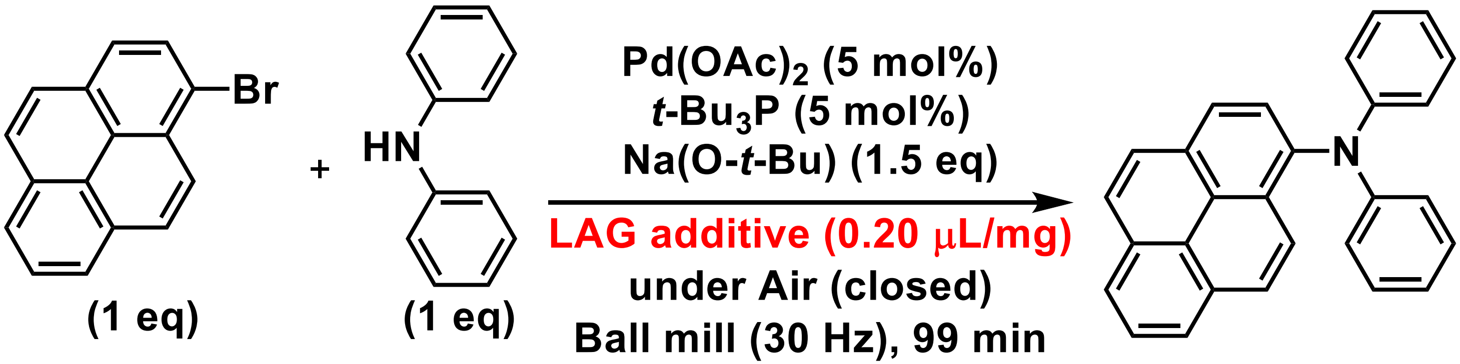


Xantphos
0 %

[a] 10 mol% of Pd(OAc)$_2$ and ligand was used.

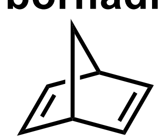
H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

Screening of LAG Additives



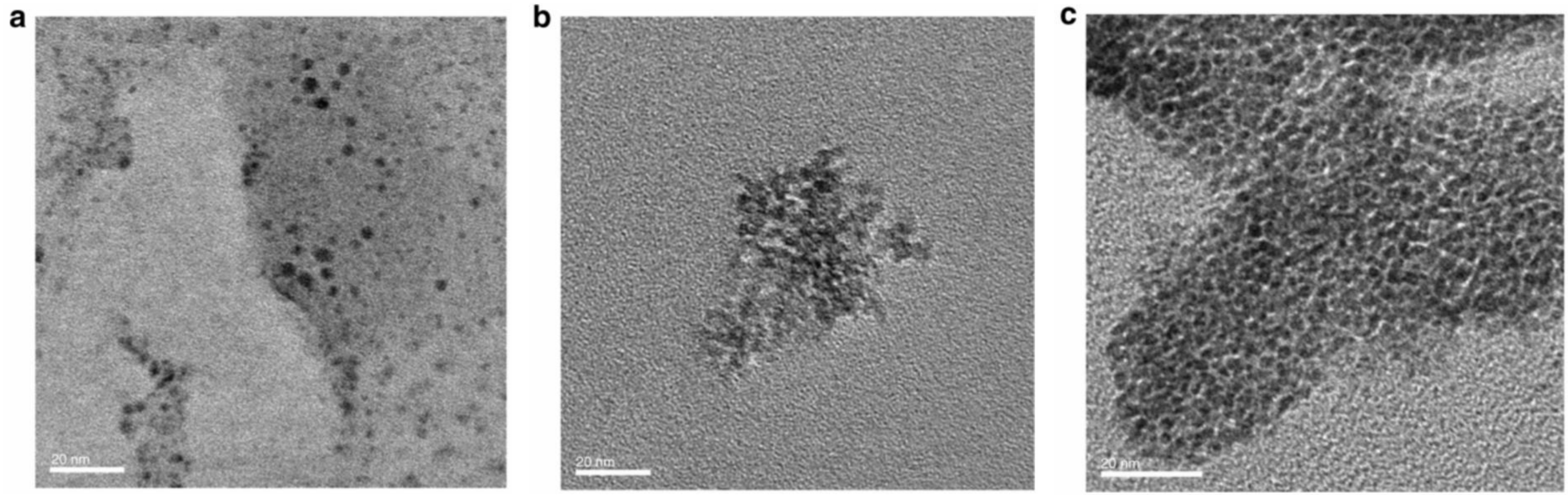
entry	LAG additives	TM(%)
1	none	28
2	toluene	48 (37)[a]
3	benzene	20
4	THF	55
5	MeCN	10
6	DMSO	0
7	hexane	16
8	cyclohexane	54
9	cyclooctane	46

[a] Toluene (0.13 μL/mg) was used.

entry	LAG additives	TM(%)
10	1,5-cod	99
11	cyclooctene	96
12	1-hexene	98
13	(E)-hex-3-ene	89
14	cyclohexene	92
15	oct-4-yne *n*-Pr—≡—*n*-Pr	66
16	norbornadiene 	12

H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

Transmission Electron Microscopy (TEM)



(a)with 1,5-cod (b)with cyclooctane (c)no additives

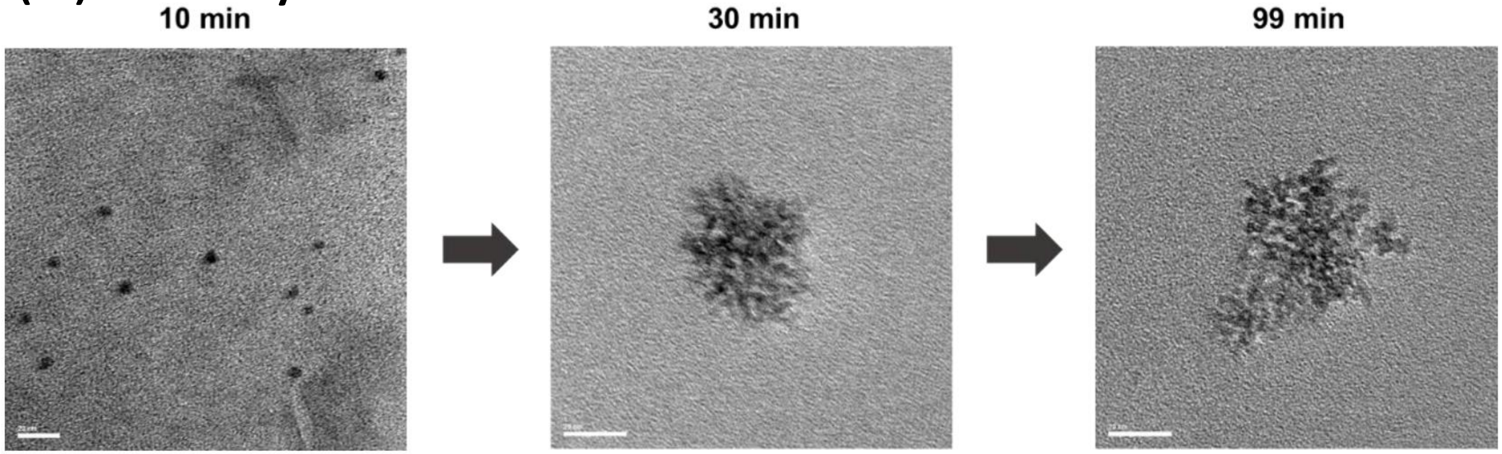
Palladium nanoparticles in the crude reaction mixture.

✓ ***1,5-cod suppressed palladium aggregations.***

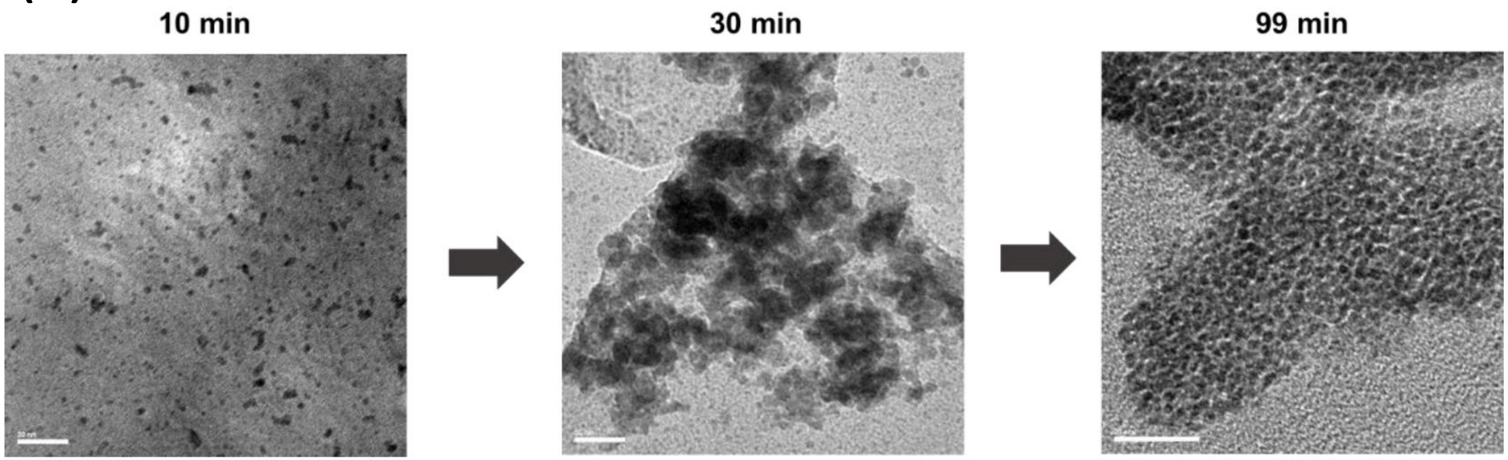
H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

Transmission Electron Microscopy (TEM) (2)

(b)with cyclooctane



(c)no additives



✓ ***Palladium was highly aggregated within 30 mins.***

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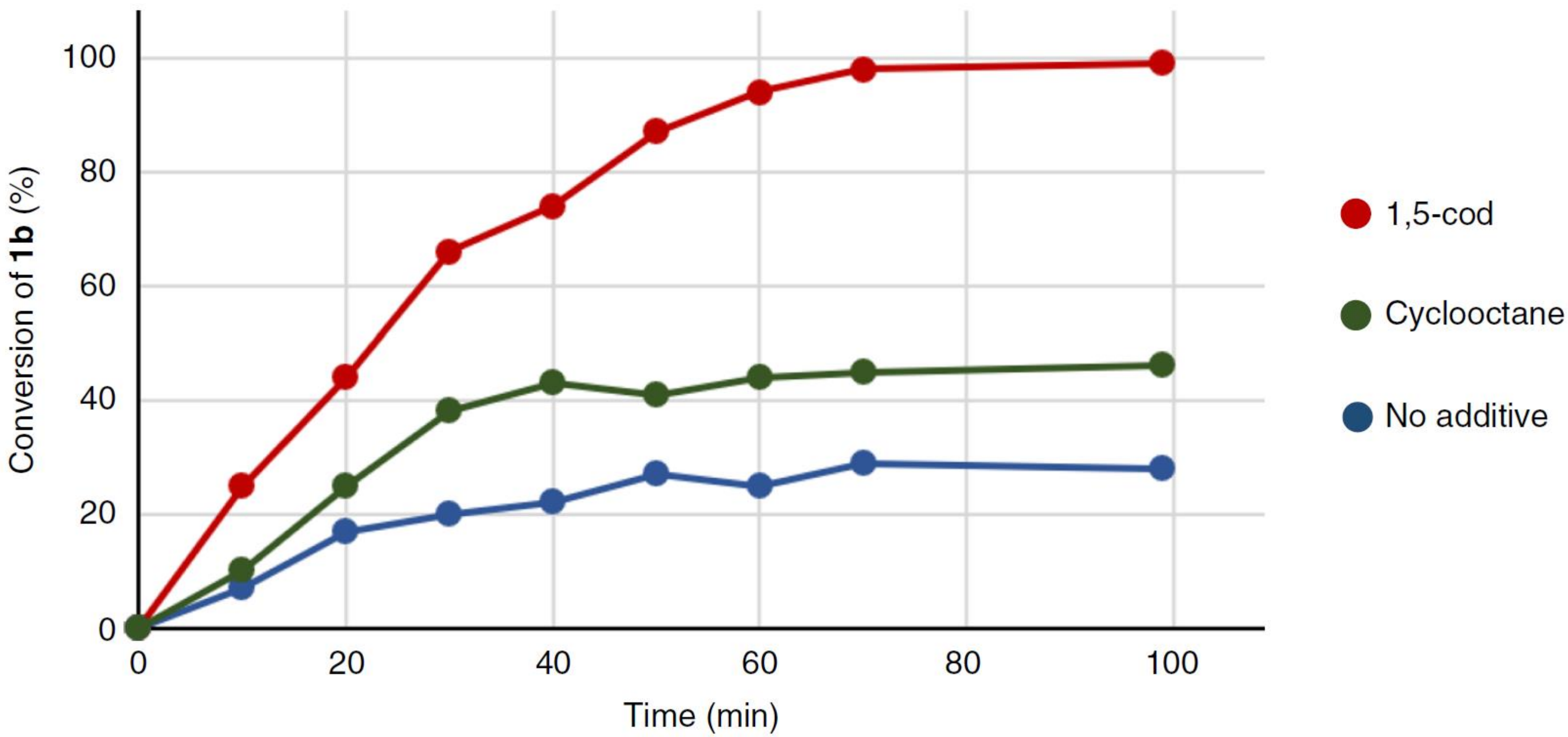
Kinetic Study



✓ ***The reactions stopped after about 30 mins.***

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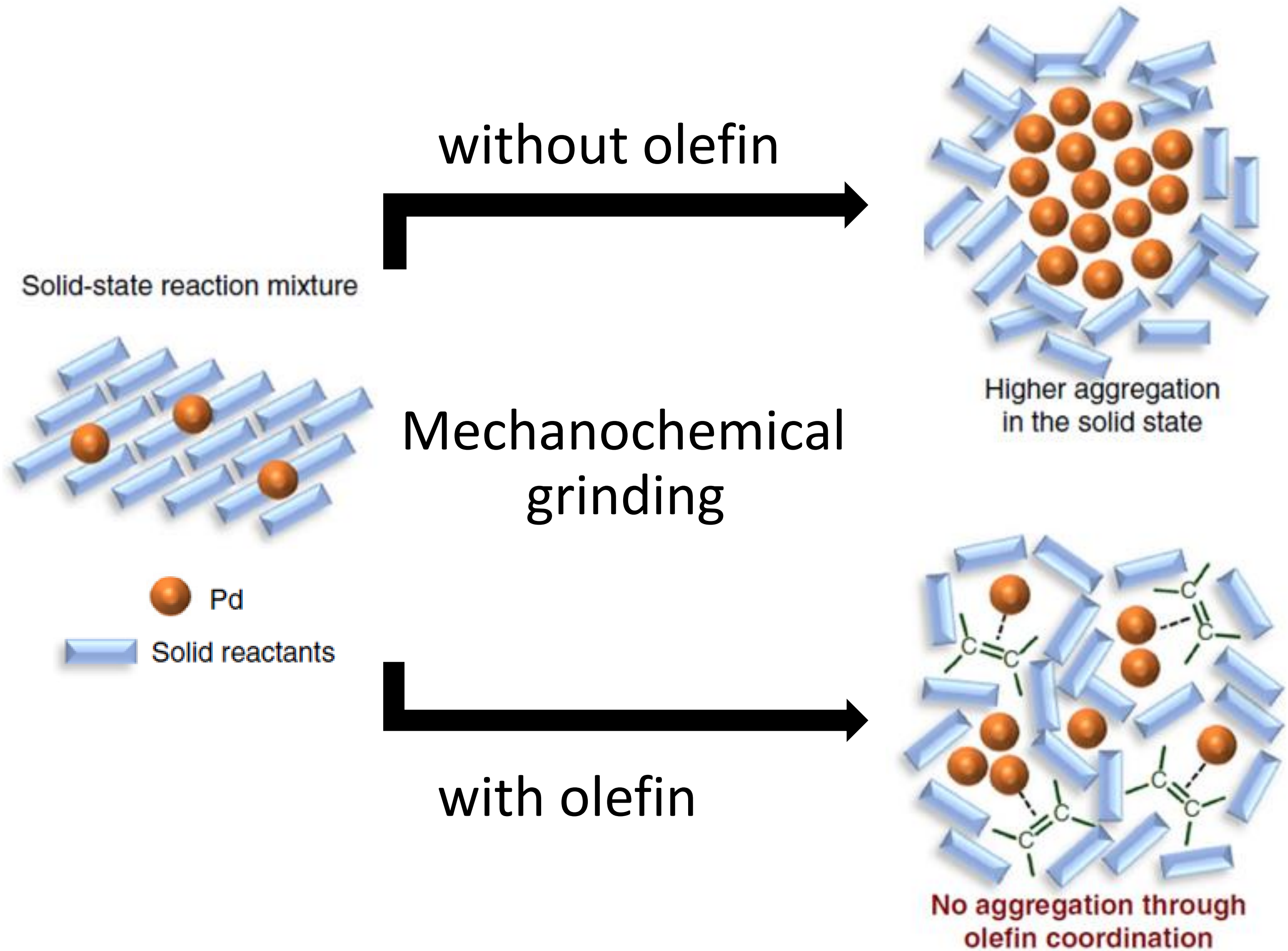
Proposed Acceleration Mechanism



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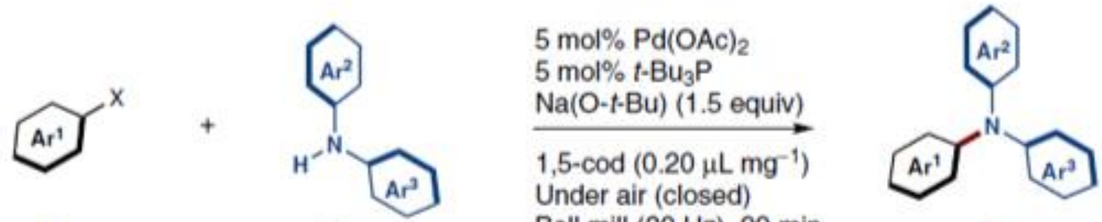
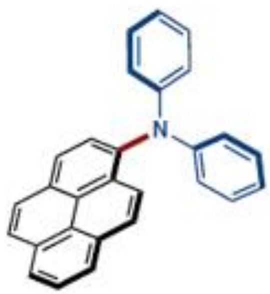
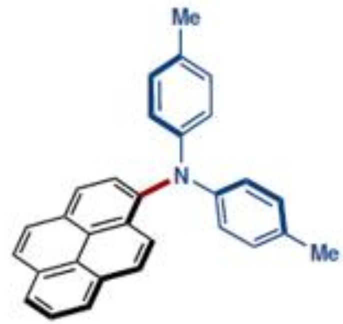
Substrate Scope (Amines)



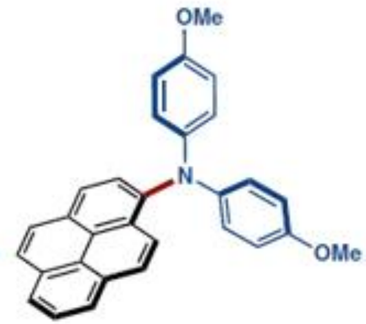
1 **2** **3**



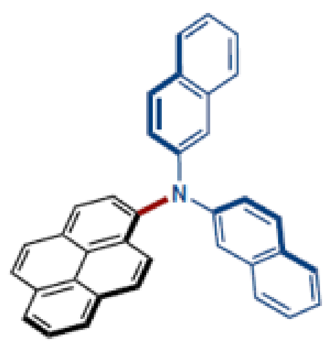
3b
93% yield



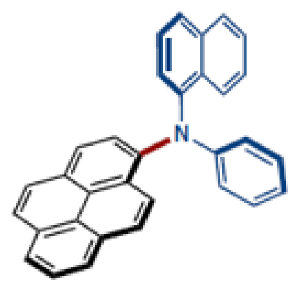
3c
88% yield



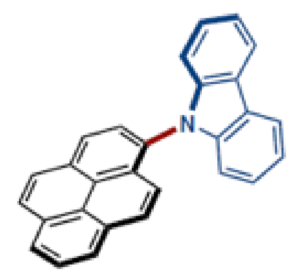
3d
68% yield



3e
72% yield



3f
81% yield



3g
<5% yield

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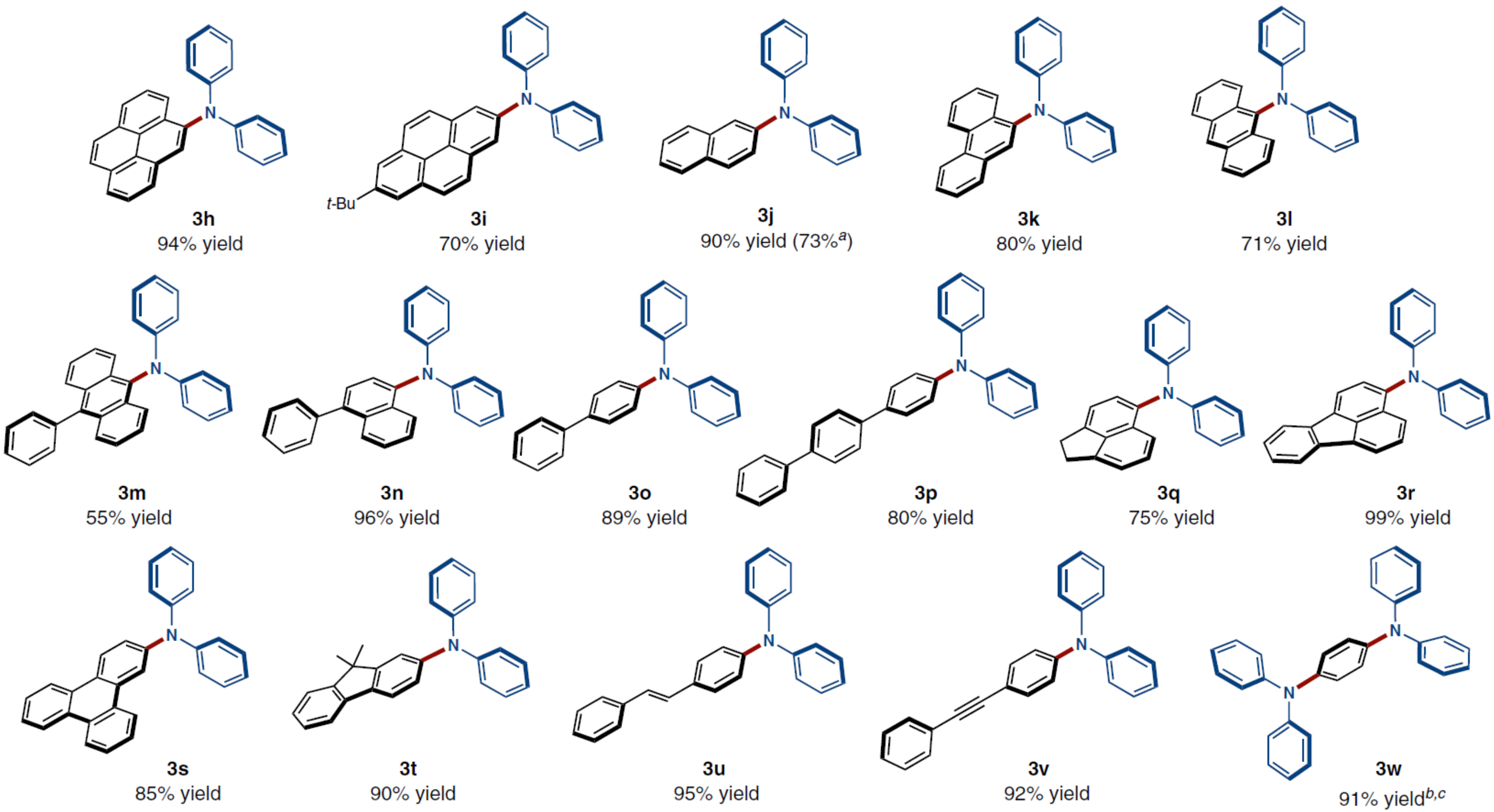
Substrate Scope (Aryl Halides) (1)



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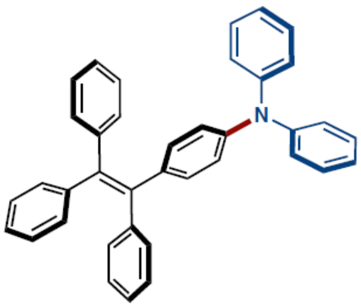
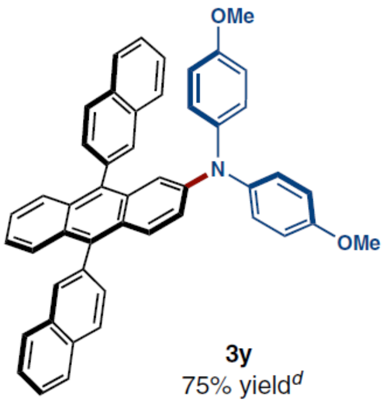
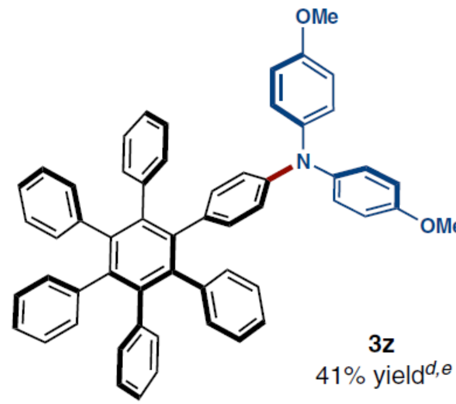
Substrate Scope (Aryl Halides) (2)



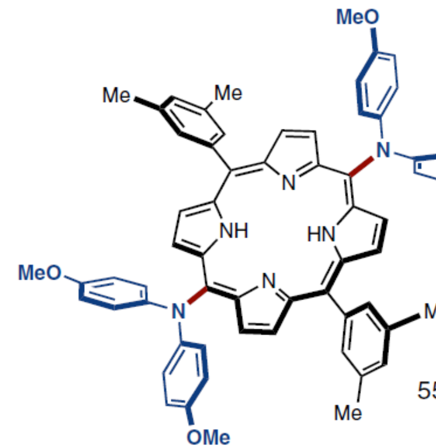
3x
67% yield



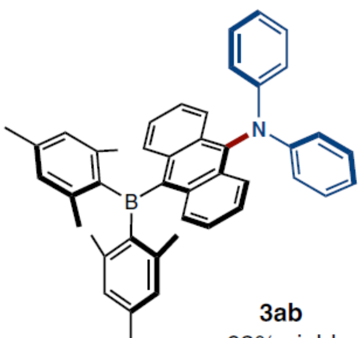
3y
75% yield[d]



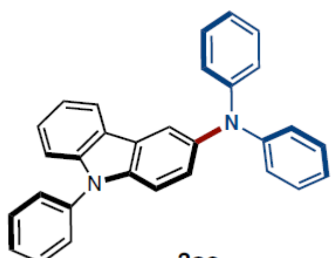
3z
41% yield[d,e]



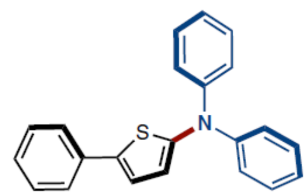
3aa
55% yield[c,f]



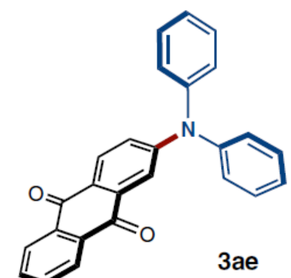
3ab
62% yield



3ac
82% yield



3ad
55% yield



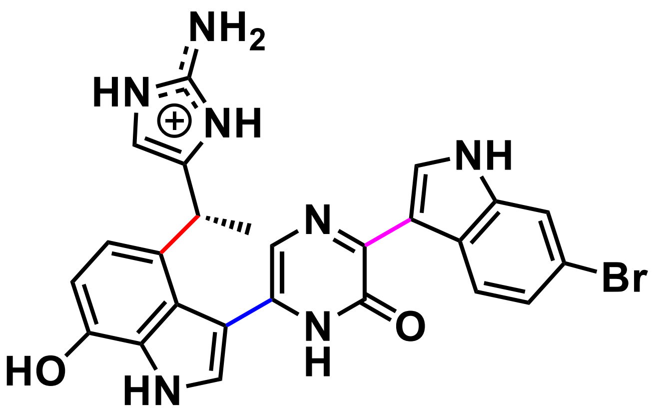
3ae
57% yield

H. Ito *et al. Nat. Commun.* **2019**, *10*, 111.

C-H Functionalization

The Importance of C-H Functionalization

✓ New & Shorter Synthetic Route

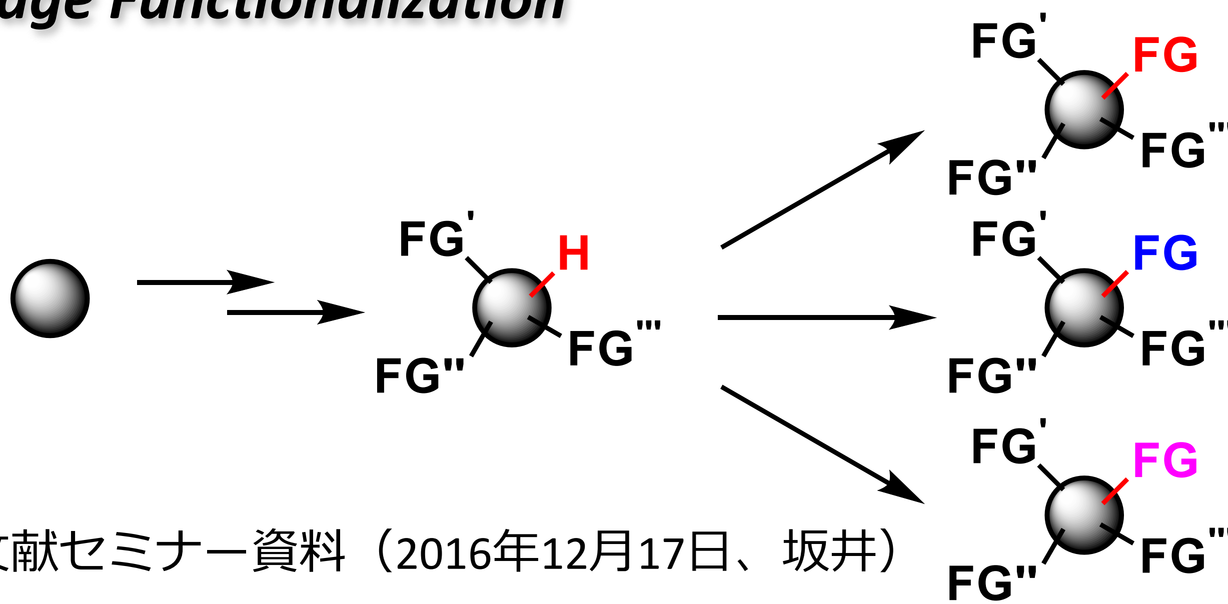


(±)-dragmacidine D

chemist	C-H functionalization	total steps
Itami	yes	15
Stoltz	no	25

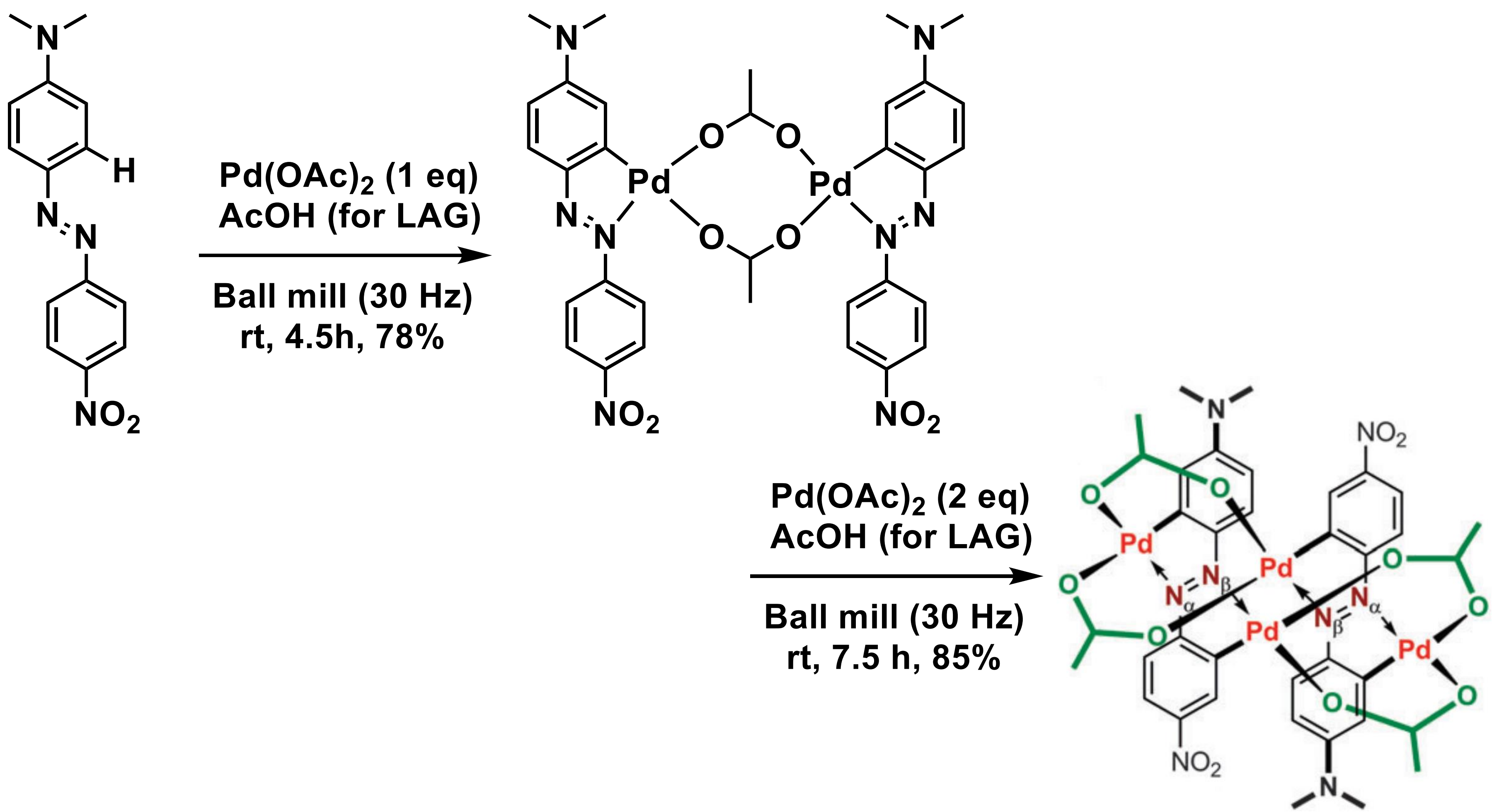
K. Itami *et al. J. Am. Chem. Soc* **2011**, *133*, 19660.
B. M. Stoltz *et al. J. Am. Chem. Soc* **2002**, *124*, 13179.

✓ Late-stage Functionalization



参考資料：文献セミナー資料（2016年12月17日、坂井）

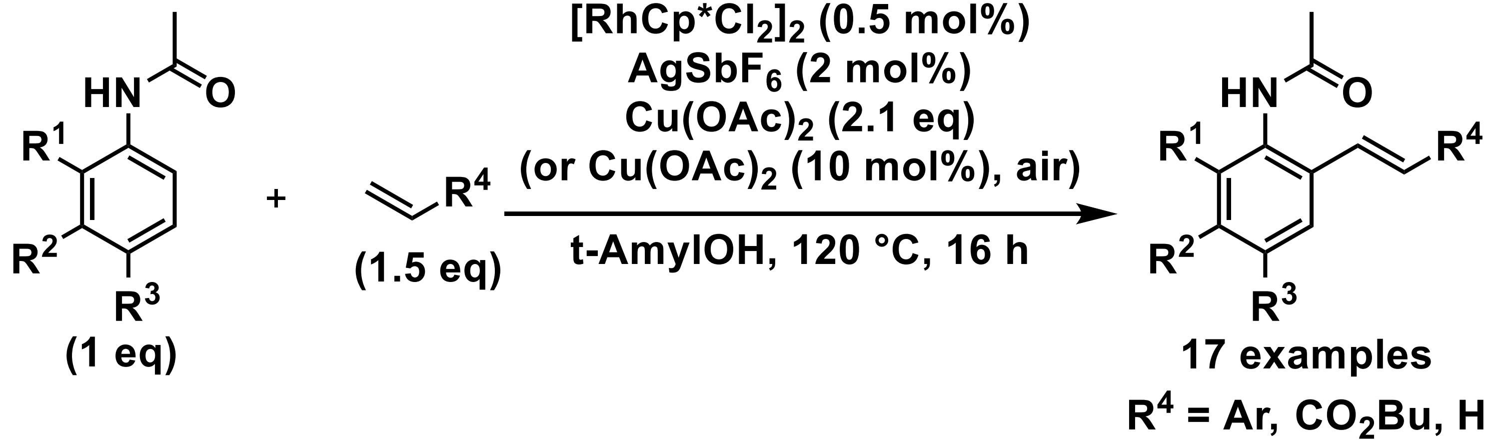
C-H Activation in Mechanochemistry



M. Ćurić *et al. Chem. Commun.* **2014**, *50*, 10287.

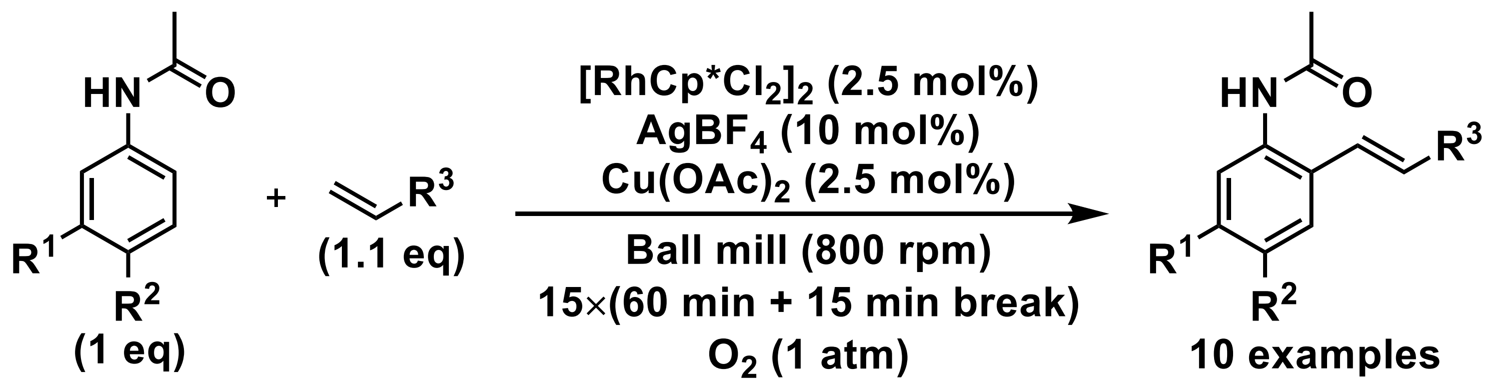
First Example of Catalytic C-H Functionalization

Solution-based reaction



F. Glorius *et al. J. Am. Chem. Soc.* **2010**, *132*, 9982.

Mechanochemical reaction



C. Bolm *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 7414.

Various C-H Functionalization in Mechanochemistry

Rh

- Olefination (C. Bolm *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 7414.)
- Halogenation (Br, I) (C. Bolm *et al. Chem. Commun.* **2015**, *51*, 12582.)
- alkynylation (C. Bolm *et al. Green. Chem.* **2017**, *19*, 2520.)
- amidation (C. Bolm *et al. ACS Catal.* **2017**, *7*, 4592.)

Ir

- amidation (C. Bolm *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 3781.)
- borylation (H. Ito *et al. Chem. Eur. J.* **2019**, *25*, 4654.)

Co

- allylation (C. Yu *et al. J. Org. Chem.* **2017**, *82*, 10665.)
- amidation (C. Bolm *et al. Adv. Synth. Catal.* **2018**, *360*, 1800.)

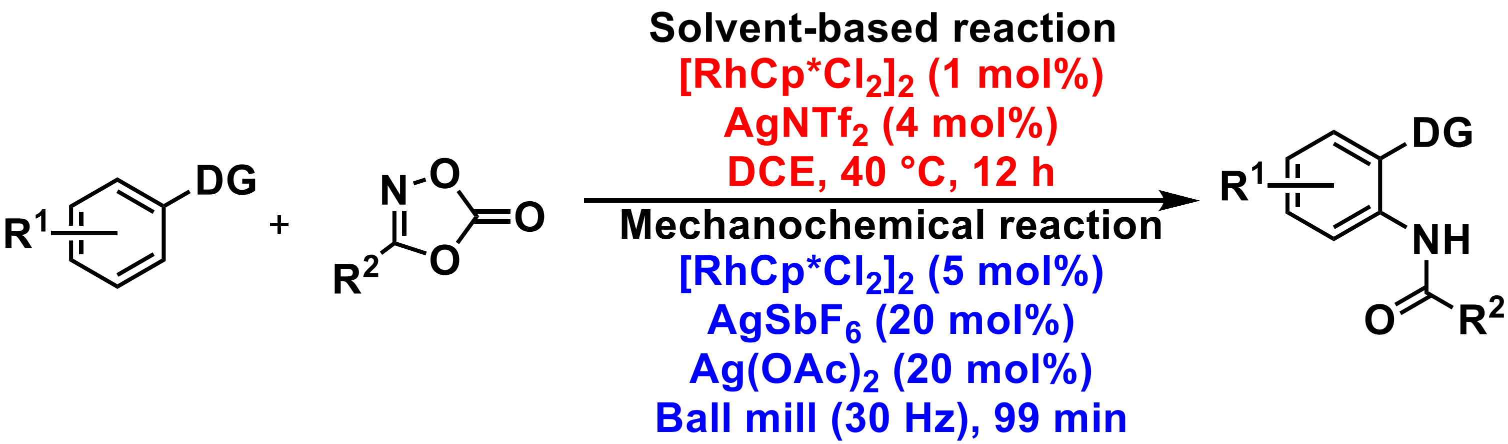
Pd

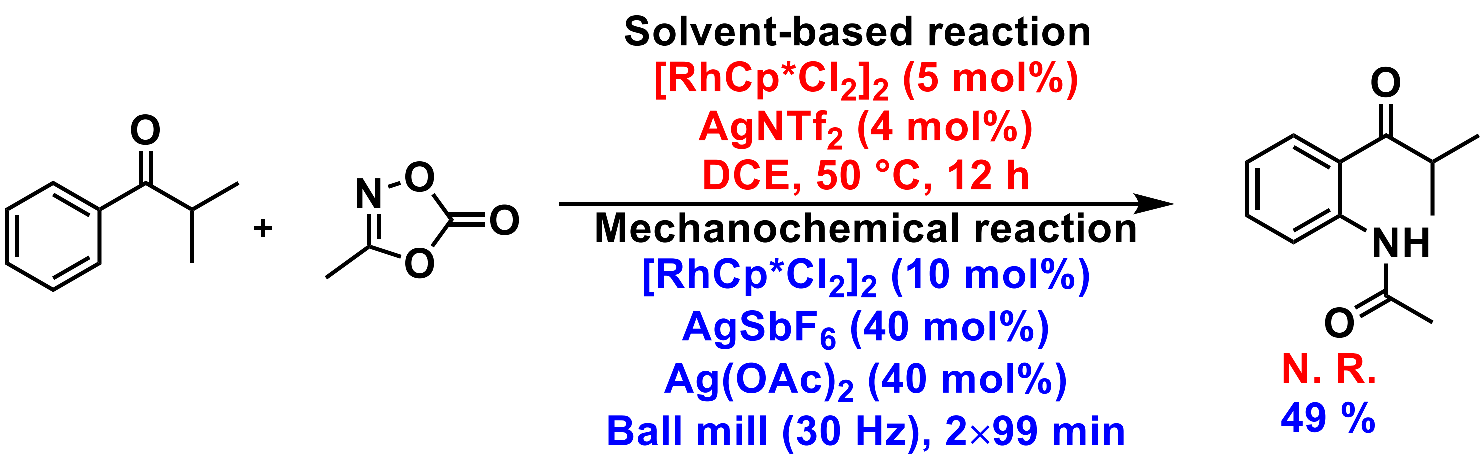
- arylation (D.-Q. Xu *et al. ACS Catal.* **2016**, *6*, 3890.)
- C-H/C-H oxidative coupling (W.-K. Su *et al. J. Org. Chem.* **2016**, *81*, 6049.)

Au

- alkynylation (C. Bolm *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 10723.)

1. Weakly Coordinating DG Can Work

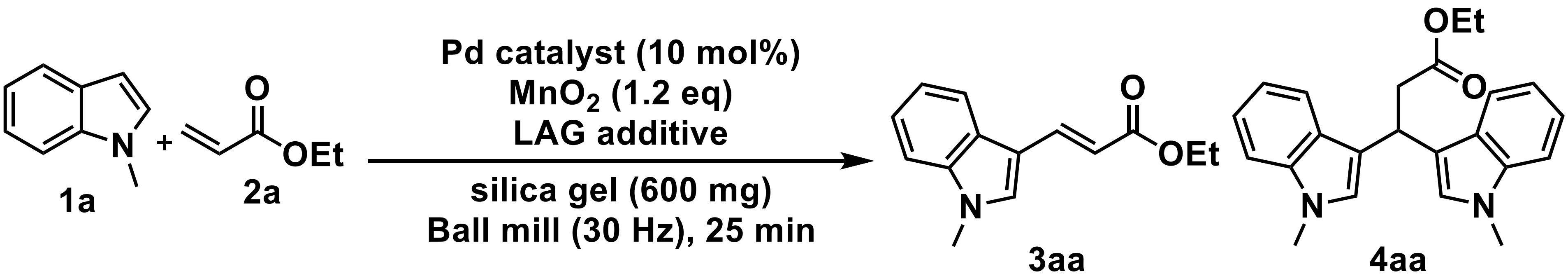




S. Chang *et al. J. Am. Chem. Soc.* **2015**, *137*, 4534.

C. Bolm *et al. ACS Catal.* **2017**, *7*, 4592.

2. Solvent Sensitive Metal Intermediate

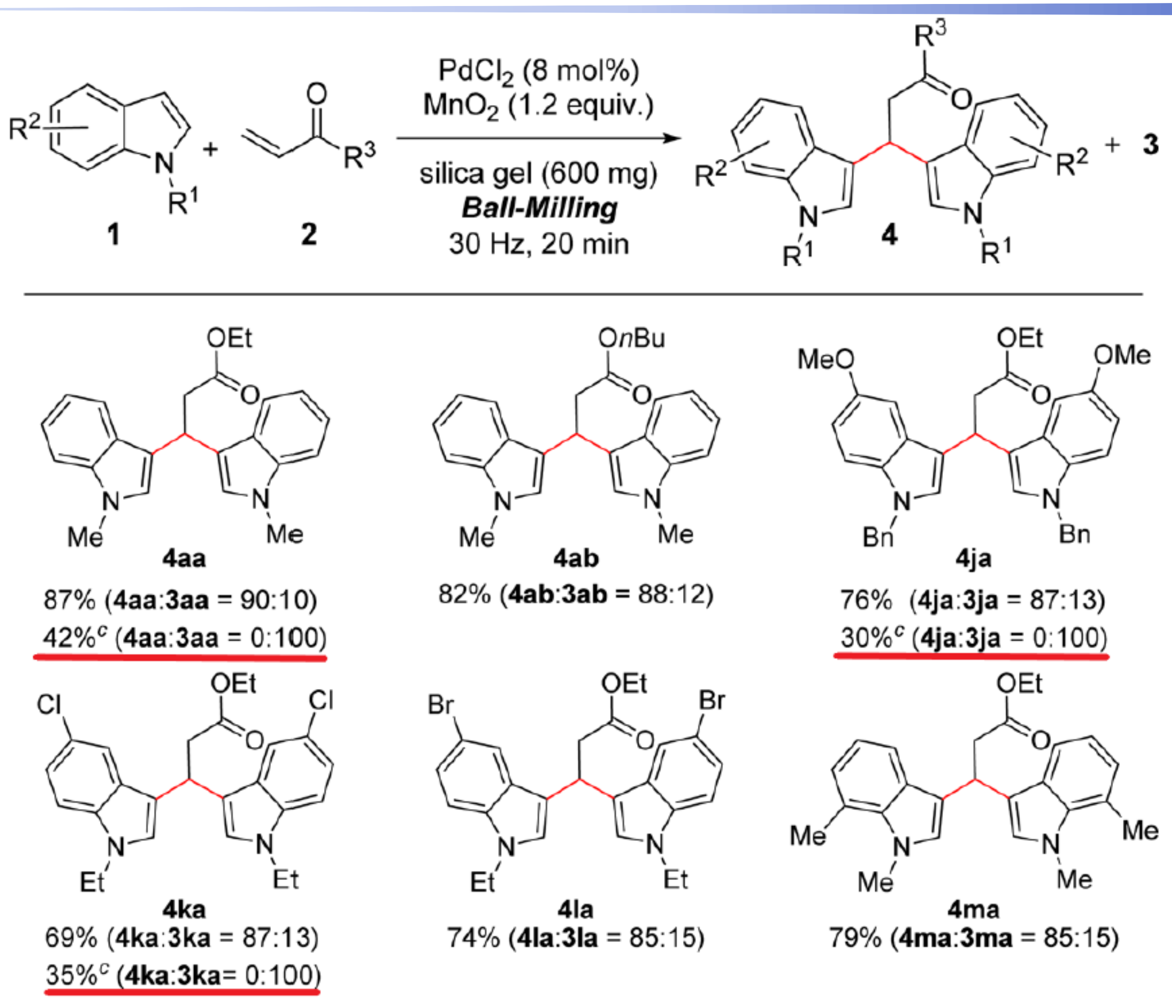


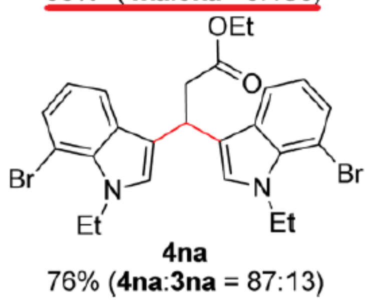
entry	Pd catalyst	LAG additives	3aa(%)	4aa(%)	
1	$Pd(OAc)_2$	none	61	-	
2	$Pd(OAc)_2$	AcOH (η = 0.17)	83	-	condition A
3	$Pd(TFA)_2$	none	31	-	
4	$PdCl_2$	AcOH (η = 0.17)	15	68	
5	PdI_2	AcOH (η = 0.17)	20	65	
6	$PdCl_2$	none	11	78	
7	PdI_2	none	12	75	
8[a]	$PdCl_2$	none	9	78	condition B

[a] 8 mol% of Pd catalyst was used.

W.-K. Su *et al. J. Org. Chem.* **2016**, *81*, 6049.

2. Solvent Sensitive Metal Intermediate (2)





[c] comparative experiments in DMF at 100 °C, overnight

W.-K. Su *et al. J. Org. Chem.* **2016**, *81*, 6049.

2. Solvent Sensitive Metal Intermediate (3)

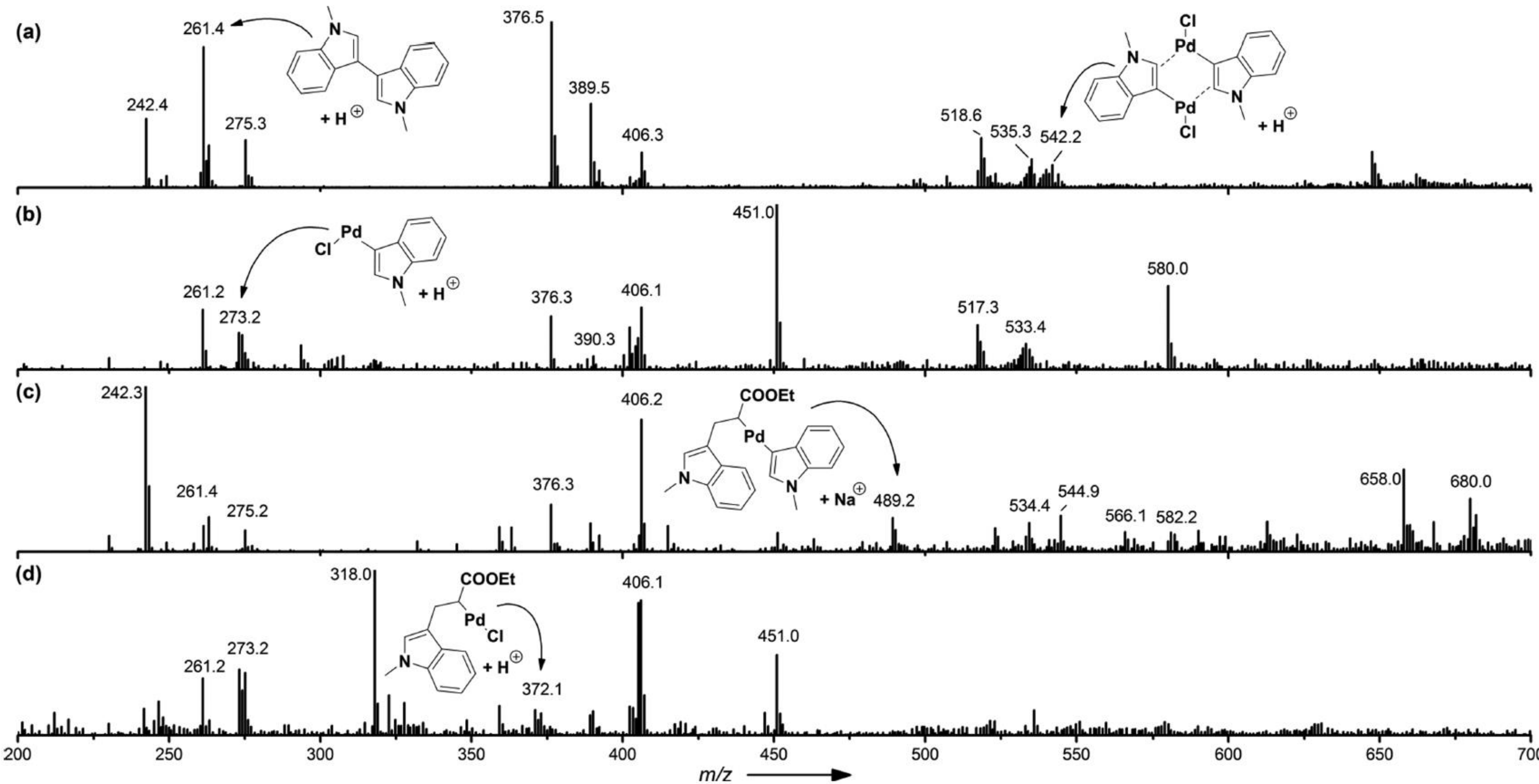


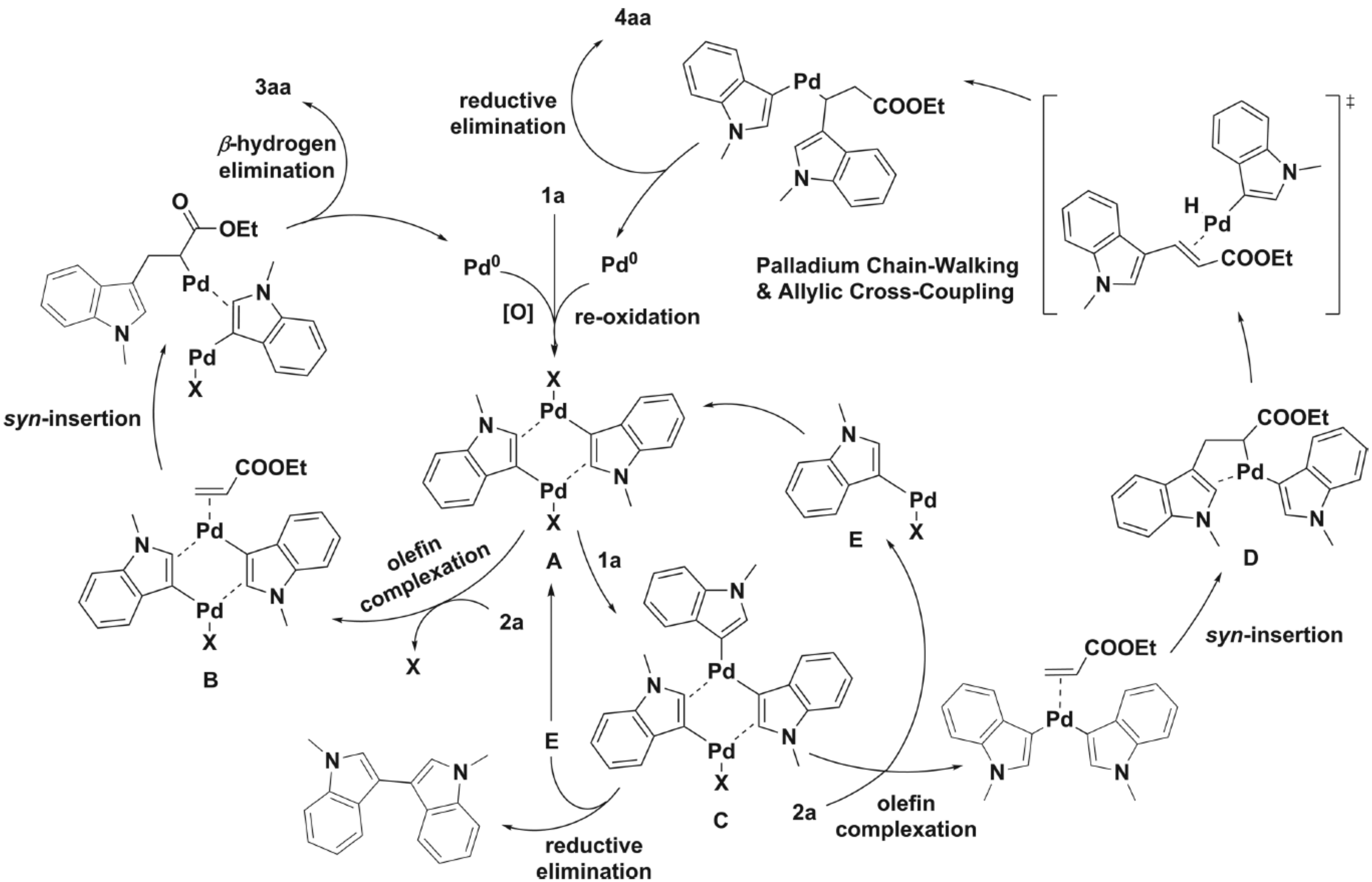
Figure 1. ESI-MS spectra of $PdCl_2$-catalyzed reactions: (a) $PdCl_2$ with **1a** with 30 Hz grinding for 30 s; (b) $PdCl_2$ with **1a** in DMF refluxed for 30 min; (c) $PdCl_2$ with **1a** and **2a** with 30 Hz grinding for 30 s; (d) $PdCl_2$ with **1a** and **2a** in DMF refluxed for 30 min.

✓ ***m/z 542.2 cluster assigned as [Pd_2(1a-H) $_2$(Cl) $_2$+H]$^+$.***

W.-K. Su *et al. J. Org. Chem.* **2016**, *81*, 6049.

2. Solvent Sensitive Metal Intermediate (4)

Proposed Mechanism of HSBM-Promoted Selective Synthesis of 3-Vinylindoles and *β*,*β*-Diindolyl Propionate



W.-K. Su *et al. J. Org. Chem.* **2016**, *81*, 6049.

Summary of Section 3

・Transition metal catalyzed cross coupling reactions between solid reactants were realized by using ball milling.

・Transition metal catalyzed C-H functionalization have been reported since 2015.

・Most of the cross coupling reaction and C-H functionalization in mechanochemistry were already realized in solution reaction.

・In mechanochemistry, it is possible to form and utilize a metal complex which is unstable to solvents.

4. Summary

Summary of Today's Literature Seminar

・Mechanochemical reactions have been studied for organic synthesis mainly in the last few decades.

・Ball mills are usually used in mechanochemistry.

・Various kinds of organic reactions such as wittig reaction, cross-coupling, C-H functionalization have been realized in mechanochemical conditions.

・ There are also some advantages in terms of reactivity.

・Mechanistic studies will lead to further progress.