

***IASOC 2024***

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***Synthetic Organic Chemistry  
Toward Sustainable Society***

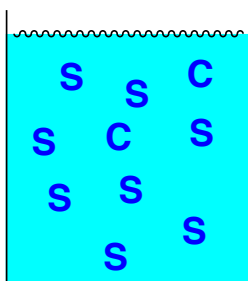
***Ischia, September 22, 2024***

***Shū Kobayashi  
The University of Tokyo***

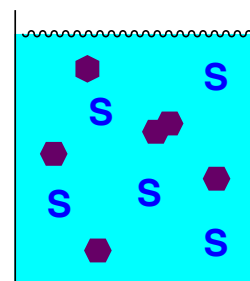
# Classification of "Catalytic Reactions in Water"

When substrate is water-soluble...

Water-soluble catalyst



Type Ia

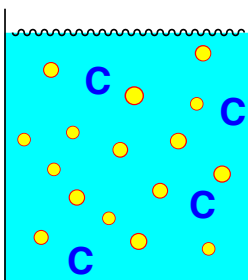


Type Ib

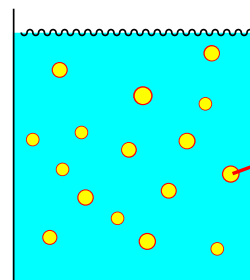
Not water-soluble catalyst

When micelle forms aggregate...

Catalyst is outside the micelle. (aqueous phase)



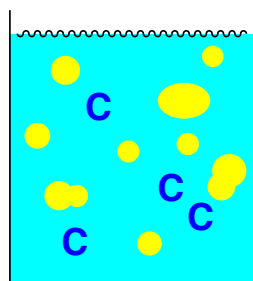
Type IIa



Type IIb

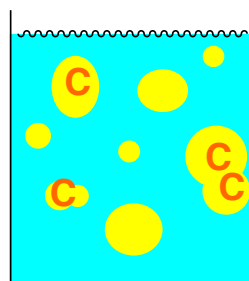
Catalyst is inside the micelle.

When substrate is not soluble in water...



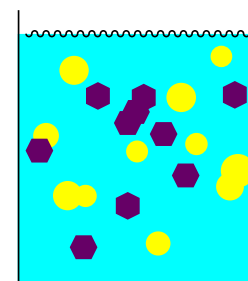
Type IIIa

Catalyst is water-soluble.



Type IIIb

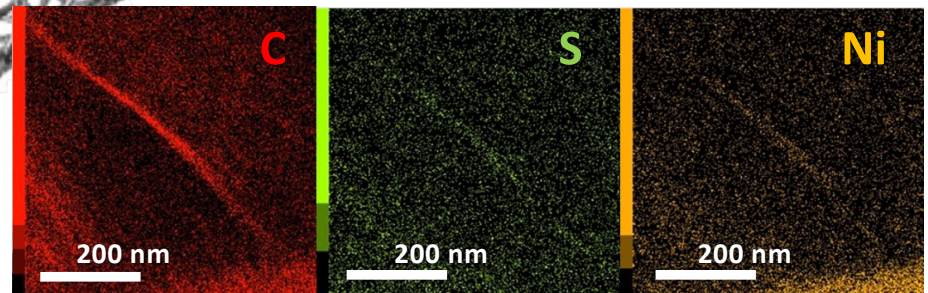
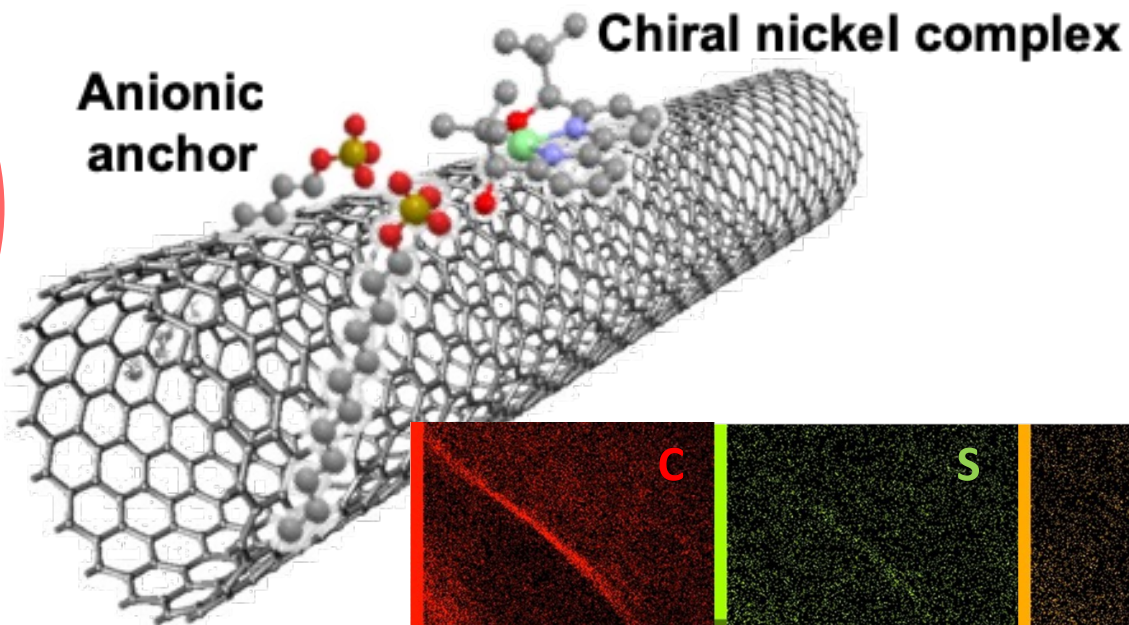
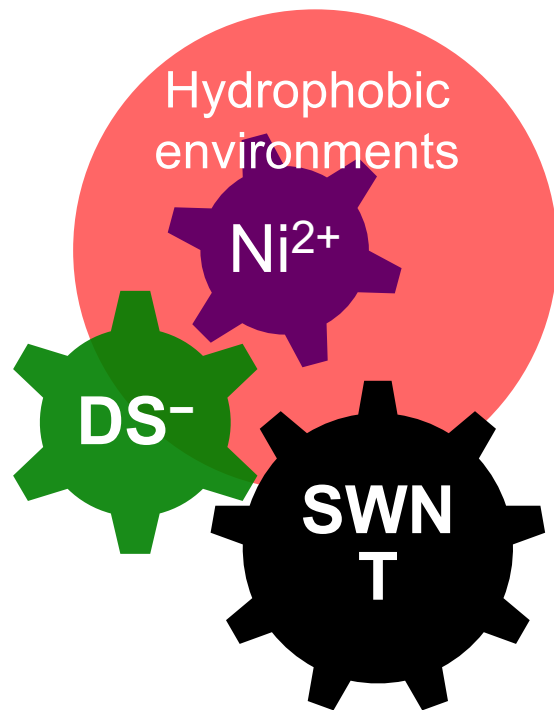
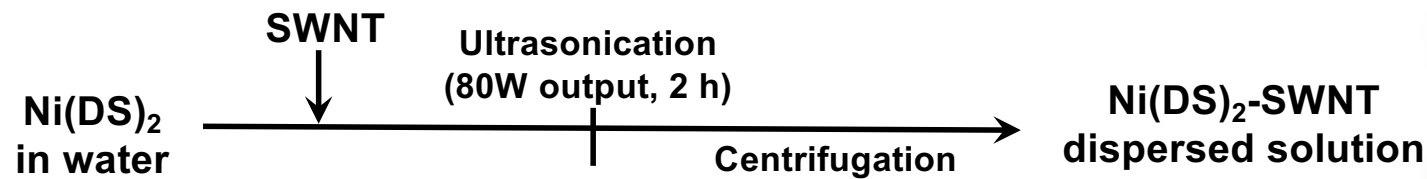
Catalyst & substrates are in the same phase.



Type IIIc

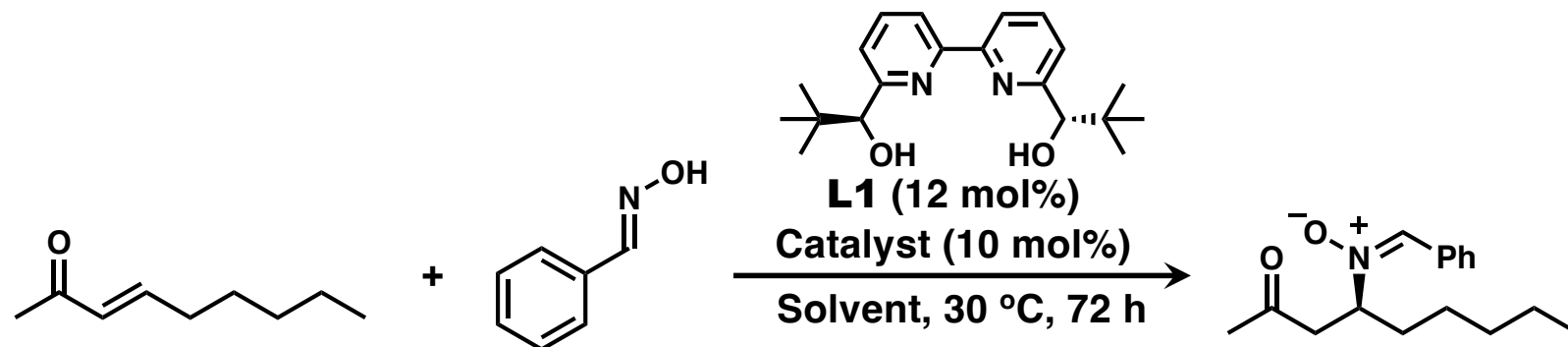
Catalyst is soluble neither in water nor in substrate.

# Type IIb Reaction: SWNT Surface as Efficient Reaction Environments



- Unique catalyst design
  - dispersed and stable environments (DLS, NMR, STEM, microscopy)
  - modified electrochemical property (UV-vis, Raman, CV, UV-vis-NIR, PLE)

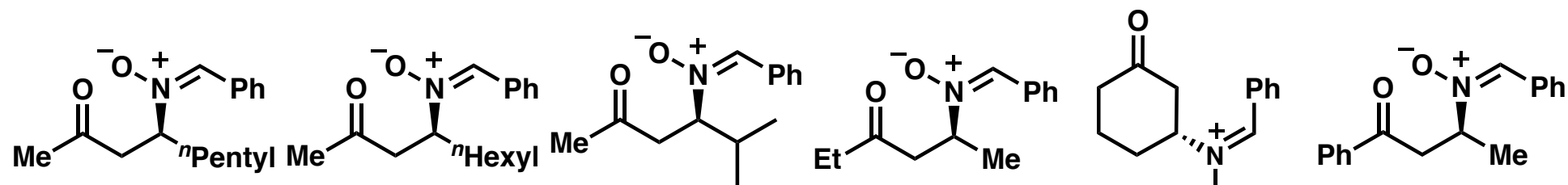
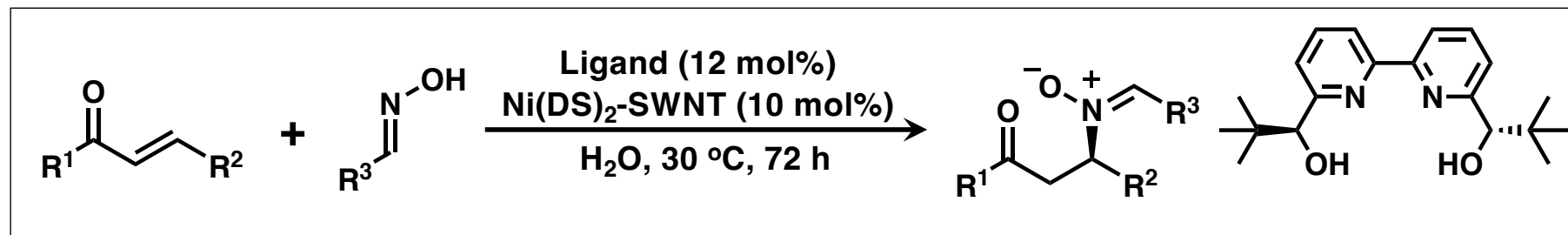
# Evaluation of Catalytic Activities



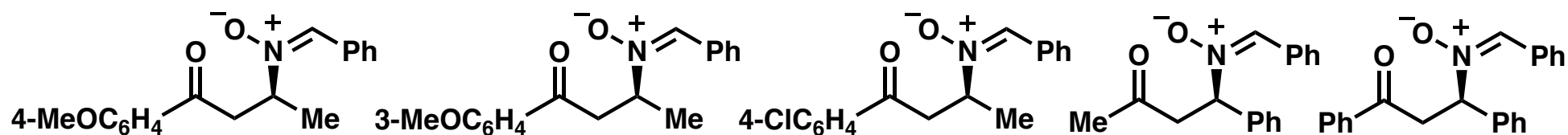
Run	Catalyst	Solvent	Yield (%)	% ee
1	Ni(DS) <sub>2</sub> -SWNT	H <sub>2</sub> O	79	95
2	Ni(DS) <sub>2</sub>	H <sub>2</sub> O	33	16
3	SWNT	H <sub>2</sub> O	Trace	–
4	NiCl <sub>2</sub> (10 mol%) + SDS-SWNT (20 mol%)	H <sub>2</sub> O	18	0
5 <sup>a</sup>			32	0
6	Ni(DS) <sub>2</sub> -SWNT	MeOH	36	3
7		EtOH	Trace	–
8		CH <sub>2</sub> Cl <sub>2</sub>	39	0
9		CHCl <sub>3</sub>	20	1
10		Et <sub>2</sub> O, THF	Trace	–
11		Toluene	NR	–

<sup>a</sup> After desalting through cellulose semipermeable membrane.

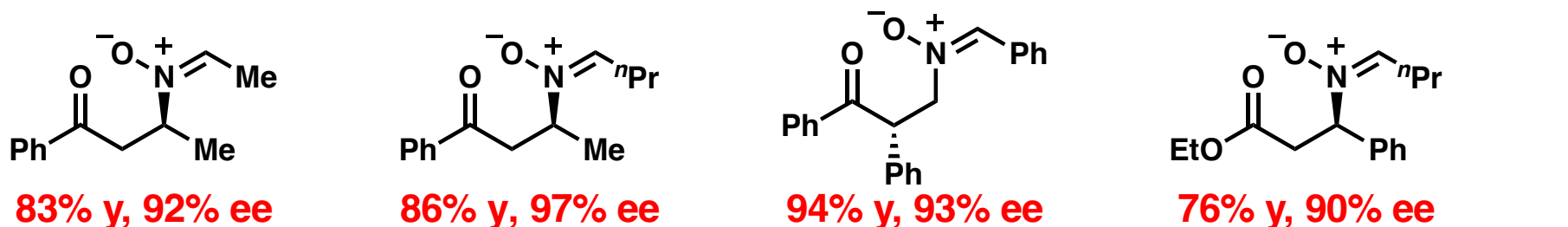
# Substrate Scope



79% y, 95% ee 76% y, 94% ee 82% y, 96% ee 88% y, 90% ee 83% y, 94% ee 86% y, 99% ee



84% y, 93% ee 80% y, 98% ee 87% y, 96% ee 81% y, 94% ee 52% y, 89% ee



83% y, 92% ee

86% y, 97% ee

94% y, 93% ee

76% y, 90% ee

# Type IIIc Reaction: Asymmetric Boron Conjugate Additions

Substrates: *Insoluble*  
Catalysts: *Insoluble*

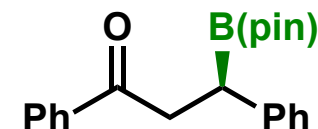
**High TOF (43,200  
h<sup>-1</sup> at 0.005 mol%)**

Cu(OH)<sub>2</sub> (5 mol%)

L1 (6 mol%)

H<sub>2</sub>O, 5 °C, 12 h

84% yield  
80% ee



Cu(OAc)<sub>2</sub> (5 mol%)

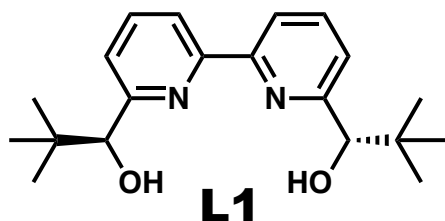
L1 (6 mol%)

H<sub>2</sub>O, 5 °C, 12 h

94% yield  
91% ee

TOF 12,800 h<sup>-1</sup>  
at 0.005 mol%

Substrates: *Insoluble*  
Catalysts: *Soluble*



Cu(OH)<sub>2</sub> (5 mol%)

L1 (6 mol%)

Organic solvent

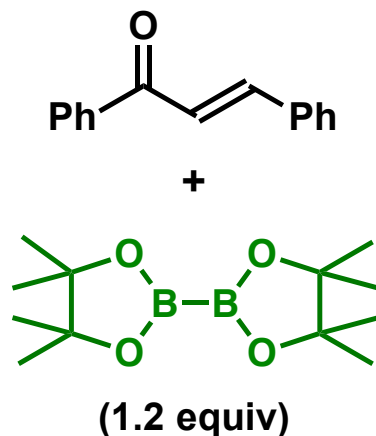
rt, 10 h

0% yield

Substrates: *Soluble*

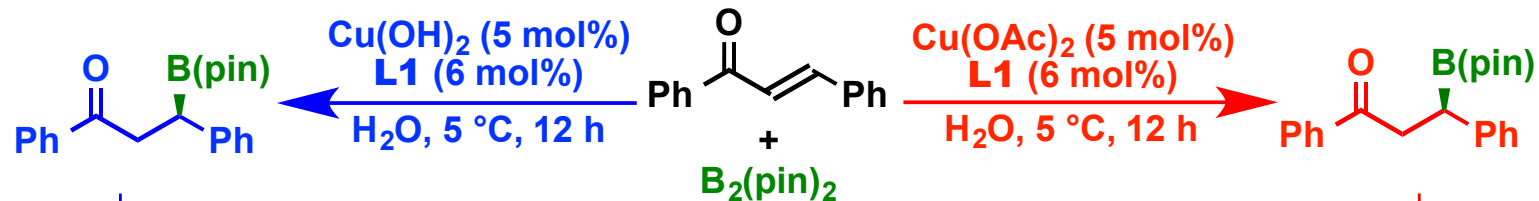
Catalyst: *Insoluble*

(Toluene, CH<sub>2</sub>Cl<sub>2</sub>, THF, DMF,  
DMSO, EtOH, neat (no solvent))



**Both catalysts &  
substrates are solid  
materials.**

# Heterogeneous vs. Homogeneous

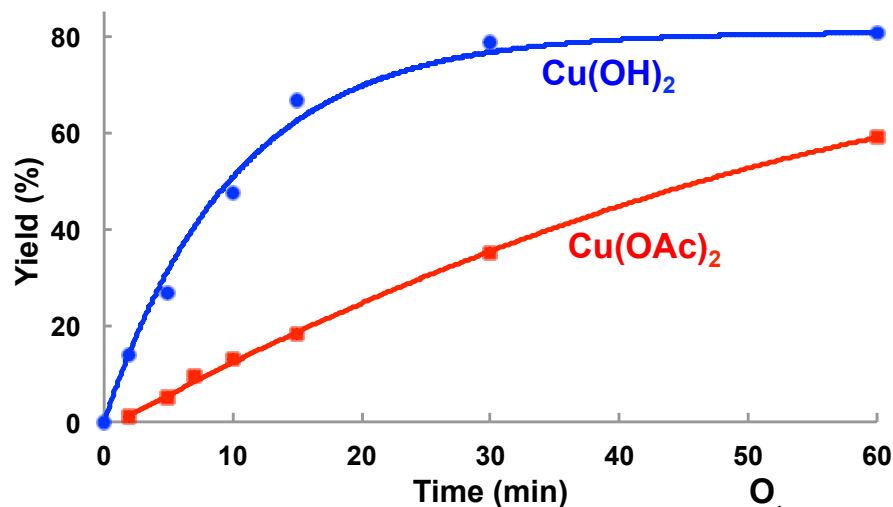


**Filtration experiments**

Left side (Cu(OH)<sub>2</sub>):  
 Filtrate: 83% yield, 81% ee  
 Second run: **Cu(OH)<sub>2</sub> No reaction**

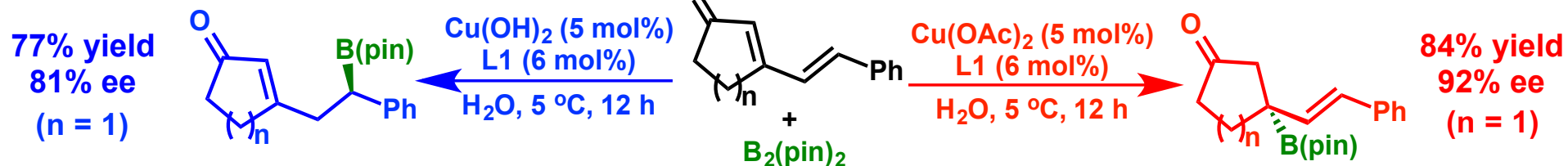
Right side (Cu(OAc)<sub>2</sub>):  
 Filtrate: 94% yield, 91% ee  
 Second run: **Cu(OAc)<sub>2</sub> 89% y, 91% ee**

ICP analysis of the filtrate: Cu content <10 ppb



	Cat. Solubility	Sub. Solubility
<b>Cu(OH)<sub>2</sub> in H<sub>2</sub>O</b>	X	X
<b>Cu(OAc)<sub>2</sub> in H<sub>2</sub>O</b>	✓	X

✓ = highly soluble, X = practically insoluble

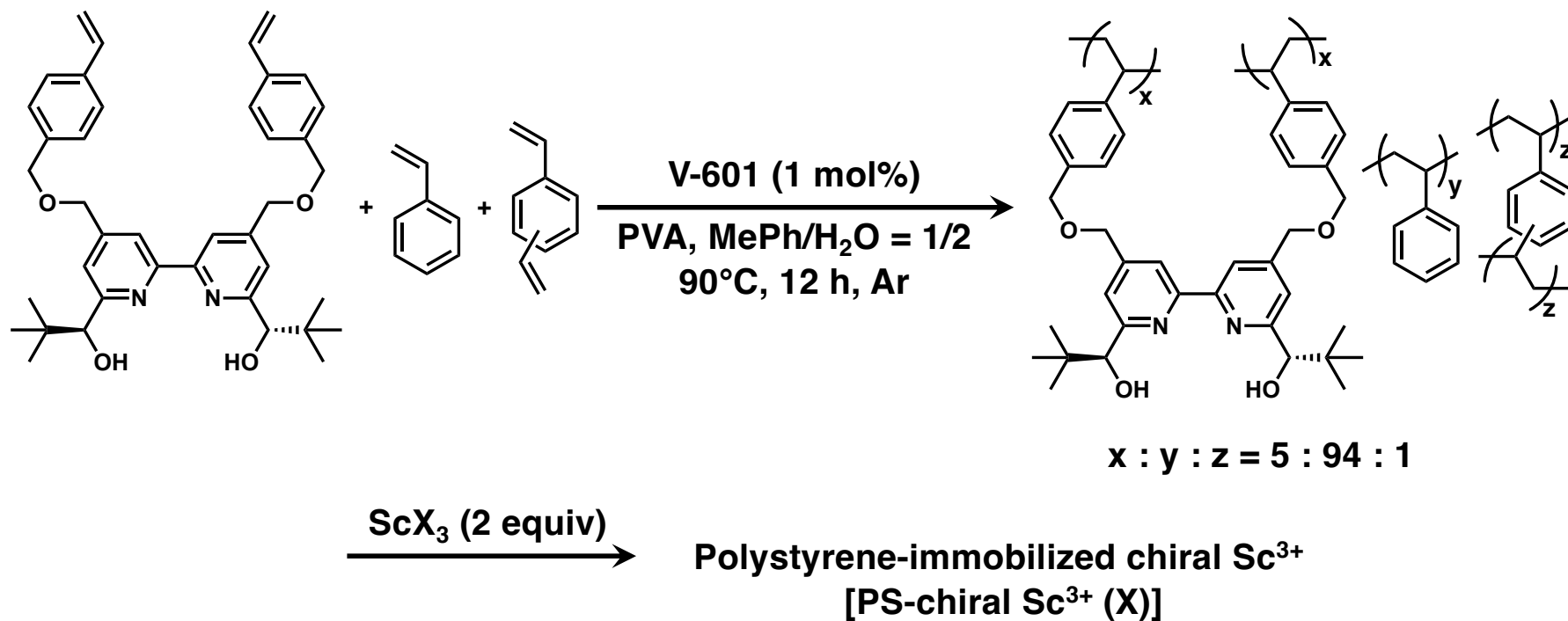


# Recycling of Catalyst-Solvent Couples from Lewis Acid-Catalyzed Asymmetric Reactions (Type IIIb Reaction)

## ■ Solvent recycling & catalyst recycling in asymmetric synthesis

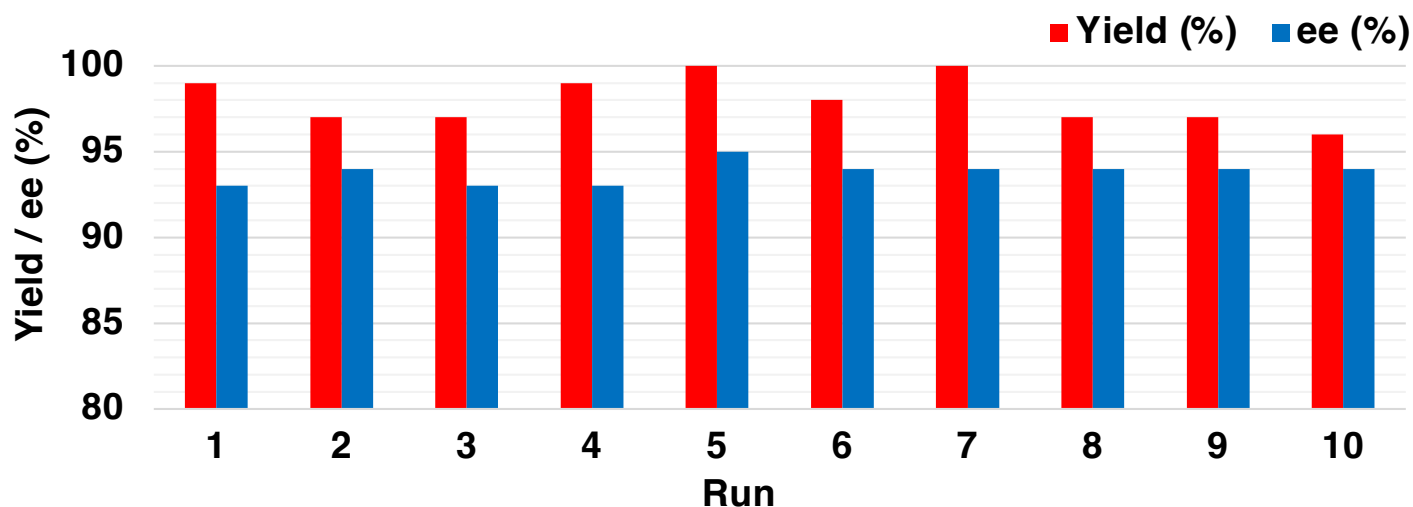
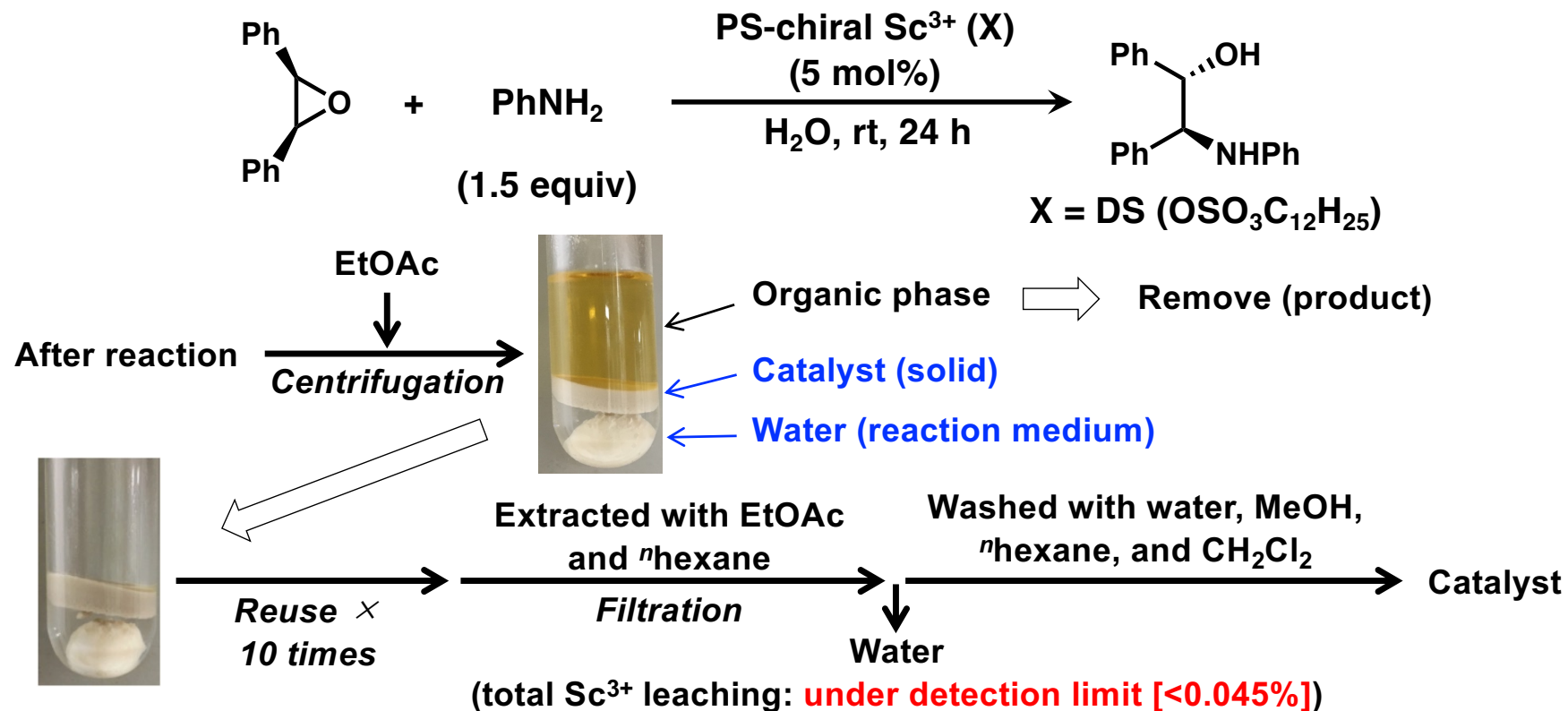
- ✓ How can you separate products from solvent?
- ✓ How can you suppress the catalyst deactivation?

⇒ Reactions in water may be suitable.

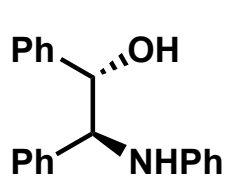
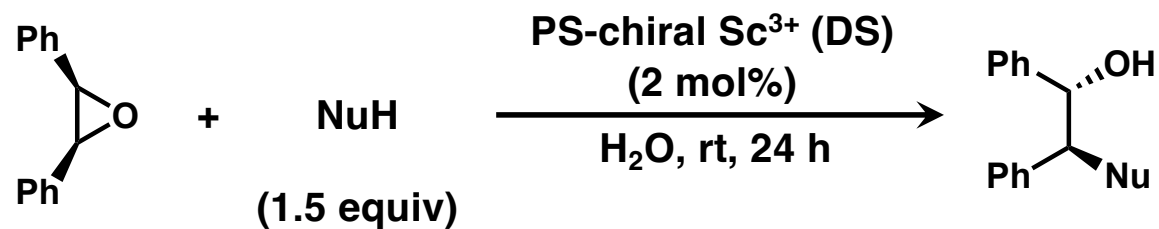




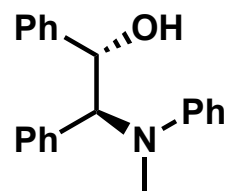
# Recycling of Catalyst-Solvent Couples



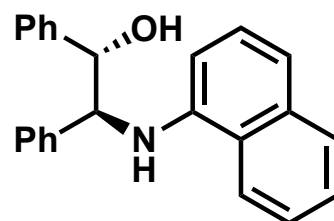
# Recycling of Catalyst-Solvent Couples



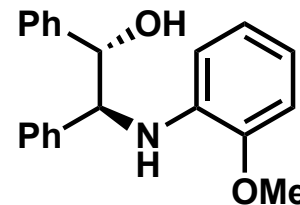
92% yield  
94% ee



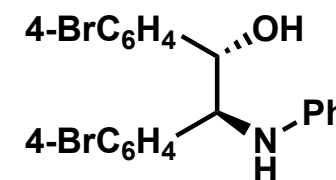
91% yield  
97% ee



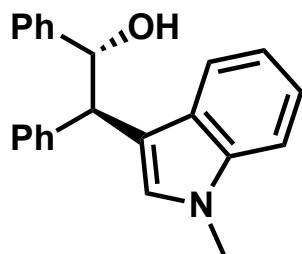
94% yield<sup>a</sup>  
87% ee



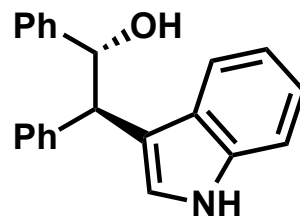
97% yield  
90% ee



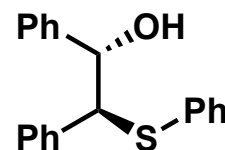
76% yield  
93% ee



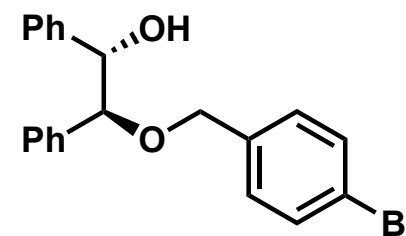
78% yield<sup>b</sup>  
89% ee



81% yield<sup>b,c</sup>  
90% ee



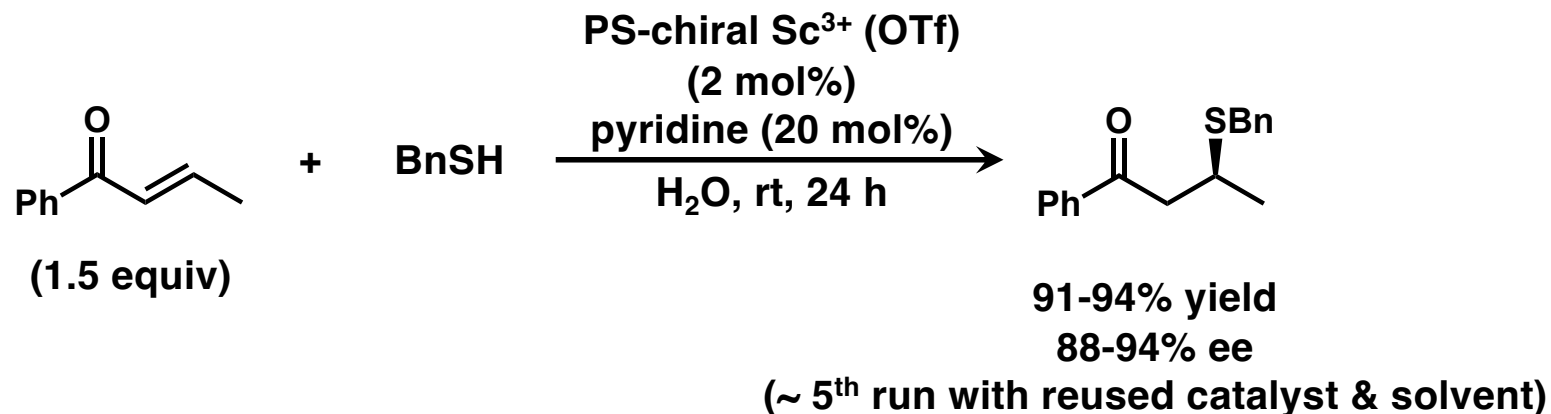
78% yield<sup>b,c</sup>  
88% ee



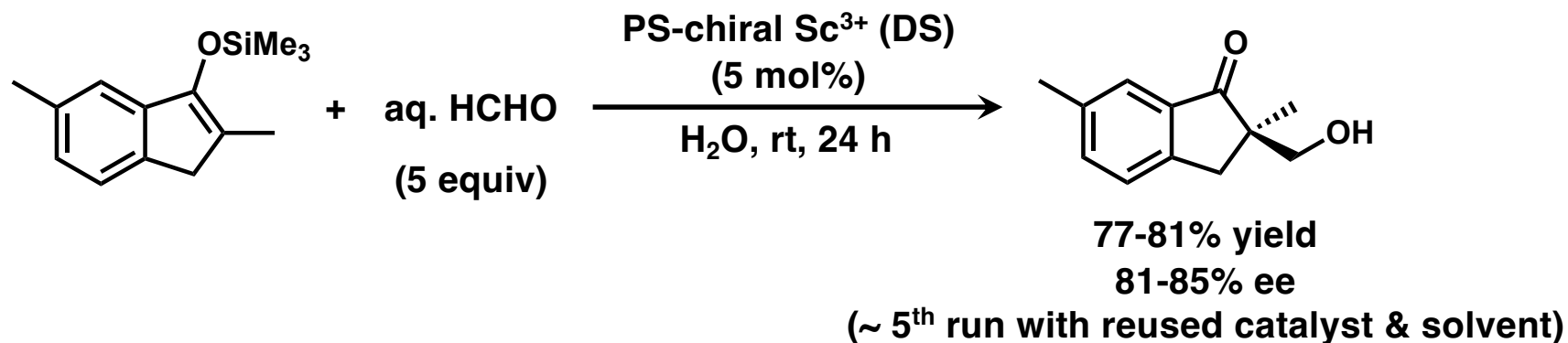
53% yield<sup>a,c</sup>  
70% ee

<sup>a</sup> Run at 40°C. <sup>b</sup> Run at 5 mol% catalyst loading for 48 h. <sup>c</sup> Run with NuH (3 equiv) for 48 h.

# Recycling of Catalyst-Solvent Couples

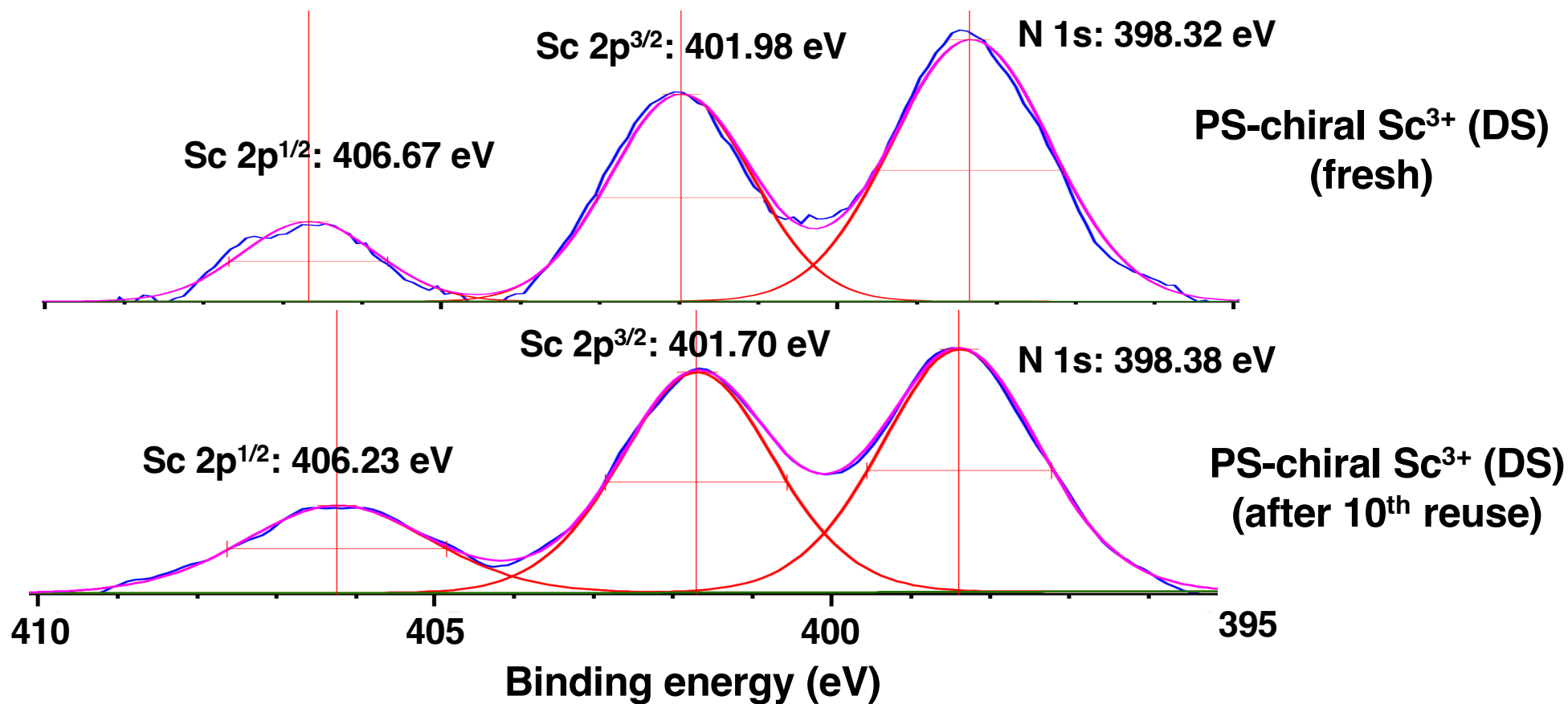
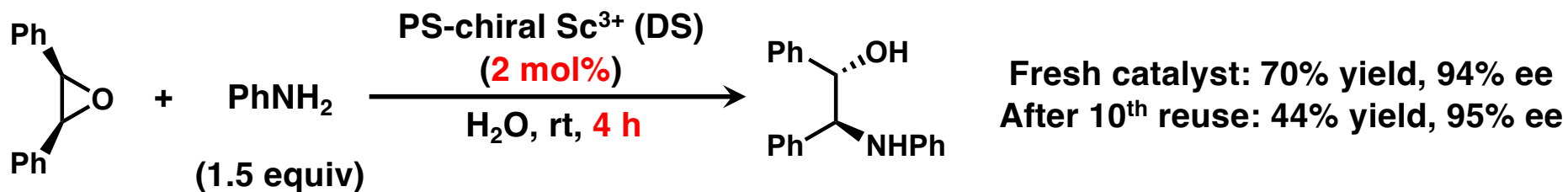


- Total Sc<sup>3+</sup> leaching: 1.71%
- Pyridine was not added from the second run onward.



- Total Sc<sup>3+</sup> leaching: 0.035%
- Three equiv. of aq. HCHO were added from the second run.

# Catalyst Deactivation

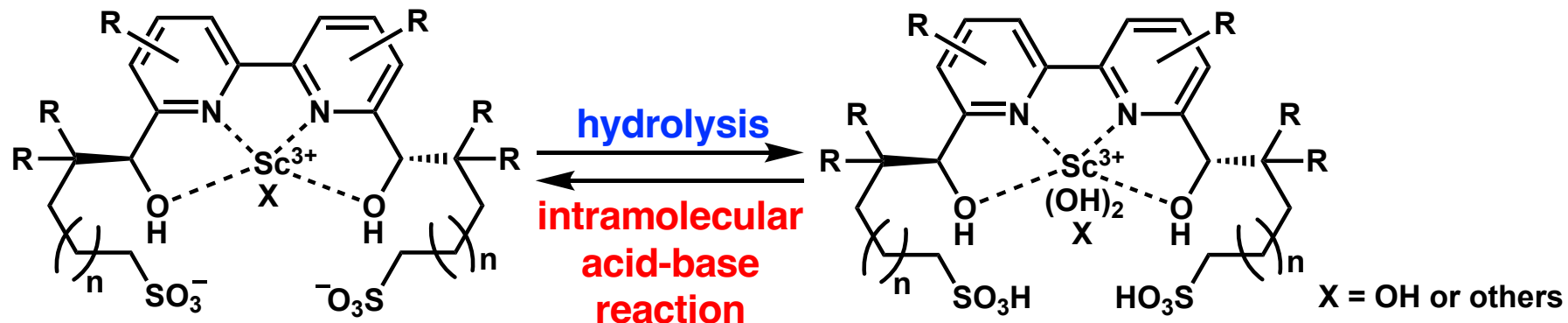


➤ Electron density of Sc<sup>3+</sup> decreased after the 10<sup>th</sup> reuse.

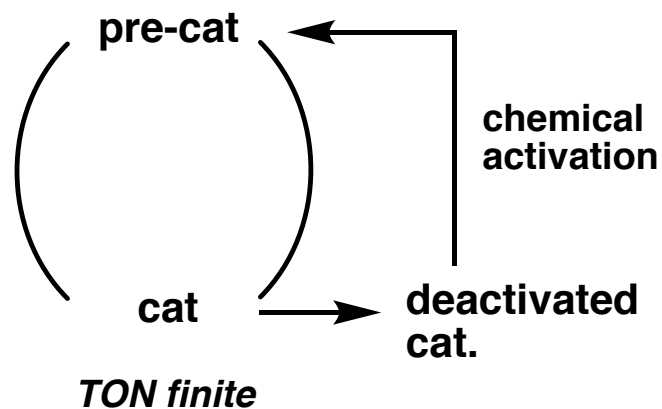
# Anionic Chiral Ligand

- **Intramolecular acid-base reaction** may avoid the deactivation?

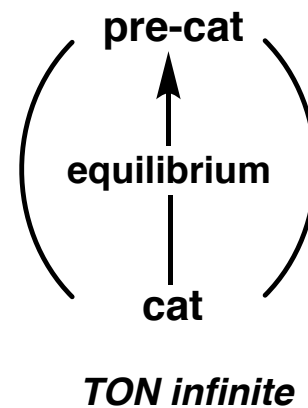
The proprio motu mechanism = “self-repairing”



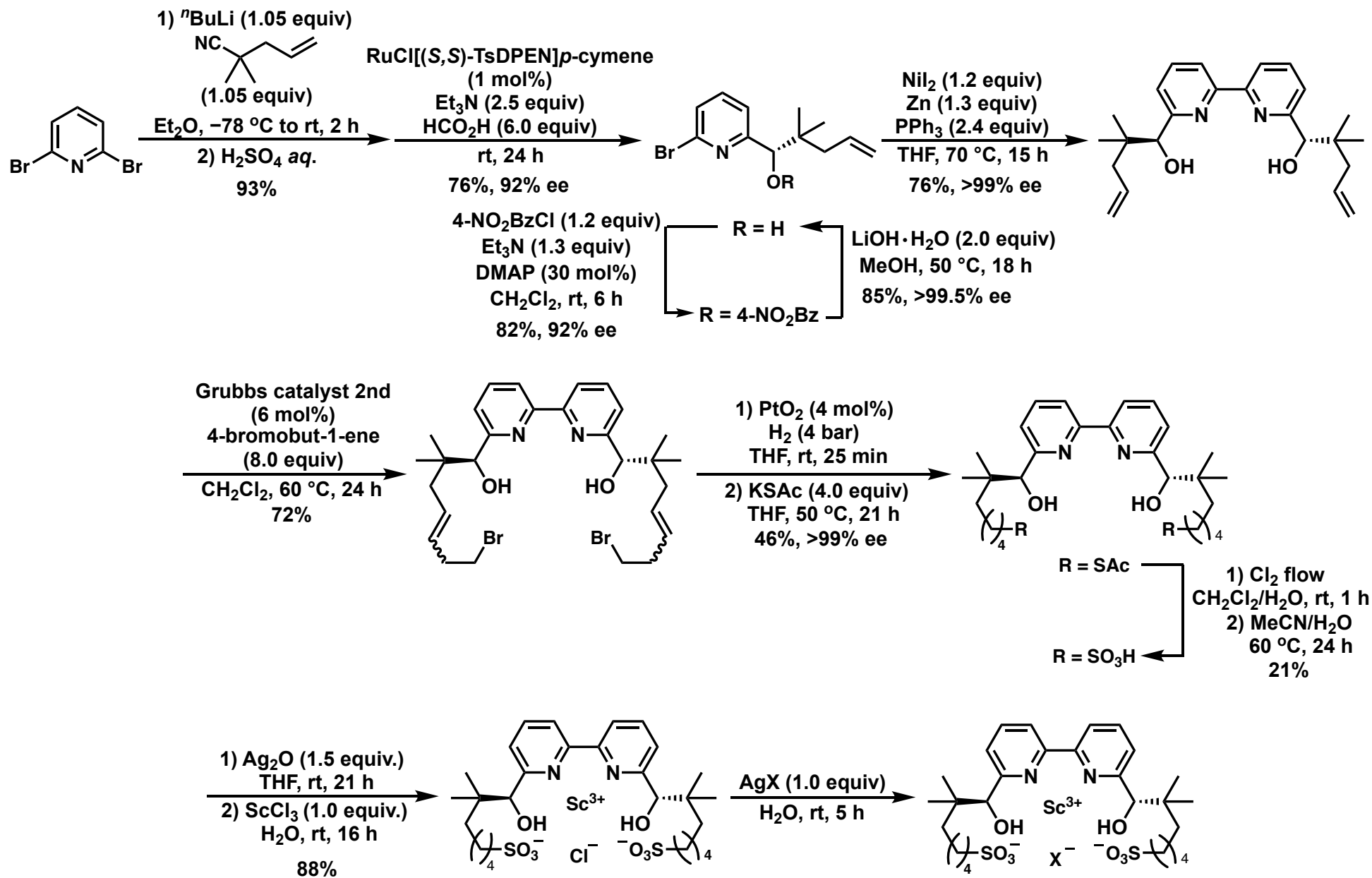
General catalyst  
“regeneration”



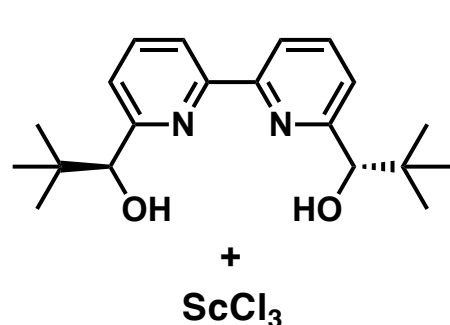
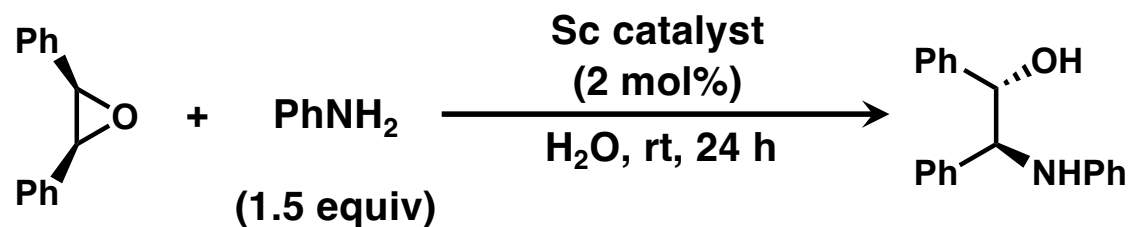
“Self-repairing”



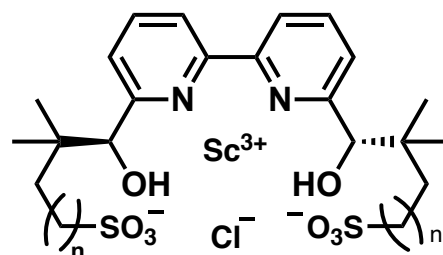
# Synthesis of Anionic Chiral Ligand



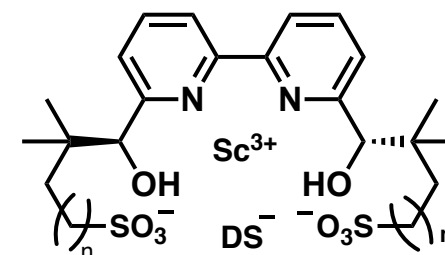
# Evaluation of Catalytic Activity



6% yield, 81% ee



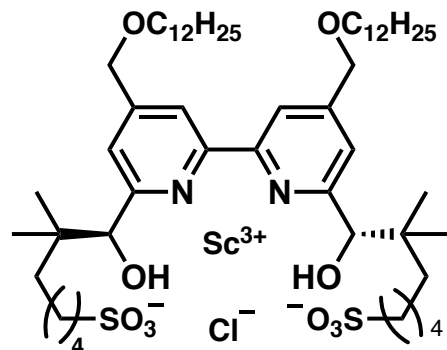
n = 2: 21% yield, 27% ee  
n = 4: 18% yield, 86% ee  
n = 5: 6% yield, 86% ee



DS = OSO<sub>3</sub>C<sub>12</sub>H<sub>25</sub>

n = 2: 33% yield, 35% ee  
n = 4: 37% yield, 73% ee

## ■ Revised structure: introduction of alkyl chain

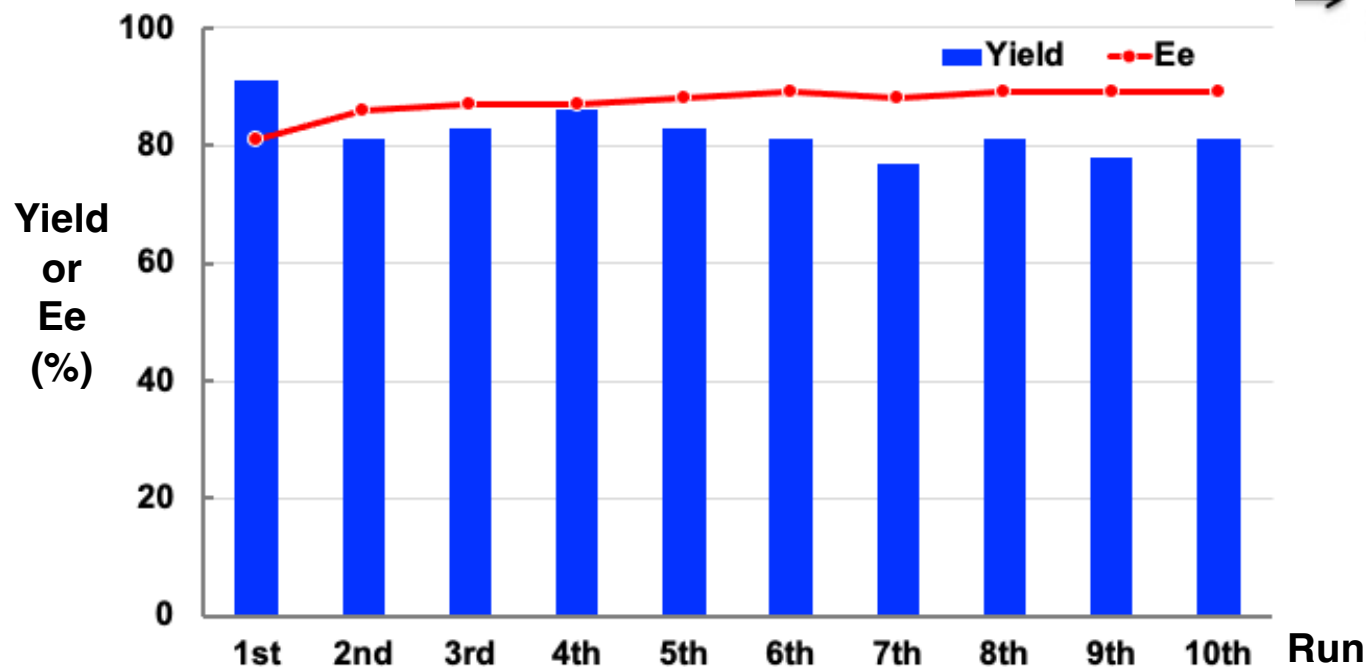
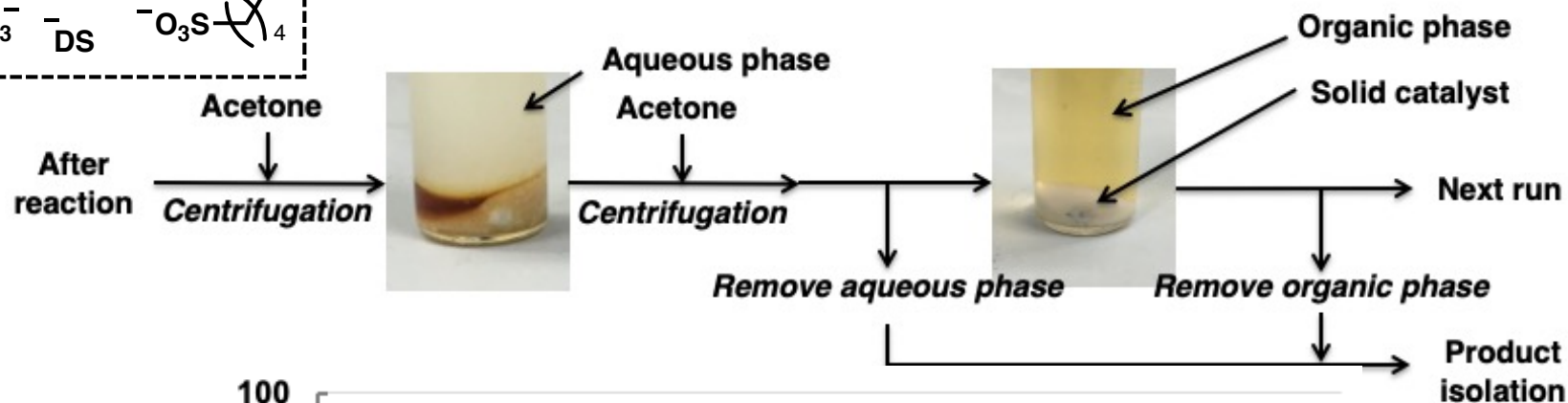
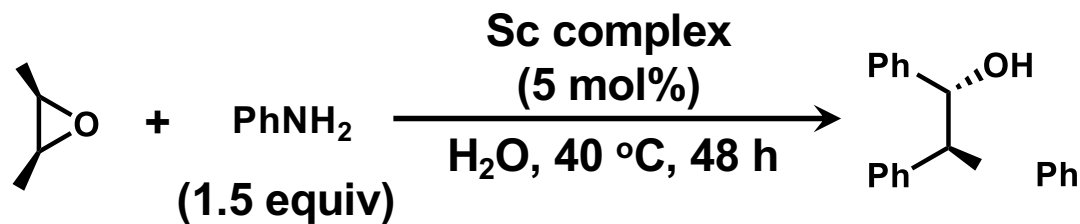
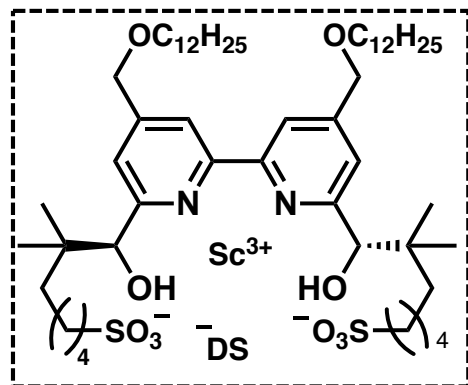


36% yield, 76% ee

5 mol%: **77% yield, 90% ee**

- ✓ Improved enantioselectivity
- ✓ Investigations to prove self-repairing nature are now in progress.

# Reusability Experiments

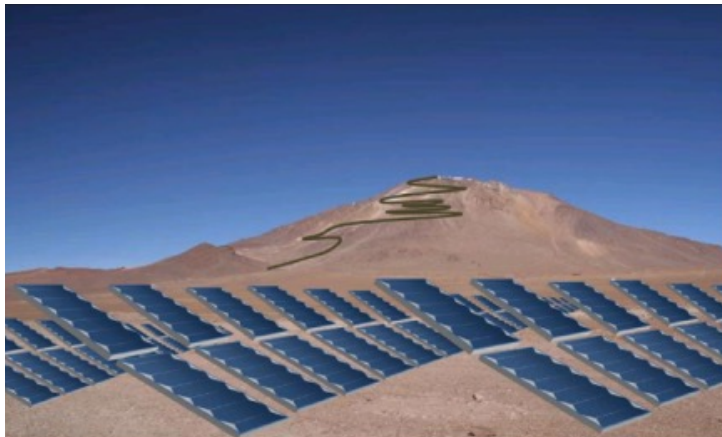




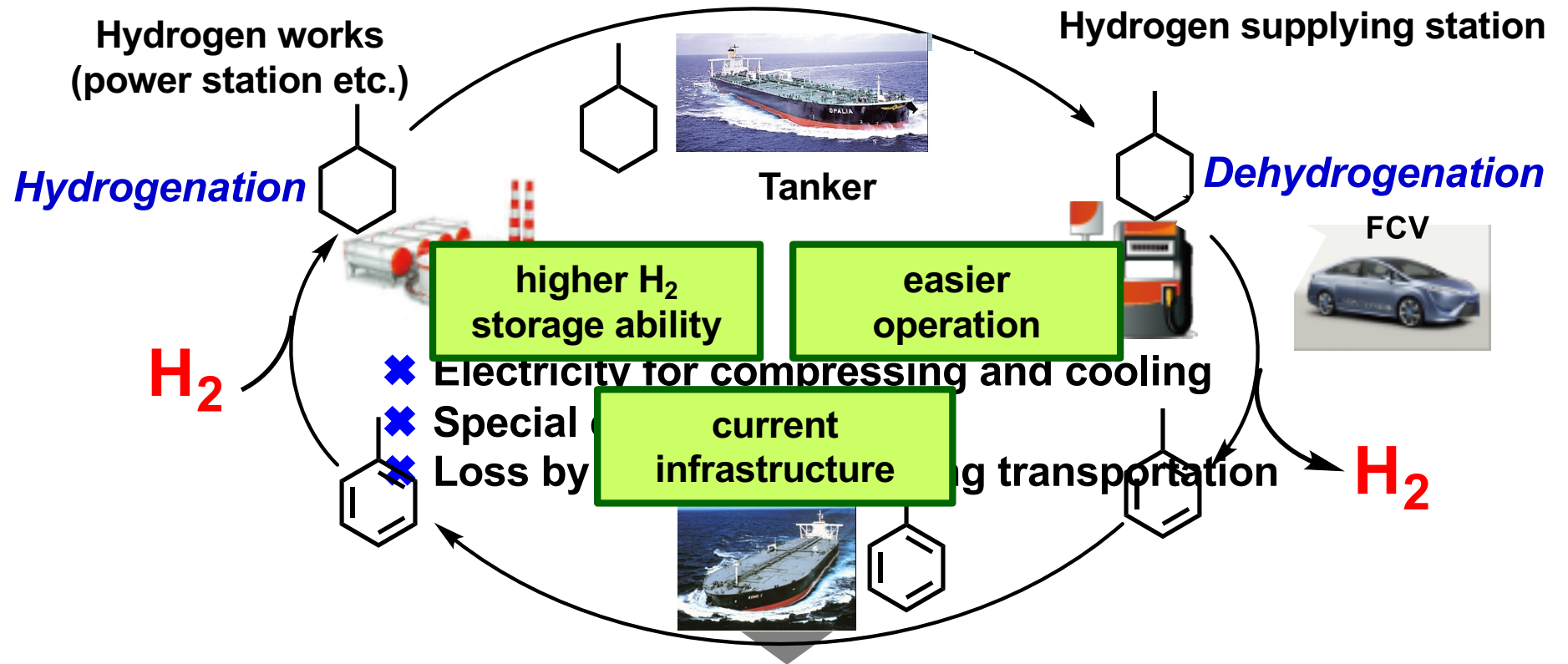
# *Alternative Energy Resources of Fossil Fuels*



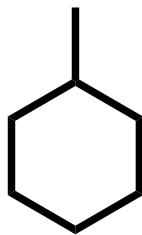
*Fossil fuels*



# Hydrogen Transport and Supply System

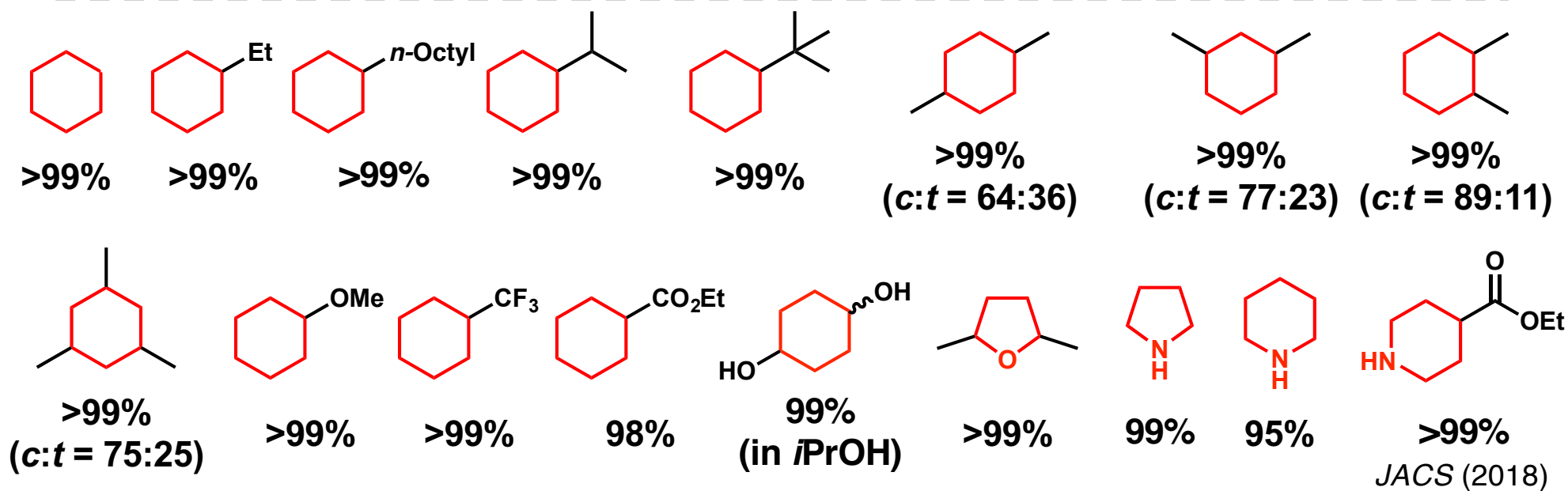
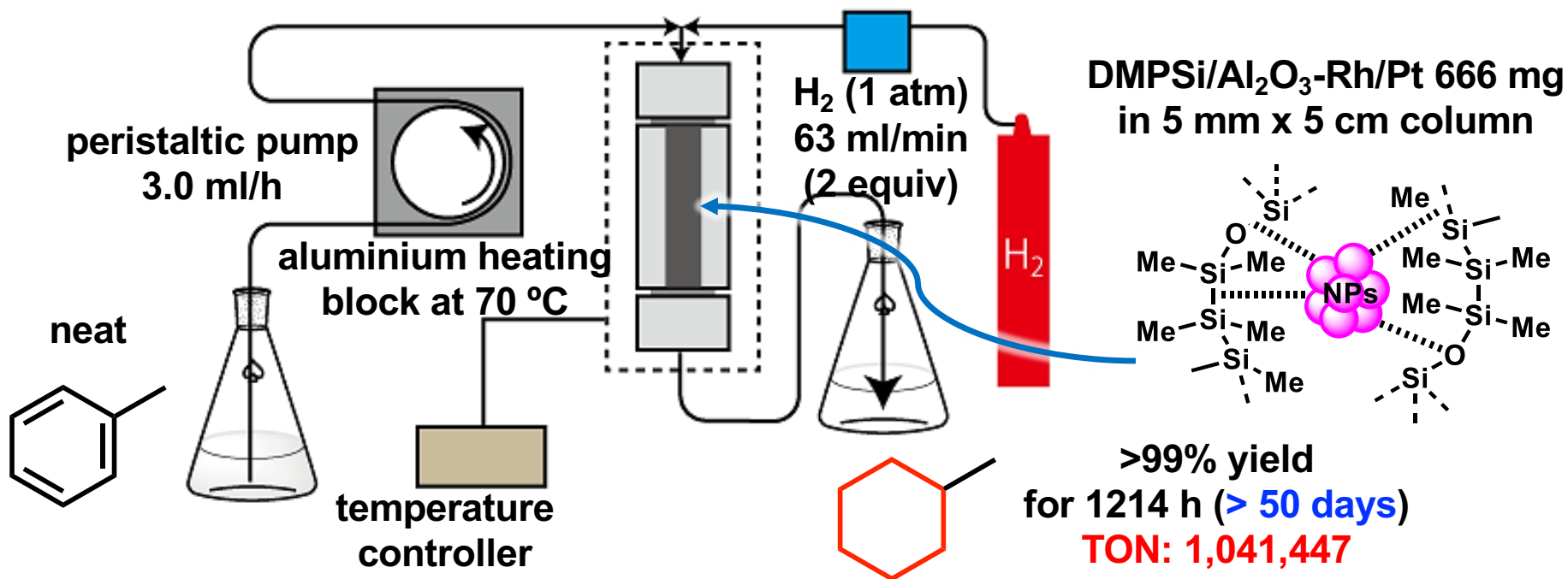


*organic hydride as a hydrogen reservoir*



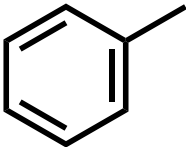
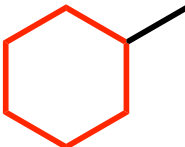
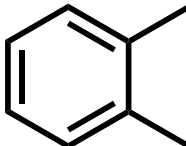
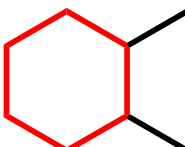
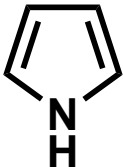
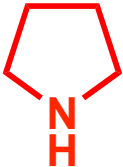
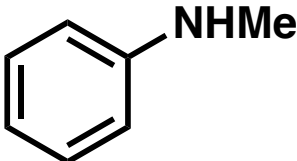
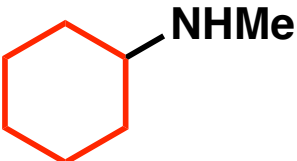
methylcyclohexane  
(MCH)

# Hydrogenation Using Continuous-flow Reactor



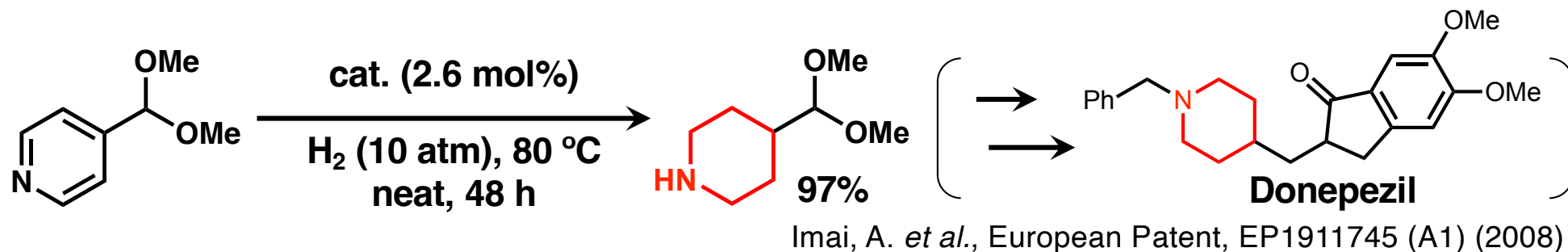
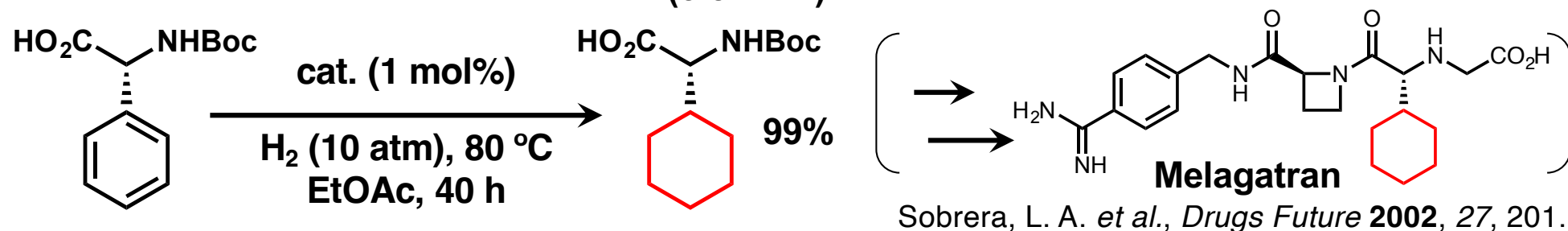
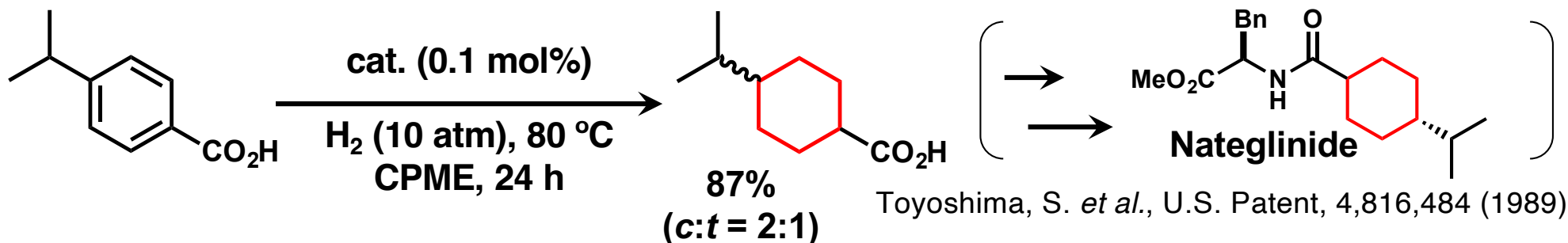
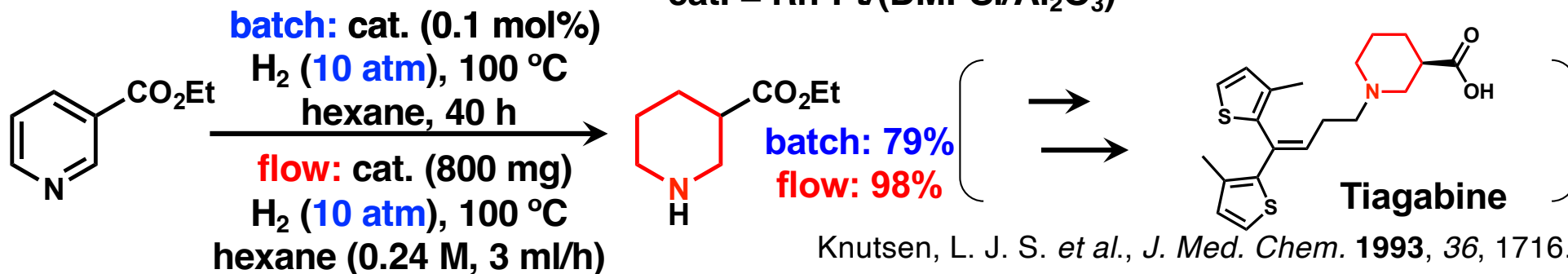
# Batch System vs. Flow System in Kinetic Study

Conditions (for both batch and flow): 50 °C, neat, H<sub>2</sub> (1 atm)

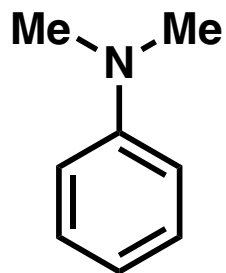
Substrate	Product	TOF (Batch)	TOF (Flow)	TOF (Flow) / TOF (Batch)
		604 h <sup>-1</sup>	3390 h <sup>-1</sup>	5.6
		90 h <sup>-1</sup>	681 h <sup>-1</sup>	7.6
		41 h <sup>-1</sup>	1118 h <sup>-1</sup>	27
		43 h <sup>-1</sup>	1507 h <sup>-1</sup>	25

# Application to API Precursor Syntheses

cat. = Rh-Pt/(DMPSi/Al<sub>2</sub>O<sub>3</sub>)

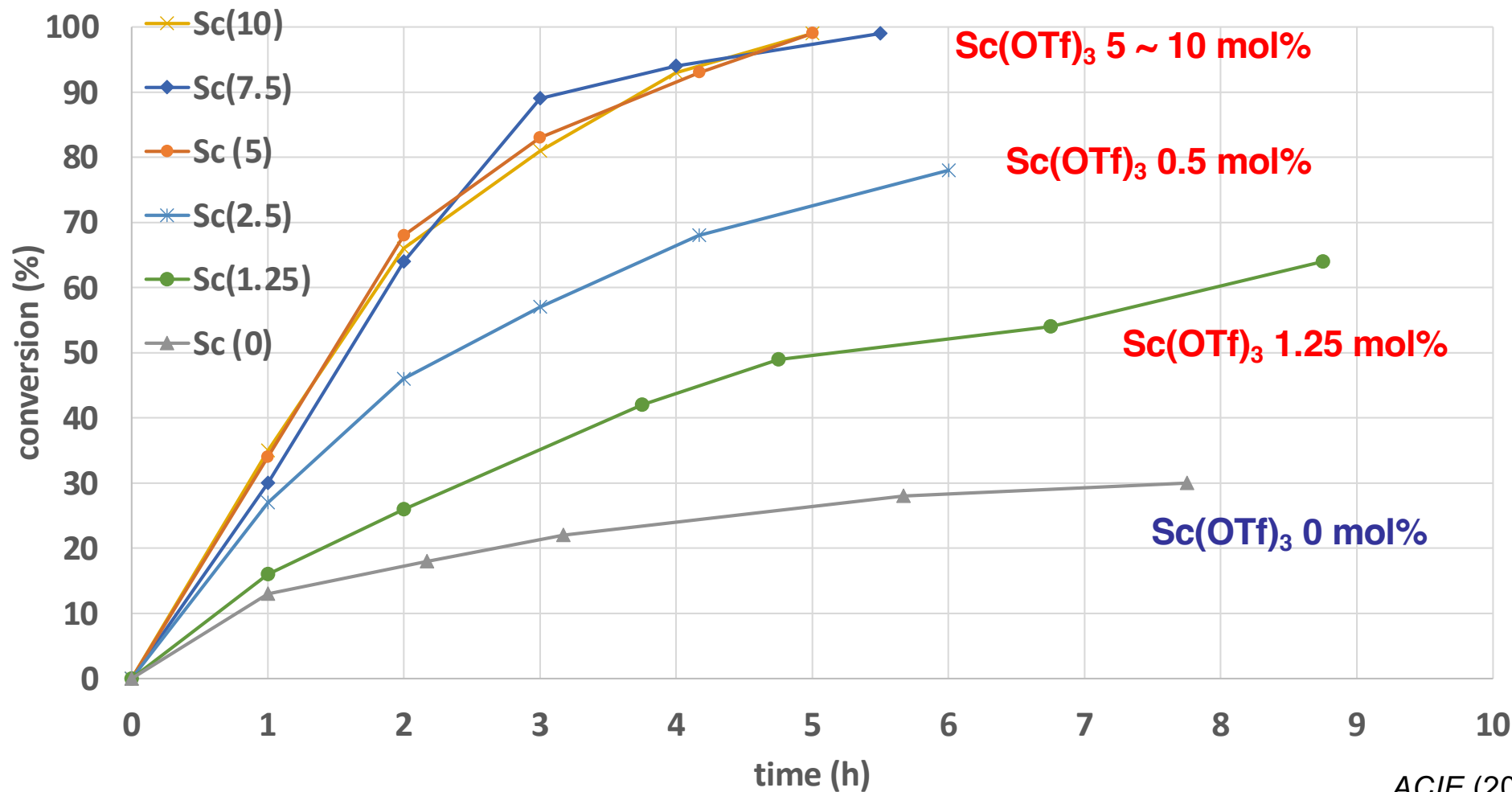
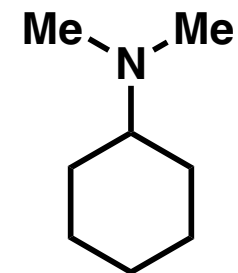


# With $Sc(OTf)_3$



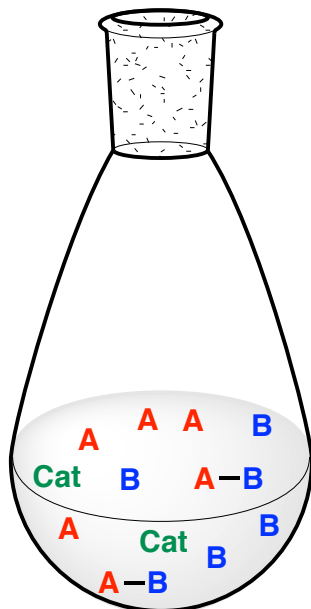
Rh-Pt/DMPSi- $Al_2O_3$  (Rh: 0.56, Pt: 0.28 mol%)  
 $Sc(OTf)_3$  (x mol%)

methylcyclohexane, 50 °C,  $H_2$  (1 atm)



# Batch and Flow Methods

## Batch Method

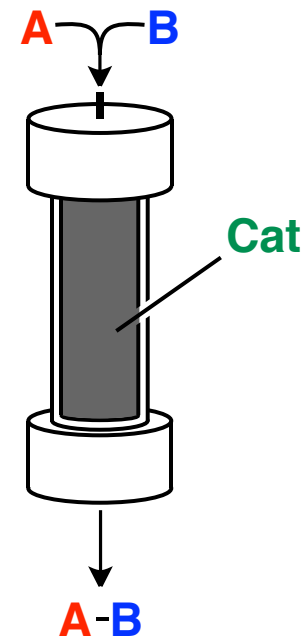


All materials are charged before the start of processing and discharged after processing



**Fine Chemicals**  
**Organic Synthesis**

## Flow Method

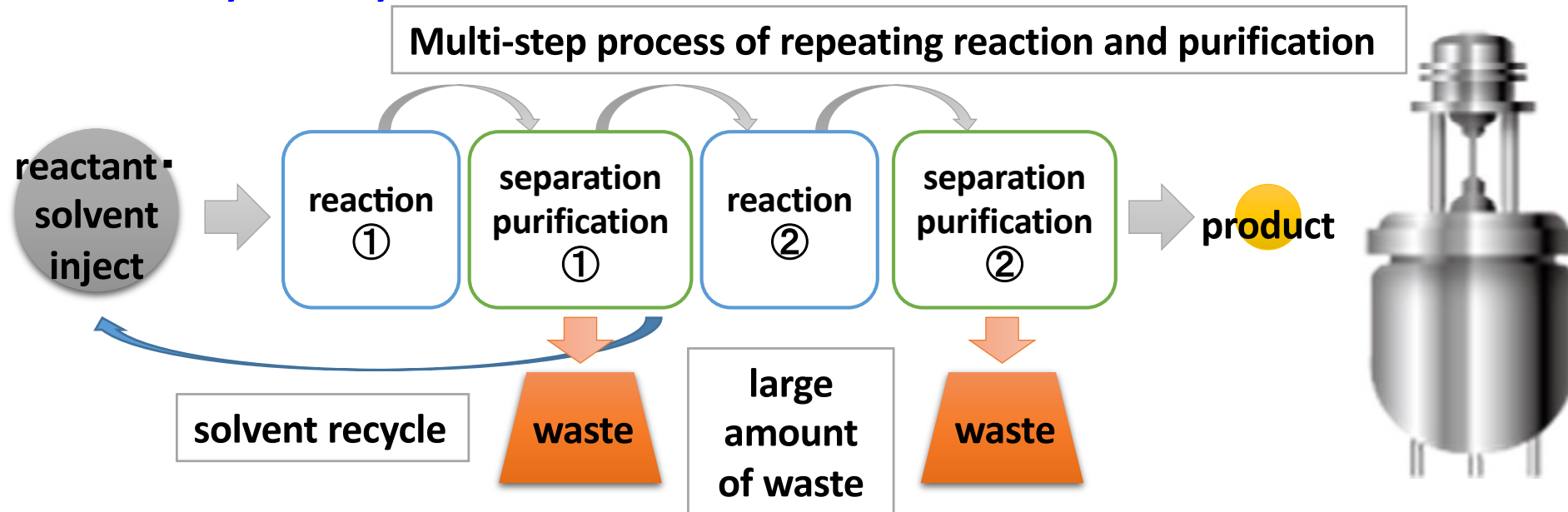


Materials are simultaneously charged and discharged

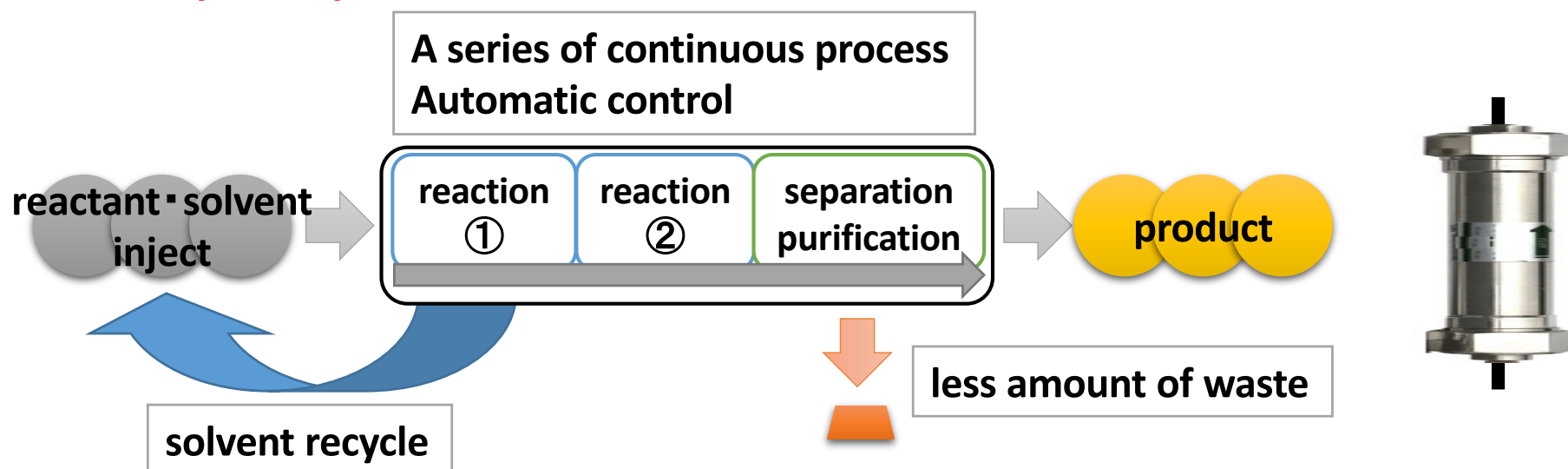


**Chemical Industry**  
**Bulk Chemicals**

## Production by batch system



## Production by flow system





# Efficiency

- **High energy productivity**
- **Saving space, energy, and time**
- **“Just in time” production**
- **Automation**
- **Unique reactivity and selectivity**
- **Avoidance of product inhibition**
- **Multistep flow system**

# ***Advantages of Flow Methods***

**Environment**

**Efficiency**

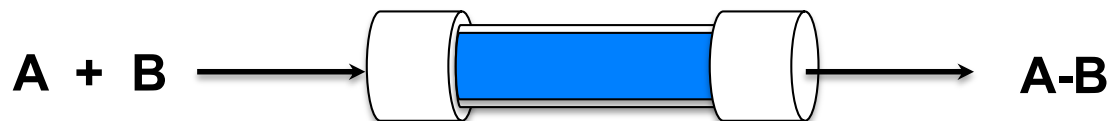
**Safety**

***Flow methods are suitable for  
Sustainable Society***

# Types of Flow Reactions

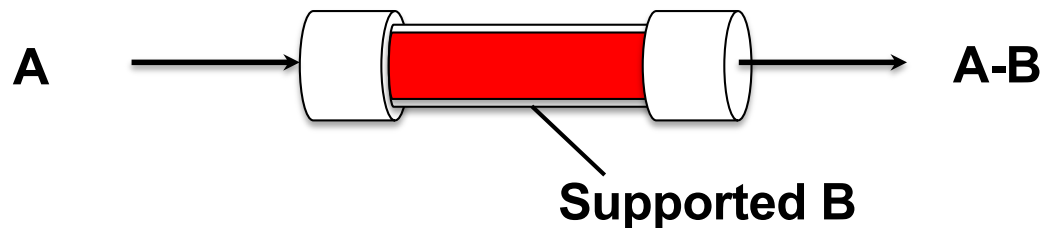
## ■ No Catalyst

*Type I*



## ■ Supported Reagent

*Type II*



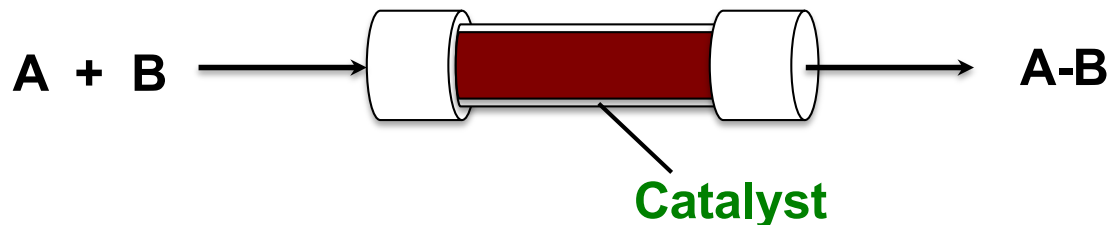
## ■ Homogeneous Catalyst

*Type III*

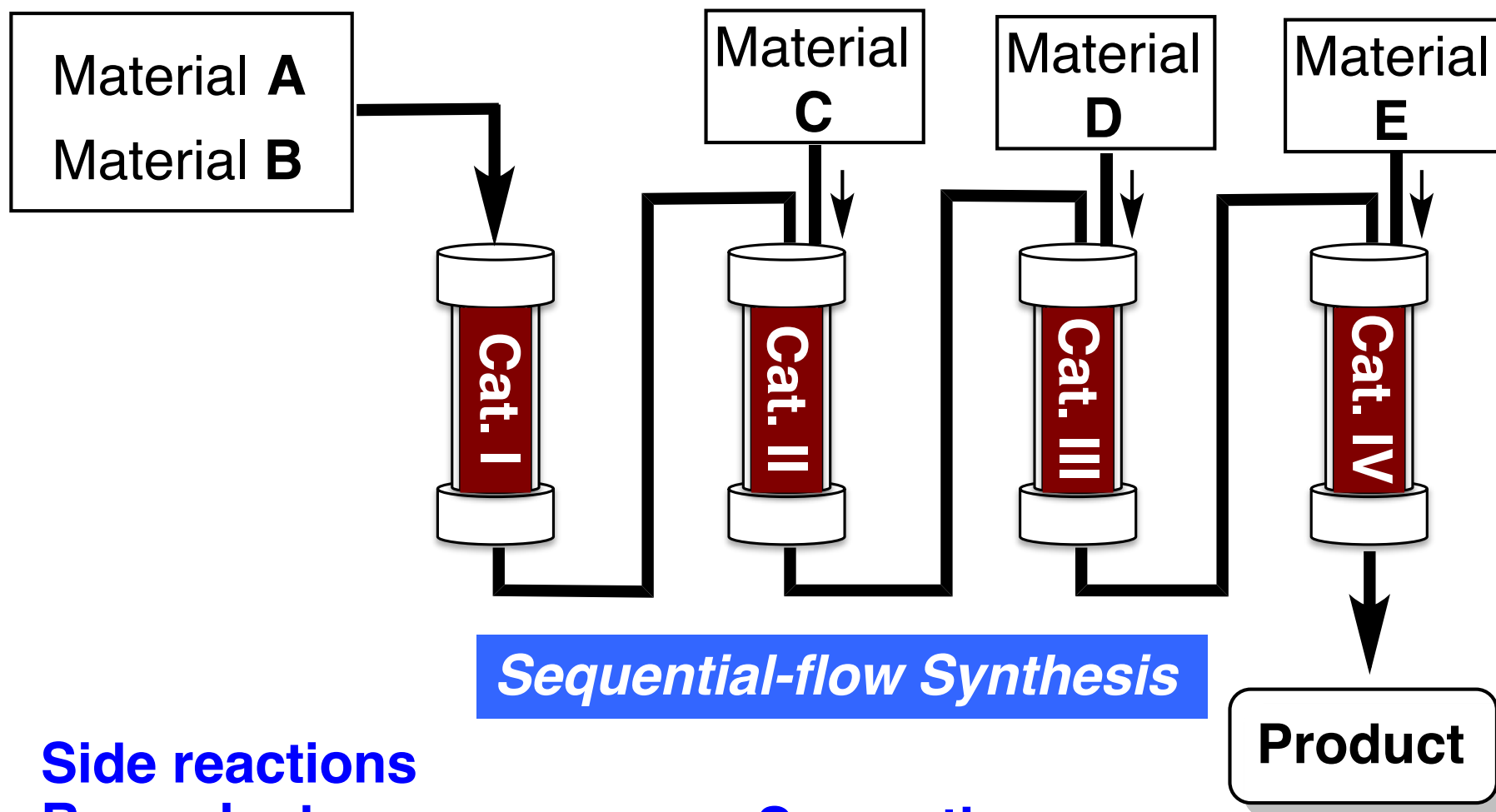


## ■ Heterogeneous Catalyst

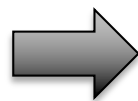
*Type IV*



# *Ideal Continuous-flow Synthesis*



Side reactions  
Byproducts  
Unreactive materials  
Excess reagents, etc



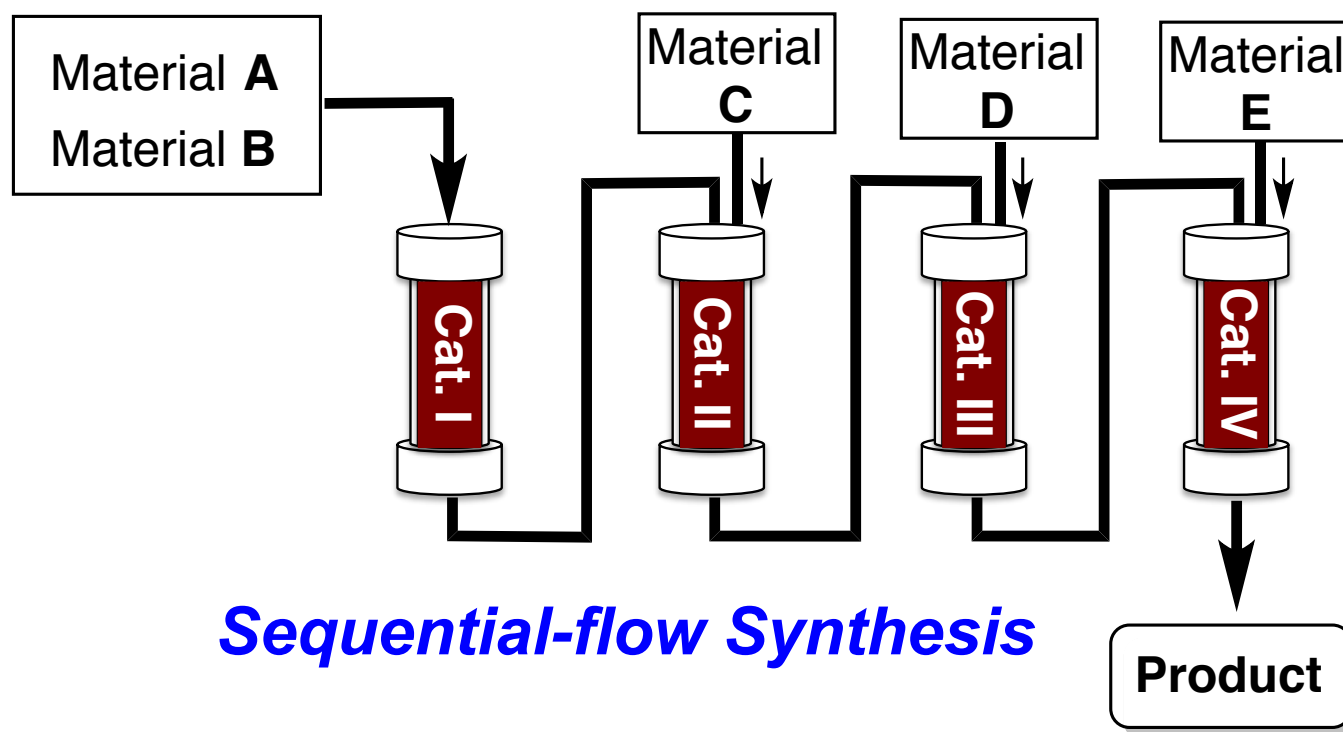
Separation  
Purification

*Only at the Final Stage!*

# *Our Goal*

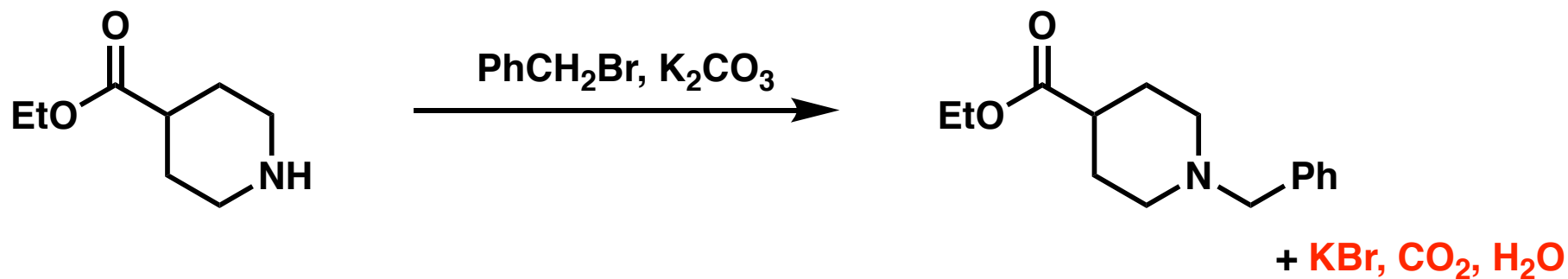
## Continuous-flow Synthesis of Fine Chemicals

- *New Synthetic Methods for Continuous-Flow*
- *Addition Reactions, Condensation Reactions*
- *New Heterogeneous Catalysts*

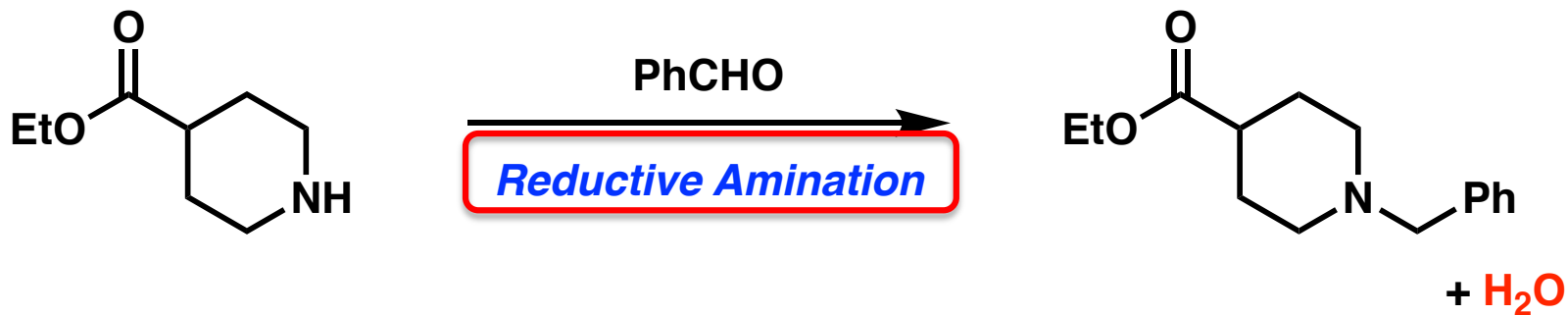


# *C–N Bond Formation*

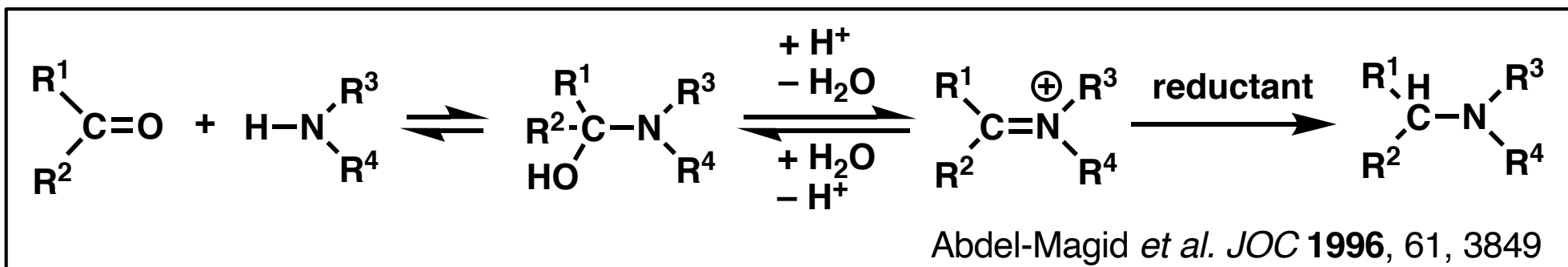
## Conventional route



## New route



# Reductive Amination



- **Direct Reductive Amination (*carbonyl* DRA)**

Not *stepwise* or *indirect* reaction (no imine or iminium intermediate)

- Reductant

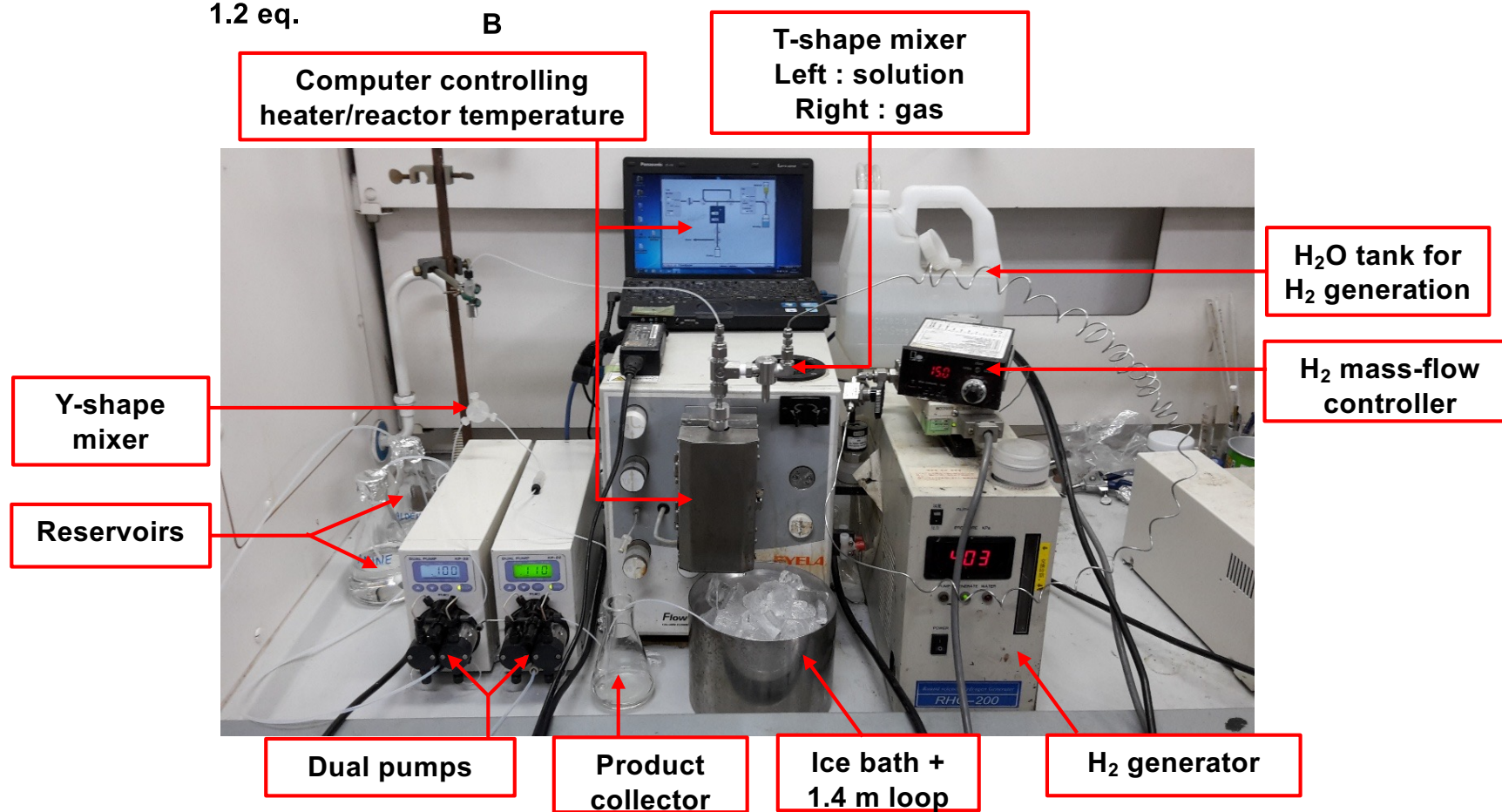
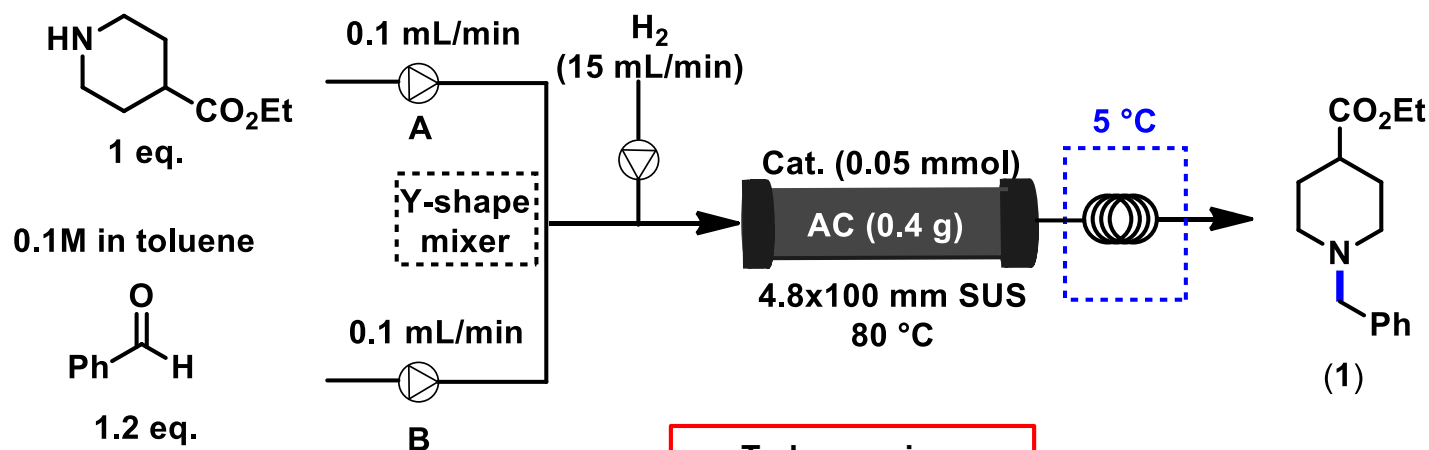
- ✓ **Catalytic hydrogenation *in flow***

- ✓ NaBH<sub>3</sub>CN ···· successful in batch

- Carbonyl DRA with H<sub>2</sub> is very limited

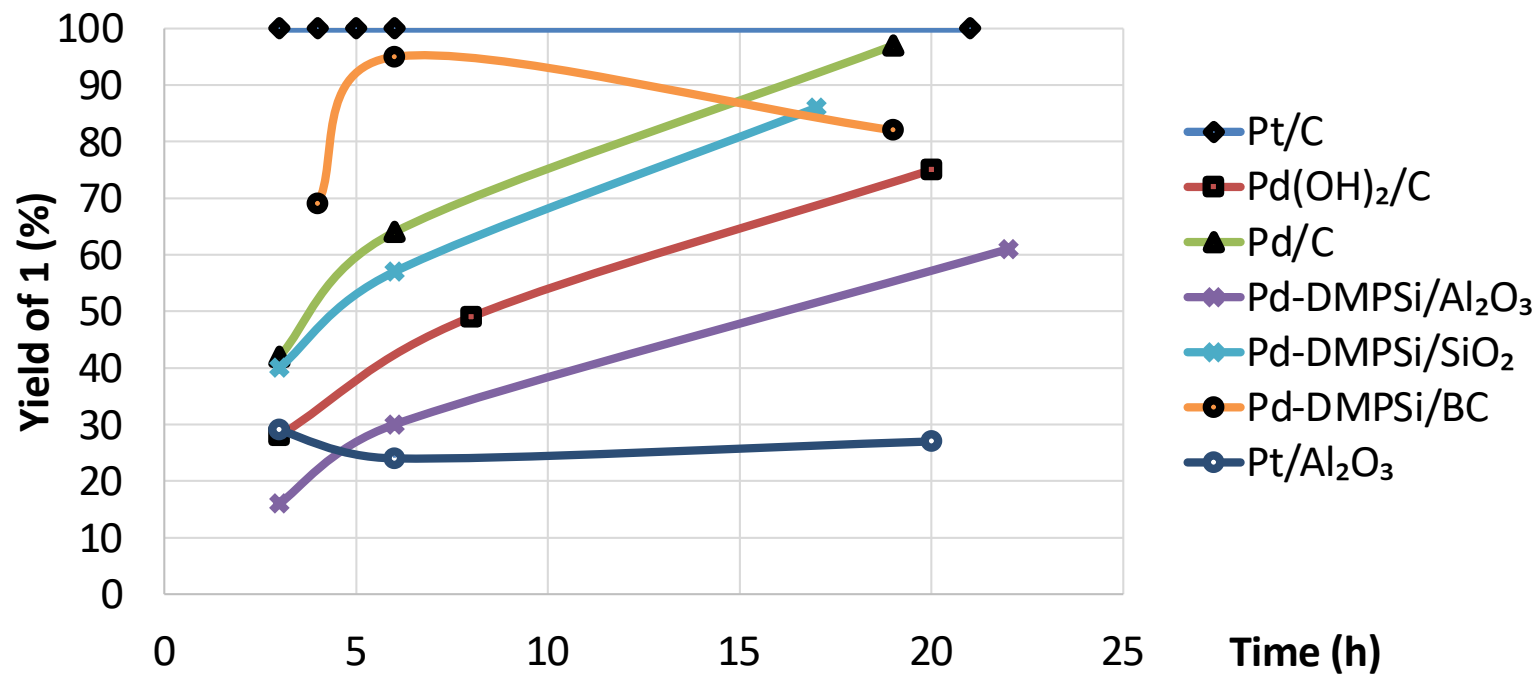
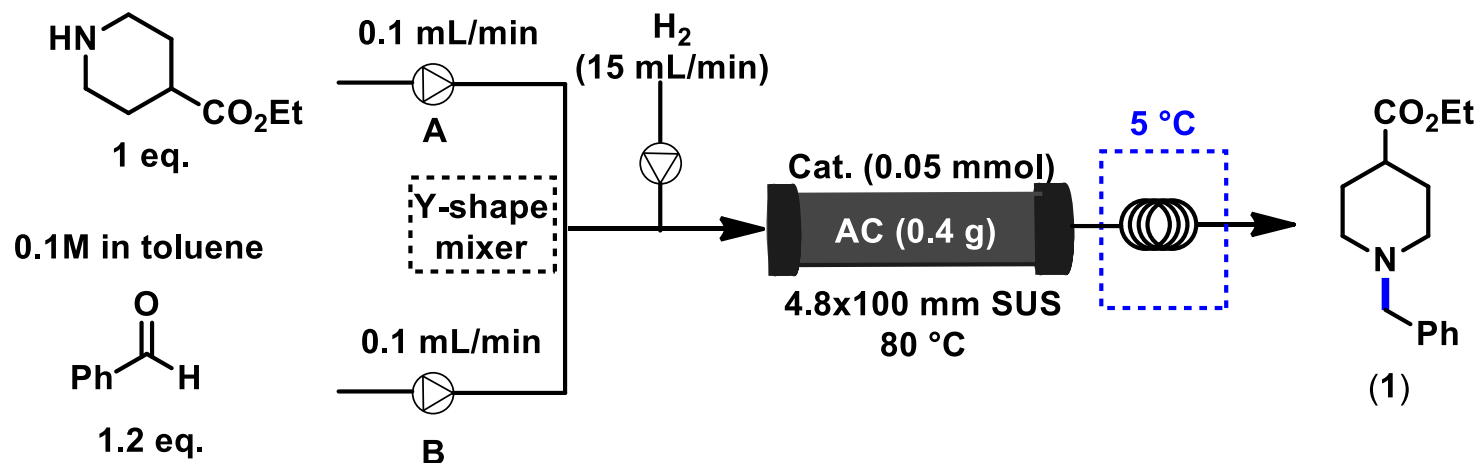
- DRAs starting from nitrile, nitrobenzene, pyridines with H<sub>2</sub> in flow; Williams (2013), Shirkhanyan (2017), Bukhtiyarov (2015, 2016, 2017), Kappe (2017)

# Direct Reductive Amination in Flow: Set-up

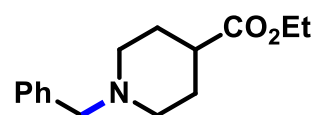
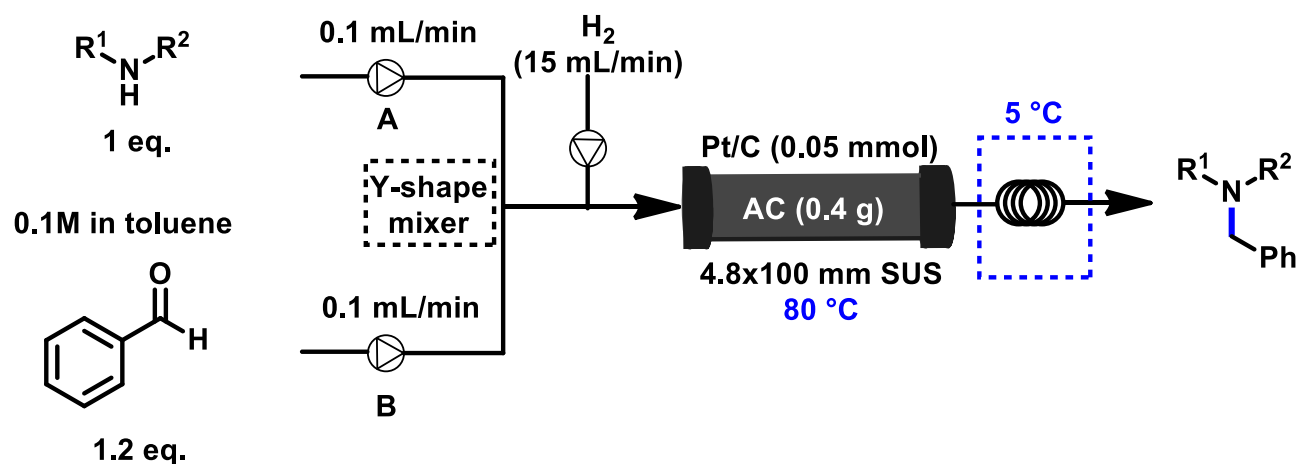




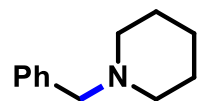
# Screening of Catalysts



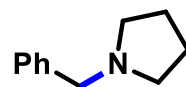
# Substrate Scope of Secondary Amines



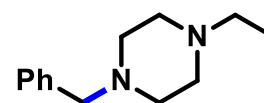
Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 3.9 kg/(L.day)



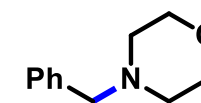
97-99%  
TOF : 23.5 h<sup>-1</sup>  
STY: 2.7 kg/(L.day)



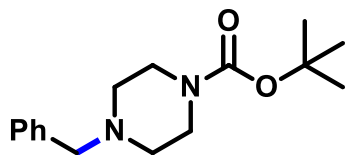
93-98%  
TOF : 23 h<sup>-1</sup>  
STY: 2.45 kg/(L.day)



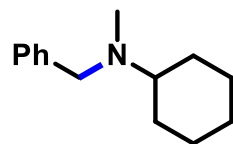
94-100%  
TOF: 23.3 h<sup>-1</sup>  
STY: 3.2 kg/(L.day)



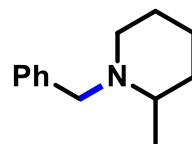
Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 2.8 kg/(L.day)



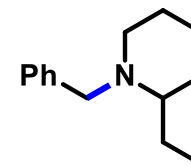
Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 4.4 kg/(L.day)



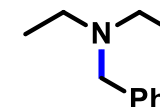
Quant. (100 °C)  
TOF: 24 h<sup>-1</sup>  
STY: 3.2 kg/(L.day)



97-100% (100 °C)  
TOF : 24 h<sup>-1</sup>  
STY: 3.0 kg/(L.day)



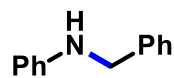
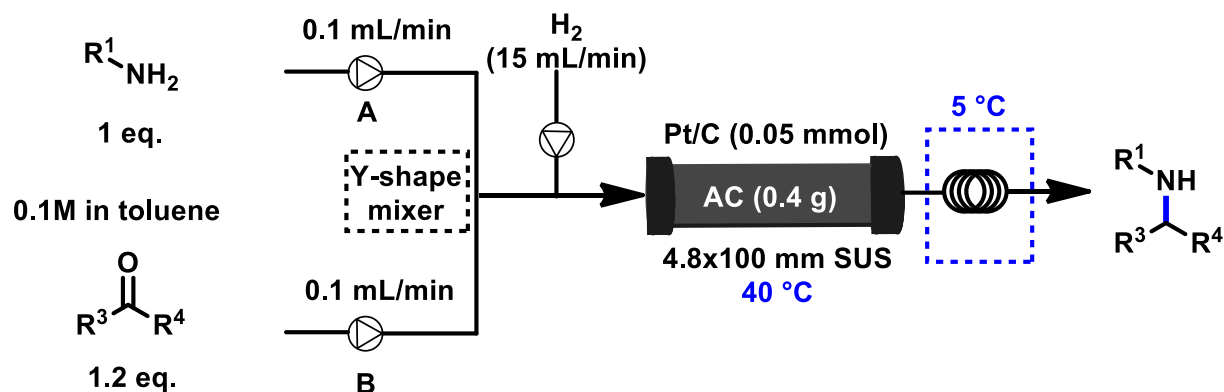
Quant. (100 °C)  
TOF : 24 h<sup>-1</sup>  
STY: 3.2 kg/(L.day)



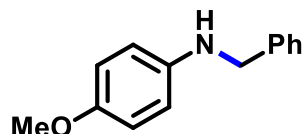
98-100% (100 °C)  
TOF : 23.8 h<sup>-1</sup>  
STY: 2.6 kg/(L.day)

Yield was calculated with <sup>1</sup>H NMR using 1,2,4,5-tetramethylbenzene as internal standard, relying on three measurements from 3 to 24 h to provide accurate yields ranges during this period.

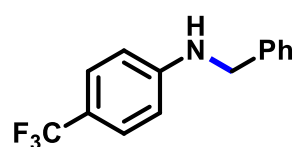
# Substrate Scope of Primary Amines



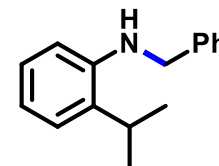
Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 2.9 kg/(L.day)



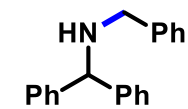
99-100%  
TOF: 23.9 h<sup>-1</sup>  
STY: 3.4 kg/(L.day)



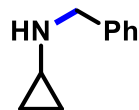
Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 4.0 kg/(L.day)



Quant. (60 °C)  
TOF: 22.4 h<sup>-1</sup>  
STY: 3.4 kg/(L.day)

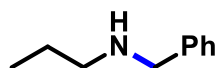


Quant.  
TOF: 24 h<sup>-1</sup>  
STY: 4.3 kg/(L.day)



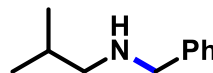
88-90%

\*10% of double benzylation  
TOF: 21.4 h<sup>-1</sup>  
STY: 2.1 kg/(L.day)



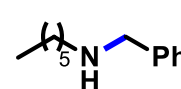
89-94% (AC: 0.2 g)

\*6-11% of double benzylation  
TOF: 22.6 h<sup>-1</sup>  
STY: 2.2 kg/(L.day)



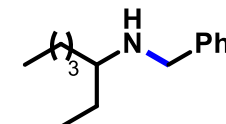
94-95% (AC: 0.2 g)

\*5-6% of double benzylation  
TOF: 22.7 h<sup>-1</sup>  
STY: 2.5 kg/(L.day)



97-99% (AC: 0.2 g)

\*1-3% of double benzylation  
TOF: 23.5 h<sup>-1</sup>  
STY: 3.0 kg/(L.day)

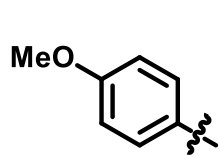
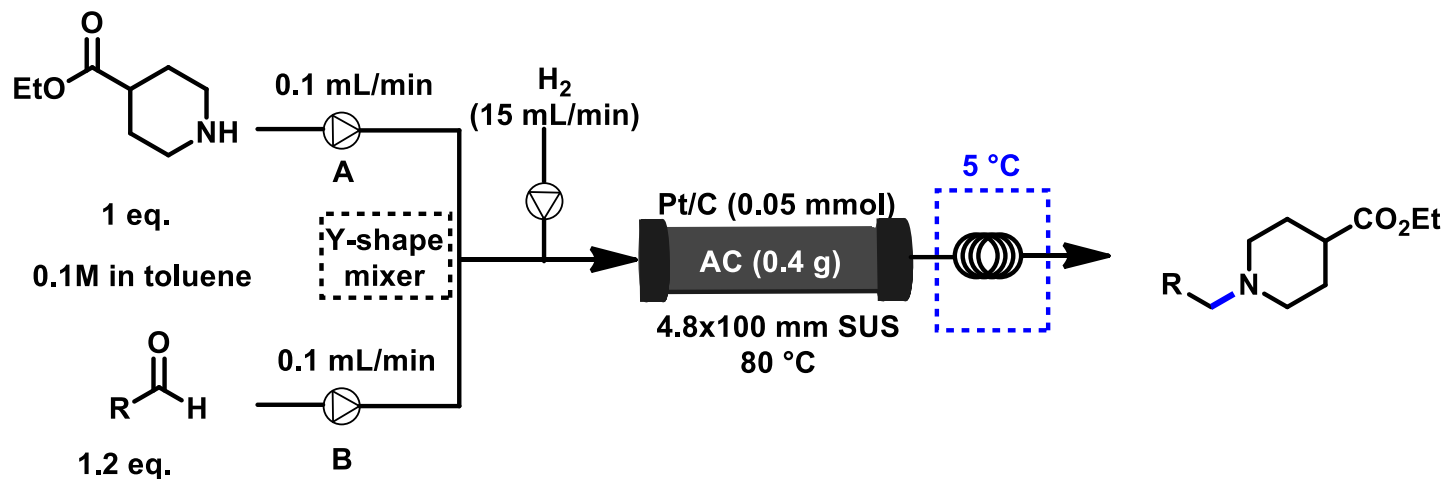


94-95% (AC: 0.2 g)

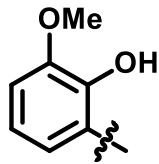
\*5-6% of double benzylation  
TOF: 22.7 h<sup>-1</sup>  
STY: 3.3 kg/(L.day)

Yield was calculated with <sup>1</sup>H NMR using 1,2,4,5-tetramethylbenzene as internal standard, relying on three measurements from 3 to 24 h to provide accurate yields ranges during this period.

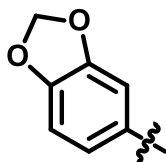
# Functional Group Tolerance



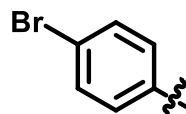
93-96%  
 TOF: 22.7 h<sup>-1</sup>  
 STY: 4.2 kg/(L.day)



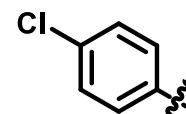
92-99%  
 TOF: 22.9 h<sup>-1</sup>  
 STY: 4.5 kg/(L.day)



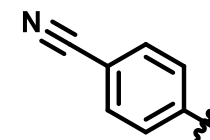
96-100%  
 TOF: 23.5 h<sup>-1</sup>  
 STY: 4.5 kg/(L.day)



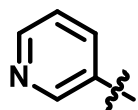
98-100%  
 TOF: 23.8 h<sup>-1</sup>  
 STY: 5.1 kg/(L.day)



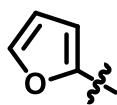
Quant.  
 TOF: 24 h<sup>-1</sup>  
 STY: 4.5 kg/(L.day)



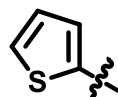
63-65%  
 TOF: 15.4 h<sup>-1</sup>  
 STY: 2.8 kg/(L.day)



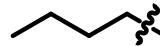
99-100% (100 °C)  
 TOF: 23.9 h<sup>-1</sup>  
 STY: 3.9 kg/(L.day)



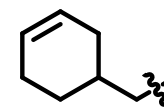
88-91% (100 °C)  
 TOF: 21.5 h<sup>-1</sup>  
 STY: 3.4 kg/(L.day)



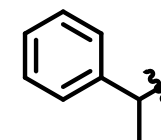
90-91% (100 °C)  
 TOF: 21.7 h<sup>-1</sup>  
 STY: 3.6 kg/(L.day)



Quant. (60 °C)  
 TOF: 24 h<sup>-1</sup>  
 STY: 3.4 kg/(L.day)



Quant. (60 °C)  
 TOF: 24 h<sup>-1</sup>  
 STY: 4.0 kg/(L.day)



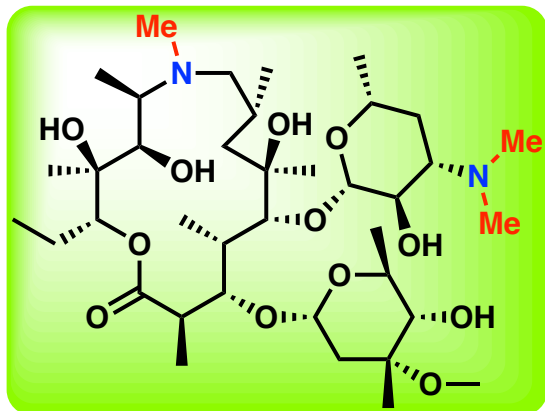
87% (140 °C)  
 TOF: 20.9 h<sup>-1</sup>  
 STY: 3.6 kg/(L.day)

Yield was calculated with <sup>1</sup>H NMR using 1,2,4,5-tetramethylbenzene as internal standard, relying on three measurements from 3 to 24 h to provide accurate yields ranges.

# N-Methylation

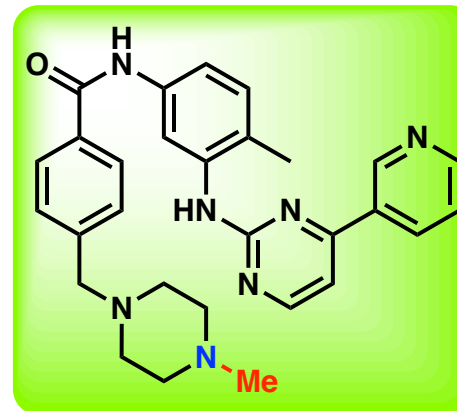
## ■ N-Methylation reaction of amines

- Surfactants, pesticides, medical intermediates, and so on

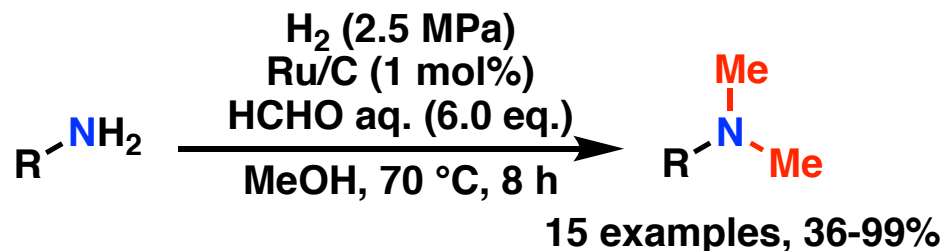


Azithromycin  
Highly effective for  
COVID-19

Imatinib  
\$ 1.561 Billion  
(2018)  
Anticancer



## ■ Reported example using H<sub>2</sub> and heterogeneous catalyst



- Solubility of HCHO
- × Very high pressure of H<sub>2</sub>

Ma L. *et al.* *Green Chem.* 2020, 22, 7387.

Ma L. *et al.* *ACS Omega* 2021, 6, 22504.

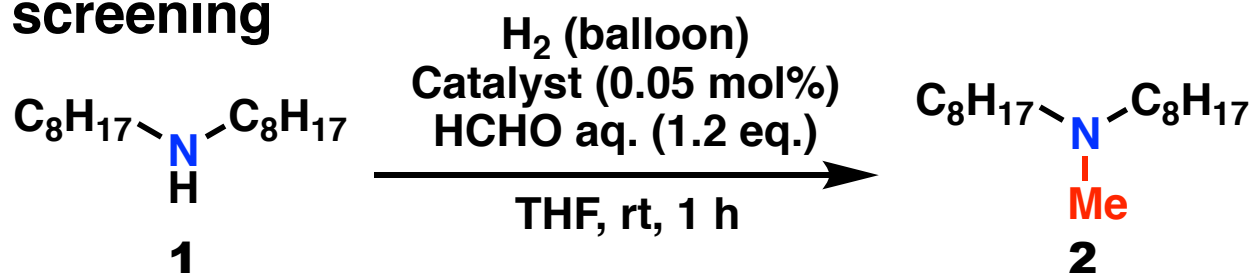
- Difficult to apply to continuous-flow system
- More active hydrogenation catalysts

### Research goal

Development of N-methylation of amines using HCHO aq., H<sub>2</sub> and heterogeneous catalysts under mild flow conditions

# Optimization under Batch Conditions

## ■ Catalyst screening

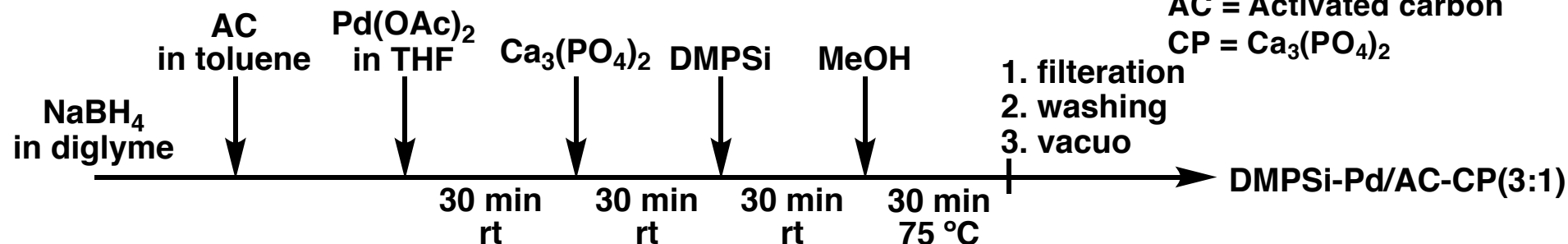


Entry	Catalyst	Yield (2) (%) <sup>b</sup>
1	Pd/C	36
2	Pt/C	<5
3	Rh/C	<5
4	Ru/C	N.D.
5	Ir/C	N.D.
6	DMPSi-Pd/AC-CP(3:1) <sup>a</sup>	48
7	DMPSi-Pt/AC-CP(3:1) <sup>a</sup>	13
8	PhMePSi-Pd/SiO <sub>2</sub> <sup>c</sup>	8

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis

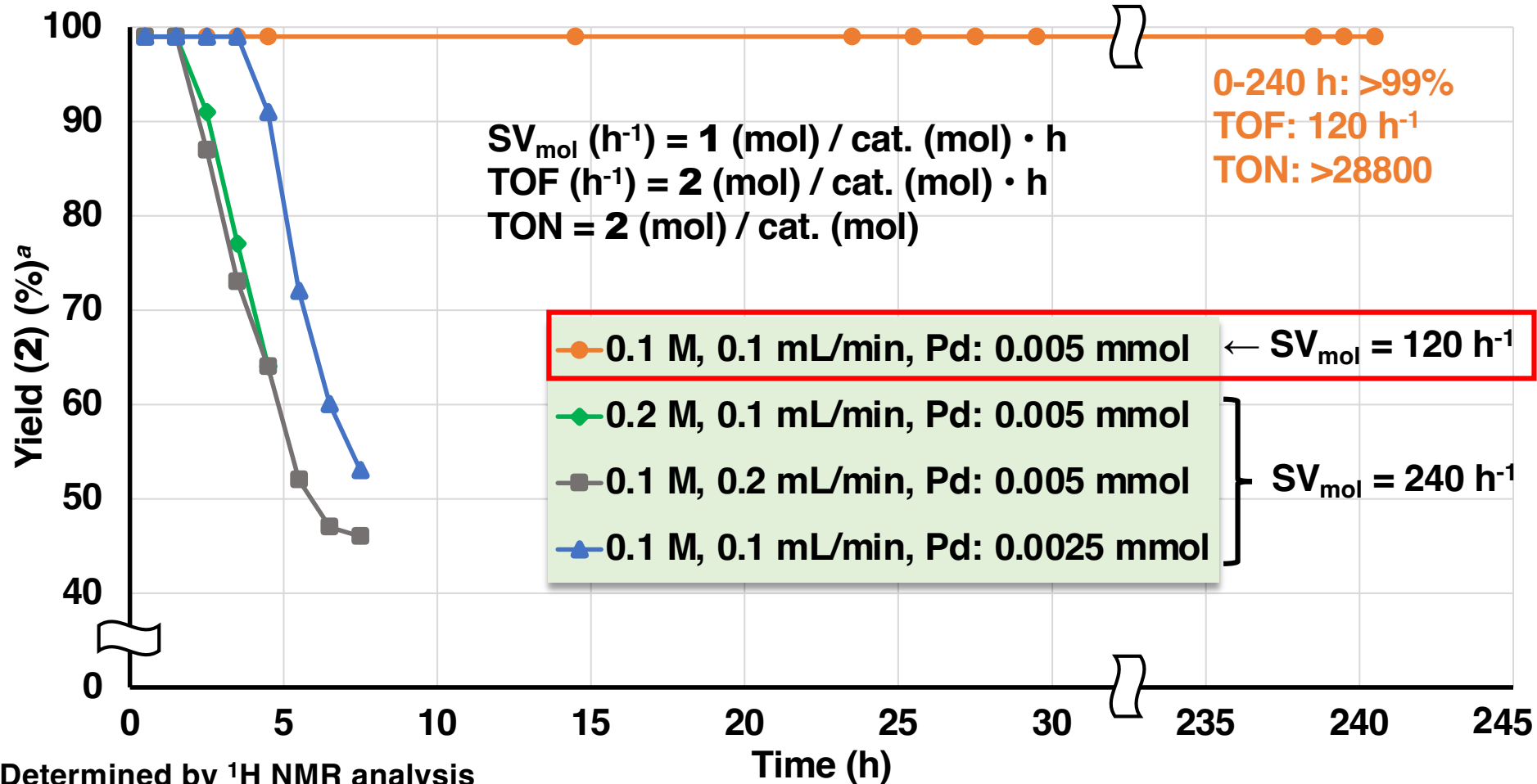
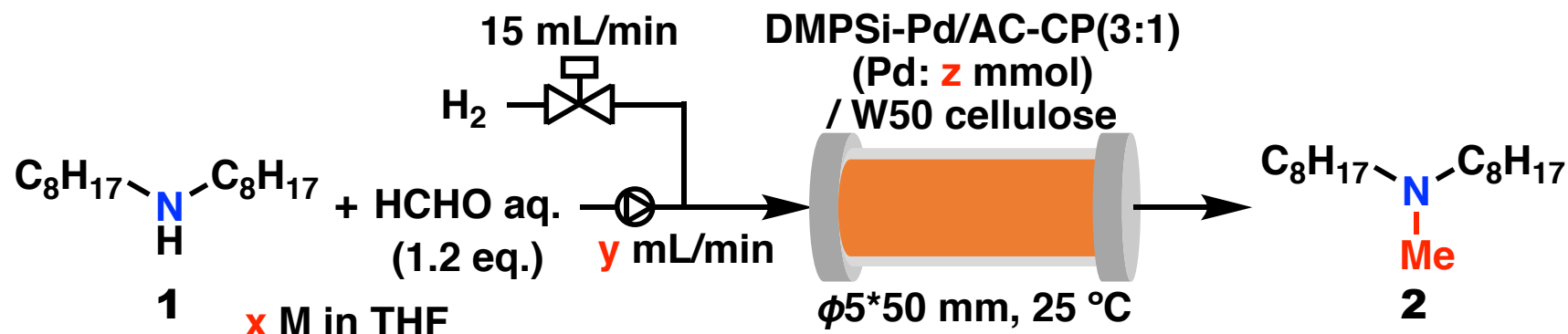
<sup>c</sup> Kobayashi S. *et al. Angew. Chem. Int. Ed.* **2022**, *61*, e202115643.

## ■ Catalyst preparation: DMPSi-Pd/AC-CP(3:1)<sup>a</sup>

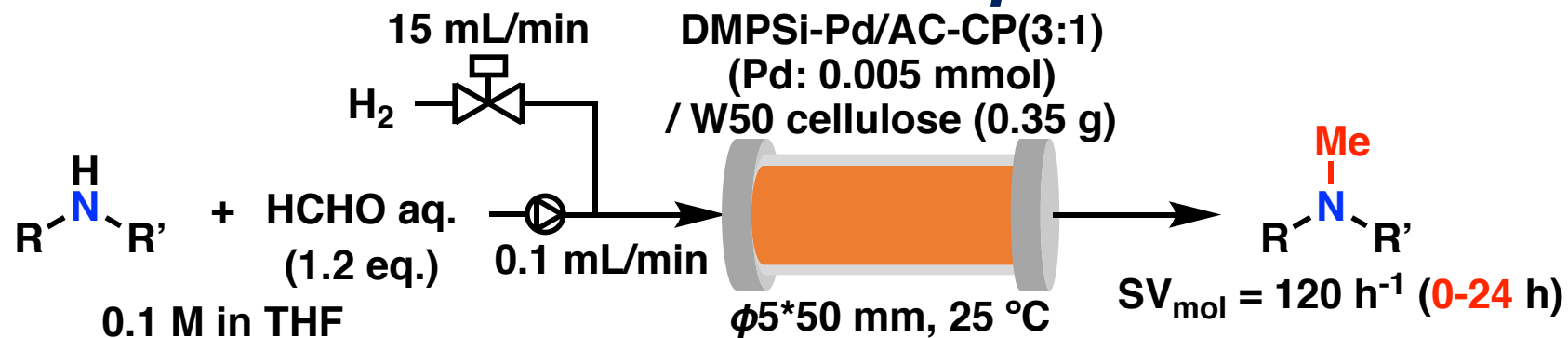


<sup>a</sup> Kobayashi S. *et al. Chem. Asian J.* **2020**, *15*, 1688.

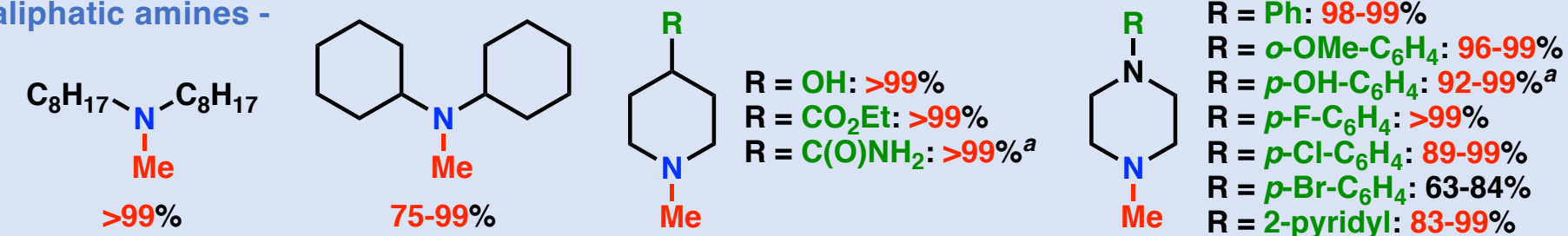
# Optimization under Flow Conditions



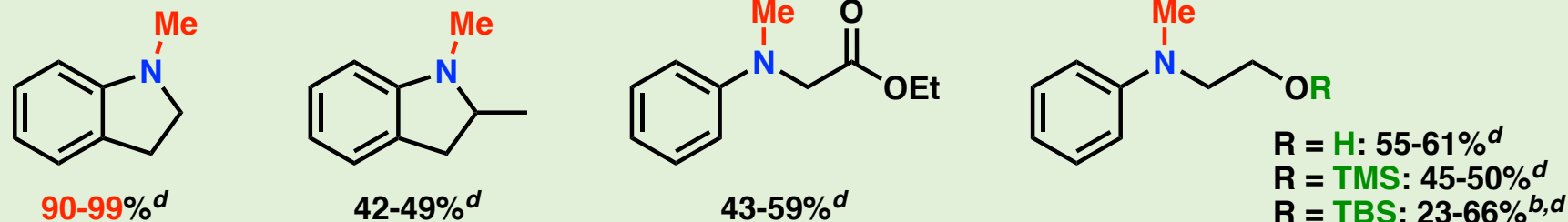
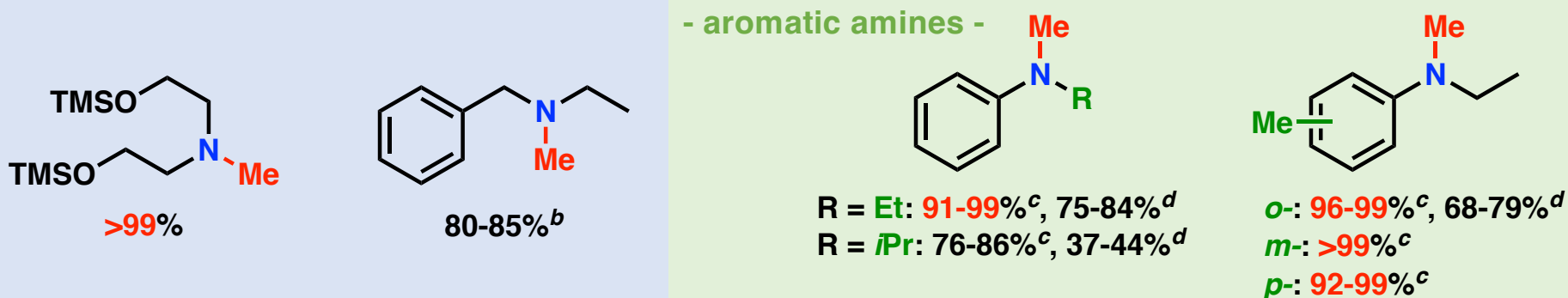
# Substrate Scope



## - aliphatic amines -



## - aromatic amines -



Yields: Determined by <sup>1</sup>H NMR analysis; <sup>a</sup> THF/MeOH(1:1); <sup>b</sup> 0-8 h; <sup>c</sup> 50 °C; <sup>d</sup> 25 °C, 0.05 M, SV<sub>mol</sub> = 60 h<sup>-1</sup>

Green Chem. (2023)



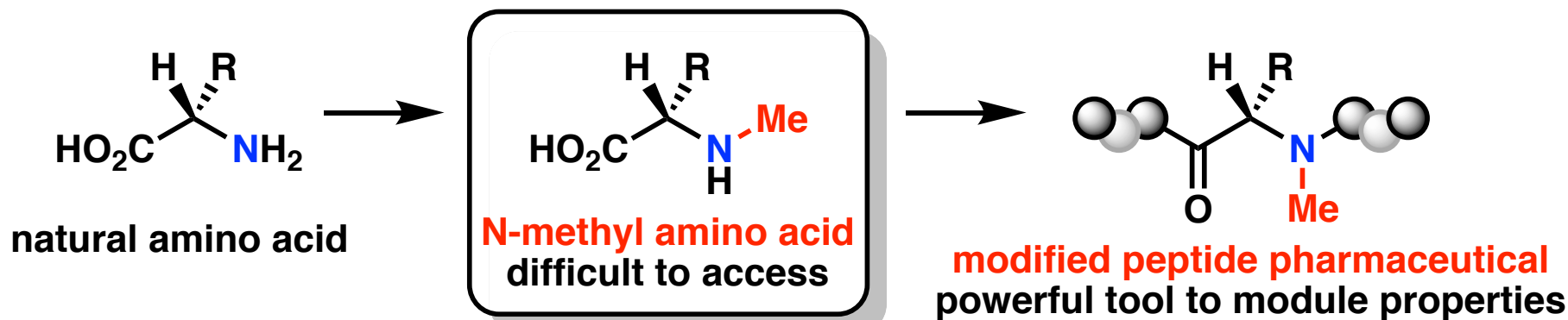
# Application to N-Monomethylation

## ■ N-Monomethylation of primary amines



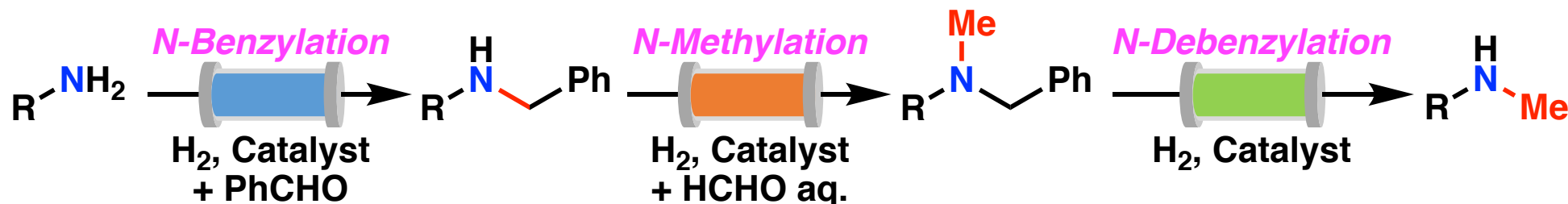
- × Limited substrate scope
- × Harsh conditions

## • N-Monomethylated amino acids



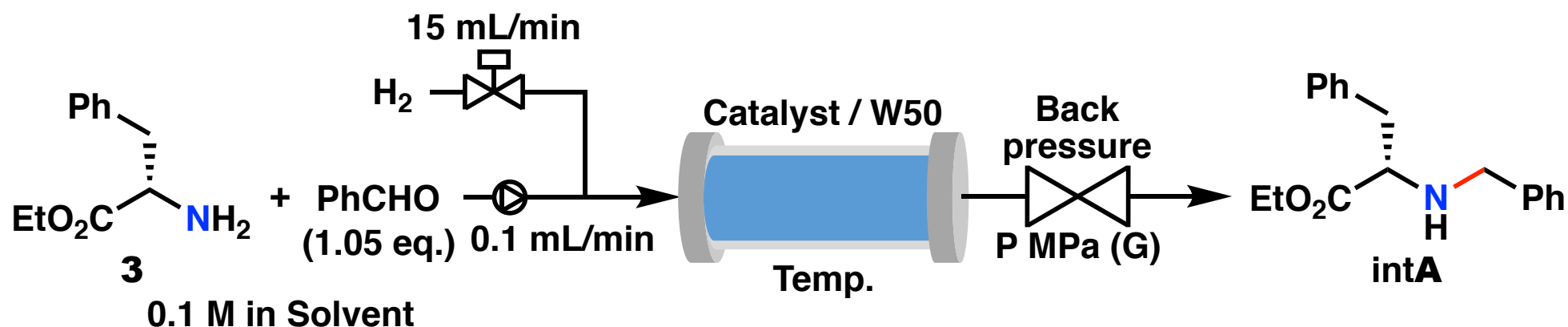
*Biopolymers* 2018, 109, e23110.

## ■ Reaction design



- Benzylation, methylation, debenylation process
  - Three reactions with  $\text{H}_2$  and heterogeneous catalysts
- **Sequential-flow system** is advantageous.

# *N*-Monomethylation: 1<sup>st</sup> step (*N*-Benzylation)



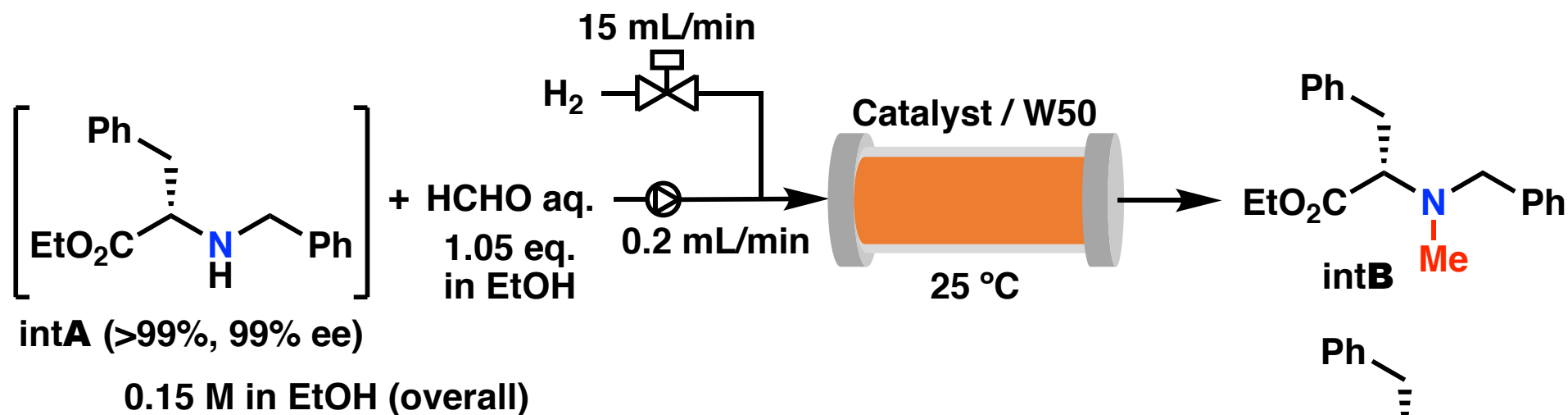
Entry	Catalyst (x mmol)	Solvent	Conditions	Yield (%) <sup>a</sup> (int A)	Ee (%) <sup>b</sup> (int A)	Yield (%) <sup>a</sup> (BnOH)
1	Pt/C (0.05 mmol)	THF	80 °C, 0.3 MPa	49	92	<5
2 <sup>c</sup>	Pt/C (0.1 mmol)	THF	130 °C, 0.6 MPa	>99	36	<5
3	DMPSi-Pd/AC-CP(3:1) (0.005 mmol)	THF	25 °C	24	99	80
4	DMPSi-Pd/AC-CP(3:1) (0.005 mmol)	THF	0.3 M, 25 °C	83	99	18
5	DMPSi-Pd/AC-CP(3:1) (0.005 mmol)	EtOH	0.3 M, 25 °C	93	99	6
6 <sup>d</sup>	DMPSi-Pd/AC-CP(3:1) (0.005 mmol)	EtOH	0.3 M, 25 °C PhCHO (1.5 eq.)	97-99	99	~50

<sup>c</sup> 2,4,6-Trimethylbenzaldehyde was used instead of benzaldehyde;

<sup>d</sup> Catalyst activity was kept for 5 days (>99%).

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis; <sup>b</sup> Determined by HPLC analysis

# N-Monomethylation: 2<sup>nd</sup> step (N-Methylation)



Entry	Catalyst (x mmol)	Yield (%) <sup>a,c</sup> (intB)	Yield (%) <sup>a,c</sup> (5)
1	DMPSi-Pd/AC-CP(3:1) (0.015 mmol)	27	18
3	DMPSi-Pt/AC-CP(3:1) (0.1 mmol)	77	N.D.
4	Pt/C (0.1 mmol)	81	N.D.
5	Pt/C (0.2 mmol)	90	N.D.
6 <sup>d,e</sup>	Pt/C (0.2 mmol)	93	N.D.

<sup>c</sup> Average for 0-4 h; <sup>d</sup> 0.3 MPa;

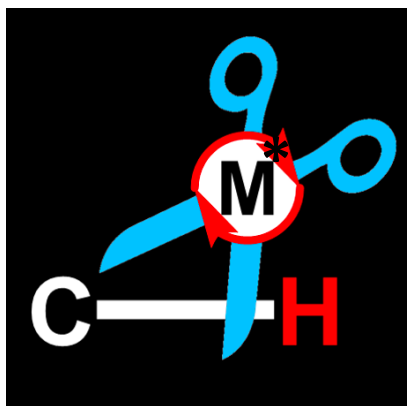
<sup>e</sup> Catalyst activity was kept for 3 days (85-93%).

✓ Pd catalysts: high **activity**    ✓ Pt catalysts: high **chemoselectivity**

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis; <sup>b</sup> Determined by HPLC analysis

# Enantioselective C–H Functionalization

## ◆ Transition Metal-Catalyzed Enantioselective C–H Functionalization



Powerful synthetic strategy for optically active molecules



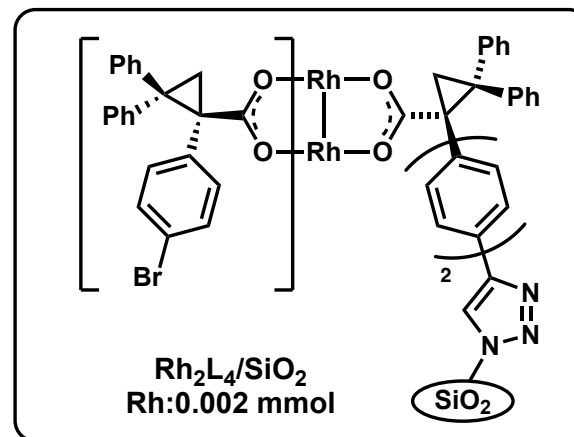
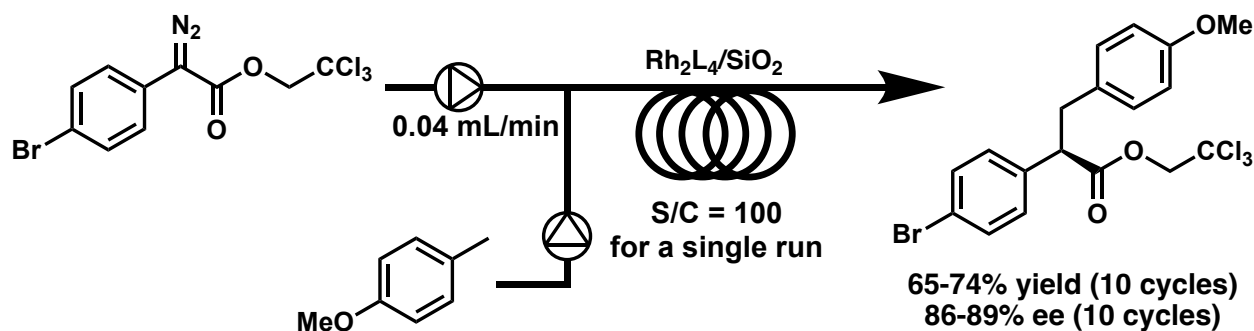
Use of precious/toxic metals with high catalyst loading

**Catalyst immobilization** + **Continuous-flow reaction**



Separation/reuse of catalysts, Efficient synthesis

## ◆ Previous Report on Chiral Heterogeneous Catalysis



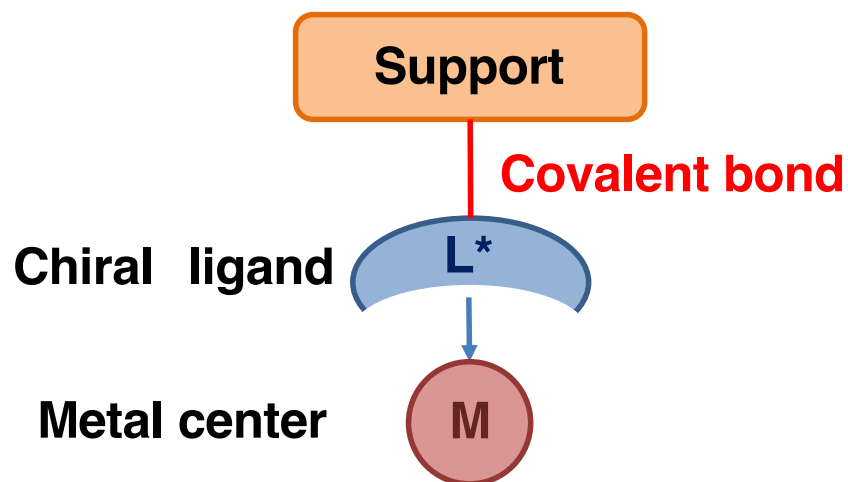
The **ONLY** example in C–H functionalization  **Complicated catalyst preparation**

H. M. L. Davies, C. W. Jones *et al.* *Angew. Chem. Int. Ed.* **2020**, *59*, 19525.

Highly **efficient and versatile** immobilization for continuous-flow catalysis

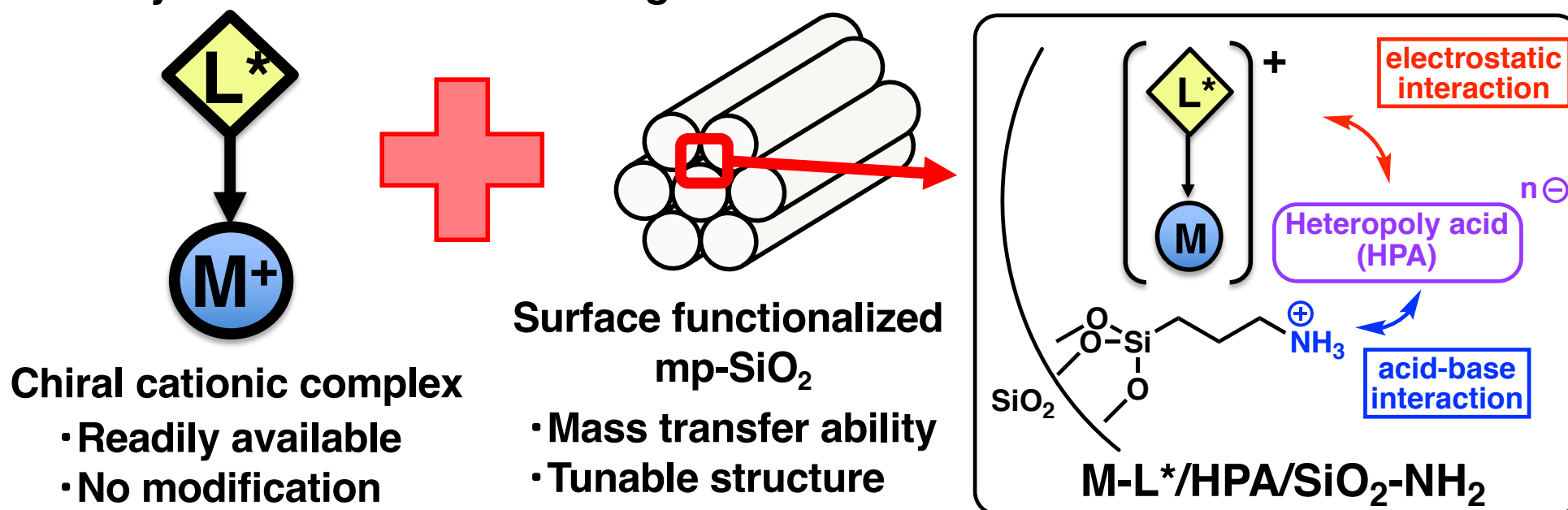
# Immobilization of Metal Complexes

## ◆ Conventional method: **covalent** immobilization of chiral ligands

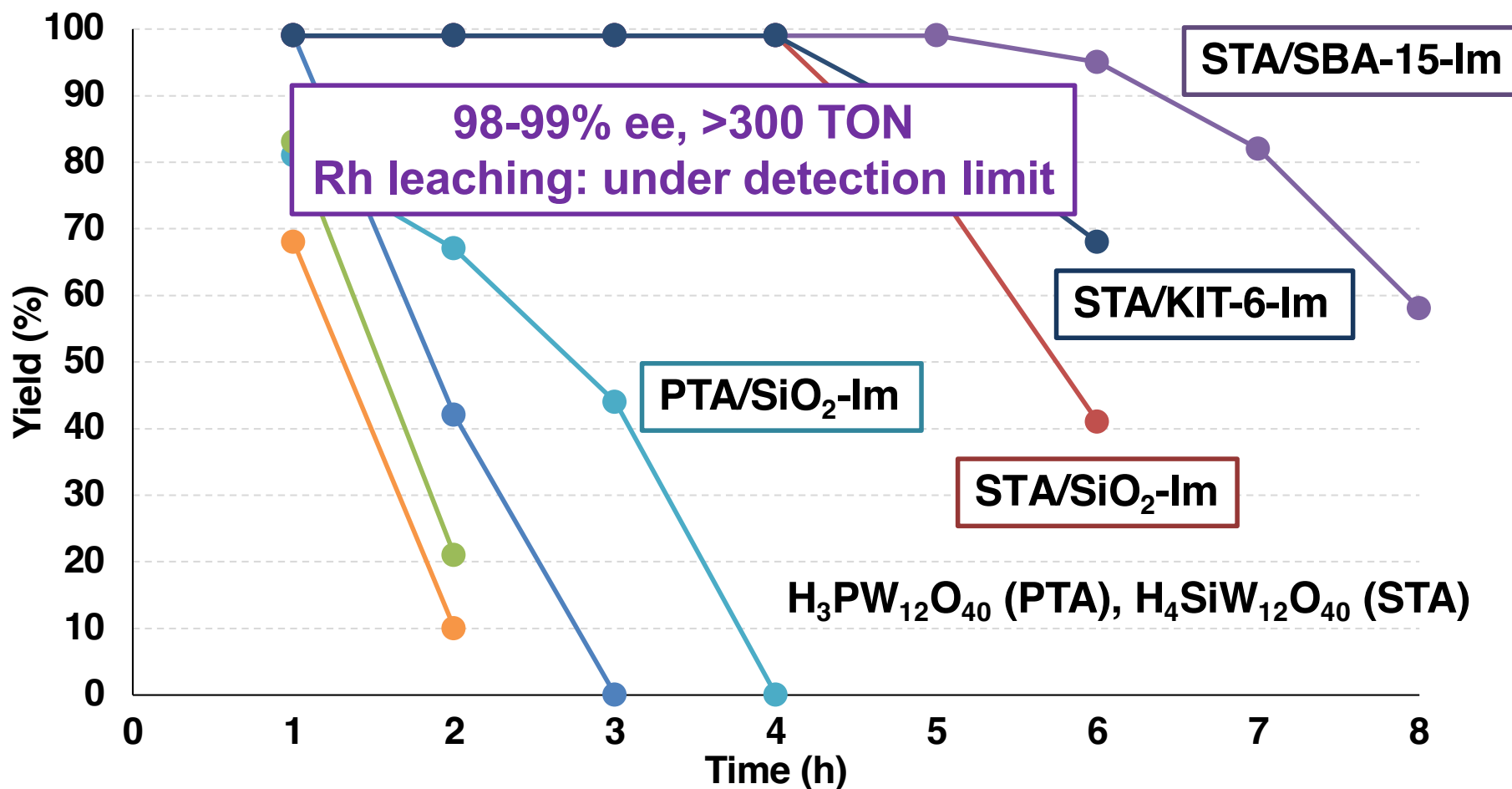
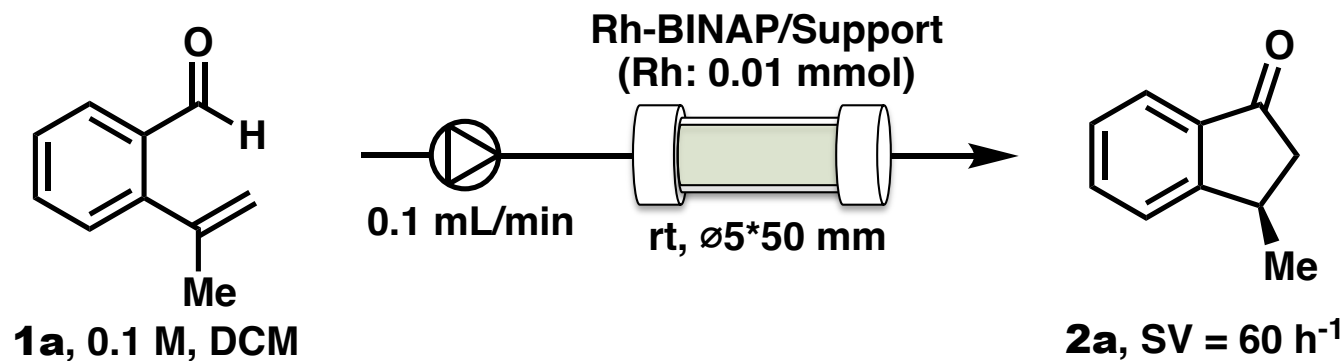


- ✓ The most straightforward
- ✗ Low activity, selectivity
- ✗ Tedious catalyst preparation

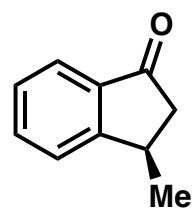
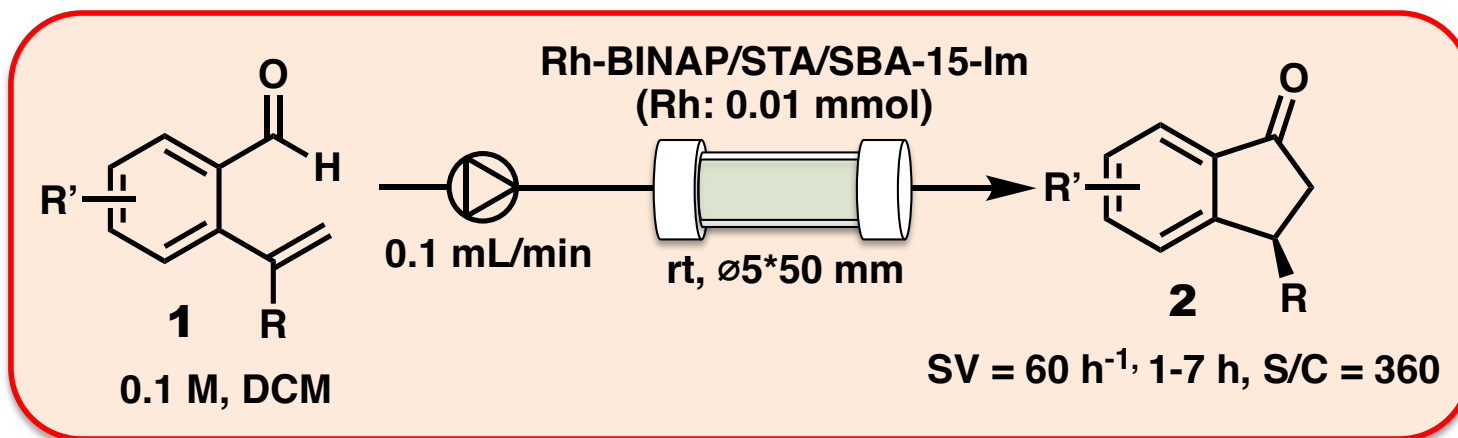
## ◆ Catalyst Immobilization Utilizing Non-Covalent Interactions



# Flow Enantioselective Hydroacylation

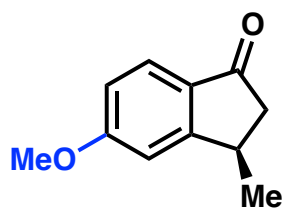


# Flow Hydroacylation: Substrate Scope (1)



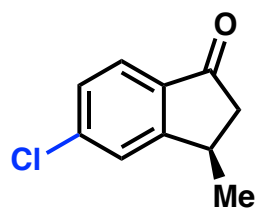
**2a**

83->99% yield  
98-99% ee



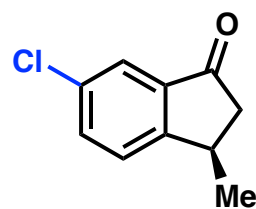
**2b**

91->99% yield  
99% ee



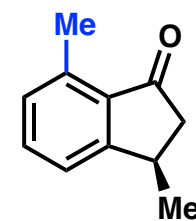
**2c**

90-98% yield  
99% ee



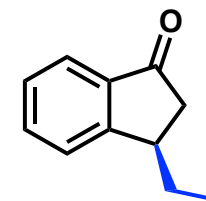
**2d**

88->99% yield  
99% ee



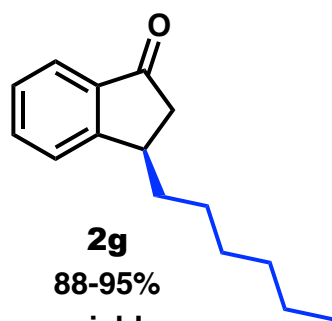
**2e**

88->99% yield  
99% ee  
(0.05 M, SV = 30 h<sup>-1</sup>)



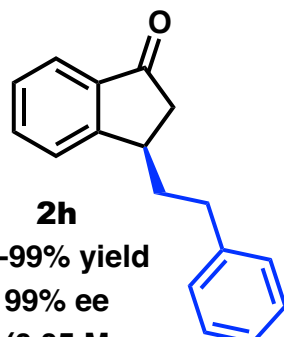
**2f**

92->99% yield  
99% ee



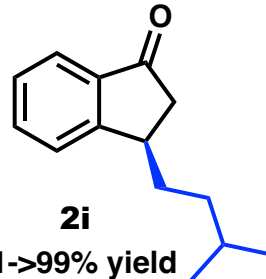
**2g**

88-95% yield  
99% ee



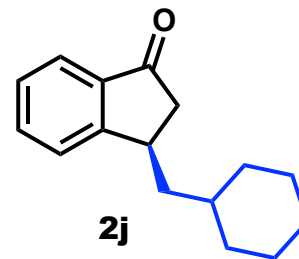
**2h**

88-99% yield  
99% ee  
(0.05 M, SV = 30 h<sup>-1</sup>)



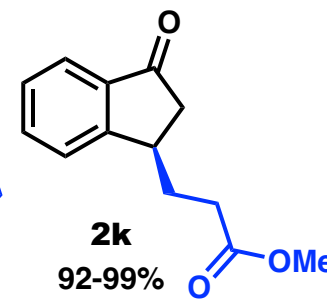
**2i**

91->99% yield  
99% ee  
(0.05 M, SV = 30 h<sup>-1</sup>)



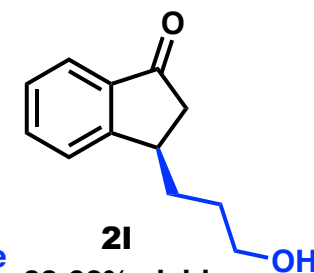
**2j**

87-95% yield  
99% ee  
(0.05 M, SV = 30 h<sup>-1</sup>)



**2k**

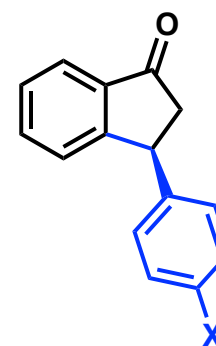
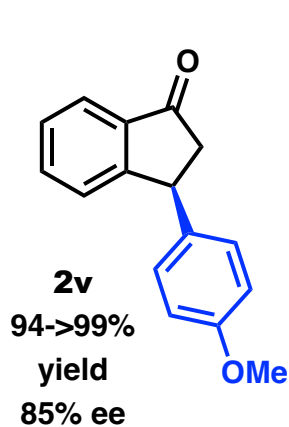
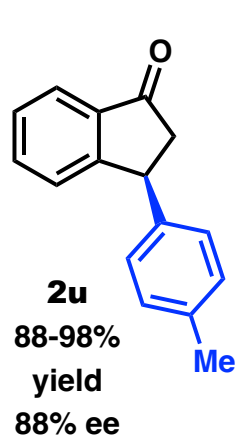
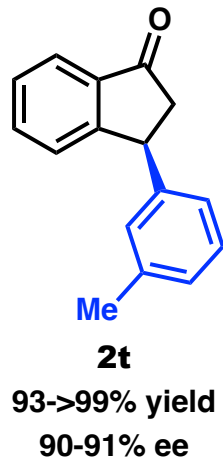
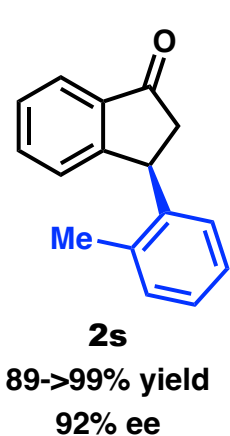
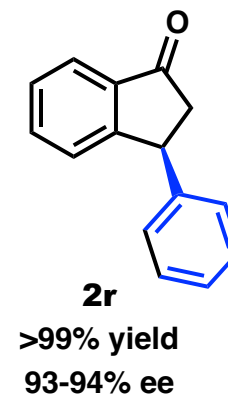
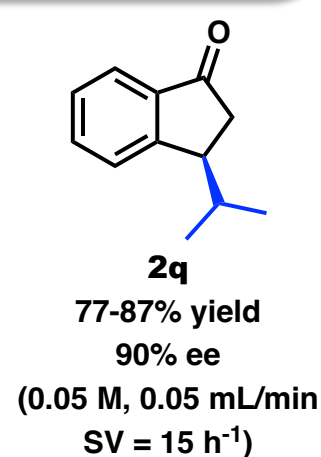
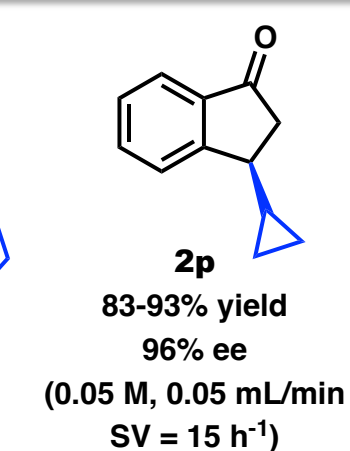
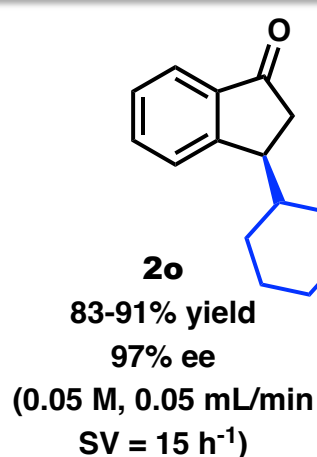
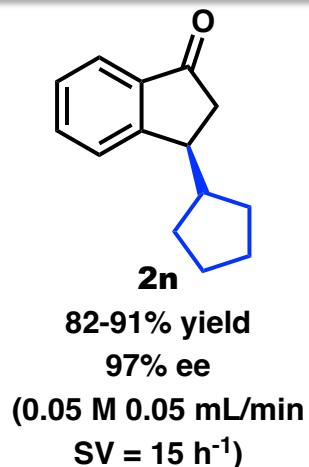
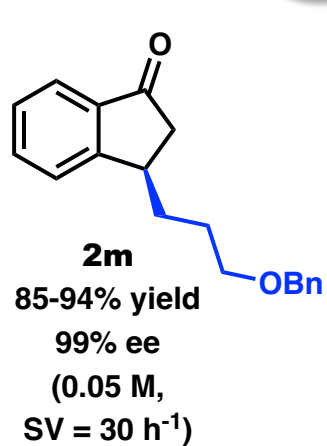
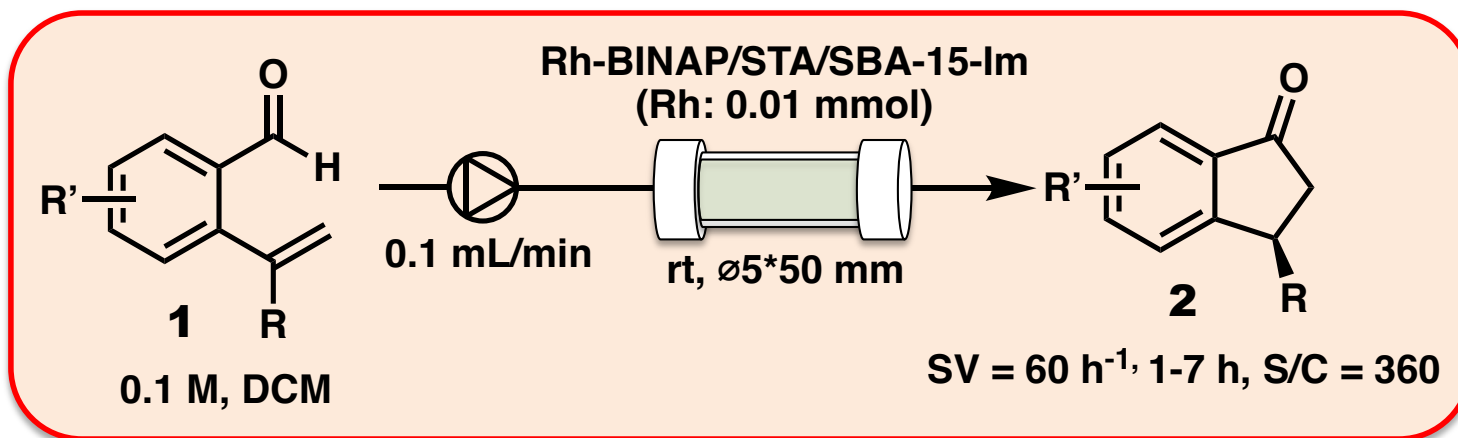
92-99% yield  
99% ee



**2l**

88-93% yield  
99% ee

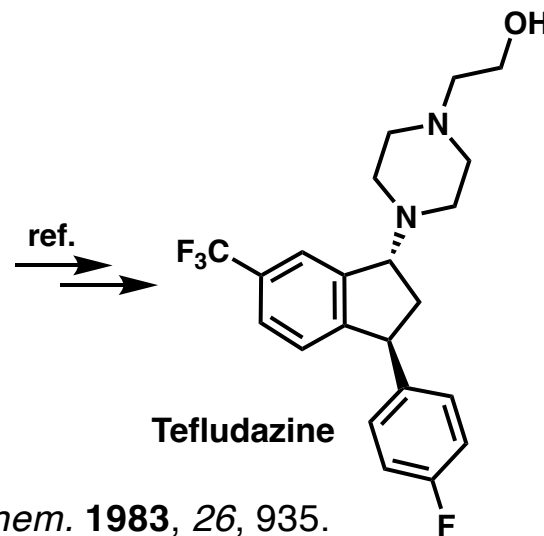
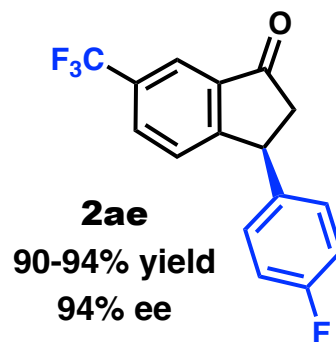
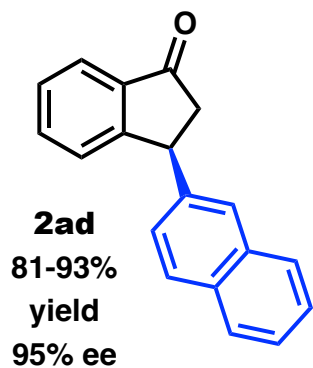
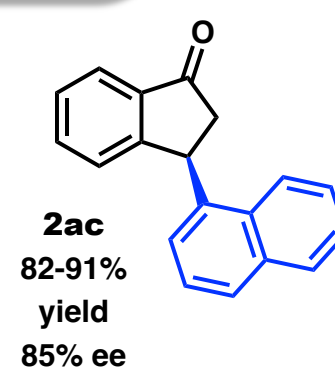
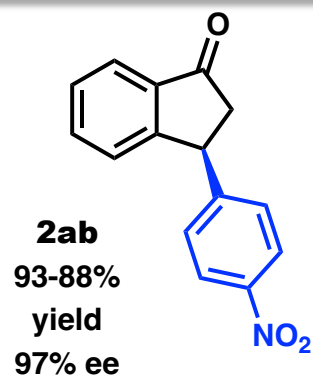
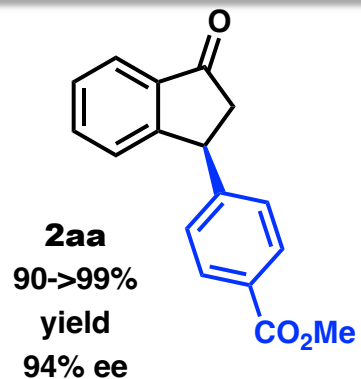
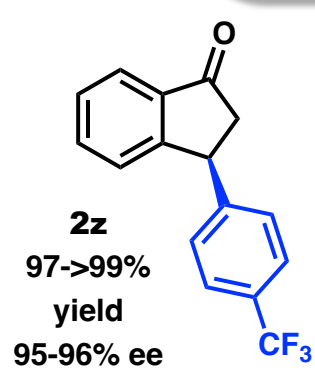
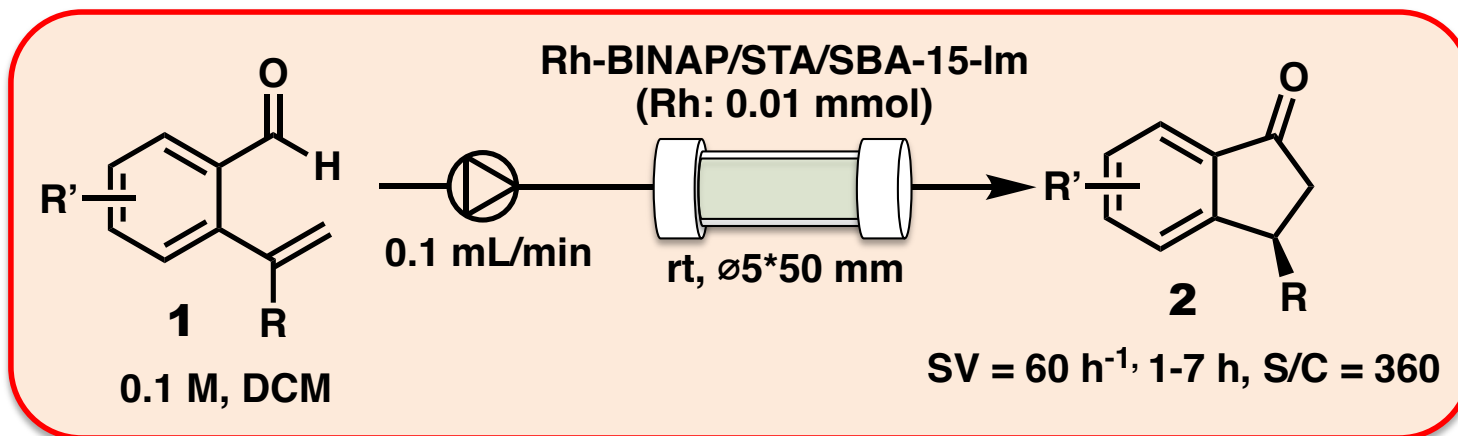
# Flow Hydroacylation: Substrate Scope (2)



**X = F(2w);**  
89-95% yield, 94% ee  
**= Cl(2x);**  
88-97% yield, 94-95% ee  
**= Br(2y);**  
90-92% yield, 95% ee

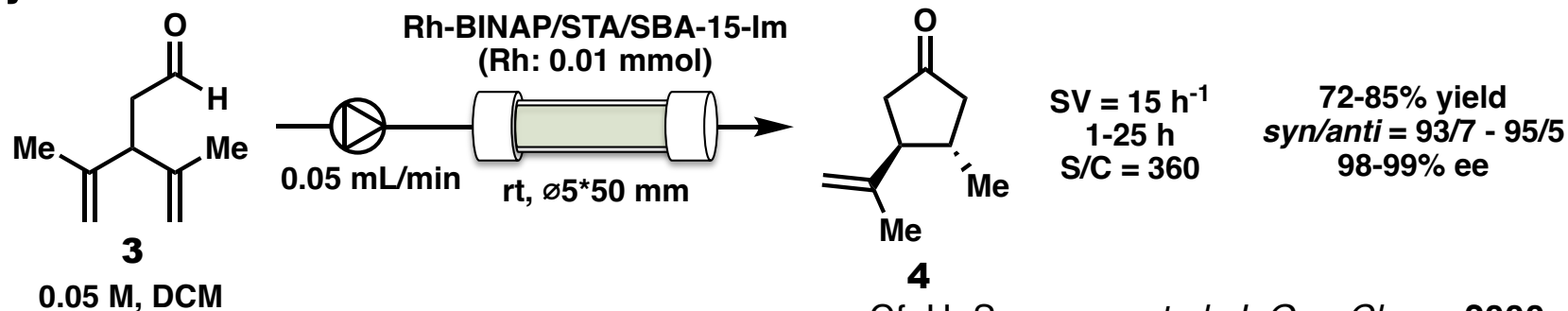


# Flow Hydroacylation: Substrate Scope (3)



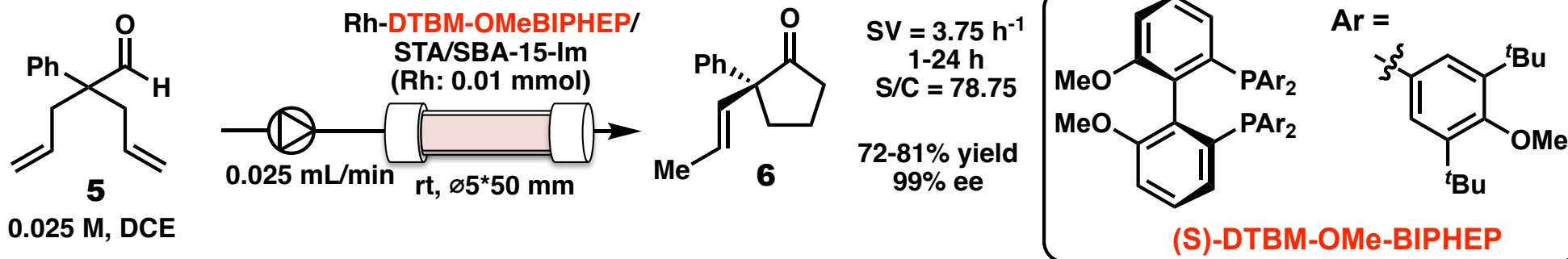
# Hydroacylations with Aliphatic Aldehydes

## ◆ Desymmetrization of Akenes



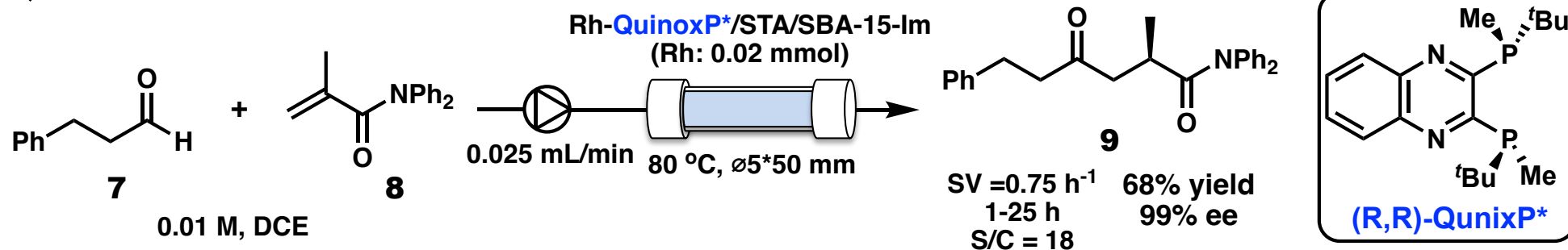
Cf. H. Suemune *et al.* *J. Org. Chem.* **2000**, *65*, 5806.

## ◆ Isomerization/Hydroacylation Sequence



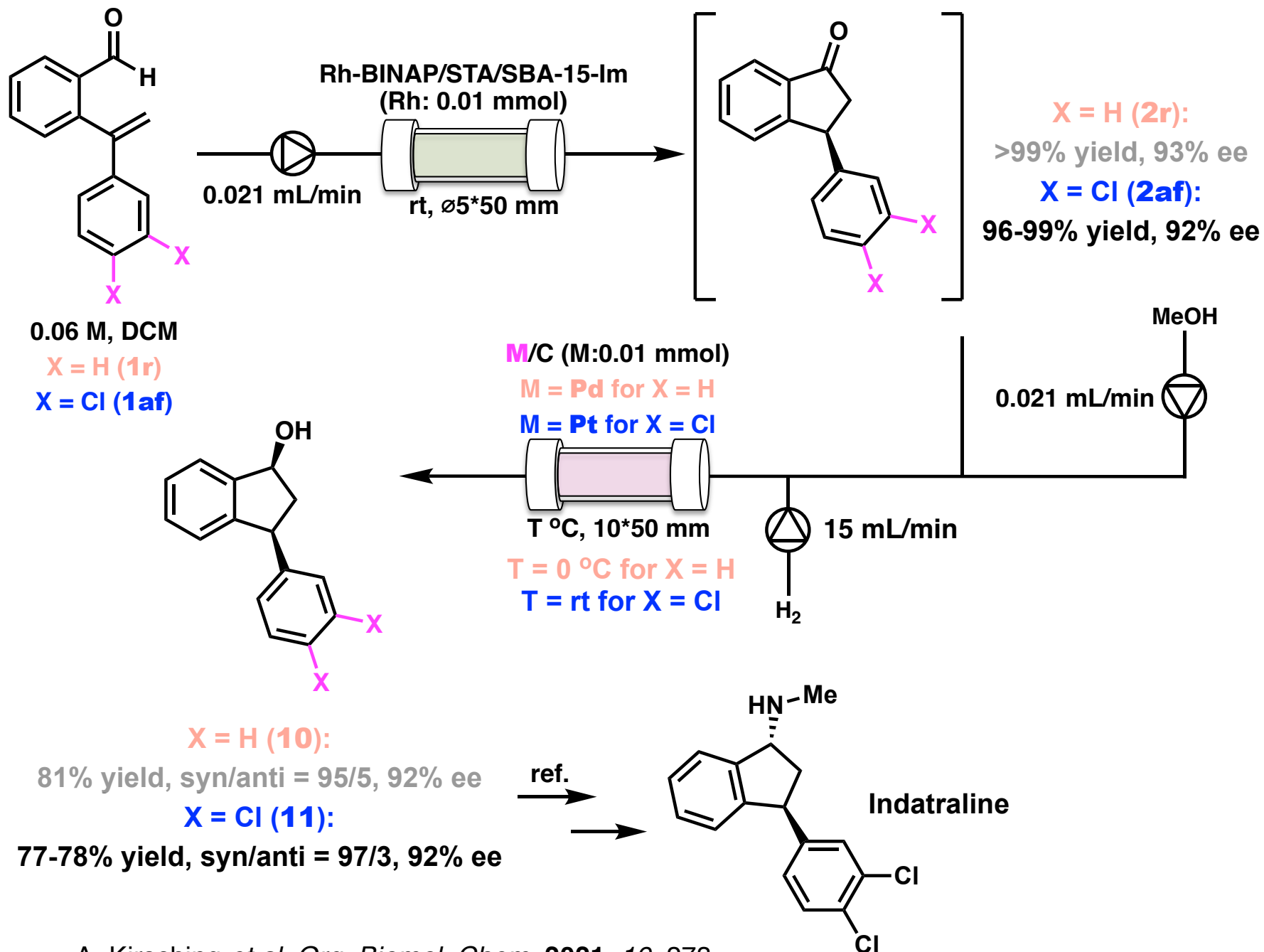
Cf. V. M. Dong *et al.* *Chem. Sci.* **2015**, *6*, 4479.

## ◆ Intermolecular Reaction

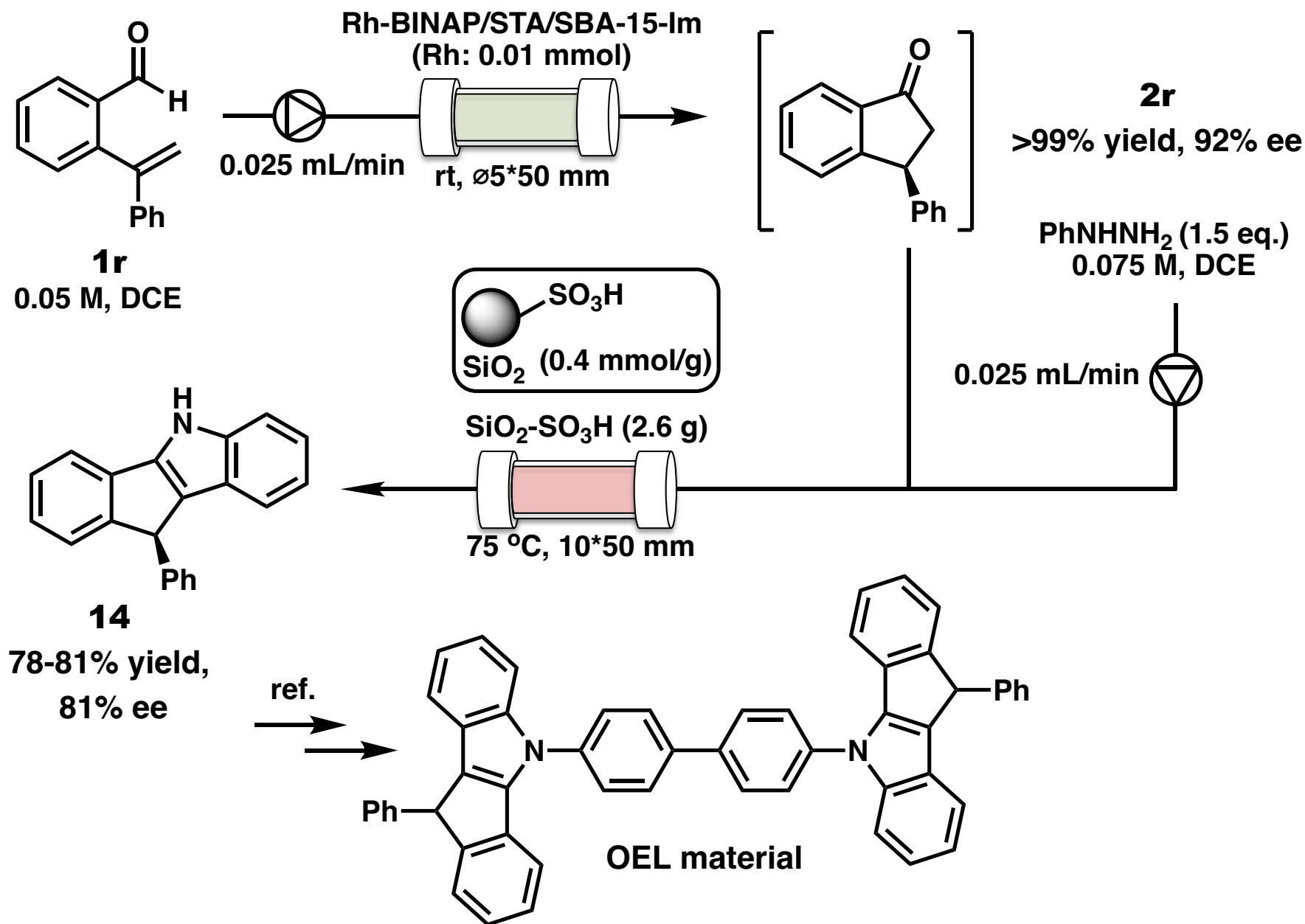


Cf. K. Tanaka *et al.* *J. Am. Chem. Soc.* **2009**, *131*, 12552.

# Sequential Hydroacylation/Hydrogenation

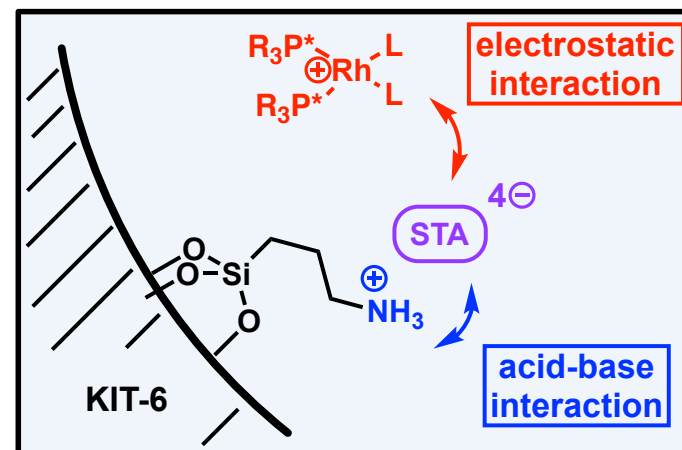
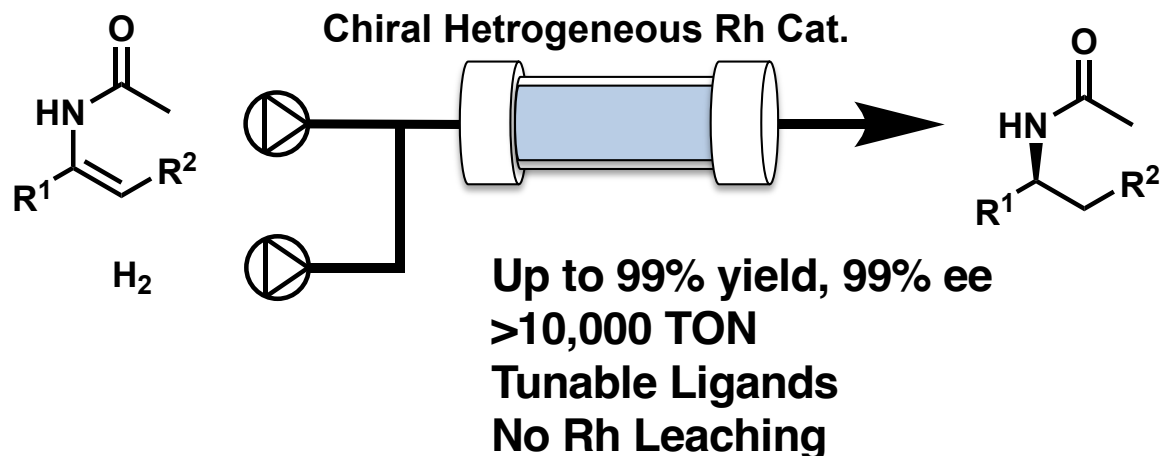


# Sequential Hydroacylation/Fischer Indole Synthesis



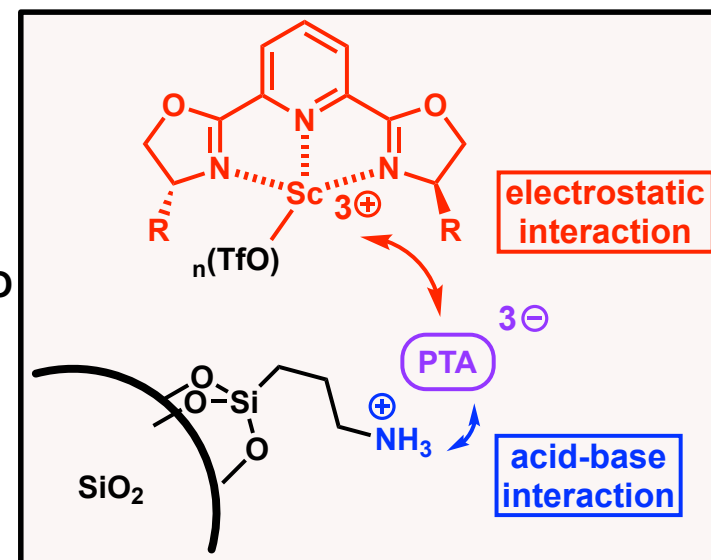
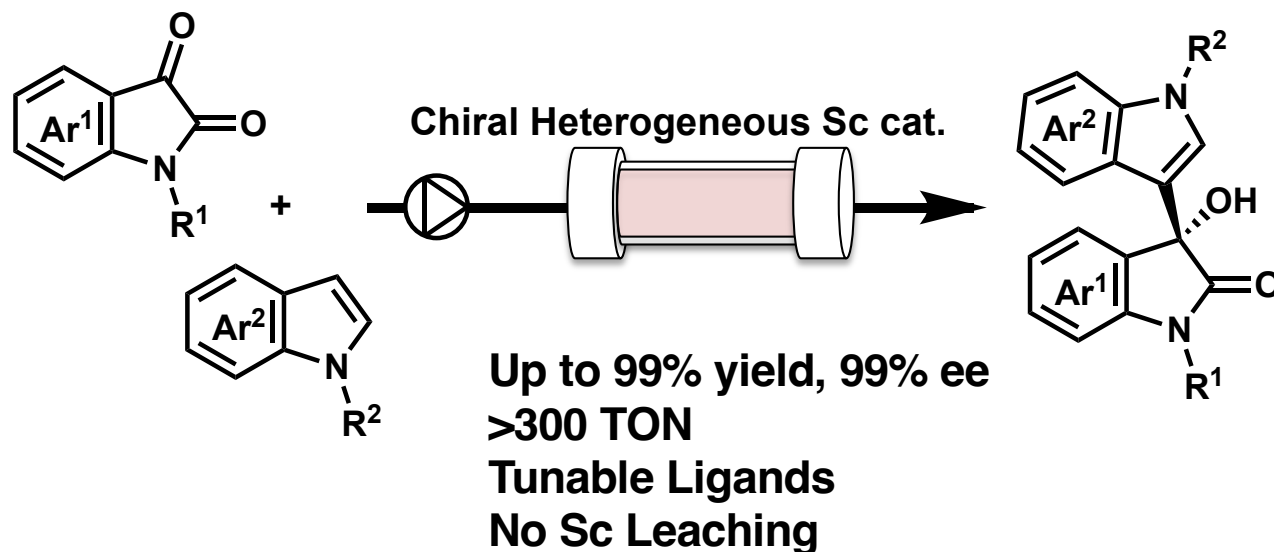
# Versatile Immobilization of Chiral Metal Catalysts

## Asymmetric Hydrogenation



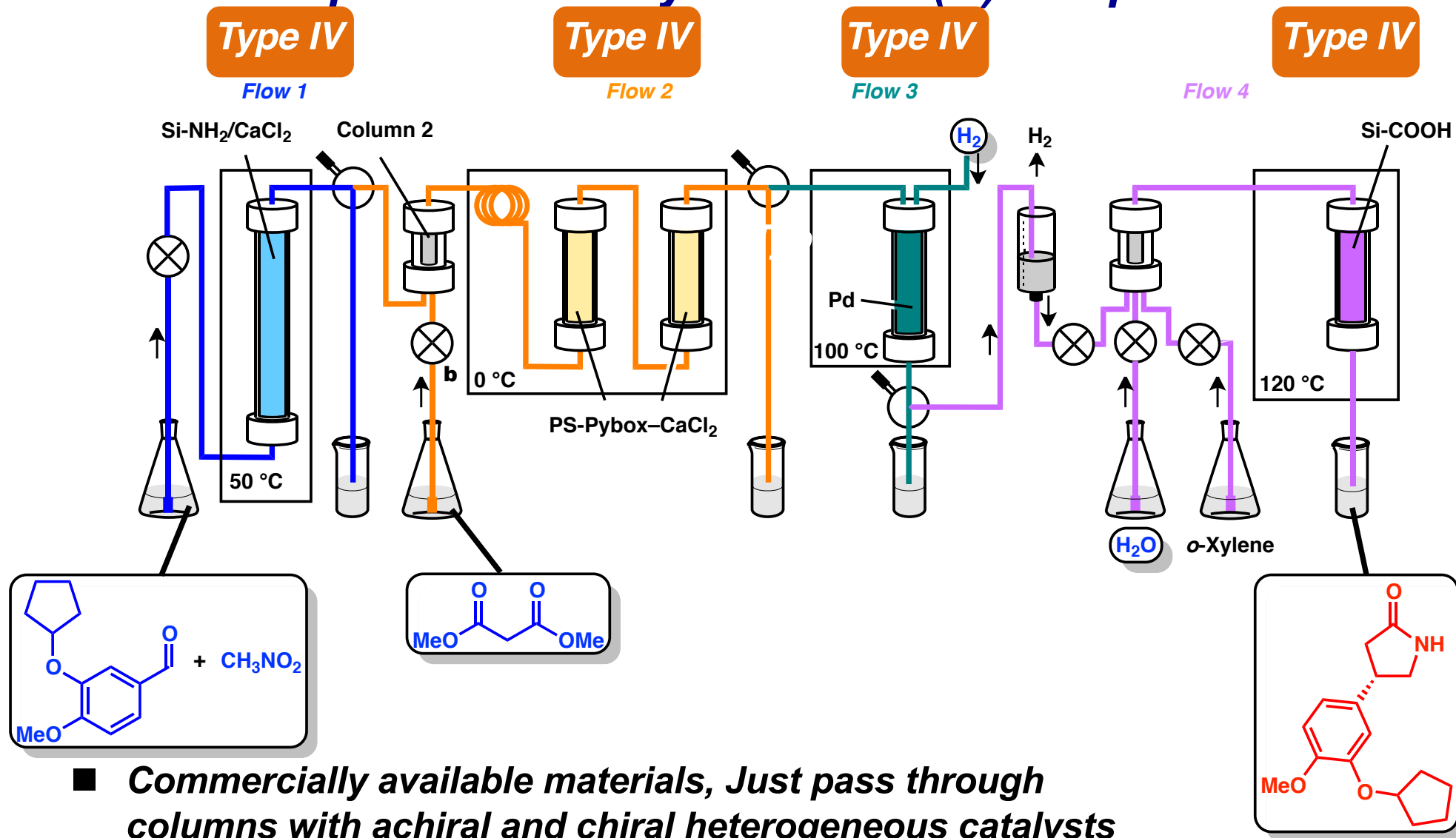
JACS (2020)

## Asymmetric Friedel-Crafts Reaction



ACIE (2021)

# Sequential-flow Synthesis of (R)-Rolipram

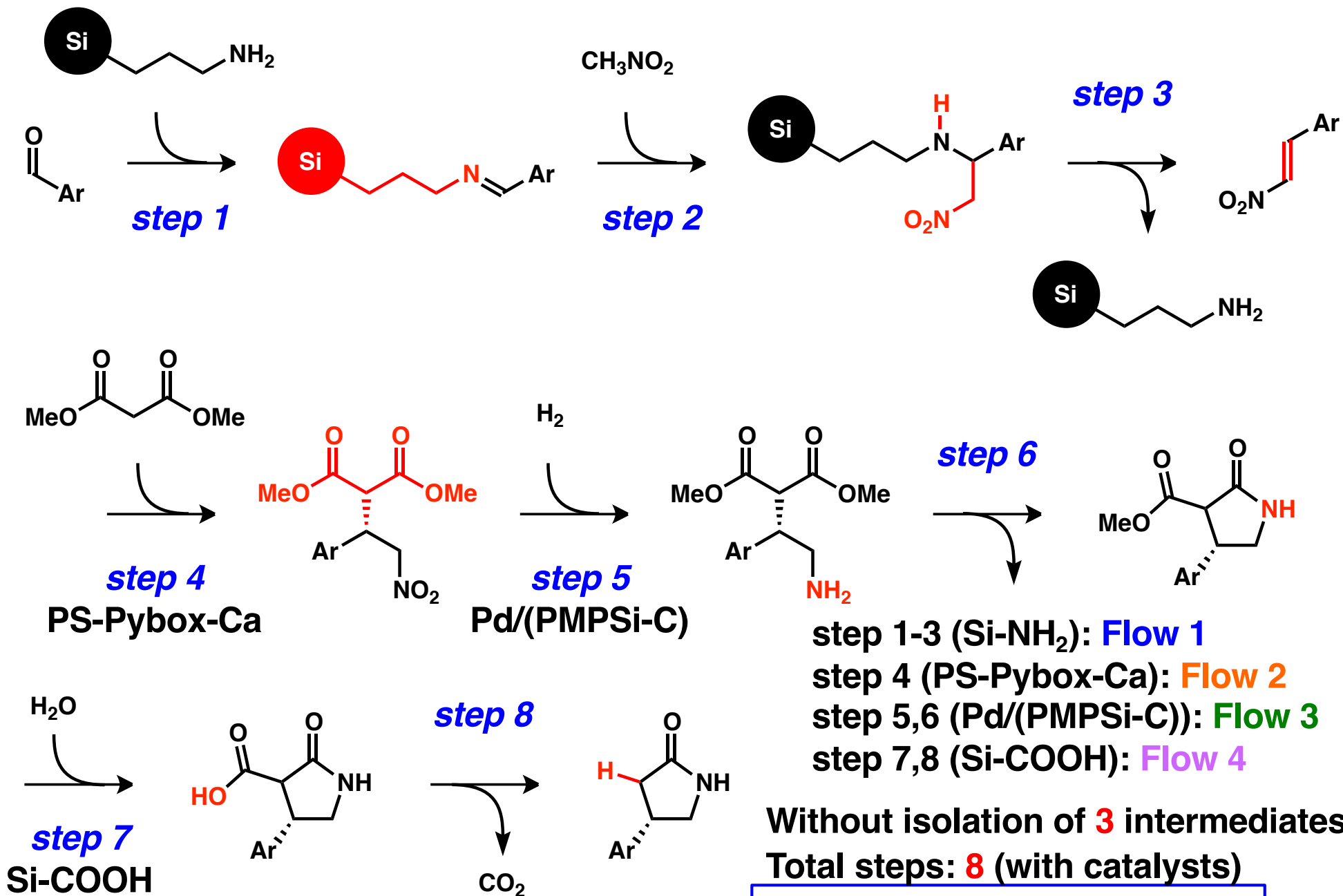


- **Commercially available materials, Just pass through columns with achiral and chiral heterogeneous catalysts**
- **Drugs are obtained directly**
- **Eight-step chemical transformations without the isolation of any intermediates and without the separation of any catalysts, co-products, byproducts, and excess reagents**

**(R)-Rolipram**  
50% yield,  
96% ee

Nature (2015)

# Rolipram Synthesis in Flow - Detail of Reactions



step 1-3 (Si-NH<sub>2</sub>): **Flow 1**

step 4 (PS-Pybox-Ca): **Flow 2**

step 5,6 (Pd/(PMPSi-C)): **Flow 3**

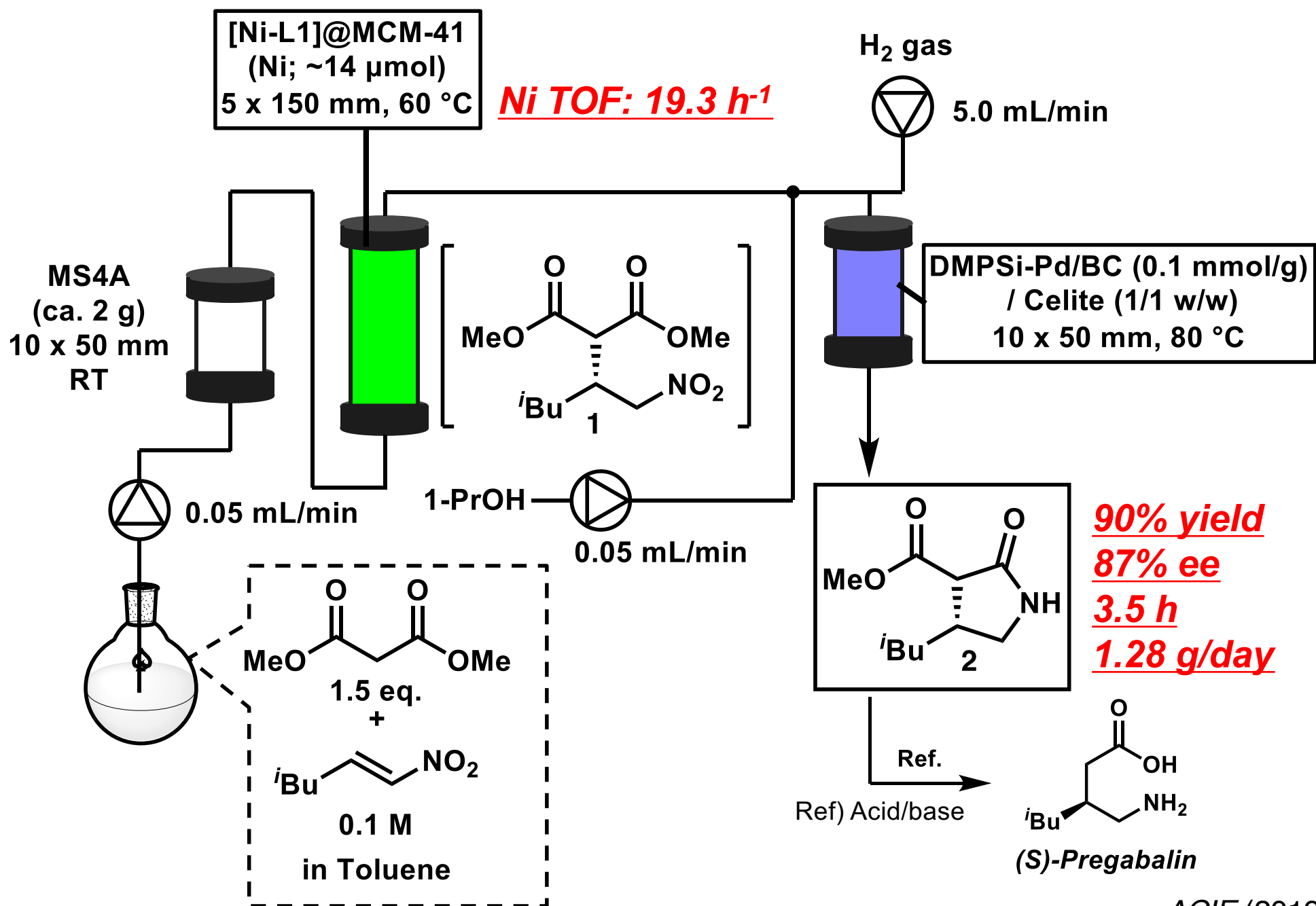
step 7,8 (Si-COOH): **Flow 4**

Without isolation of **3** intermediates

Total steps: **8** (with catalysts)

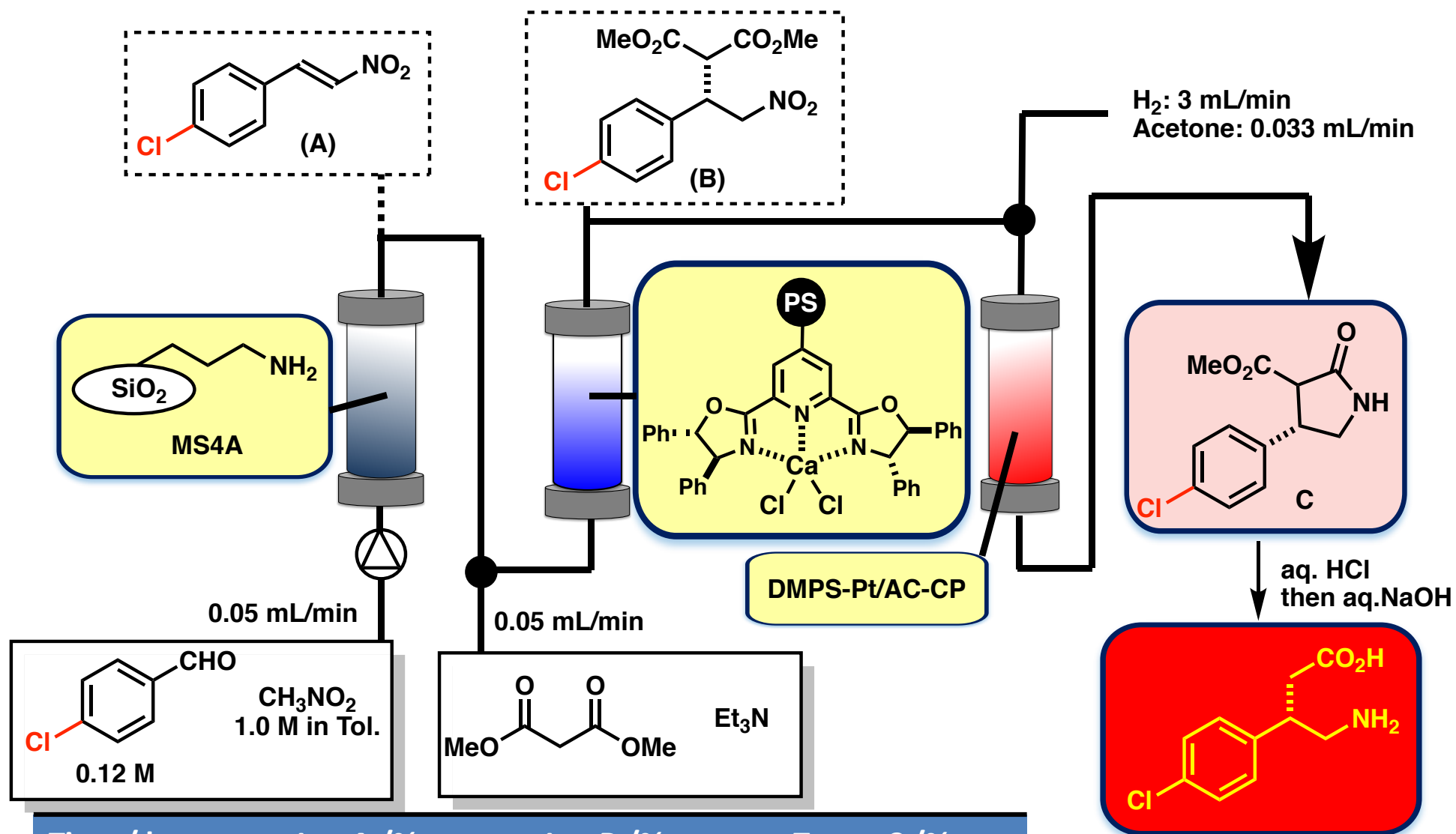
Total yield: **83% yield, 96% ee**

# Sequential-flow Asymmetric Synthesis of Pregabalin





# Sequential-flow Synthesis of Baclofen

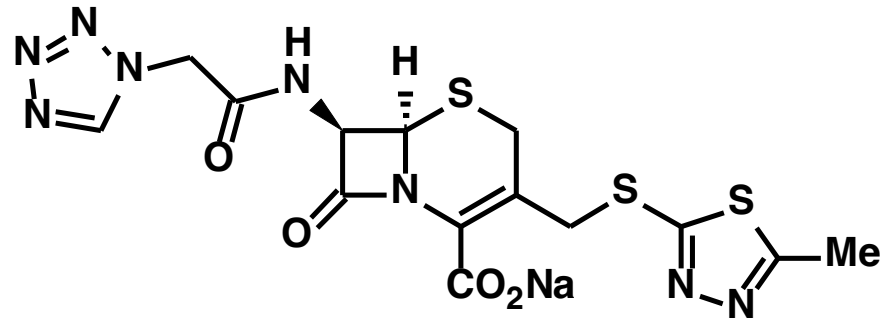


Time / h	Int. A / %	Int. B / %	Target C / %
39 - 45	98	99	96-96
63 - 69	96	99	93-94

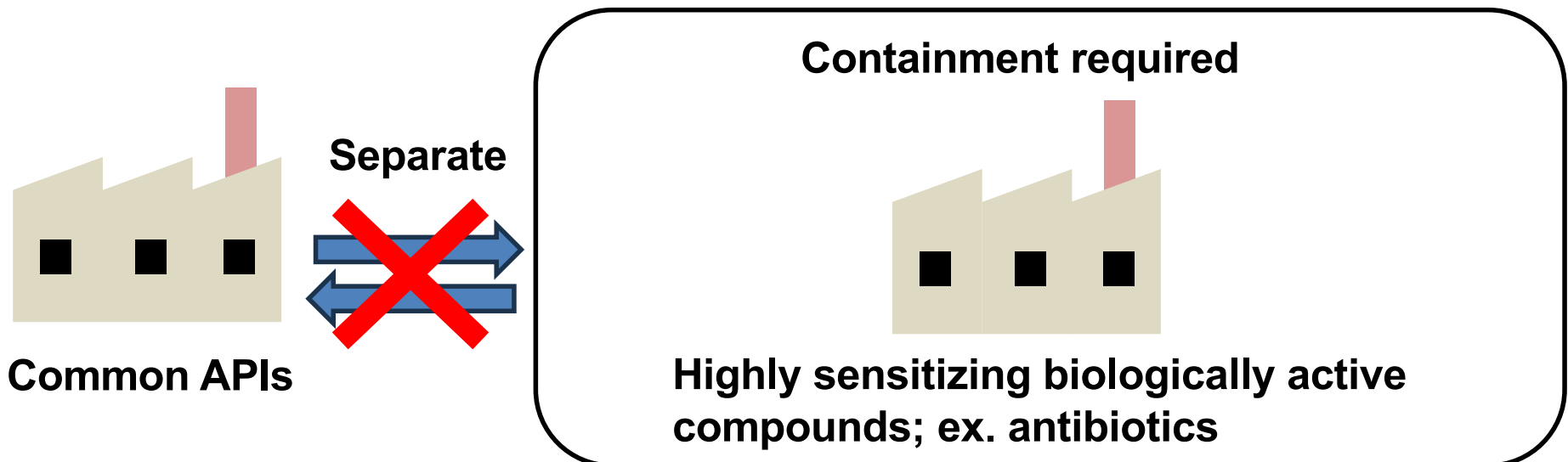
**Baclofen**

CAJ (2020)

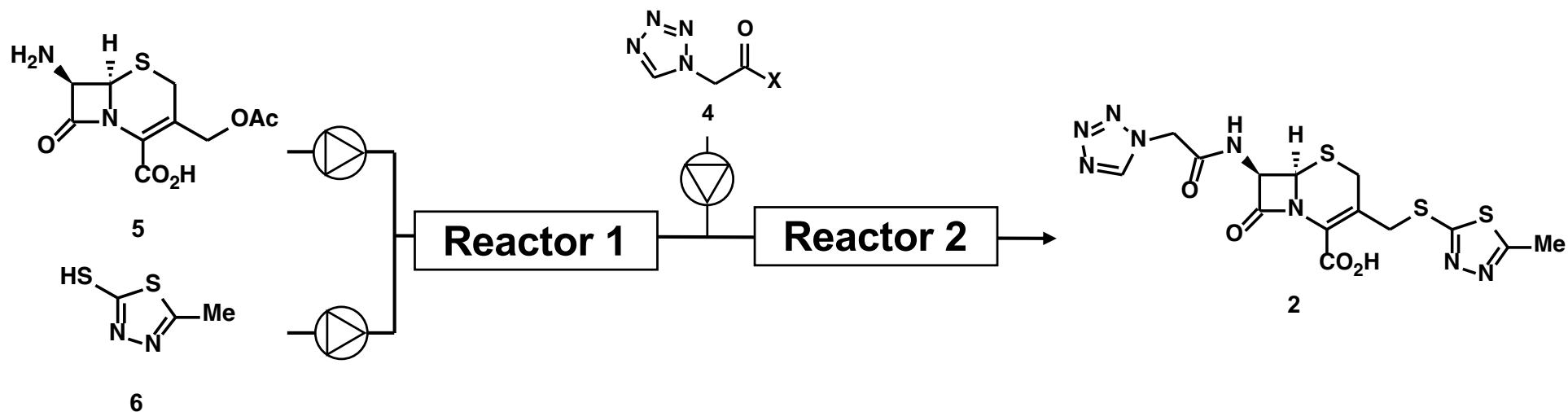
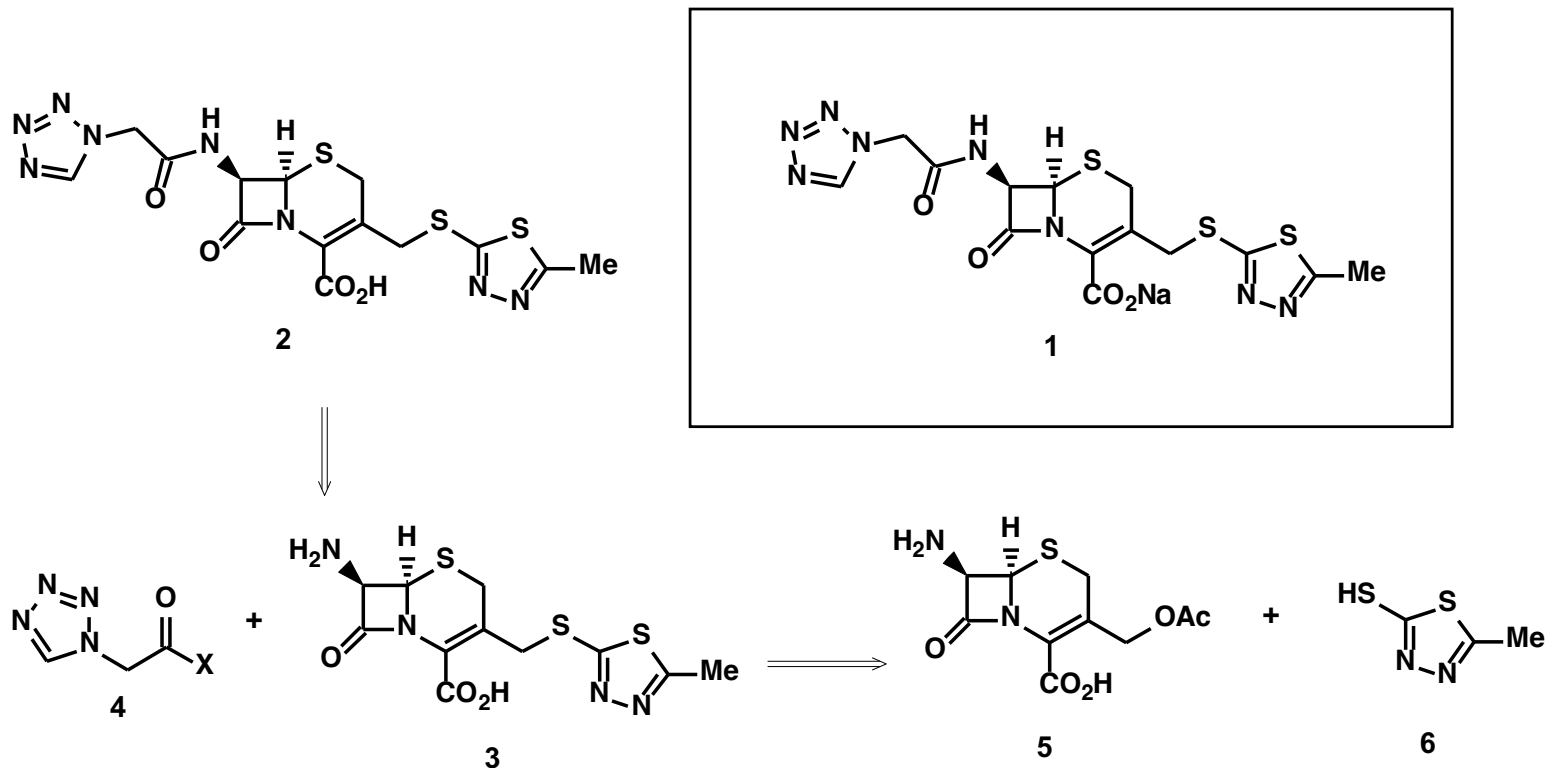
# Cefazolin Sodium



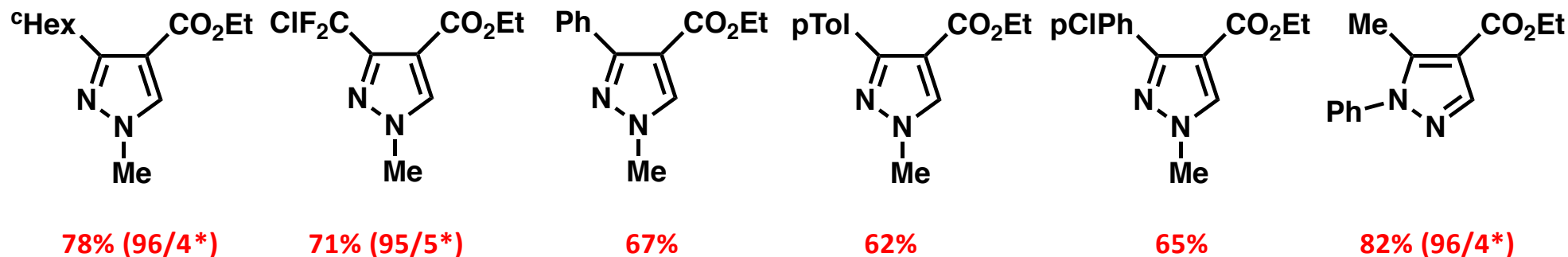
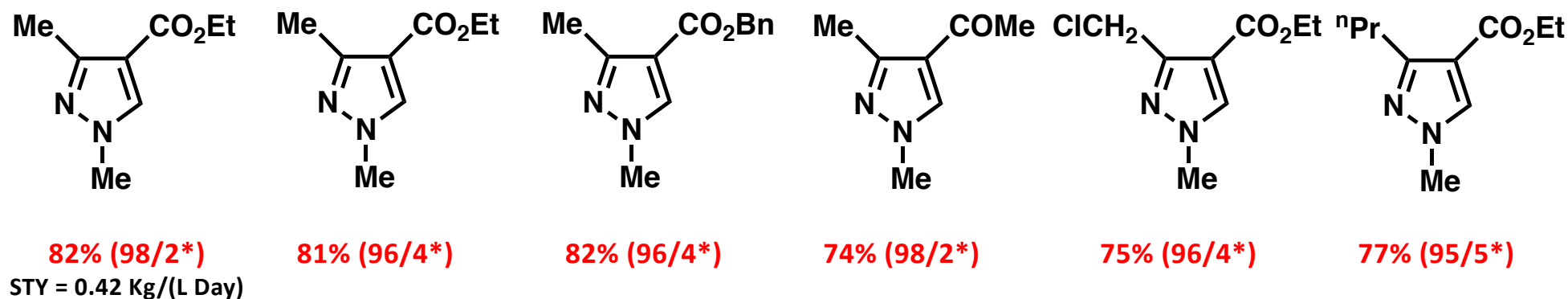
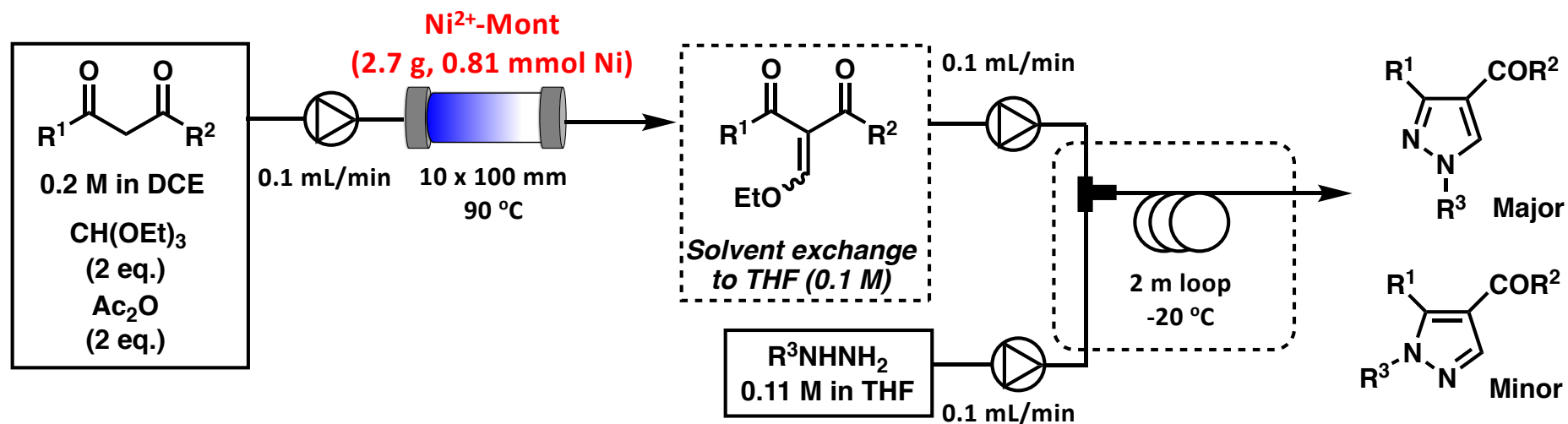
- Used for the prevention of primary infection in most surgeries
- Registered as one of the essential medicines defined by the WHO
- Growing its demand and usage worldwide
- ◆ Necessary to isolate manufacturing sites and equipment to prevent contamination and to ensure safety



# Synthetic Strategy for Continuous-flow Synthesis



# Sequential-flow Synthesis of Pyrazoles



\* : major/minor ratio

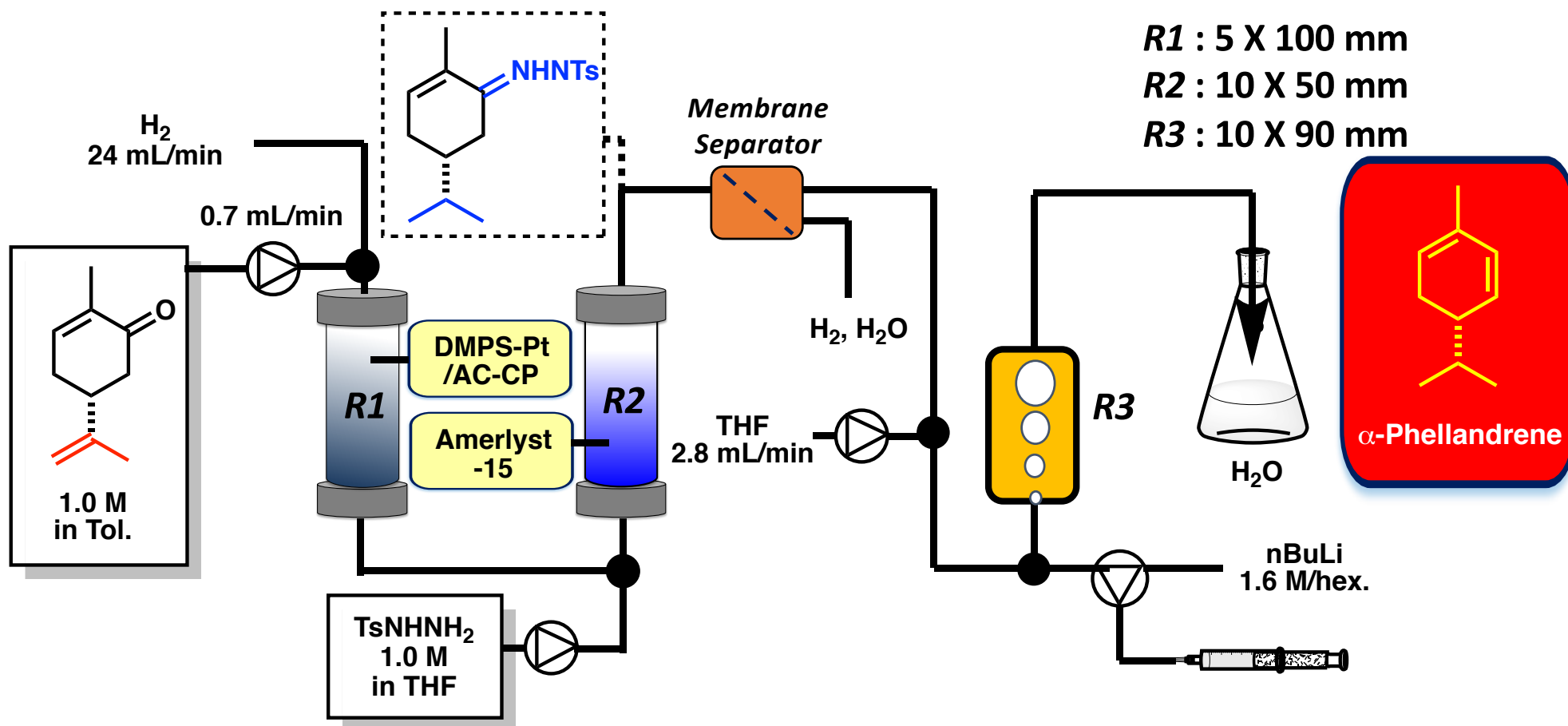
ASC (2019)

# Sequential-flow Synthesis of $\alpha$ -Phellandrene

Hydrogenation

Condensation

Shapiro Reaction



**R1** : 5 X 100 mm

**R2** : 10 X 50 mm

**R3** : 10 X 90 mm

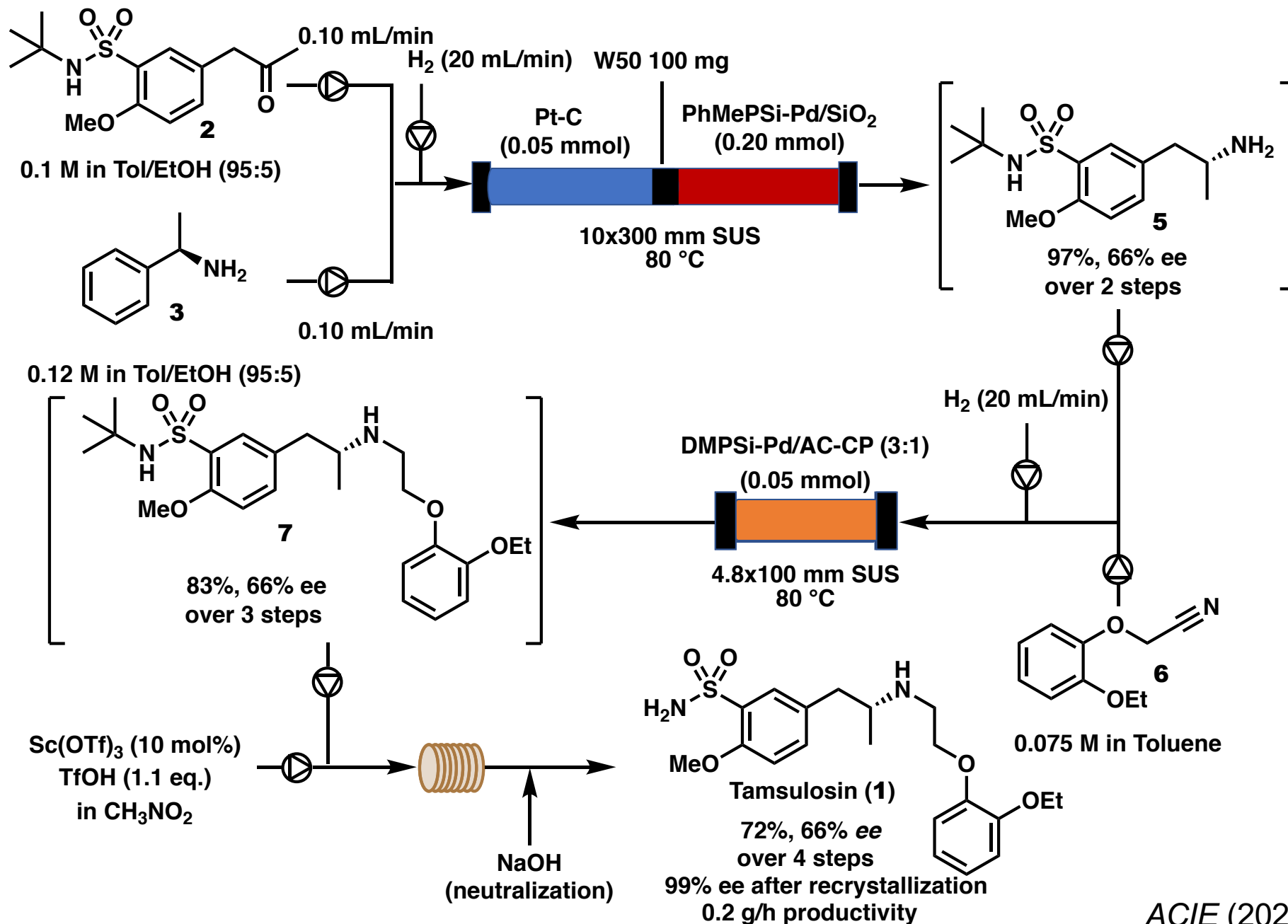
Runtime: 100 min.

Yield (3-steps): 83% (= 7.9 g/ 100 min)

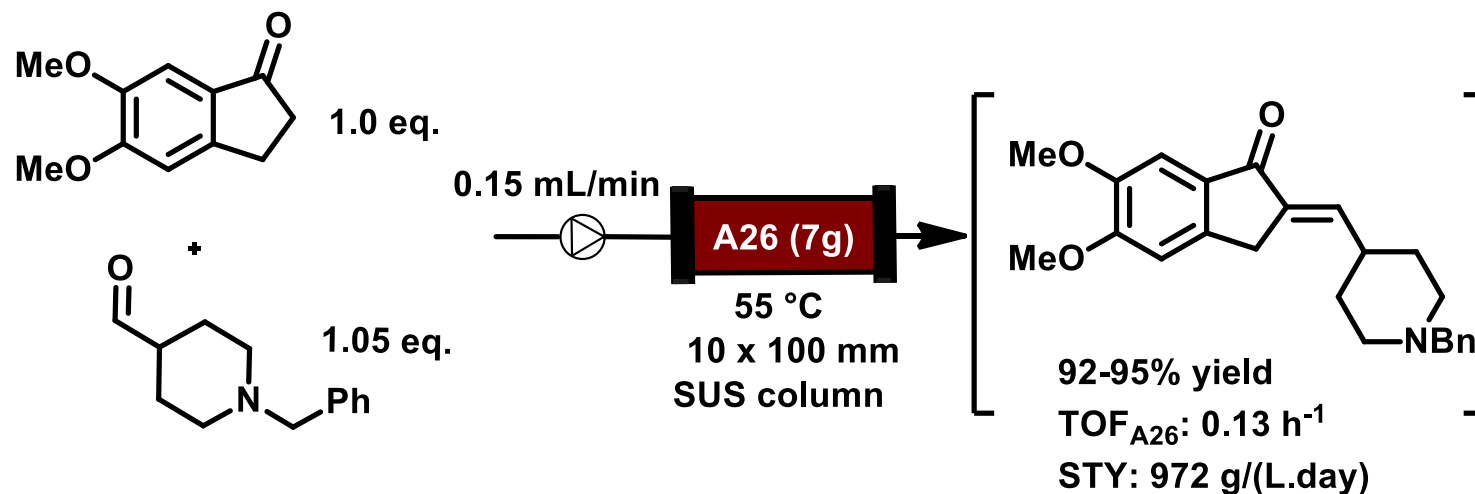
STY: 366 g/L h

OPRD (2020)

# Sequential-flow Synthesis of Tamsulosin

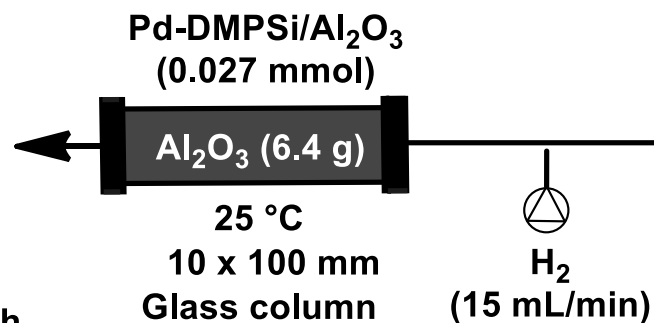
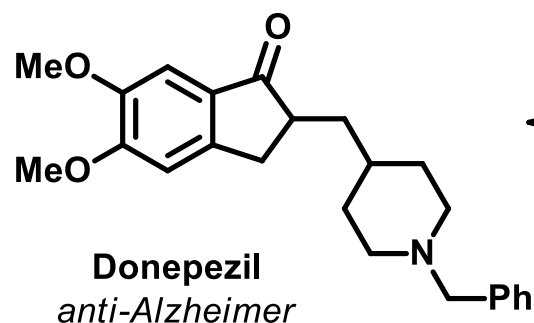


# Sequential-flow Synthesis of Donepezil



0.1 M (THF/iPrOH, 9:1)  
+2% H<sub>2</sub>O

92-95% yield for 30 h  
TOF<sub>Pd</sub>: 31.2 h<sup>-1</sup>  
STY: 488 g/(L.day)  
Productivity: 7.7 g/day



# Alternative Sequential-flow Synthesis of Donepezil

