Flow Chemistry
~“micro” flow to “fine” flow~

2018/9/22 (Sat.)

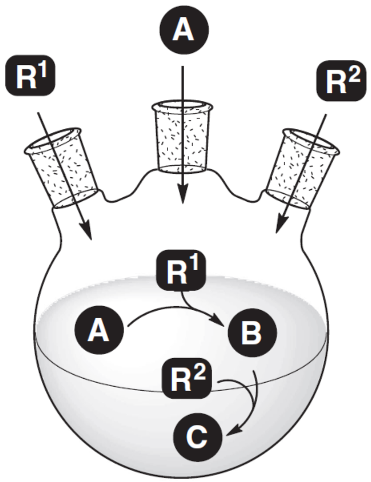
Literature Seminar

Taiki Fujita (M2)

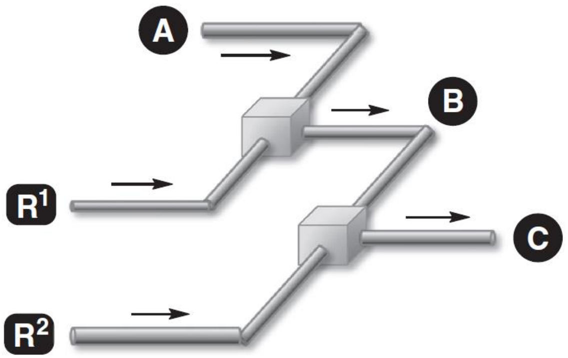
Introduction of Flow

Batch vs Flow

Batch reaction



Flow reaction



Laboratory scale
Fine chemicals

Large scale industry production

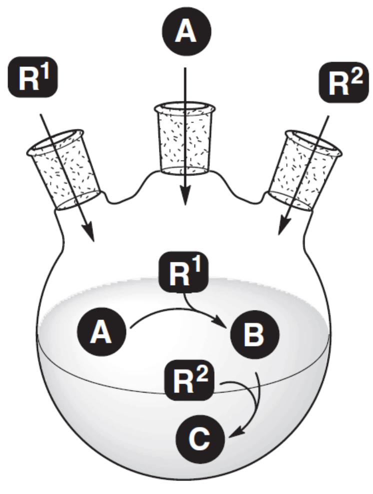
In flow reaction, introduction, reaction and recovery are conducted *continuously*.

Nagaki A. *J. Synth. Org. Chem.* 2015, *73*, 423.

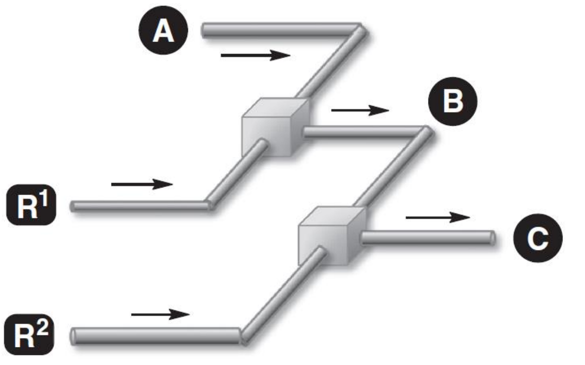
Introduction of Flow

Batch vs Flow

Batch reaction



Flow reaction



The merit of flow method

Saving space, time and cost.

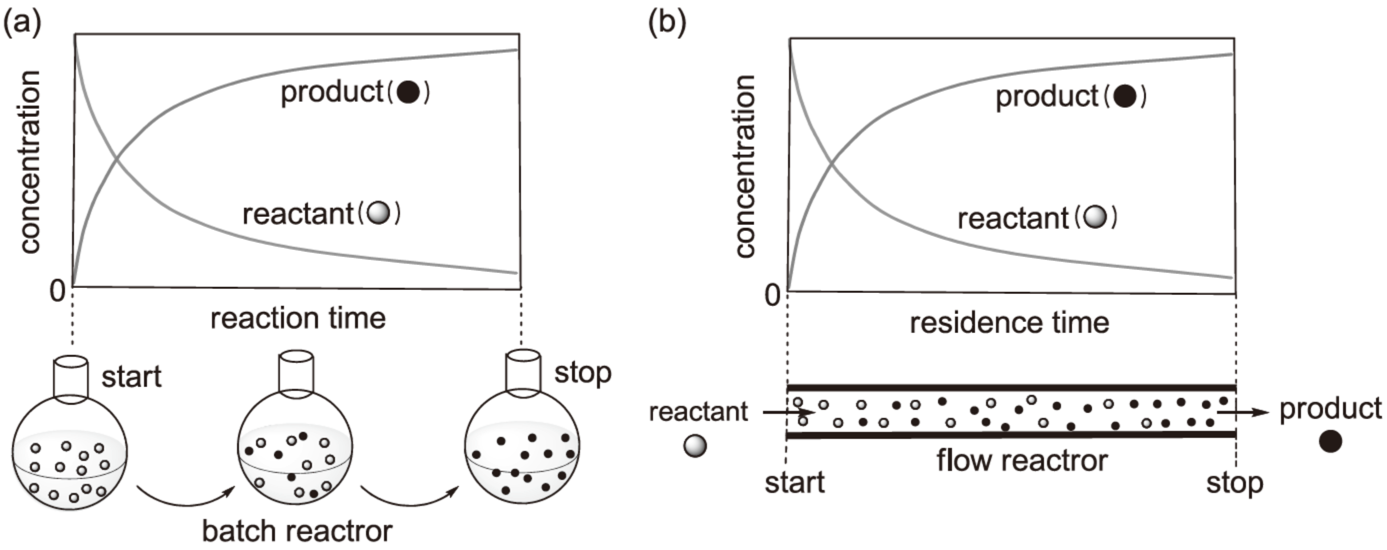
Safe reaction

Unique reactivity …

Nagaki A. *J. Synth. Org. Chem.* 2015, *73*, 423.

Character of Flow Reactor

<u>Time is controlled by space</u>



reaction time ≡ residence time

Nagaki A. *J. Synth. Org. Chem.* 2015, *73*, 423.

Flash Chemistry and Jun-ichi Yoshida

Micro flow chemistry is effective method when the reaction is very fast or unstable intermediate generate.

Flash chemistry ; using rapidly generated unstable intermediate for another reaction.

Jun-ichi Yoshida was born in Osaka, Japan in 1952. He graduated from Kyoto University in 1975, where he received his doctor's degree under the supervision of Prof. Makoto Kumada in 1981. In 1979 Yoshida joined the faculty at Kyoto Institute of Technology as an Assistant Professor. In the meantime, he visited University of Wisconsin during 1982–1983, where he joined the research group of Prof. B. M. Trost. In 1985 he moved to Osaka City University, where he was promoted to Associate Professor in 1992. In 1994 he was appointed as Full Professor of Kyoto University. His research interests include integrated organic synthesis on the basis of reactive intermediates, organic electron-transfer reactions, organometallic reactions, and flow microreactor synthesis. Awards: the Progress Award of Synthetic Organic Chemistry, Japan (1987), the Chemical Society of Japan Award for Creative Work (2001), Nagoya Silver Medal (2006), Humboldt Research Award (2007), Green and Sustainable Chemistry Award (2010), and Dogane Award (2010).

Yoshida J. *et al. Synlett*, 2011, *9*, 1189.

Characterististic Feature of Micro Reactor

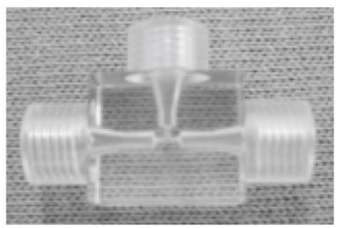
- **Extremely fast mixing**

$t \sim d^2/D$; d = diffusion distance, D = diffusion coefficient

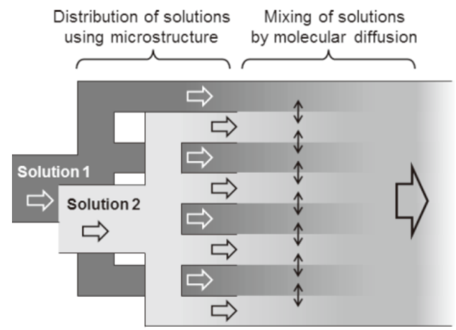
e.g. In flask, d = 100 μm $\rightarrow$ t ~ second order

e.g. In micro mixer, d ~ micro order $\rightarrow$ t ~ millisecond

High speed collision-type



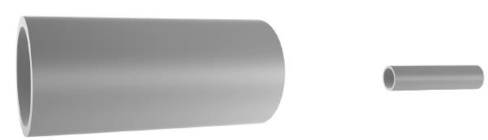
Multilamination-type



- **Precise temperature control**

Surface to volume ratio is very large

- **Heat transfer occurs rapidly**
- **Phase-boundary reaction is efficient**



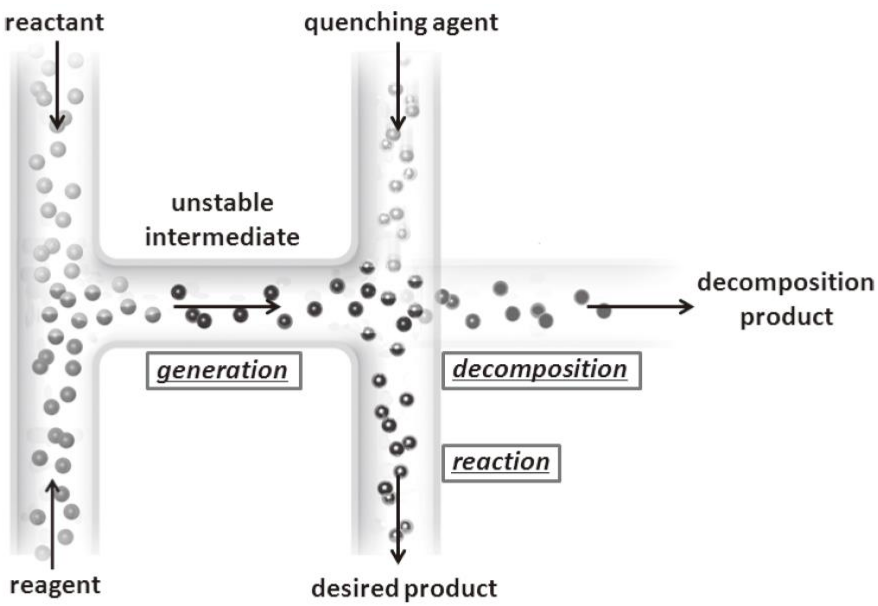
size	1/100
sueface area	1/10000
volume	1/1000000
sueface/volume	100

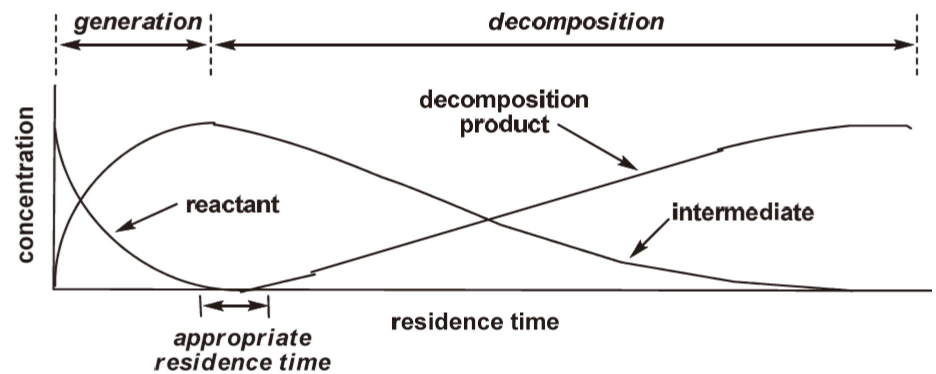
Nagaki A. *J. Synth. Org. Chem.* 2015, *73*, 423.

Characteristic Feature of Micro Reactor

- **Precise residence time control**

  lengh, flow rate and <u>fast</u> <u>mixing</u> is also important.





unstable short-lived reactive intermediates **can be used another reaction.**

Yoshida J. *et al. Chem. Sus. Chem.* 2011, *4*, 331.

Fast Mixing ~ Friedel-Crafts Reaction ~

Competitive Consecutive Reactions

$$A + B \xrightarrow{k_1} P1$$

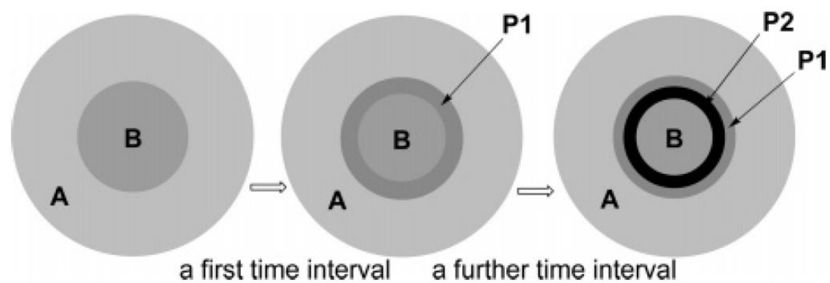
$$P1 + B \xrightarrow{k_2} P2$$

$K_1 >> K_2 \rightarrow$ <u>P_1 should be high</u>

↕

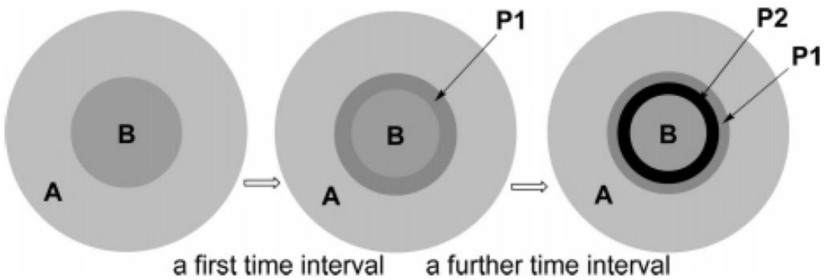
The selectivity is *not determined* by classical kinetic principles

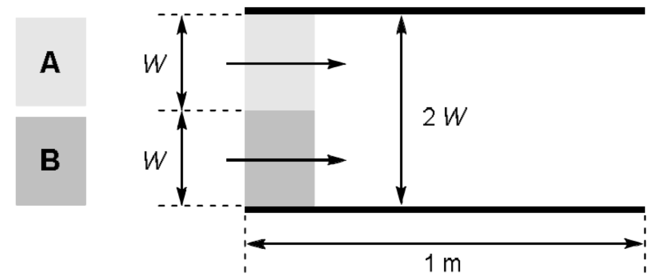
Disguised Chemical Selectivity



Yoshida J. *et al. J. Am. Chem. Soc.* 2005, *127*, 11666.
Rys P. *et al. Acc. Chem. Res*. 1976, *10*, 345.

CFD Simulation for DCS





density = $1.317*10^3$ kg/m^3, D = 10^{-9} m^2/s, v = $1.19*10^{-3}$ Pa, [A,B] = 0.01 M

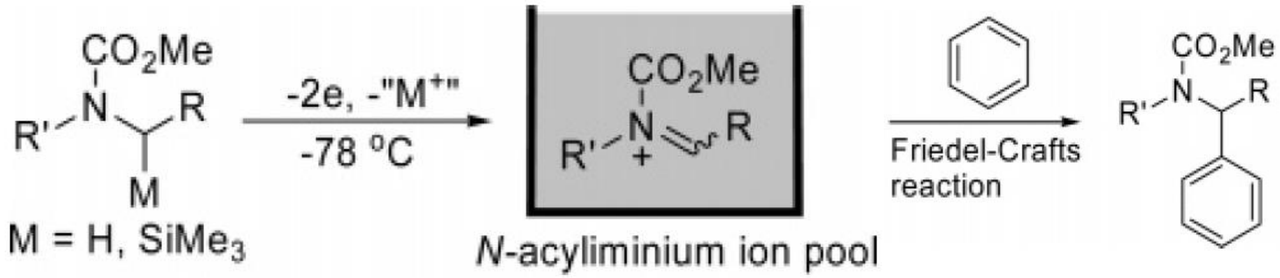
K_1 (L/(mol•s))	K_2 (L/(mol•s))	mixer	W (μm)	P_1 (%)	P_2 (%)	$P_1 : P_2$
10^4	10^2	ideal	-	94.6	2.7	97 : 3
10^4	10^2	diffusion	100	60.6	19.7	75 : 25
			25	89.6	4.5	95 : 5
			2.5	94.7	2.6	97 : 3
10^5	10^3	diffusion	100	31.1	34.3	47 : 53
			25	67.8	15.9	81 :19
			2.5	94.5	2.7	97 : 3
10^6	10^4	diffusion	100	14.5	42.7	25 : 75
			25	36.1	31.9	53 : 47
			2.5	90.5	4.7	95 : 5

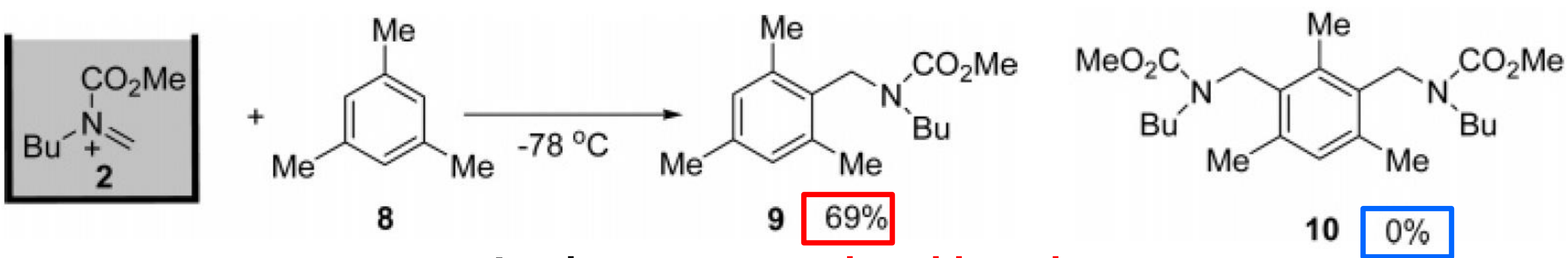
flow micro reactor is effective ***especially for fast reaction***

Yoshida J. *et al. J. Am. Chem. Soc.* 2005, *127*, 11666.

Friedel-Crafts Aminoalkylation

'Cation Pool'



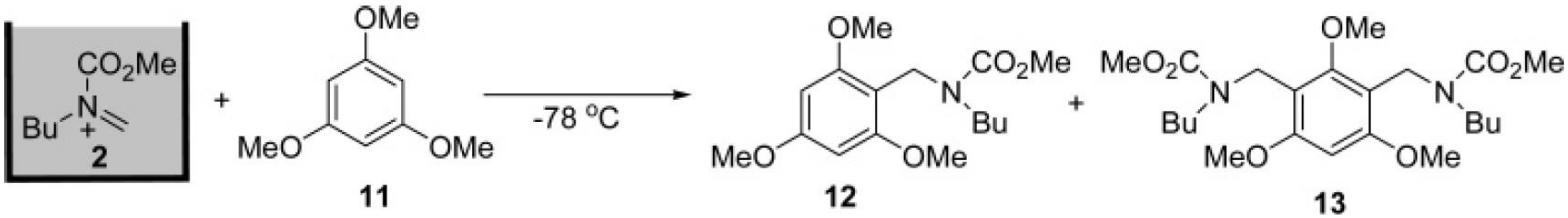


In situ, protonated and inactive

Mesitylene is not so reactive. ⟹ **Even in batch, good selectivity appears.**

Yoshida J. *et al. J. Am. Chem. Soc.* 2005, *127*, 11666.

Friedel-Crafts Aminoalkylation in Batch

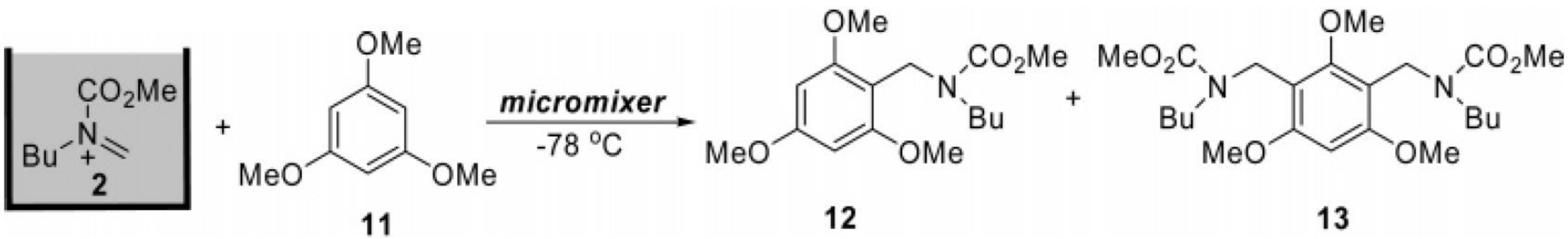


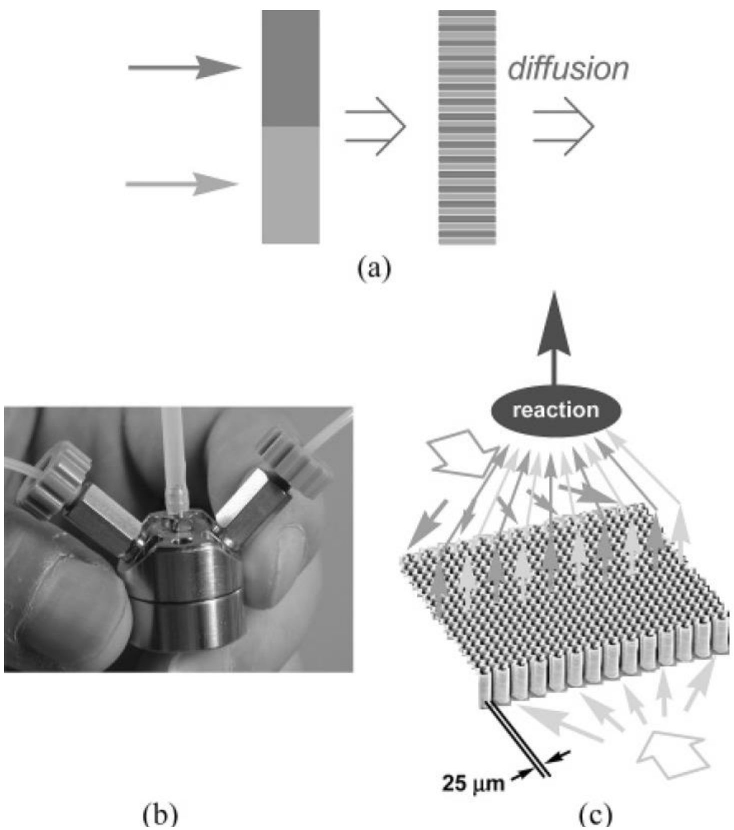
method of additon	**12** (%)	**13** (%)
addition of **2** to **11**	37	32
addition of **11** to **2**	33	33
simultaneous addition of **2** and **11**	34	30

Trimethoxybenzene is *highly reactive*. ⟹ **In batch, poor selectivity appears.**

Yoshida J. *et al. J. Am. Chem. Soc.* 2005, *127*, 11666.

Friedel-Crafts Aminoalkylation in Flow





temperature (°C)	reactor	conversion of 11 (%)	**12** (%)	**13** (%)
−78	micromixer[a]	91	92	4
	batch reactor[b]	75	37	32
−47	micromixer[a]	92	84	15
	batch reactor[b]	86	7	22
−27	micromixer[a]	85	70	19
	batch reactor[b]	99	1	7
0	micromixer[a]	93	30	15
	batch reactor[b]	quantitative	0	1

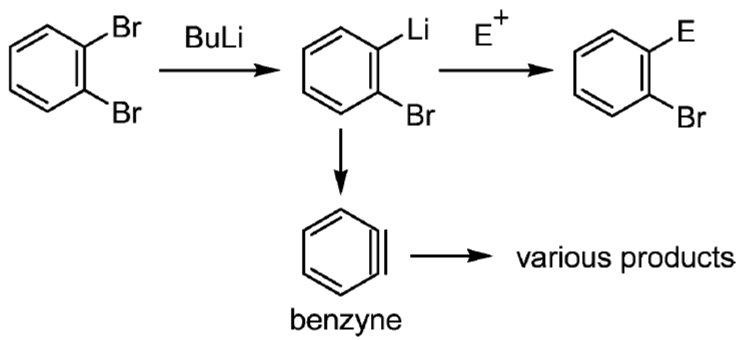
flow rate (mL/min)[a]	**12** (%)	**13** (%)
1	14	19
3	52	14
5	92	4

Flow rate **is also important factor for mixing efficiency.**

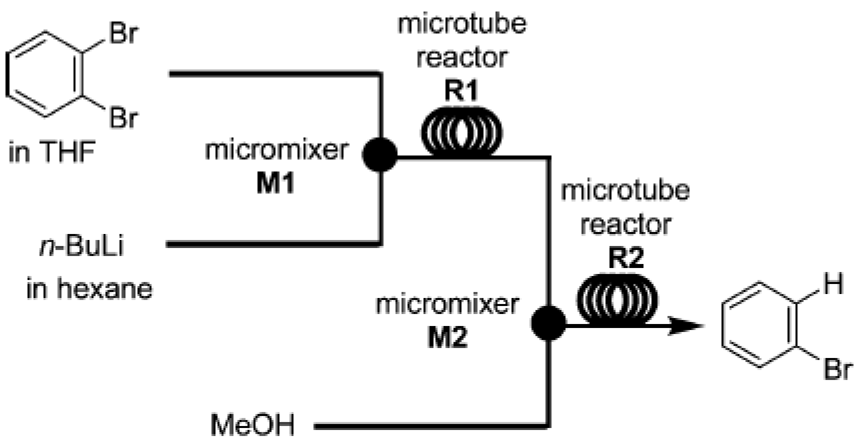
Yoshida J. *et al. J. Am. Chem. Soc.* 2005, *127*, 11666.

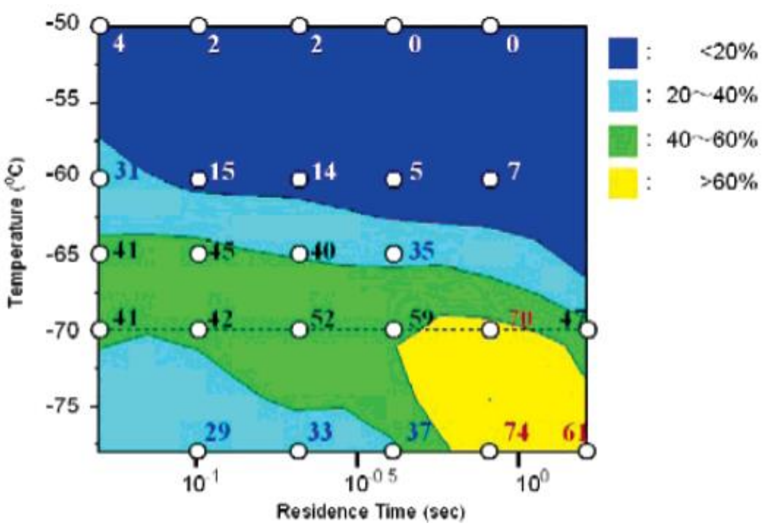
Precis Temperature Control

-110 ºC



At -78 ºC, desired product was not obtained completely.

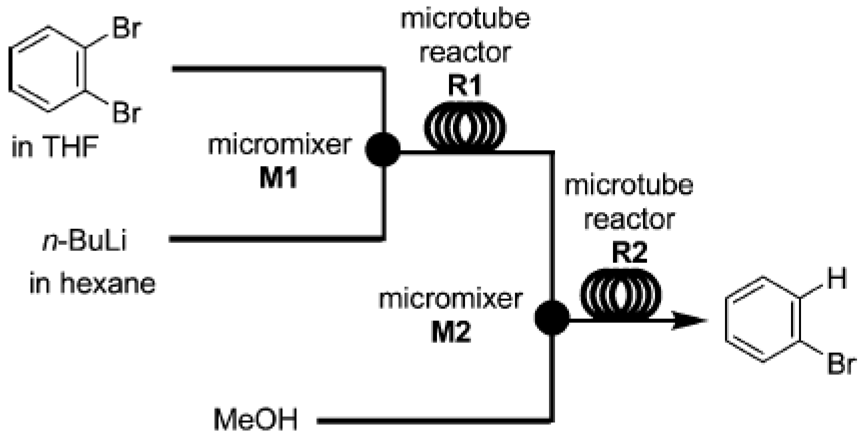


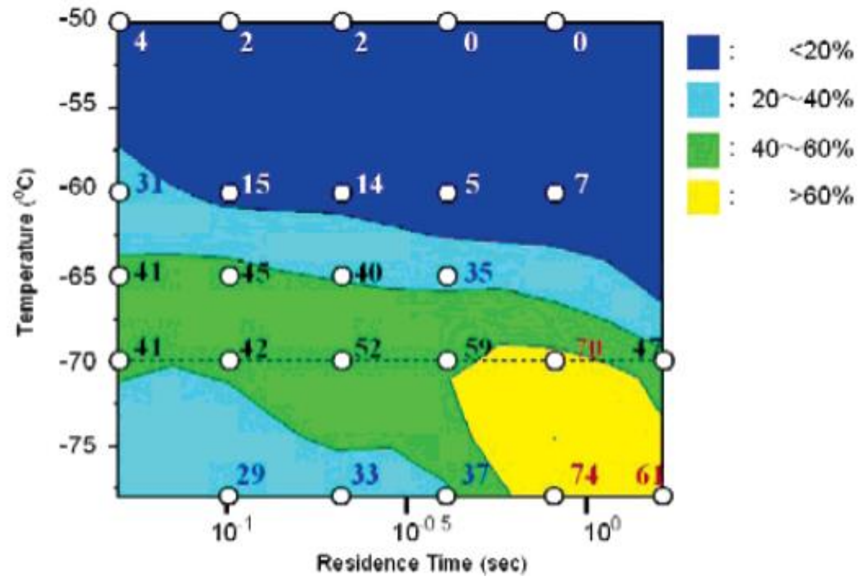


Temperature-residence time map is effective to optimize reaction condition.

Yoshida J. *et al. J. Am. Chem. Soc.* 2007, *129*, 3046.

Temperature-residence time map



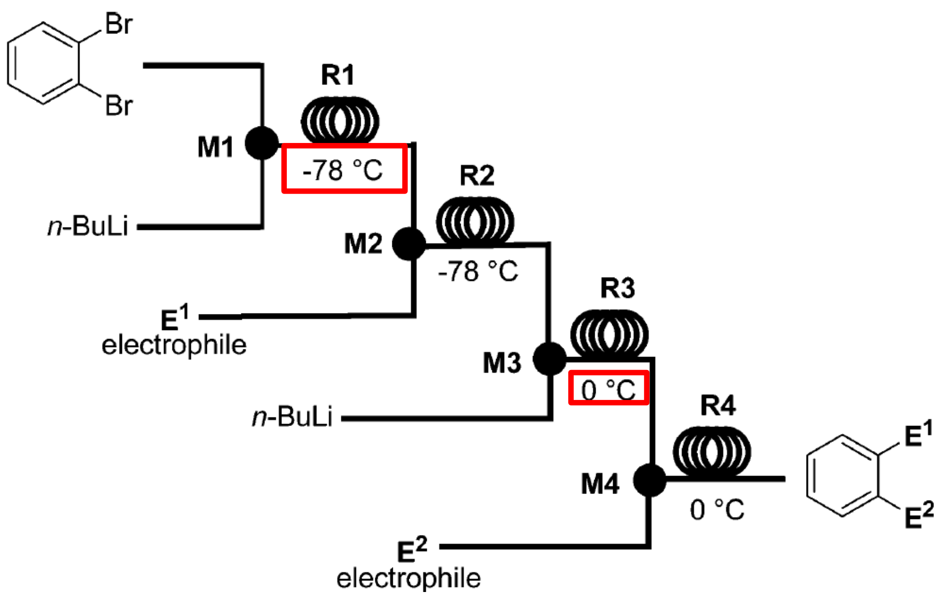


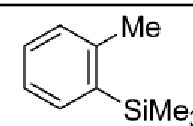
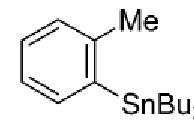
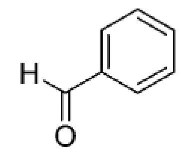
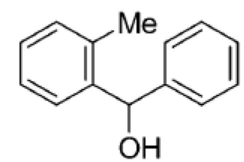
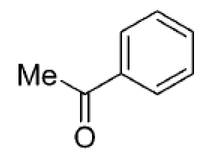
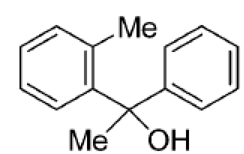
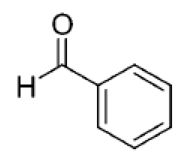
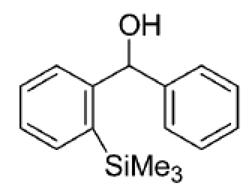
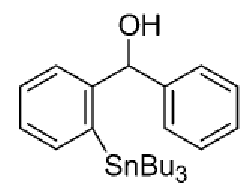
Decompose to benzyne

Insufficient generation of ArLi

Yoshida J. *et al. J. Am. Chem. Soc.* 2007, *129*, 3046.

Sequential Reactions



electrophile (E^1)	electrophile (E^2)	product	% yield
MeOTf	Me_3SiCl		67[a]
	Bu_3SnCl		62[a]
			61[a]
			53[a]
	Me_3SiCl		74[a]
	Bu_3SnCl		58[b]

Even at higher temperature, reaction proceed smoothly.

Yoshida J. *et al. J. Am. Chem. Soc.* 2007, *129*, 3046.

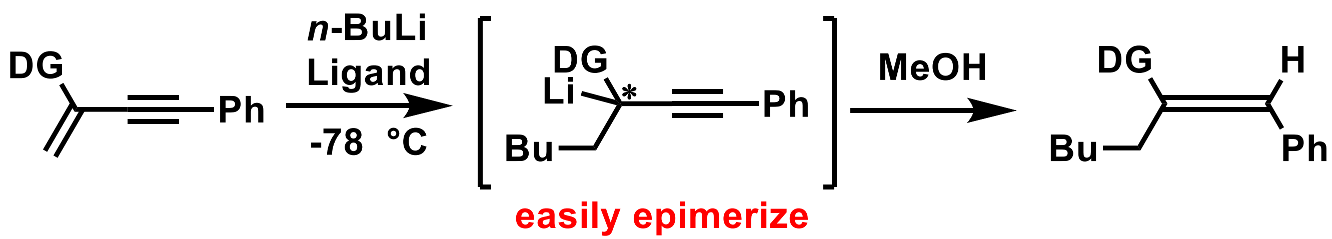
Precise Residence Time Control

Configurationally unstabele organometallics are not used.
(e.g.) asymmetric carbolithiation

↑

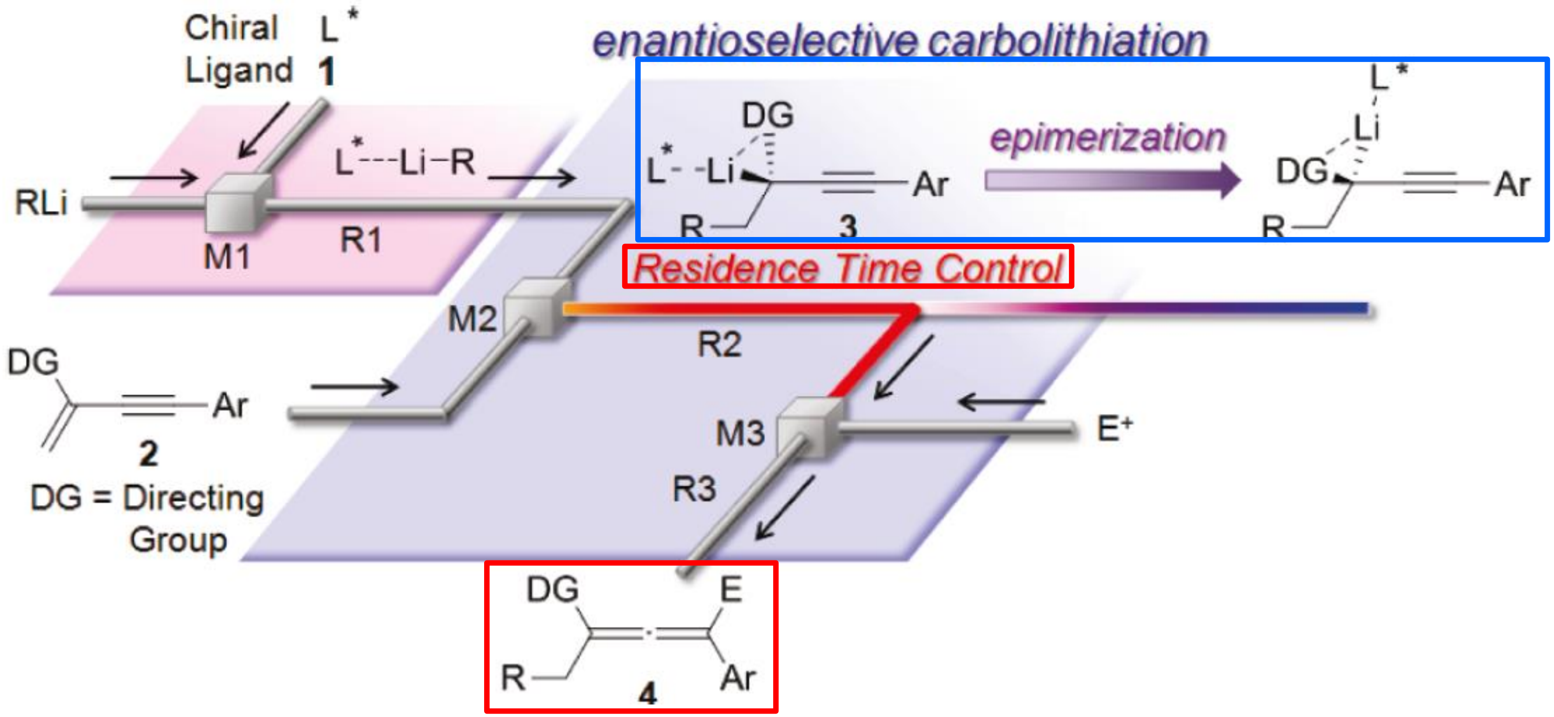
- **decompositon**
- **rapid epimerization**

Key ***: HIgh resolution control of residence time by microreactor***



Yoshida J. *et al. J. Am. Chem. Soc.* 2011, *133*, 3744.

Asymmetric Carbolithiation



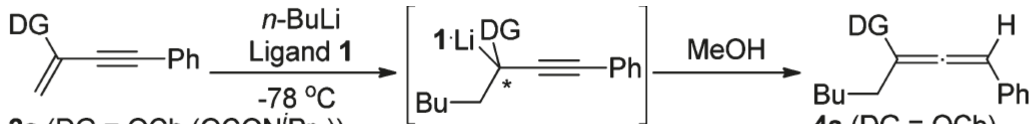
Reaction must be quenched before epirize.

↕

Reaction must proceed sufficiently.

Yoshida J. *et al. J. Am. Chem. Soc.* 2011, *133*, 3744.

Screening



2a (DG = OCb (OCON^{i}Pr$_2$))
2b (DG = H)
2c (DG = OMOM)

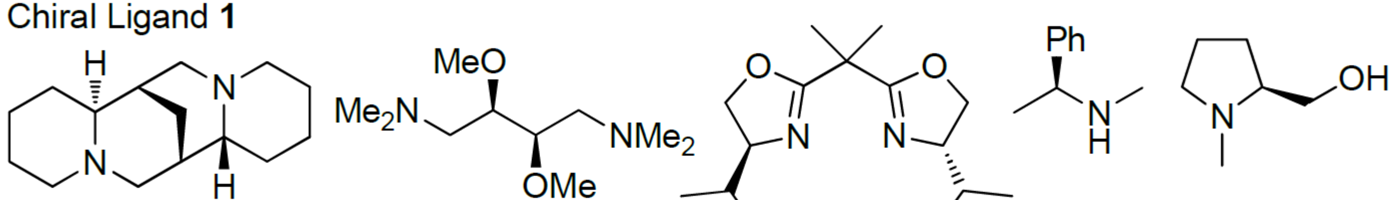
4a (DG = OCb)
4b (DG = H)
4c (DG = OMOM)

entry	substrate	ligand	product	% yield of product[b] (enantiomeric ratio)	% recovery of substrate
1	**2a**	**1a**	**4a**	91 (88:12)	4
2[c]	**2a**	**1a**	**4a**	82 (93:7)	10
3[c]	**2b**	**1a**	**4b**	83 (61:39)	1
4[c]	**2c**	**1a**	**4c**	0	91
5	**2a**	**1b**	**4a**	57 (52:48)	36
6	**2a**	**1c**	**4a**	<1 (45:55)	88
7	**2a**	**1d**	**4a**	<1 (34:66)	98
8	**2a**	**1e**	**4a**	0	>99

The importance of directing group

[c] ^{n}BuLi 0.67M in Tol, 3.0 ml/min

Chiral Ligand **1**

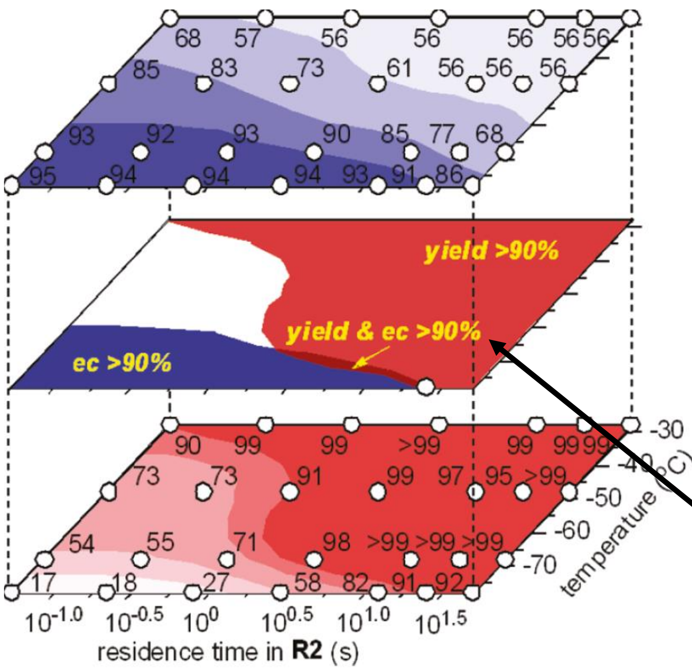


1a (-)-sparteine **1b** **1c** **1d** **1e**

Yoshida J. *et al. J. Am. Chem. Soc.* 2011, *133*, 3744.

Optimize the condition

%ec (R) = R/(R+S)*100 ; er = 93:7 → ec =93%



ec decreased with increasing t^R and temperature because of epimerization.

yield increased with increasing t^R and temperature.

Very small domain

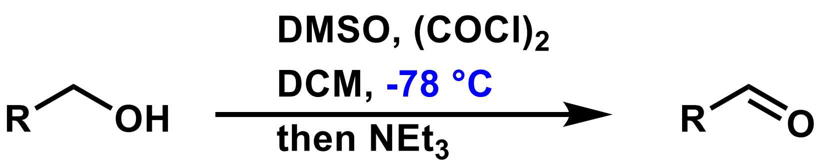
<u>Quantitative evaluation</u> of asymmetric reaction.

(t^R, T) = (25 s, -78 °C)

Flow : 91% yield, 91% ec ↔ Batch : 99% yield, 61% ec

Yoshida J. *et al. J. Am. Chem. Soc.* 2011, *133*, 3744.

Room Temperature Swern Oxidation



Swern oxidation is one of the most iportant organic reactions.

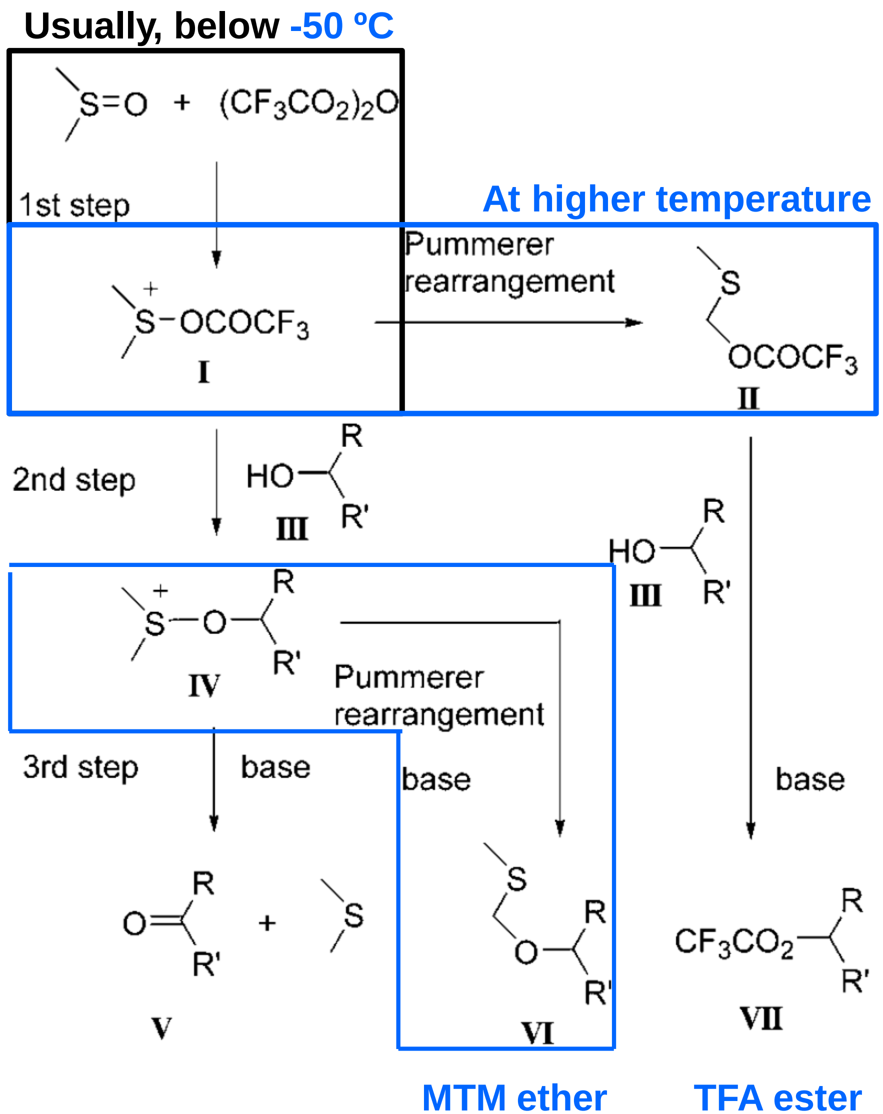
Modification, which TFAA was used instead of (COCl), is known for high reactivity.

many side reactions !

Yoshida J. *et al. Angew. Chem. Int. Ed.* 2005, *44*, 2413.

Side Reactions

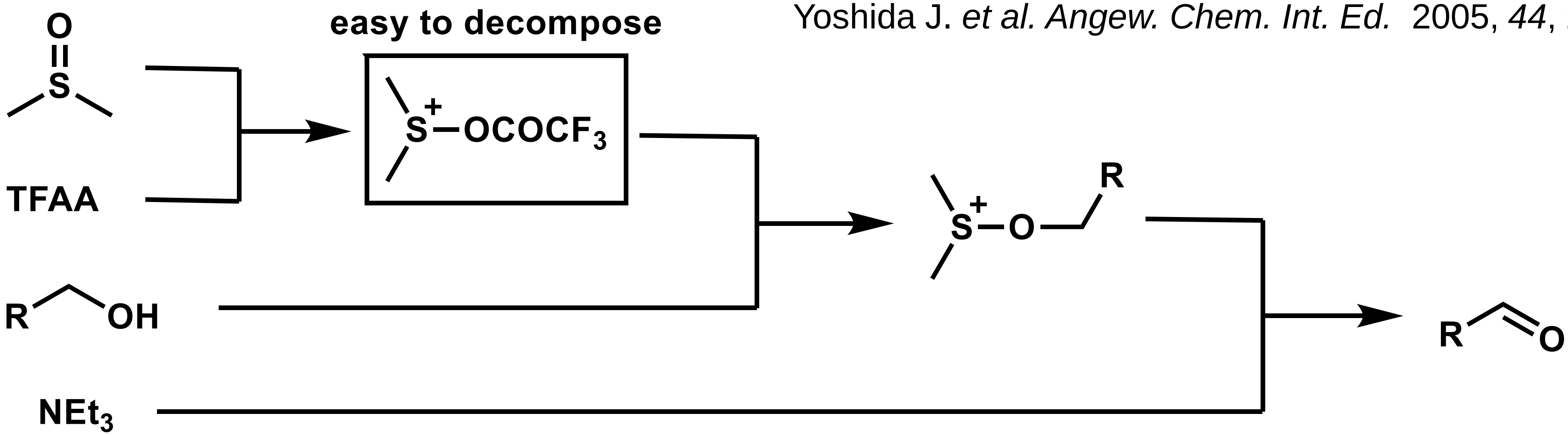
I is stabele only below -30 ºC.



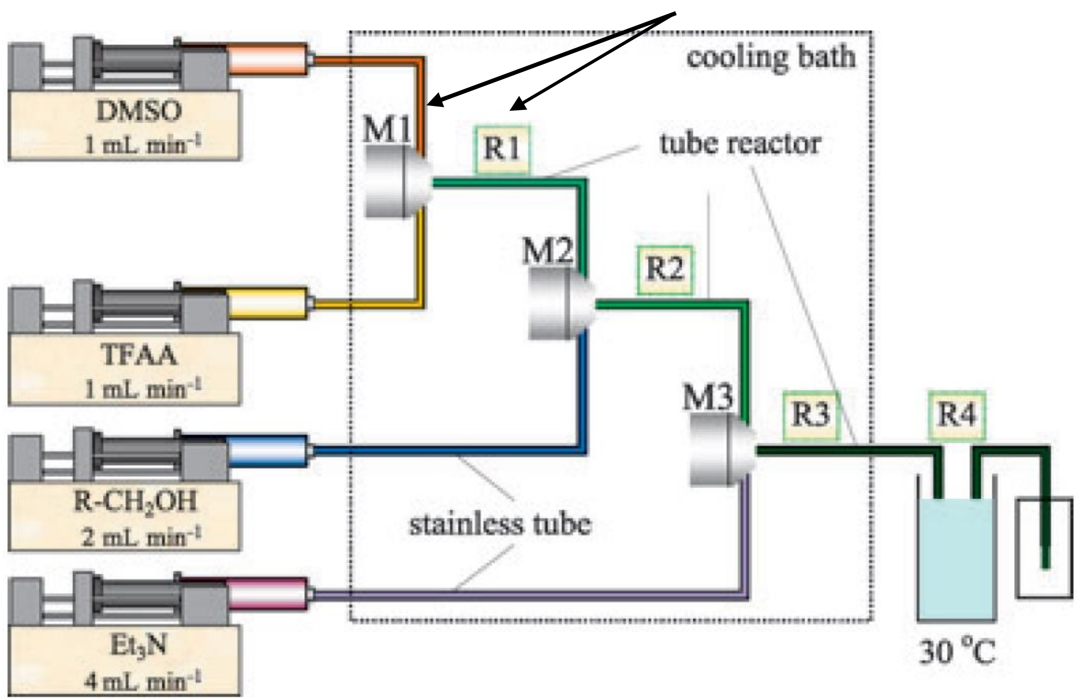
Yoshida J. *et al. Angew. Chem. Int. Ed.* 2005, *44*, 2413.

Microreactor

Yoshida J. *et al. Angew. Chem. Int. Ed.* 2005, *44*, 2413.



The Key : control of M1 and R1



Results

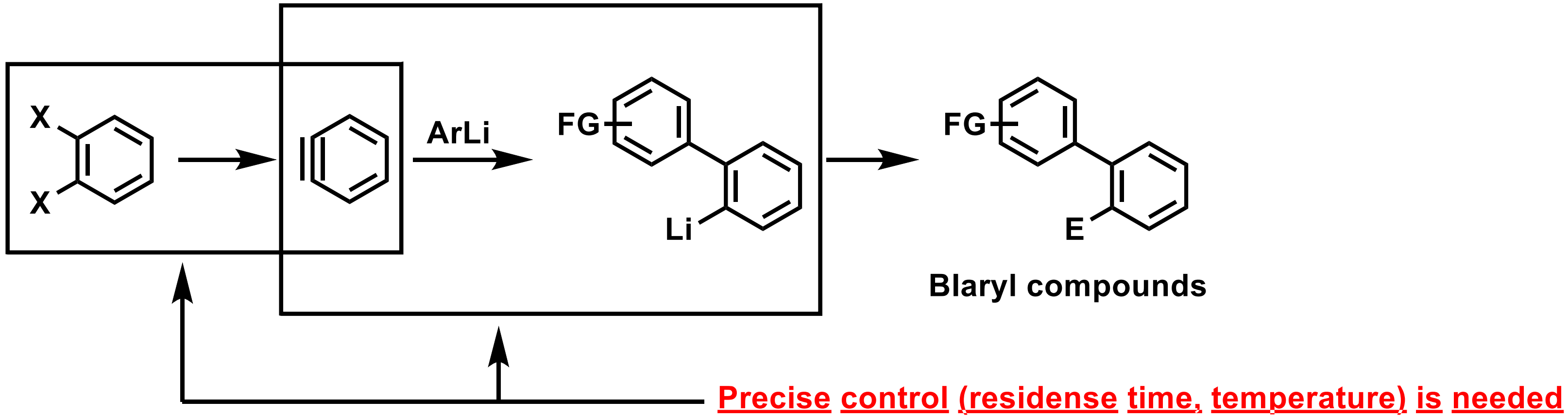
V = desired product, VI = MTM ether, VII = TFA ester

Alcohol **III**	System	Residence time in R1 [s]	*T* [°C]	Conversion [%]	Yield of **V** [%]	Yield of **VI** [%]	Yield of **VII** [%]
1-decanol	microscale flow	2.4	−20	95	75	8	19
		0.01	0	94	70	6	22
		0.01	20	96	71	6	22
	macroscale batch		−20	73	11	1	90
2-octanol	microscale flow	2.4	−20	92	95	5	2
		0.01	0	91	86	4	3
		0.01	20	88	89	3	2
	macroscale batch		−20	51	20	2	75
cyclohexanol	microscale flow	2.4	−20	88	88	6	5
		0.01	0	90	89	7	1
		0.01	20	81	88	5	2
	macroscale batch		−20	86	19	2	70
			−70	88	83	10	5
benzyl alcohol	microscale flow	2.4	−20	97	91	n.d.[b]	8
		0.01	0	100	78	n.d.[b]	14
		0.01	20	100	75	n.d.[b]	16
	macroscale batch		−20	80	49	n.d.[b]	50

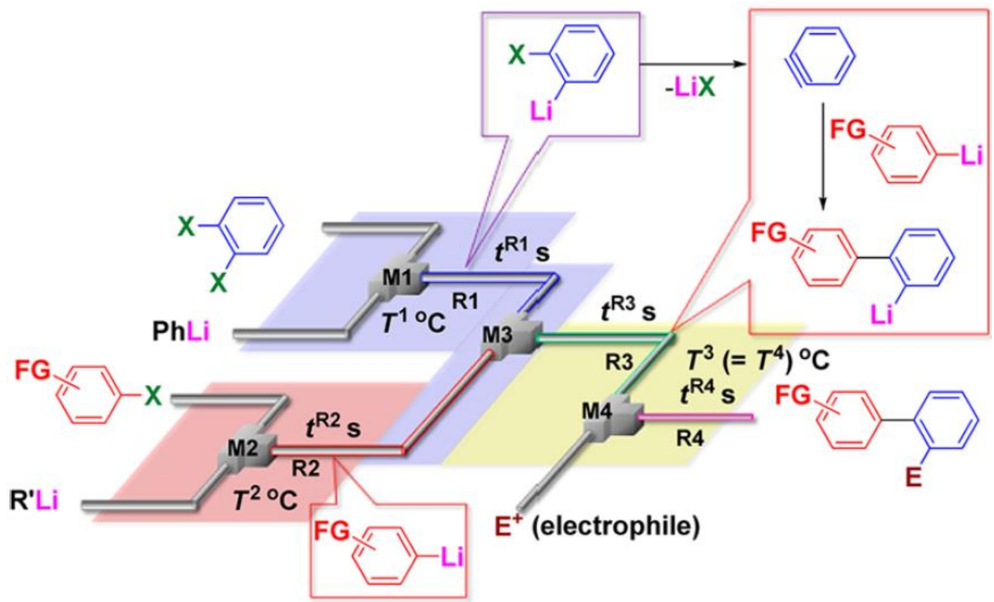
- **Precise temperature control**
- **Extremely fast and efficient mixing**
- **Short residence time**

Yoshida J. *et al. Angew. Chem. Int. Ed.* 2005, *44*, 2413.

TM-Free Three Components Coupling

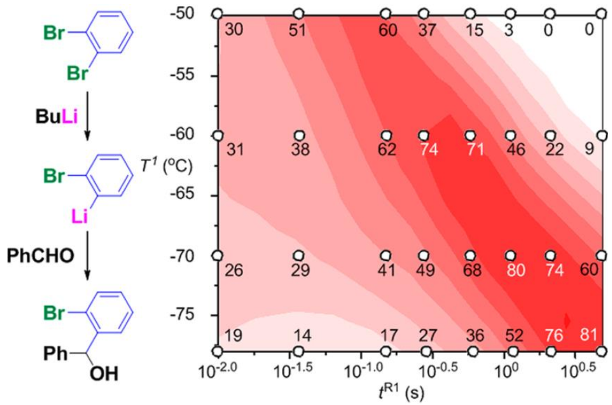


- Benzyne is difficult to use for carbolithiation.
- *o*-disubstituted biaryl synthesis with TM-free



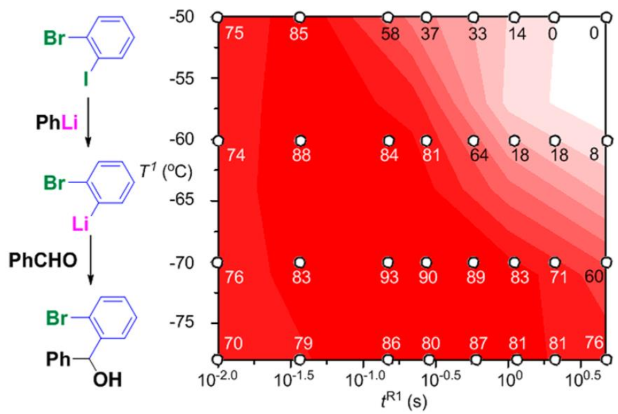
Yoshida J. *et al. J. Am. Chem. Soc.* 2014, *136*, 12245.

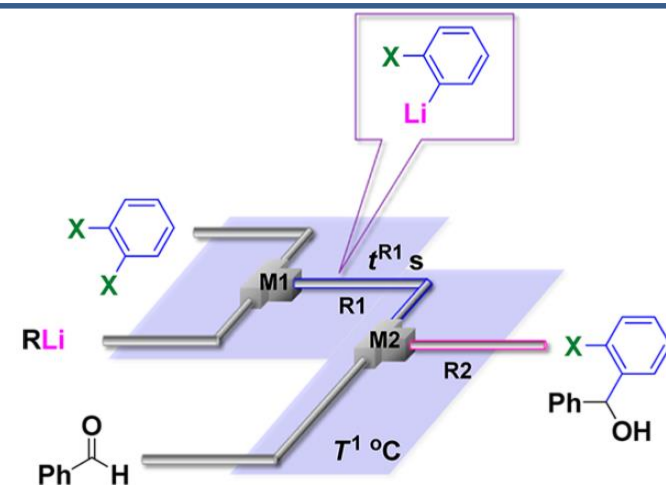
R1 : Benzyne Control

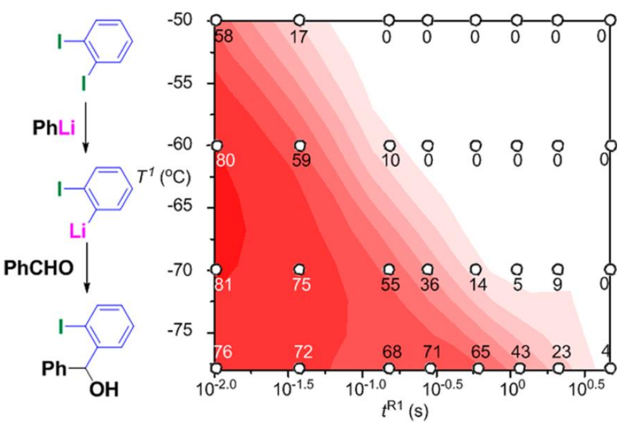


Bromine/lithium exchange is not so fast.

Key : Prevent decomposing to benzyne







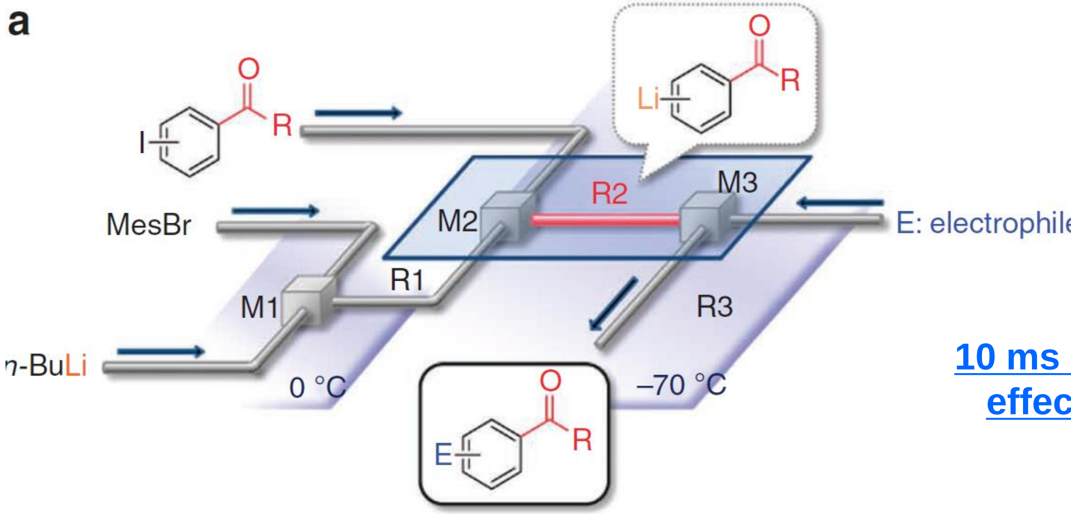
Iodine/lithium exchange is so fast.

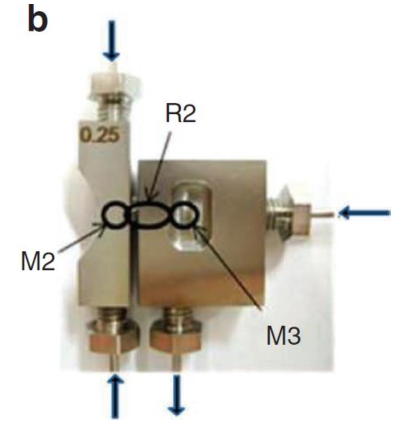
Yoshida J. *et al. J. Am. Chem. Soc.* 2014, *136*, 12245.

R2 : Carbolithiation with Functionalized ArLi

Precedent Works

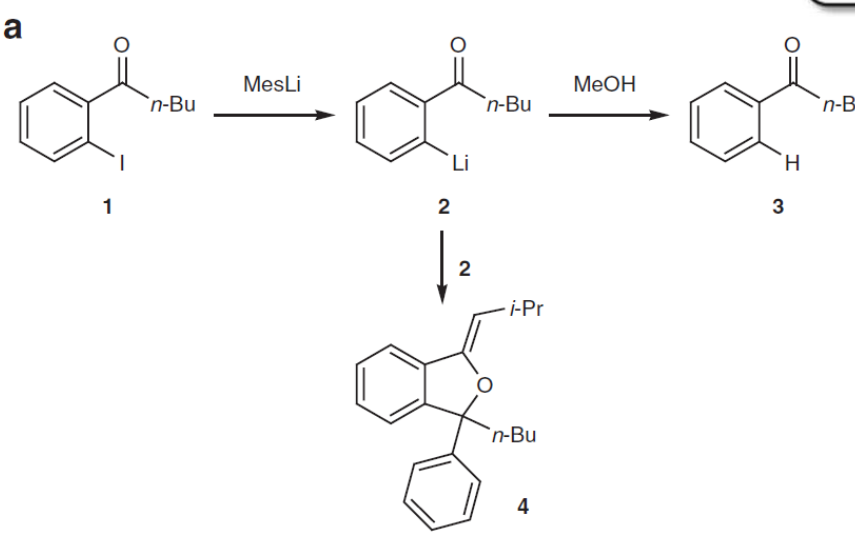
Aryl conpounds, containing electrophilic groups, can be used.
Nitrile, Nitro, Ester and even Ketone groups are tolerated.

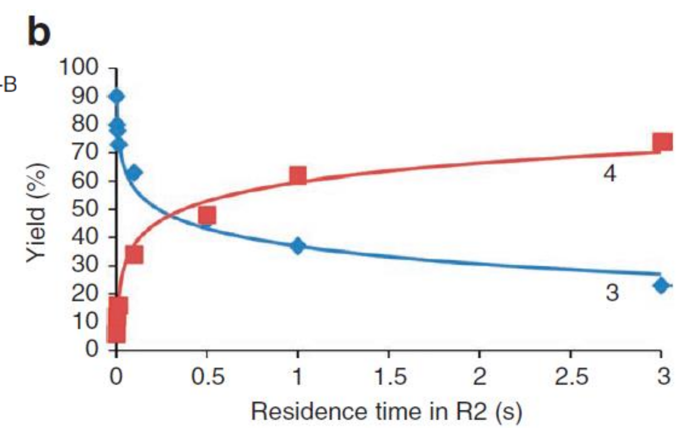


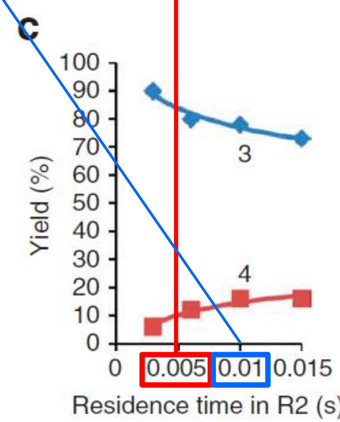


10 ms is not effective

Only 3 ms RT



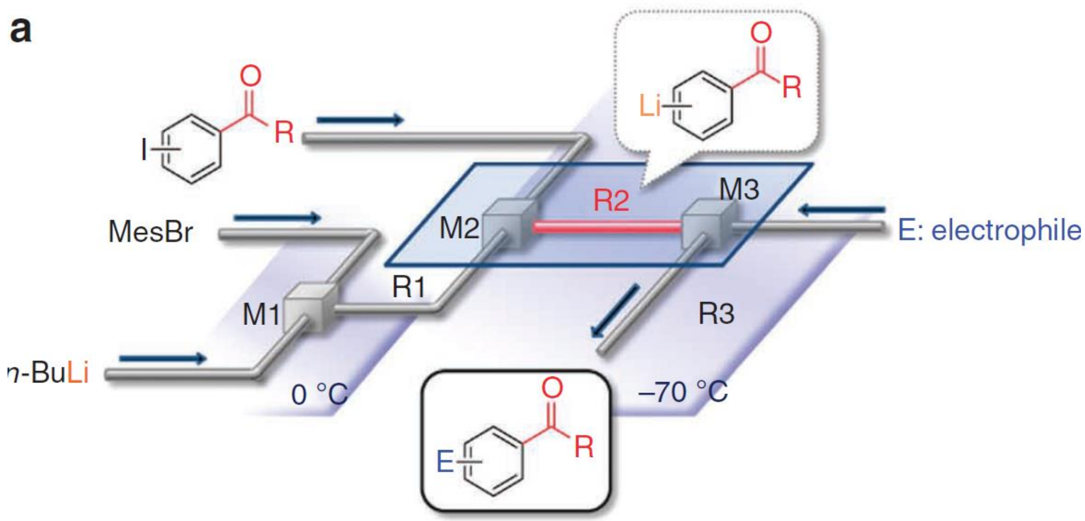


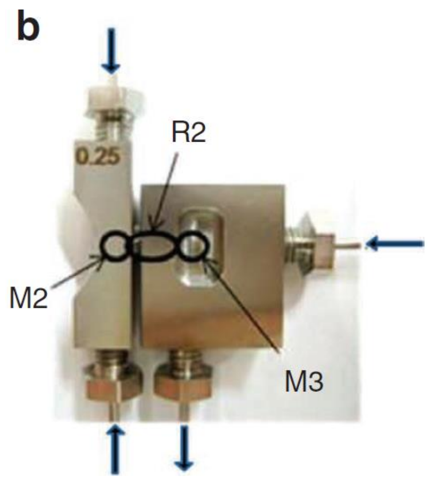


Yoshida J. *et al. Nat. Commun.* 2011, *136*, 12245.

For the Extremely Fast Mixing

Integrated devices
achieved this fast mixing.





Reynolds number ~ 10^2 !!

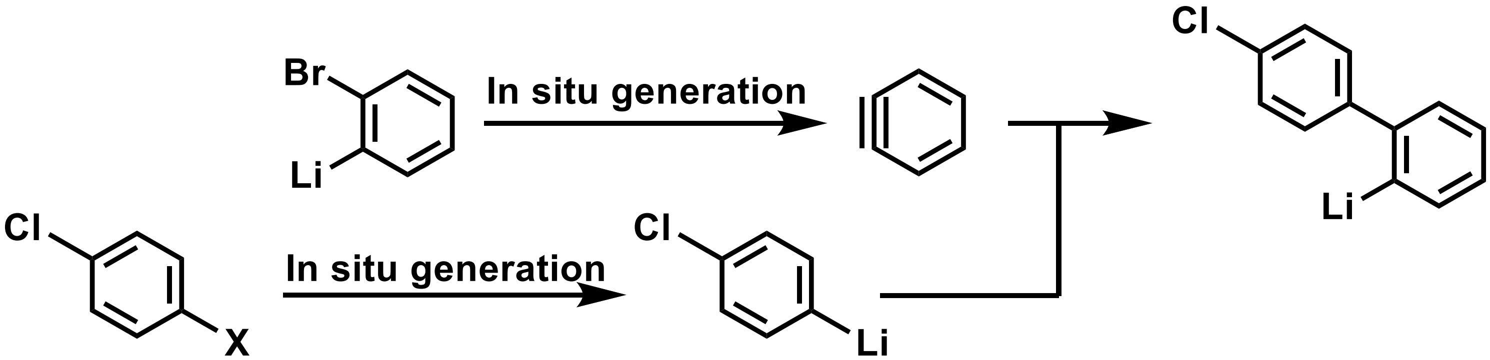
↓

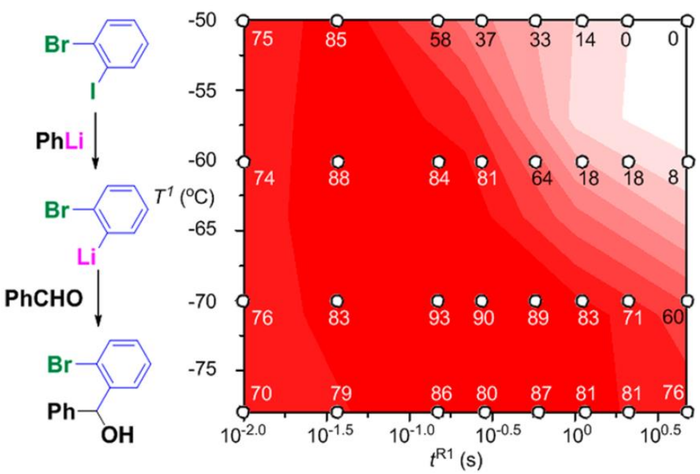
engulfment flow may occurs

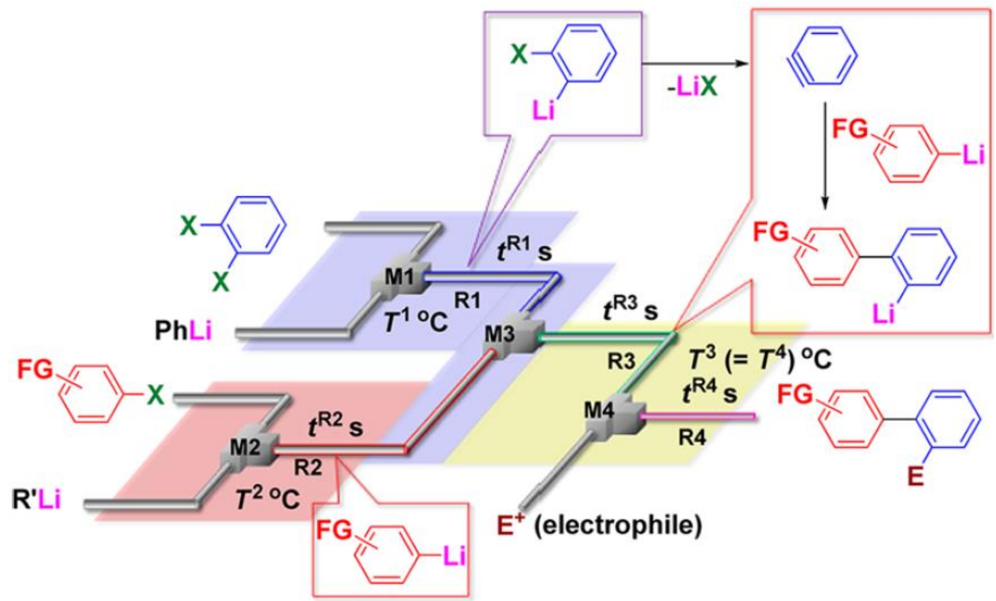
Inner diameter of R2 (μm)	Length of R2 (cm)	Residence time in R2 (s)	GC yield of product **3** (%)	GC yield of byproduct **4** (%)
250	1.0[a]	0.0030	91	7
250	2.0[a]	0.0060	80	12
250	3.3	0.010	78	16
250	5.0	0.015	73	15
500	8.3	0.10	58	31
1000	10.4	0.50	49	51
1000	20.8	1.0	37	62
1000	62.4	3.0	23	74

Yoshida J. *et al. Nat. Commun.* 2011, *136*, 12245.

R2 : Carbolithiation with Functionalized ArLi







T^1 = -70 °C, t^{R1} = 0.22 s

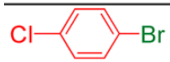
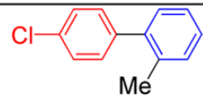
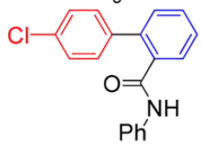
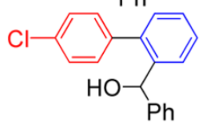
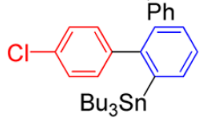
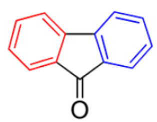
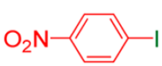
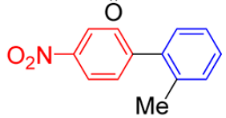
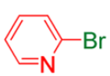
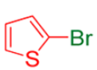
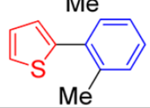
T^2 = 0 °C, t^{R2} = 0.31 s ⟶ **cooled to -70 °C**

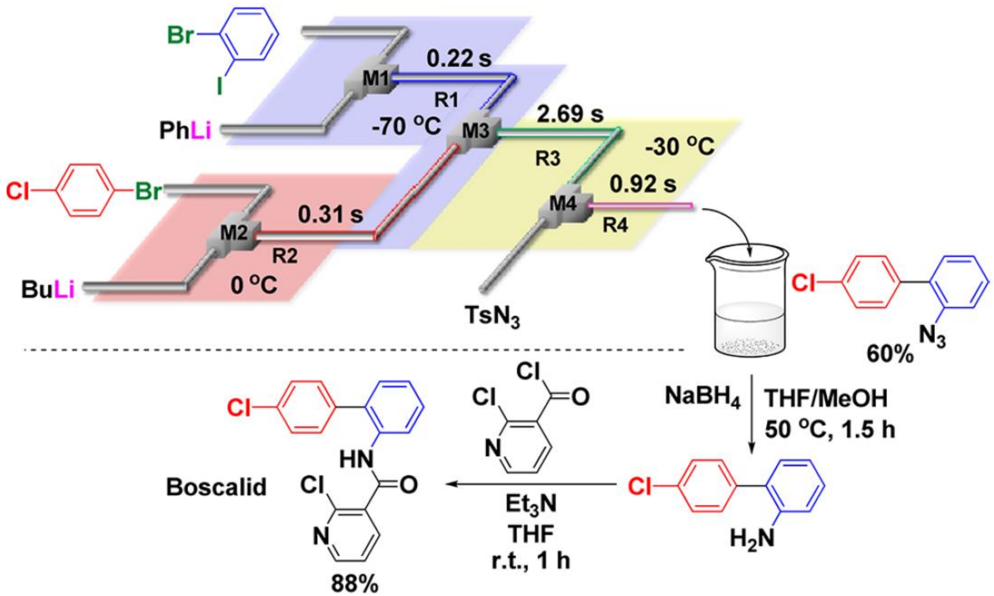
T^3 = -30 °C, t^{R3} = 2.69 s

↓

Flash generated benzyne

Substrate Scope and Application

substrate	electrophile	product	yield (%)
	MeOTf[b,c]		73
	TMSOTf[b]		53
	PhCNO[b]		63
	PhCHO[b]		69
	Bu_3SnCl[b]		58
	–[c,e]		71
	MeOTf[f]		50
	MeI[g]		50
	MeOTf[d]		58



Nitrile, Nitro are tolerated.

Short Summary of Micro Flow

Characteristics of micro flow

- **Fast mixing**
- **Temperature control**
- **Residencetime control**

⇓

Unique reactions are being developed.

Flow “Fine” Synthesis

Fine Synthesis

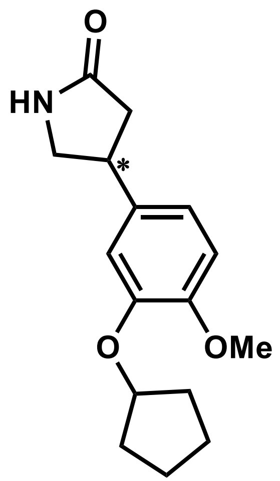
- **by *batch* method** → **Conventional organic synthesis**
- **by *flow* method** → **Flow "fine" synthesis**

Flow "fine" synthesis

- ***Reaction and synthesis that attain high yields and high selestivities by a flow method.***
- ***Synthesis of structurally complex molecules using a multistep flow system.***

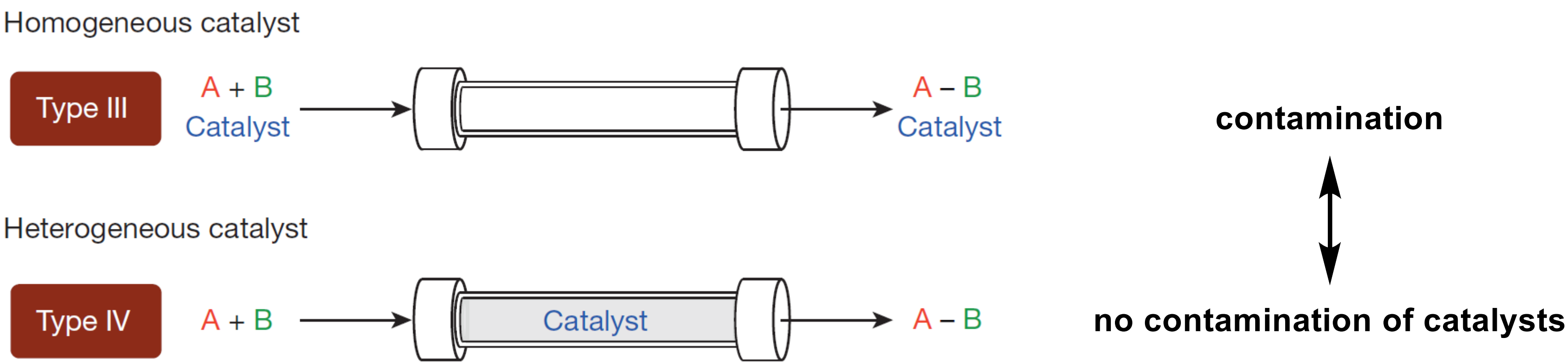
Kobayashi S. *Chem. Asian. J.* 2016, *11*, 425.

Total Synthesis of (*R*)– and (*S*)-Rolipram



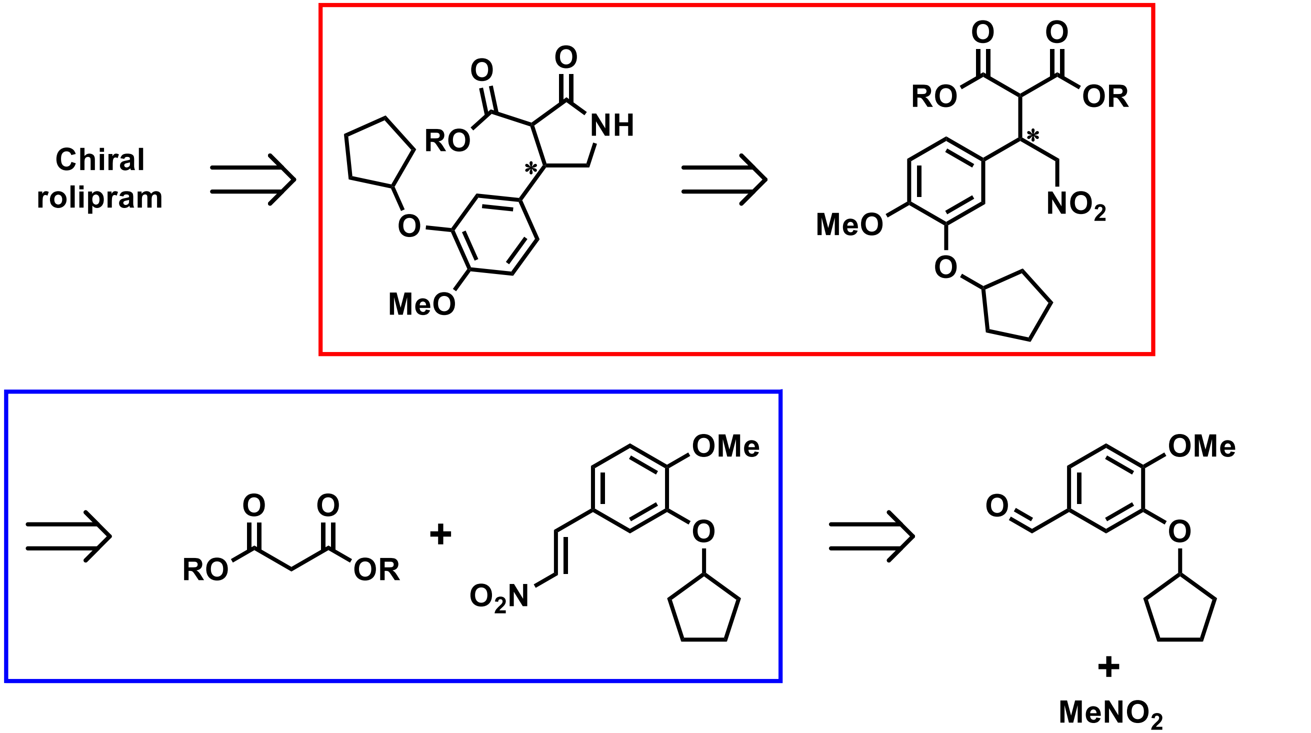
(*R*) - and (*S*) - Rolipram

- ***Continuous-flow system***
- ***Only heterogeneous catalysts***
- ***Robust Asymmetric Catalyst***
- ***No leaching Pd***



Kobayashi S. *et al*. *Nature*, 2015, *520*, 329.

Retrosynthesis of Rolipram

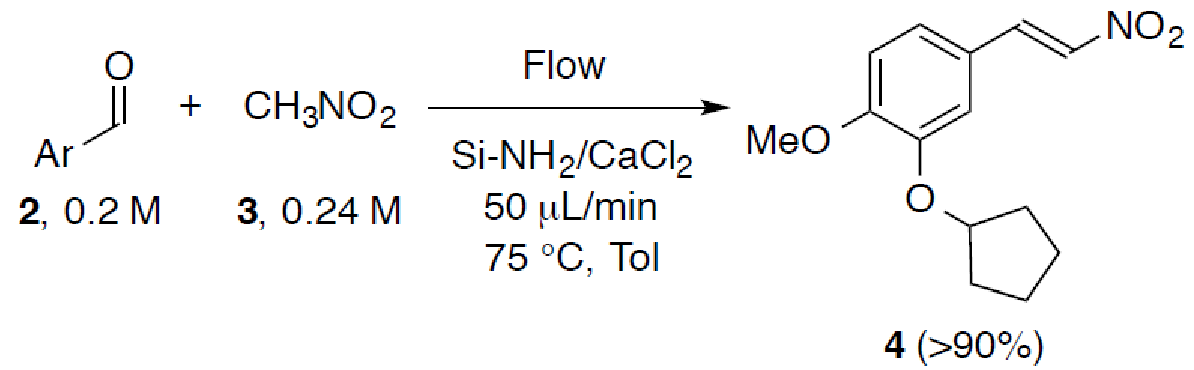


Commercially available

Key Points

- **Selective reduction by Pd catalysis and cyclization**
- **Catalytic asymmetric 1,4-addition of malonate**

Aldol Reaction



Not necessary

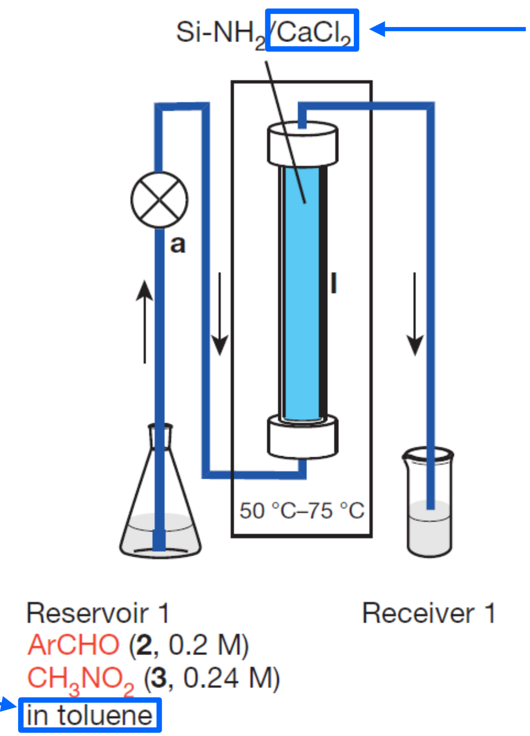
- **This system is stable for more than 1 week**
- **Just silica-supported amine works**

at 75 °C, this system found to be stable

↕

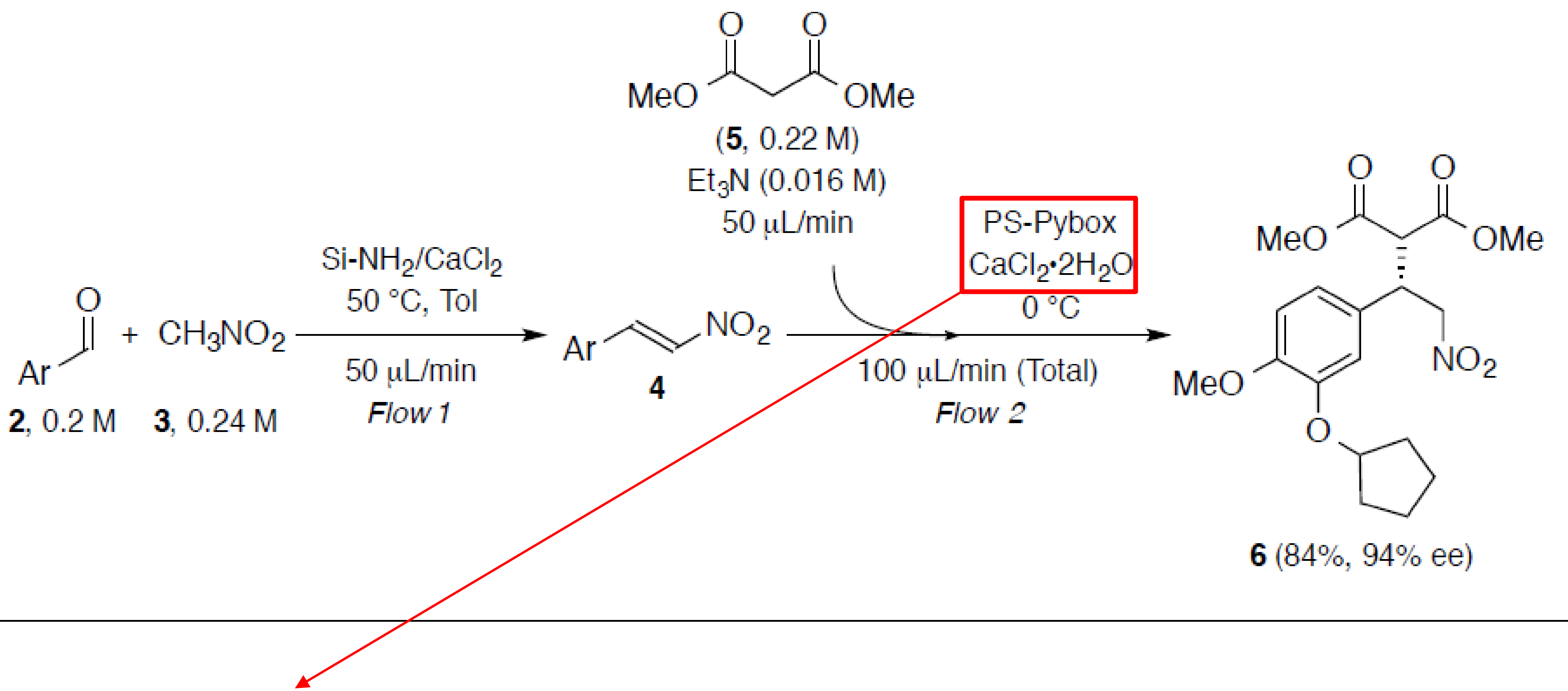
at 50 °C, >100 h the yield slightly decreased.

<u>For the following step</u>



Kobayashi S. *et al*. *Nature,* 2015, *520*, 329.

Catalytic Asymmetric 1,4-Addition



Polymer-supported (PS) chiral calcium catalyst

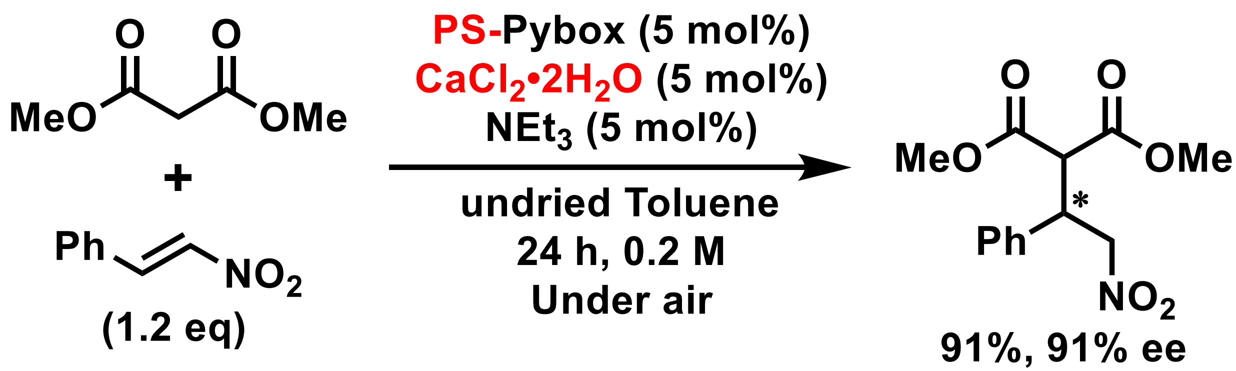
- **Stable more than one week**
- **Non-toxic Ca**

Kobayashi S. *et al*. *Nature,* 2015, *520*, 329.

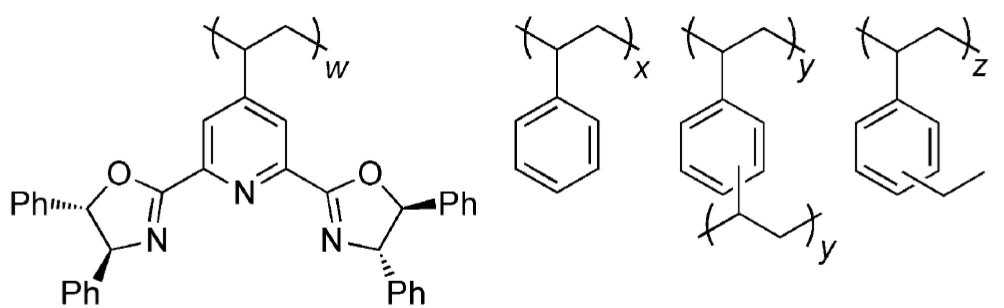
PS Chiral Ca Catalyst in Batch

In batch method

Homogenious catalyst → *Heterogenious catalyst*



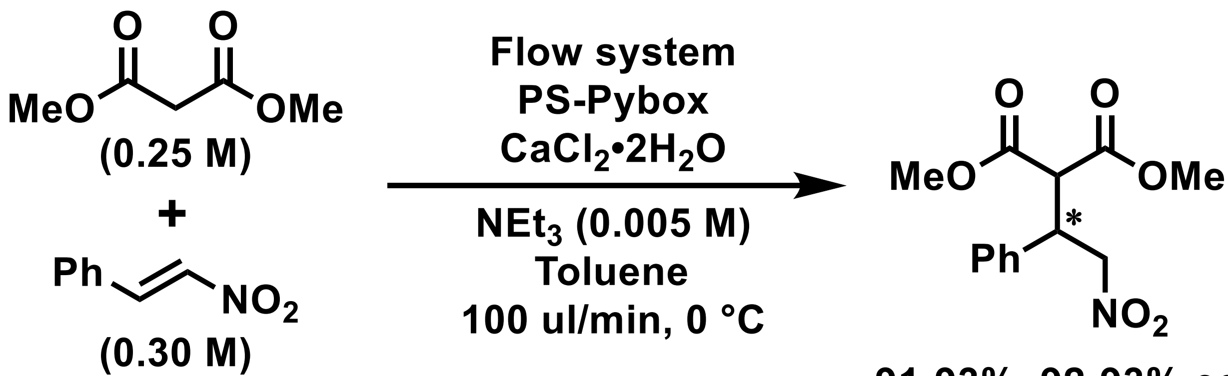
- ***Stable under Air and Water***
- ***immobilized PS-Pybox catalyst***



Polymer-Supported Pybox (PS-Pybox)

$w : x : y : z = 13 : 83 : 3 : 1$

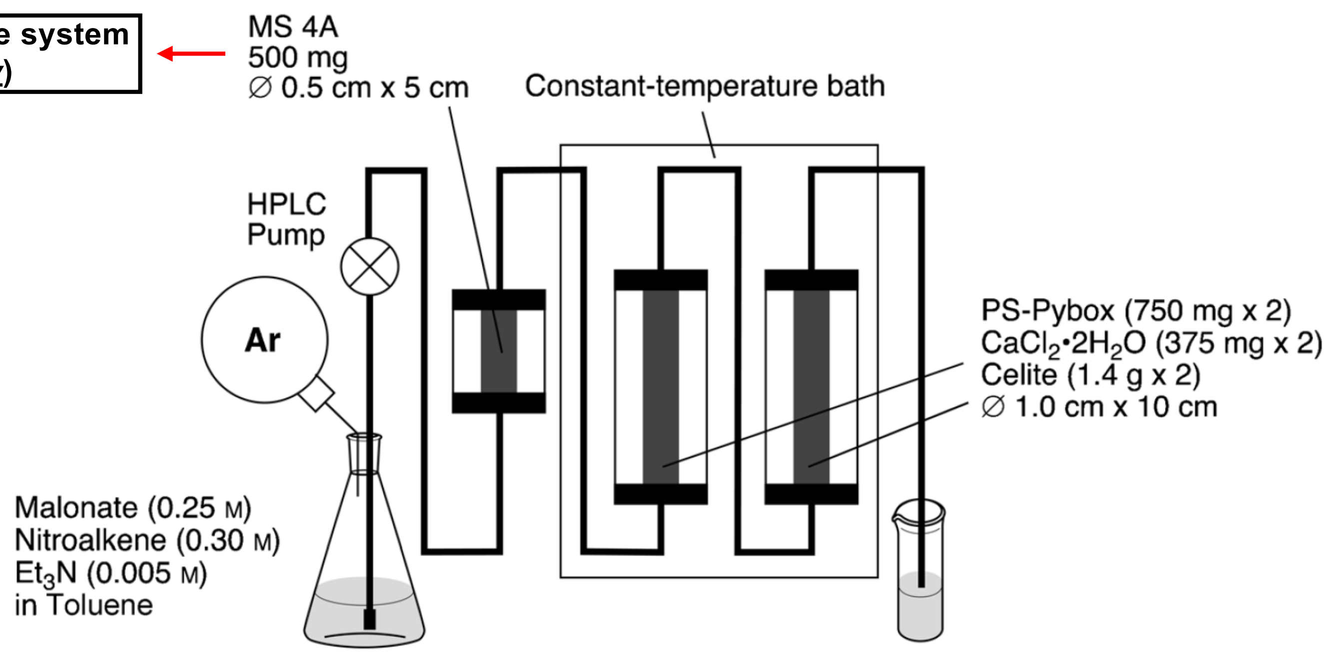
PS Chiral Ca Catalyst in Flow



91-93%, 92-93% ee

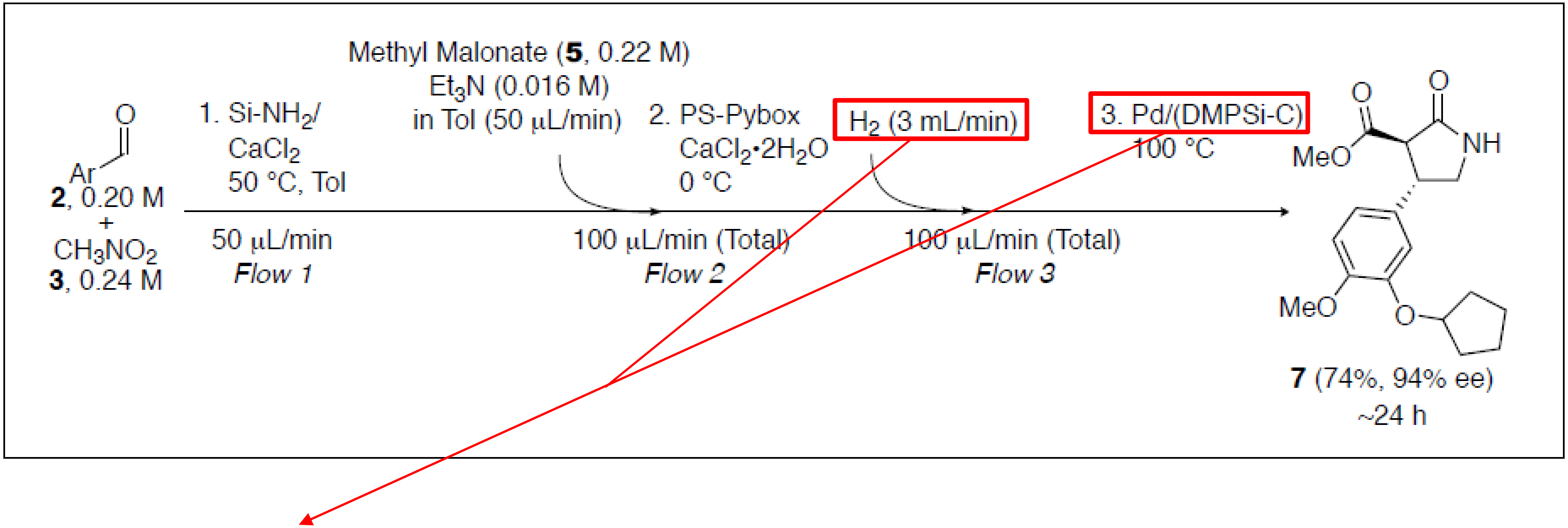
- **Robustness (average : 96% yield, 92% ee for 8.5 days)**

• Precolumn to stabilize system
(*<u>not</u>* *<u>necessary</u>*)



Kobayashi S. *et al*. *Chem. Eur. J.* 2012, *18*, 13624.

Synthesis of γ-lactams



Continuous-flow reduction

- **Microencapsulated Pd**
- **Newly developed Pd/DMPSi-C (polysilane-supported Pd/C)**

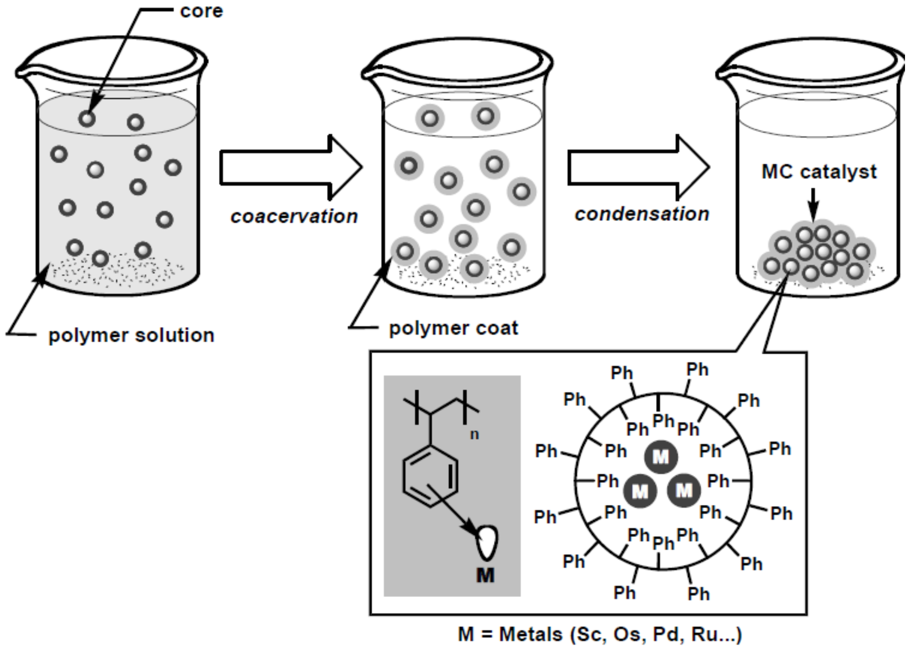
↕

Pd/PSi-Al_2O_3 cat. did not work

Kobayashi S. *et al*. *Nature*, 2015, *520*, 329.

Immobilized Catalyst for Toxic Metals

- **MC (Microencapsulated) Catalyst**



M = Metals (Sc, Os, Pd, Ru...)

- **Recycle and reuseable**
- **High activity**
- **No leaching toxic metals (Pd, Os, Ru...)**

- ***Recoverable & Reusable***
- ***Highly Active***

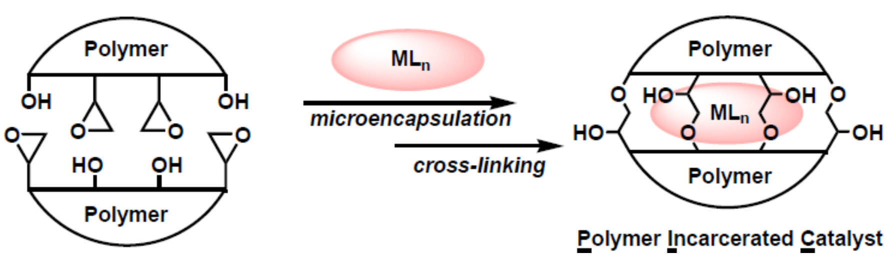
⇩

Green Chemistry

Process Chemistry

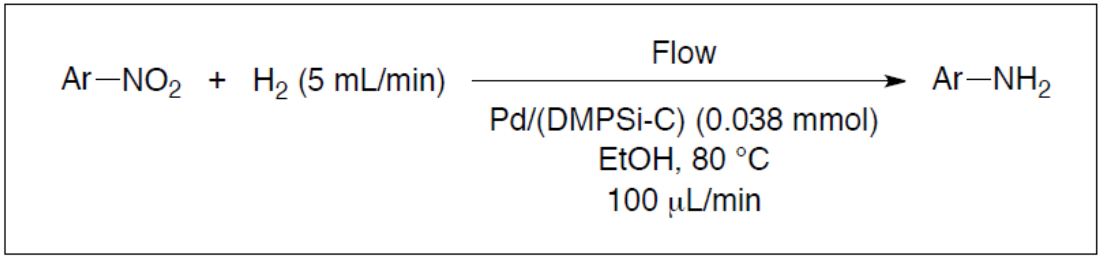
- **PI (Polymer-Incarcerated) Catalyst**

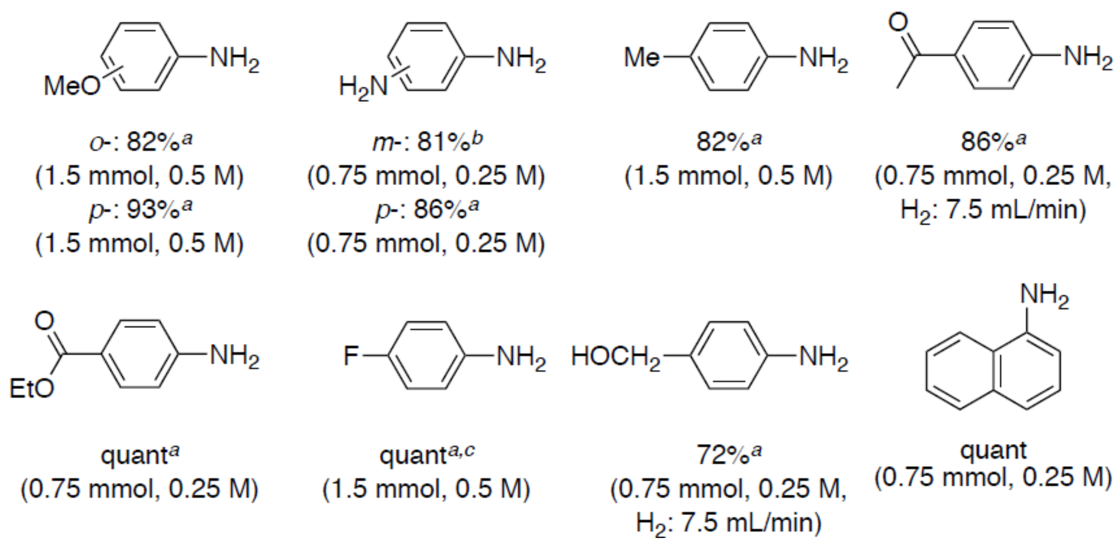
e.g. Kobayashi S. *et al*. *Science,* 2004,304, 1305.

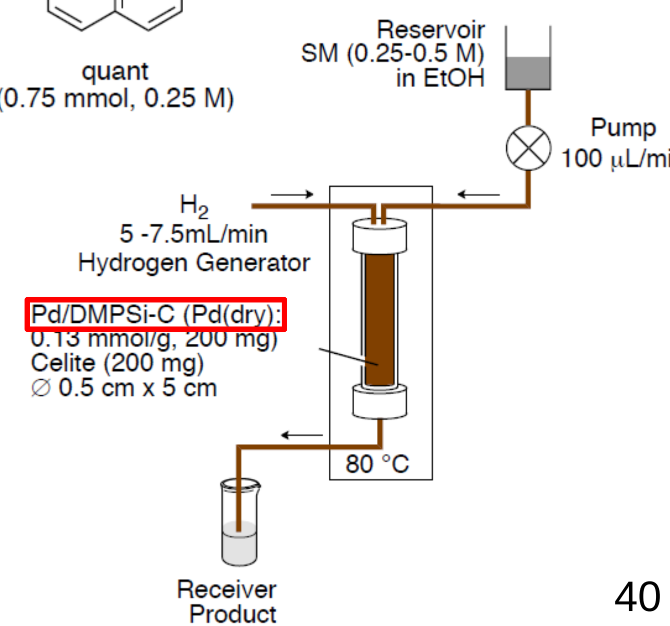


- **MC catalyst & cross-linking**
- **Many solvents can be used**

Hydrogenation in Flow





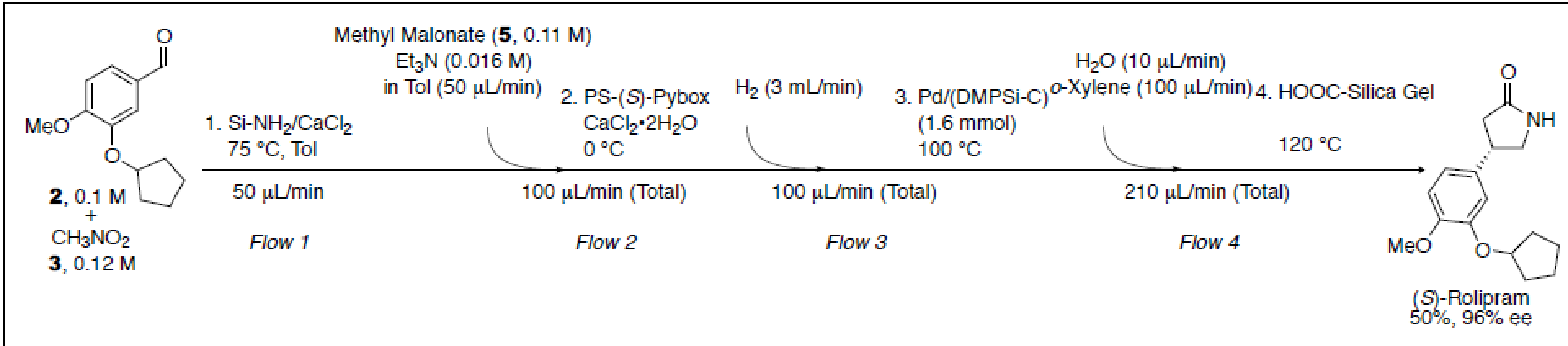


- **Pd/ PSi-xx, where xx is for prevent leaching metals.**
- **Pd/PSi, Pd/PSi-Al_2O_3, Pd/PSi-Tio_2.... are generally used for hydrogenation.**

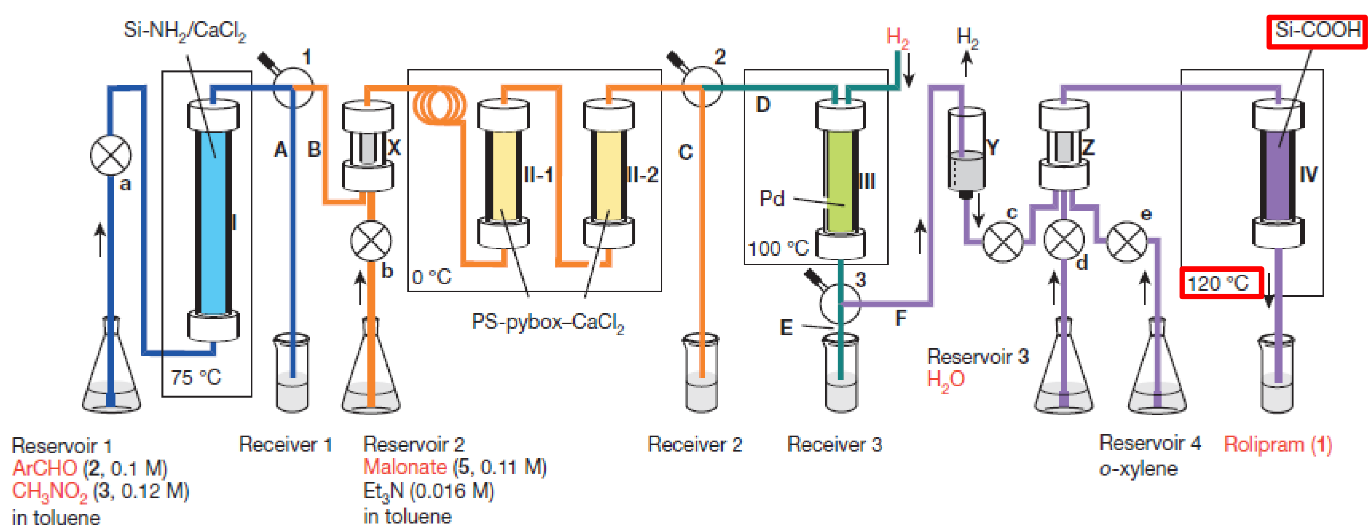
Rolipram is not suitable substrate.

Kobayashi S. *et al*. *Nature,* 2015, *520*, 329.

Hydrolysis and Decarboxylation

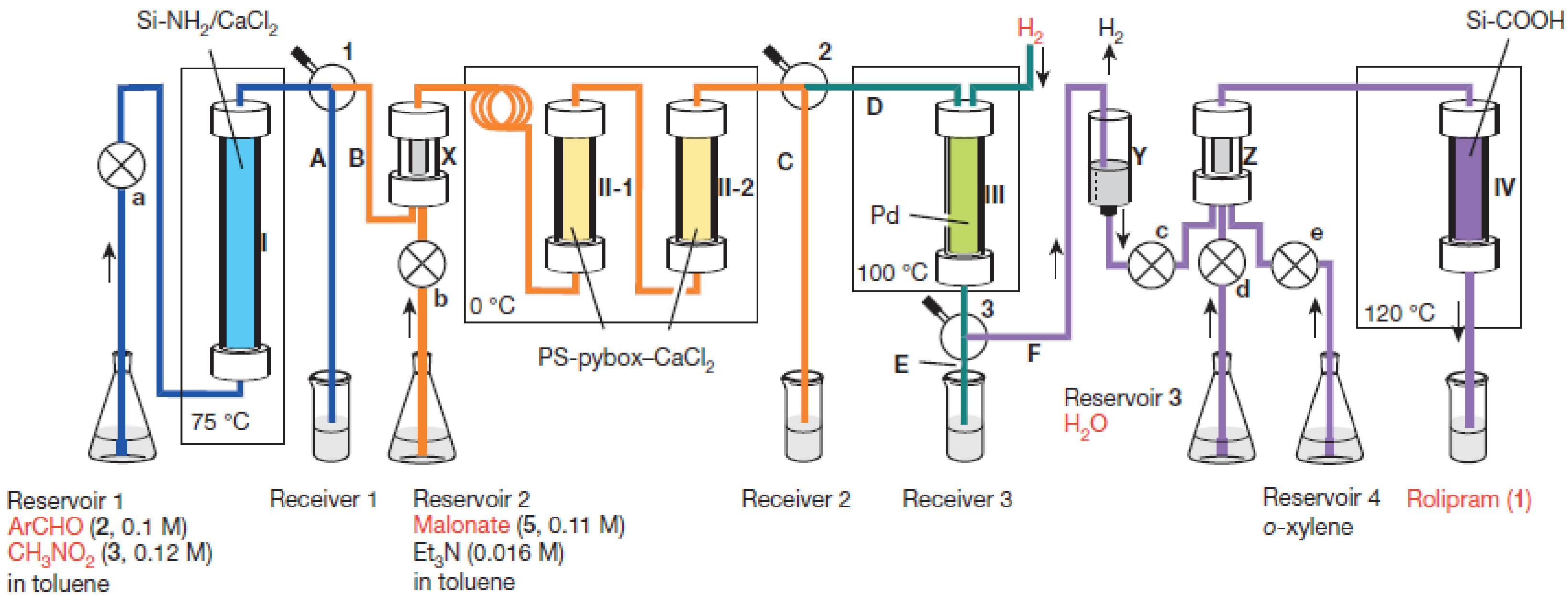


silica-supported carboxylic acid and heating promote hydrolysis and decarboxylation.



Kobayashi S. *et al*. *Nature,* 2015, *520*, 329.

Summary of Rolipram



Summary and key points

- **(*S*)-Rolipram, 50% yield (997.8 mg/ 24h), 96% ee**
- **(*R*)-Rolipram (50%, 96% ee) is also got**
- **8 steps 4 columns**
- **Stable more than 1 week**
- **Only heterogenious catalyts**
- **No leaching Pd detected by ICP**

Summary

Flow chemistry : reaction development and total synthesis

↓ **unique reactions**

↓ **fine synthesis**

In the future, flow chemistry might be the main stream of synthesizing molecules in academic and company ?!