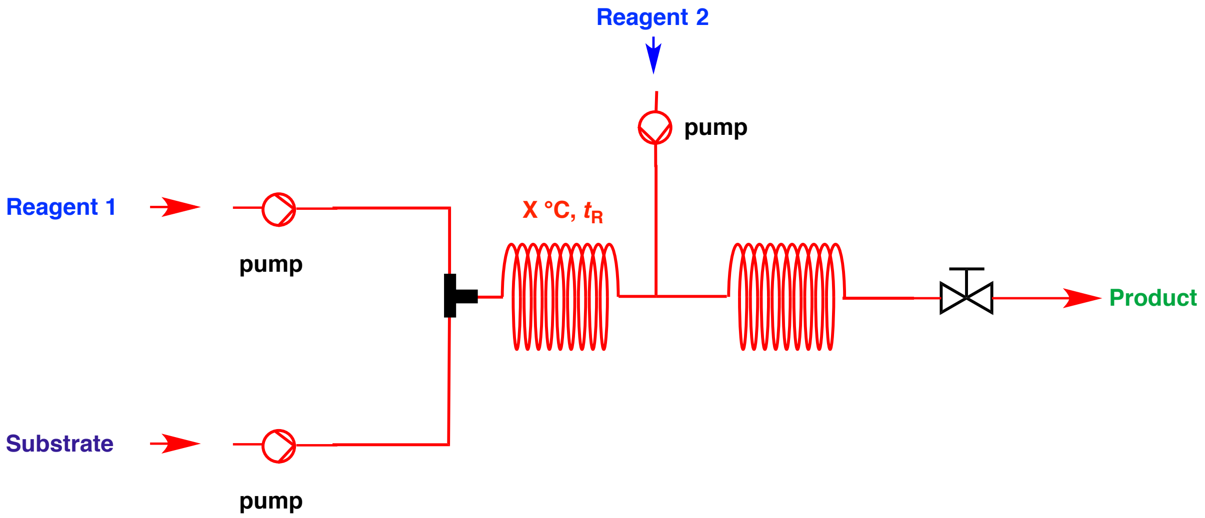
Synthesis of Reactive Intermediates in Flow - Part I

André B. Charette



Reagent 2

pump

Reagent 1

pump

X °C, t_R

Product

Substrate

pump

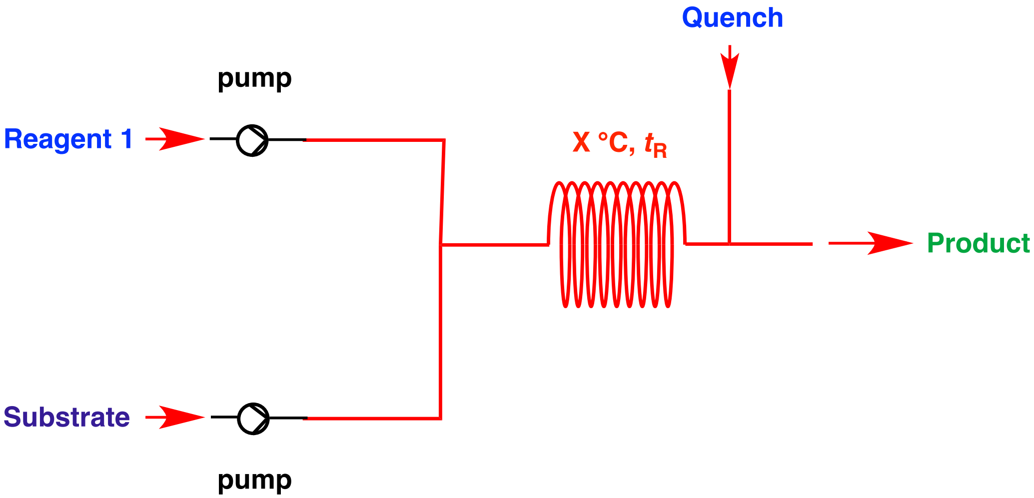
September 25, 2015

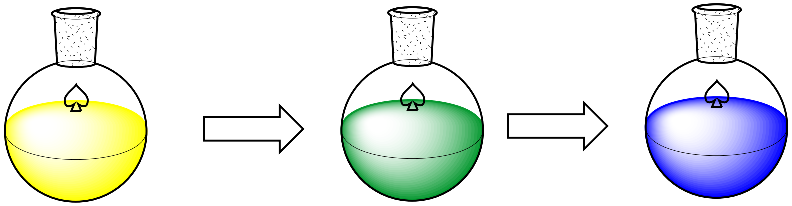
Université de Montréal

Traditional Scale-up vs Continous Flow Synthesis

Traditional Reaction Setup
Batch processes

Continuous Flow Synthesis



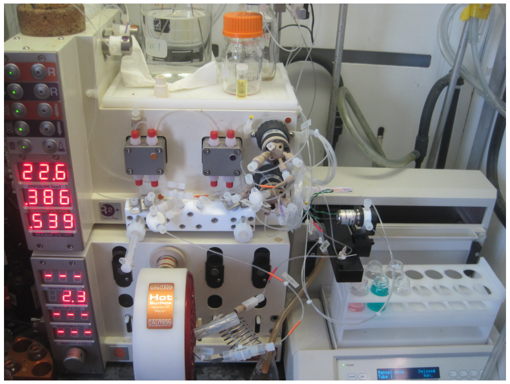


- Batch reaction time: how long a reaction vessel is held at a given temperature
- Reaction time is defined by how long the reactants stay in the reactor zone – residence time

Batch vs Flow in an Academic Setting

	Batch (>200 years)	⇨	Flow
Scenario I	works well		try to match batch yields
Scenario II	works well		works well
Scenario III	works well		small improvements vs batch (slightly better yields shorter reaction time)
Scenario IV	doesn't work very well		much better
Scenario V	impossible to achieve		works well
Scenario VI	works well (but NOT SAFE)		works well SAFER

$



≥300x$

Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502.
Baxendale, I. R.; Brocken, L.; Mallia, C. J. *Green Process Synth.* **2013**, *2*, 211.

Batch versus Continuous Flow Reactors

⇨ **Efficient organic reaction (high yield and selectivity) requires efficient mass and heat transport**

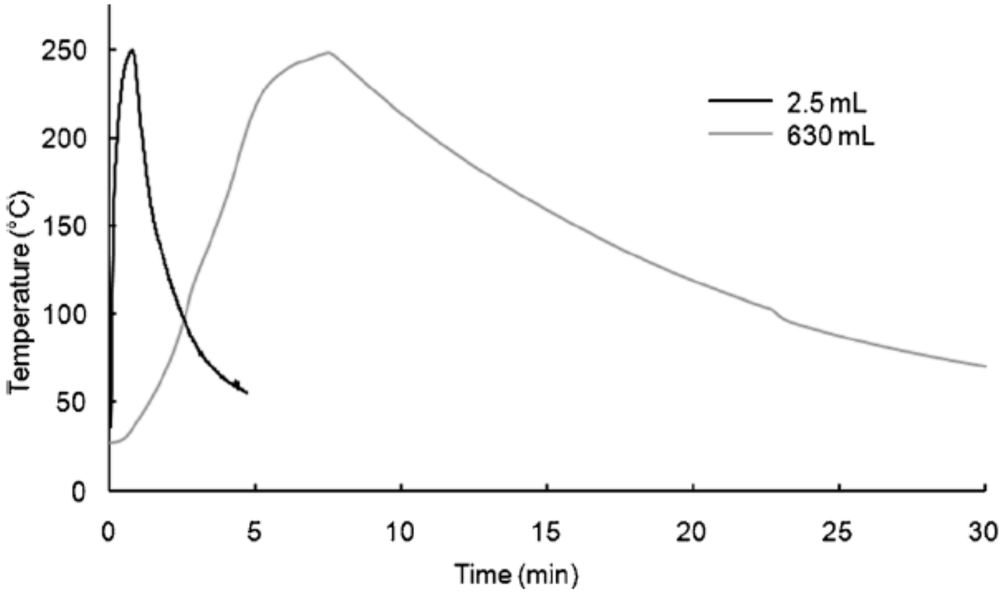


Figure 4. Temperature profiles comparing heating and cooling performances in the sealed-vessel microwave synthesis of 2-methylbenzimidazole (Table 1) at 250°C (4 s hold time at 250°C). Small scale: Monowave 300 instrument (2.5 mL volume). Large scale: Masterwave BTR (630 mL volume).[13]

Batch versus Continuous Flow Reactors

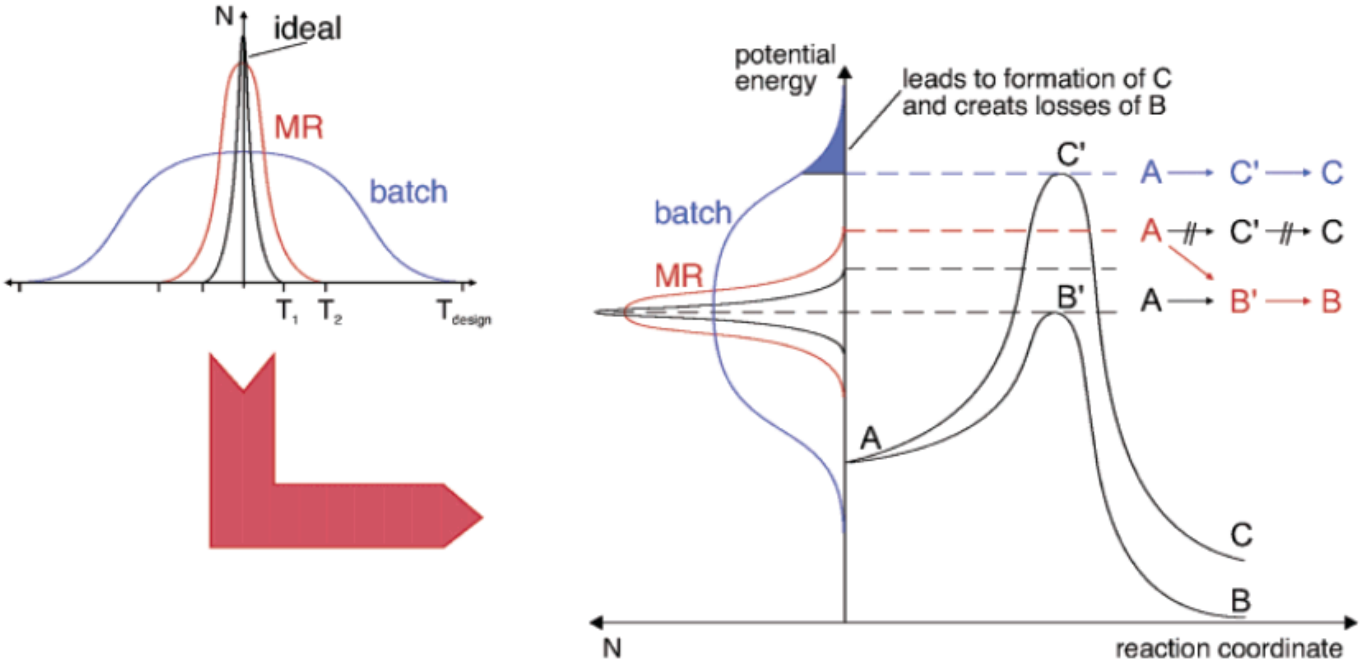
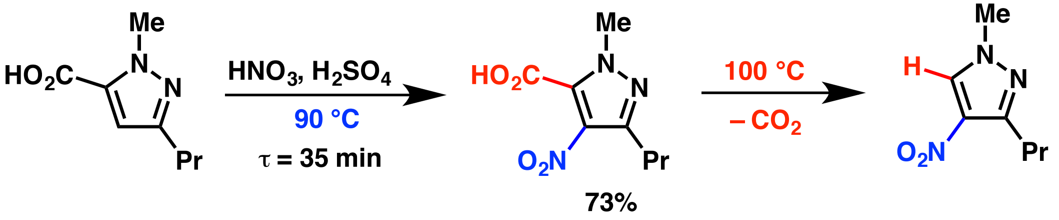
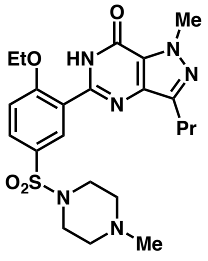


Figure 3. Temperature and activation energy, temperature quality, and activation energy.



Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, 2827.



Sildenavil
(PDE5 inhibitor)

Batch: **1.59 kg** **1.93 kg**

HNO_3, H_2SO_4
50 – 55 °C, 96%

Preparation of Reactive and Unstable Intermediates

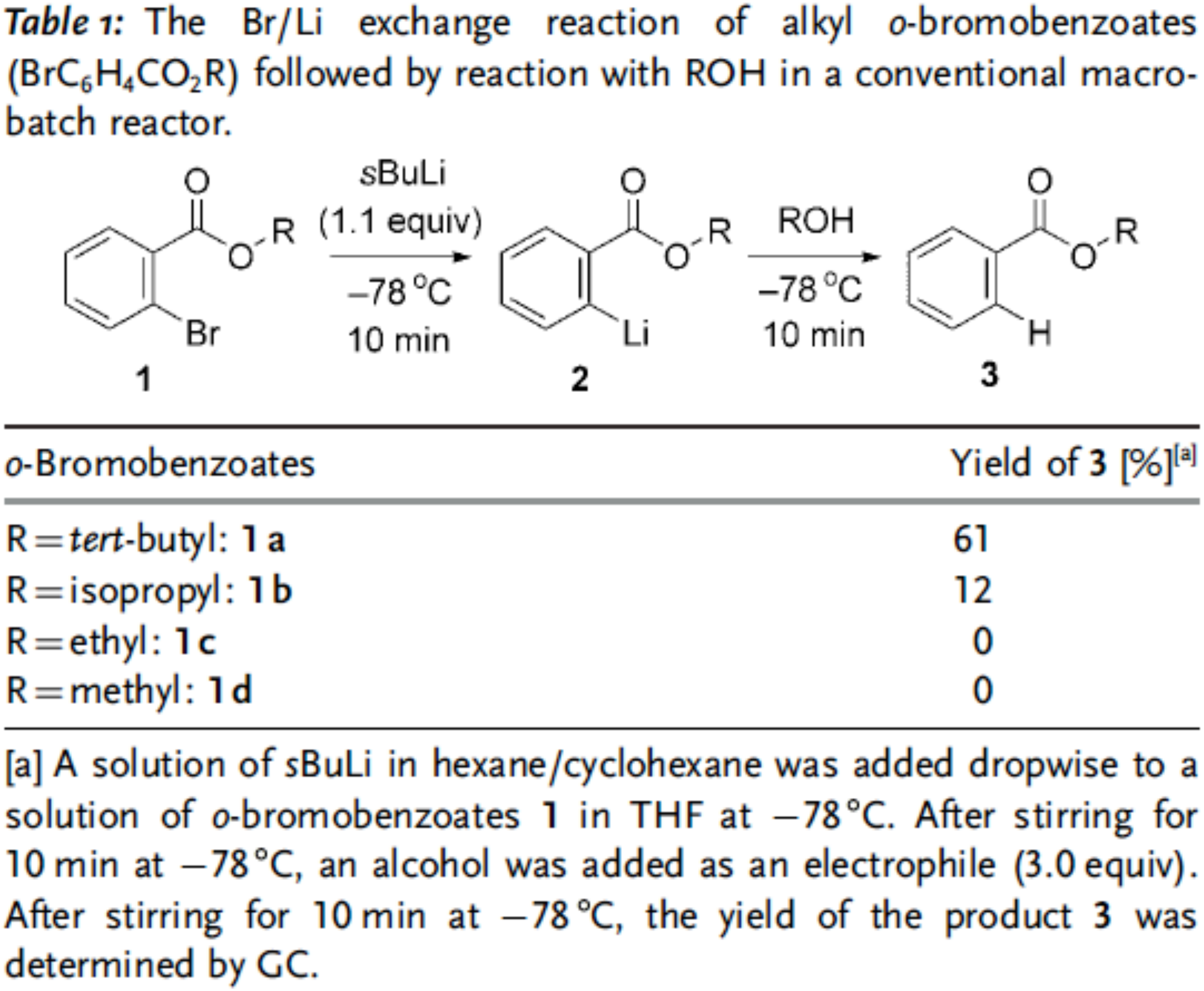


Table 1: The Br/Li exchange reaction of alkyl *o*-bromobenzoates ($BrC_6H_4CO_2R$) followed by reaction with ROH in a conventional macro-batch reactor.

o-Bromobenzoates	Yield of **3** [%][a]
R = *tert*-butyl: **1 a**	61
R = isopropyl: **1 b**	12
R = ethyl: **1 c**	0
R = methyl: **1 d**	0

[a] A solution of sBuLi in hexane/cyclohexane was added dropwise to a solution of *o*-bromobenzoates **1** in THF at −78 °C. After stirring for 10 min at −78 °C, an alcohol was added as an electrophile (3.0 equiv). After stirring for 10 min at −78 °C, the yield of the product **3** was determined by GC.

Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7833.

Preparation of Reactive and Unstable Intermediates

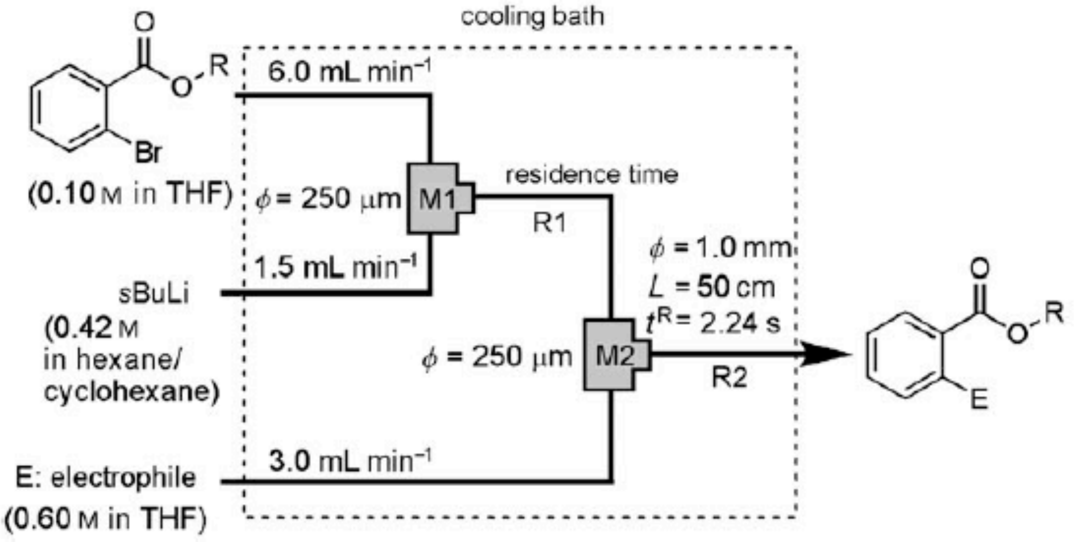
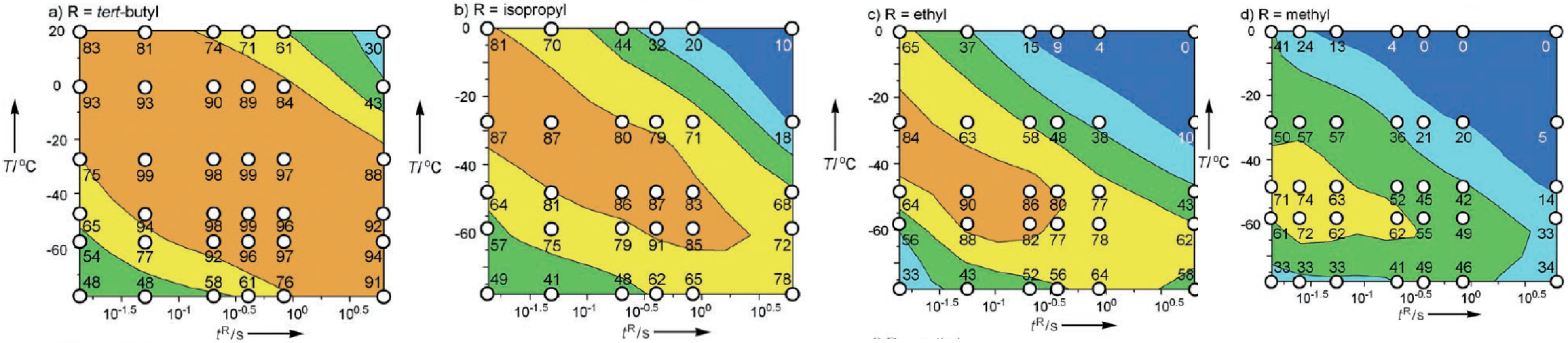


Figure 1. A microflow system for the Br/Li exchange reaction of alkyl *o*-bromobenzoates followed by reaction with electrophiles (see text for details).



Nagaki, A.; Kim, H.; Yoshida, J. *Angew Chem Int Edit* **2008**, *47*, 7833.

Preparation of Reactive and Unstable Intermediates

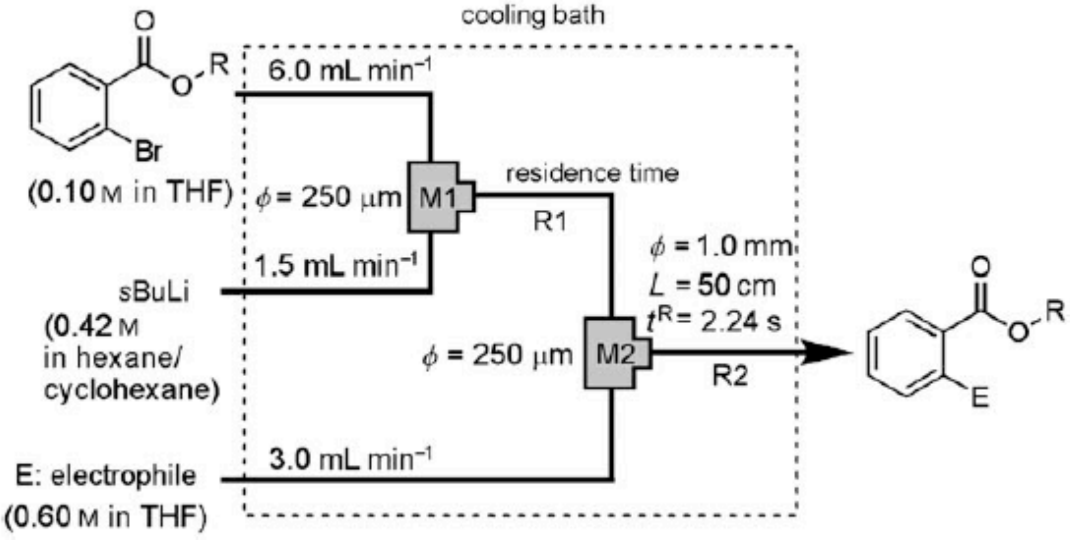
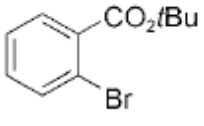
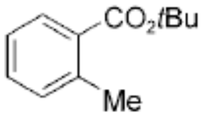
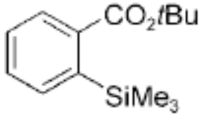
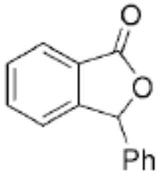


Figure 1. A microflow system for the Br/Li exchange reaction of alkyl *o*-bromobenzoates followed by reaction with electrophiles (see text for details).

	**1a**	MeI		**4a**	88
		Me_3SiCl		**5a**	96
		PhCHO		**6**	82

Nagaki, A.; Kim, H.; Yoshida, J. *Angew Chem Int Edit* **2008**, *47*, 7833.

Kinetic vs Thermodynamic Control

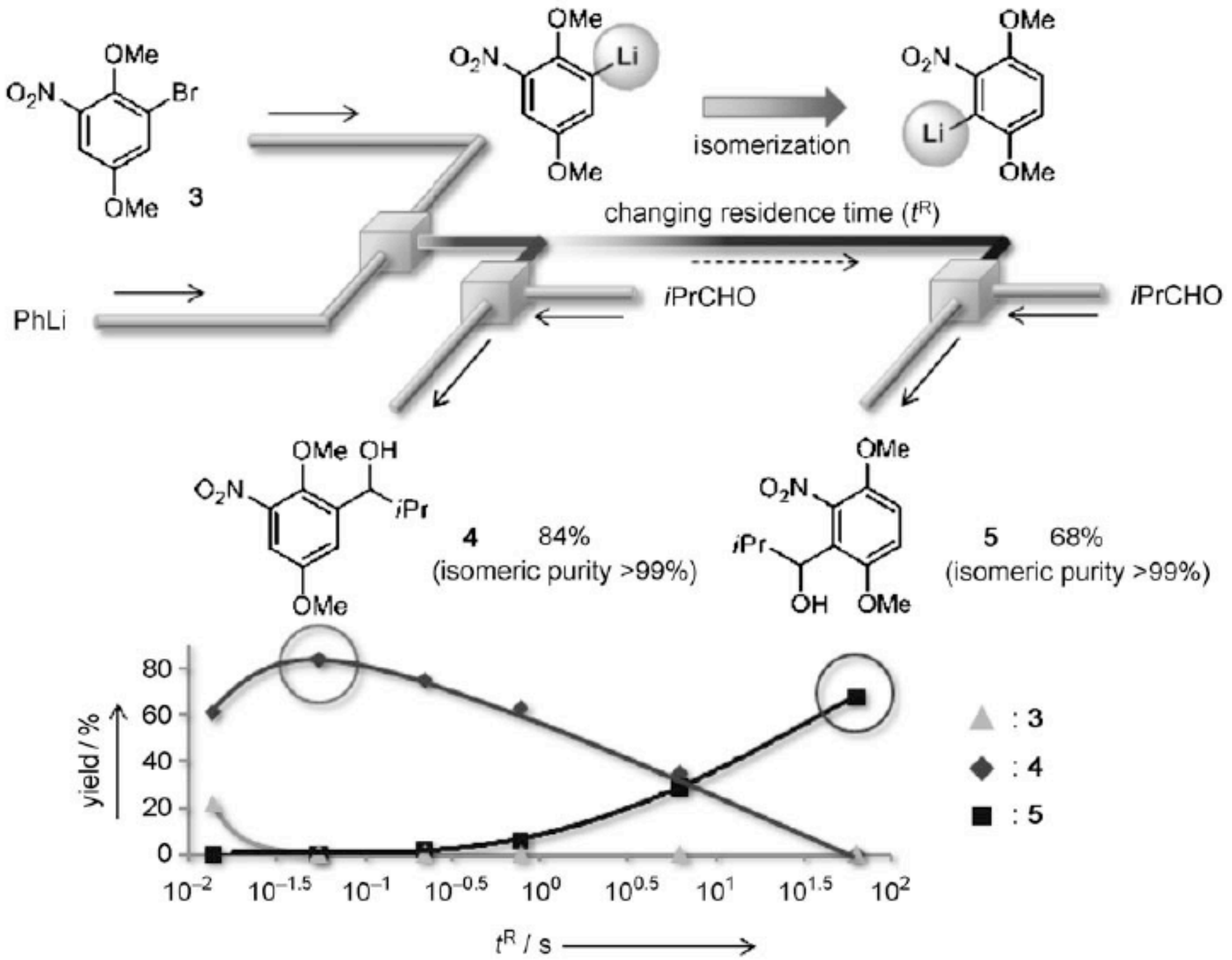
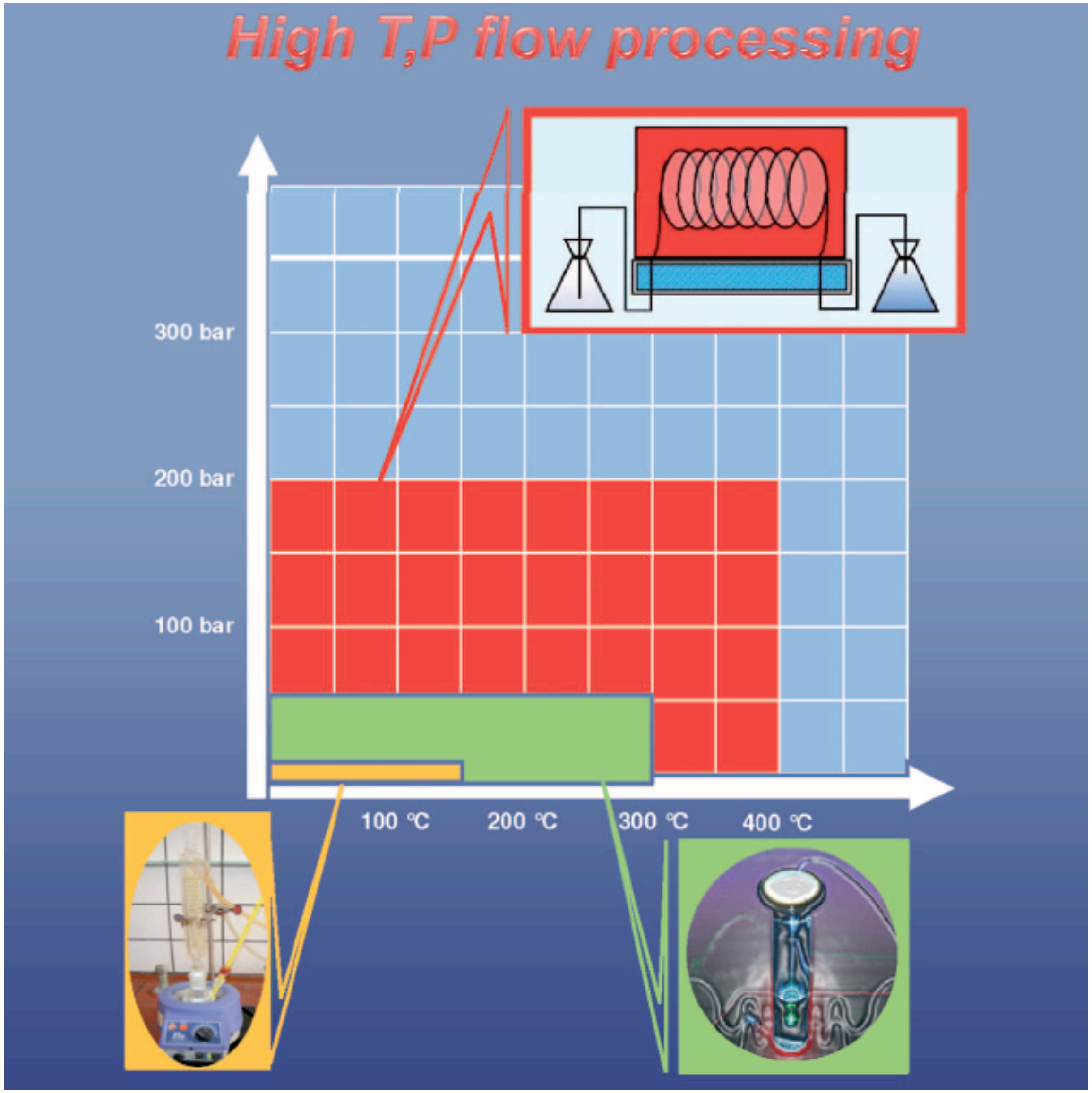


Figure 3. Switch between kinetic and thermodynamic control by changing the residence time.

Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8063.

Exploring New Reaction Windows



New Reaction Window: High temperature/high pressure

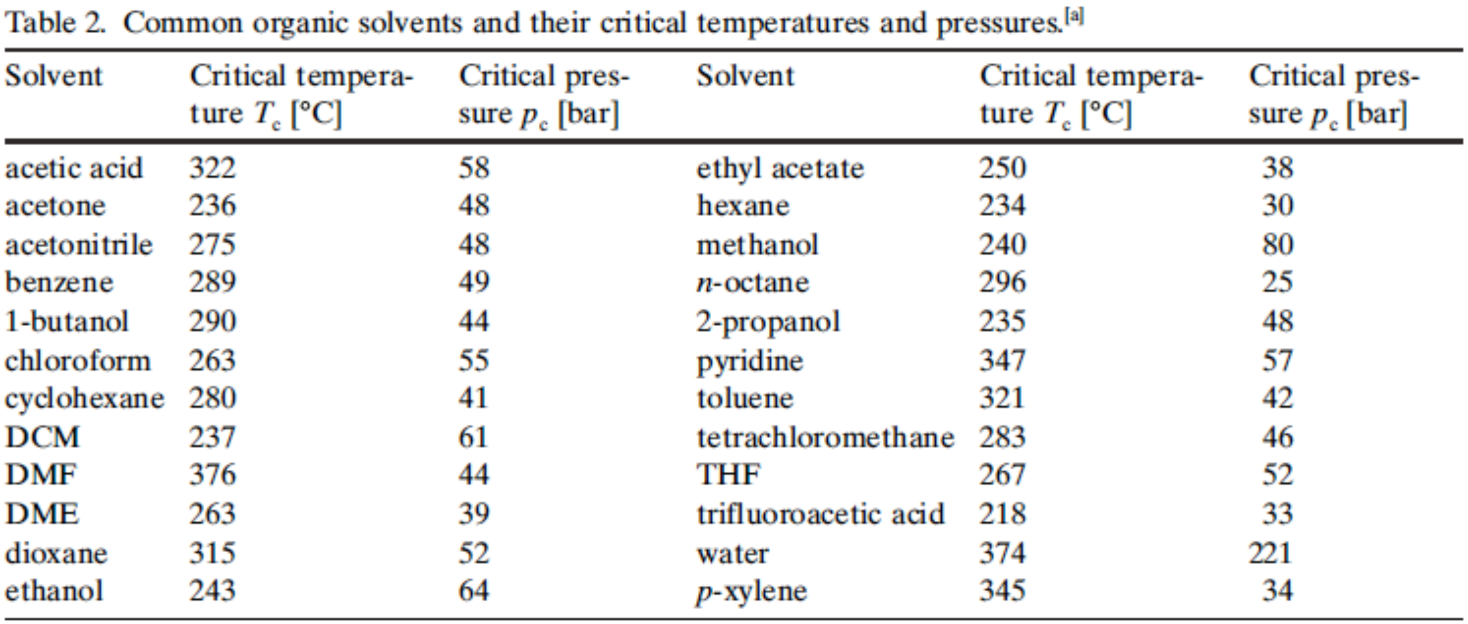


Table 2. Common organic solvents and their critical temperatures and pressures.[a]

Solvent	Critical temperature T_c [°C]	Critical pressure p_c [bar]	Solvent	Critical temperature T_c [°C]	Critical pressure p_c [bar]
acetic acid	322	58	ethyl acetate	250	38
acetone	236	48	hexane	234	30
acetonitrile	275	48	methanol	240	80
benzene	289	49	*n*-octane	296	25
1-butanol	290	44	2-propanol	235	48
chloroform	263	55	pyridine	347	57
cyclohexane	280	41	toluene	321	42
DCM	237	61	tetrachloromethane	283	46
DMF	376	44	THF	267	52
DME	263	39	trifluoroacetic acid	218	33
dioxane	315	52	water	374	221
ethanol	243	64	*p*-xylene	345	34

The ***critical temperature*** of a substance is the temperature at and above which vapor of the substance cannot be liquefied, no matter how much pressure is applied.

The ***critical pressure*** of a substance is the pressure required to liquefy a gas at its critical temperature.

Back Pressure Regulators

Table 2. Common organic solvents and their critical temperatures and pressures.[a]

Solvent	Critical temperature T_c [°C]	Critical pressure p_c [bar]	Solvent	Critical temperature T_c [°C]	Critical pressure p_c [bar]
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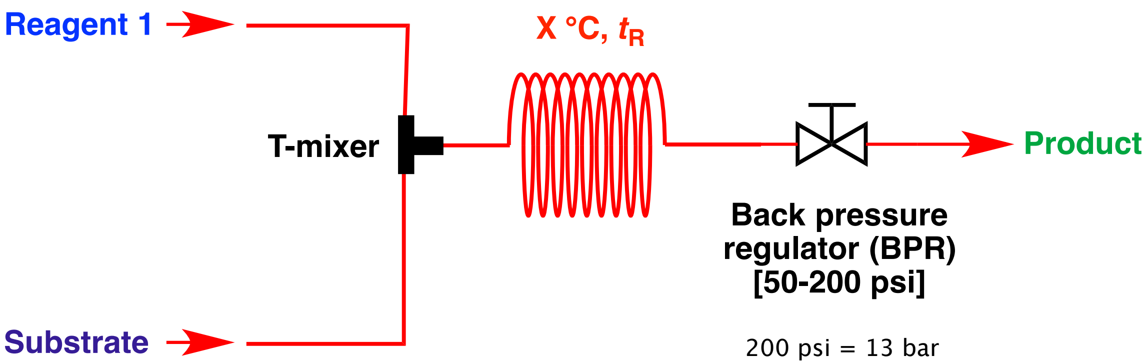
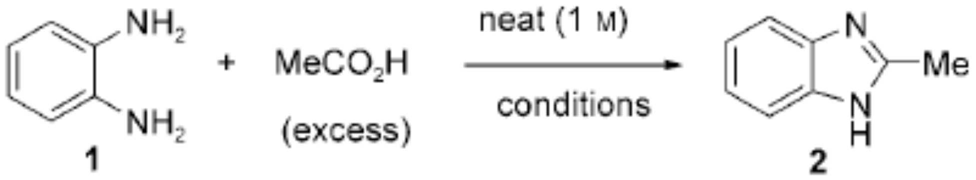


200 psi = 13 bar
50 psi = 3.4 bar

Pressure and Temperature: A Convincing Proof of Concept

Table 3. Temperature dependence for the condensation of *o*-phenylenediamine with acetic acid.



Temp. [°C]	Pressure [bar]	Time
25	–	9 weeks
60	–	3 days
100	–	5 h
130	2	1 h
160	4	10 min
200	9	3 min
270	29	ca. 1 s

Reactive Intermediates in Flow

Grignard Reagents: RMgX from EtMgBr + ArBr

Wakami, H.; Yoshida, J. Grignard exchange reaction using a microflow system: From bench to pilot plant. *Org. Process Res. Dev.* **2005**, *9*, 787-791.
Petersen, T. P.; Becker, M. R.; Knochel, P. Continuous Flow Magnesiation of Functionalized Heterocycles and Acrylates with TMPMgCl center dot LiCl. *Angew. Chem. Int. Ed.* **2014**, *53*, 7933-7937.
Brodmann, T.; Koos, P.; Metzger, A.; Knochel, P.; Ley, S. V. *Org. Process Res. Dev.* **2012**, *16*, 1102.

Alkyl, vinyl, aryl, heteroaryllithium RBr + R'Li; E$^+$

Nagaki, A.; Yamada, D.; Yamada, S.; Doi, M.; Ichinari, D.; Tomida, Y.; Takabayashi, N.; Yoshida, J. *Aust. J. Chem.* **2013**, *66*, 199.
Nagaki, A.; Tokuoka, S.; Yoshida, J. *Chem. Commun.* **2014**, *50*, 15079. (α-(trifluoromethyl)vinyllithium)
Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8063. (nitro-substituted aryllithium)
Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7833. Nagaki, A.; Kim, H.; Moriwaki, Y.; Matsuo, C.; Yoshida, J. *Chem. Eur J* **2010**, *16*, 11167. (aryllithium)
Nagaki, A.; Kim, H.; Usutani, H.; Matsuo, C.; Yoshida, J. *Org. Biomol. Chem.* **2010**, *8*, 1212. (cyano-substituted aryl lithium)
Kim, H.; Nagaki, A.; Yoshida, J. *Nat. Commun.* **2011**, *2*.

Lithiation/Borylation/Suzuki–Miyaura Cross Coupling

Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 10665.

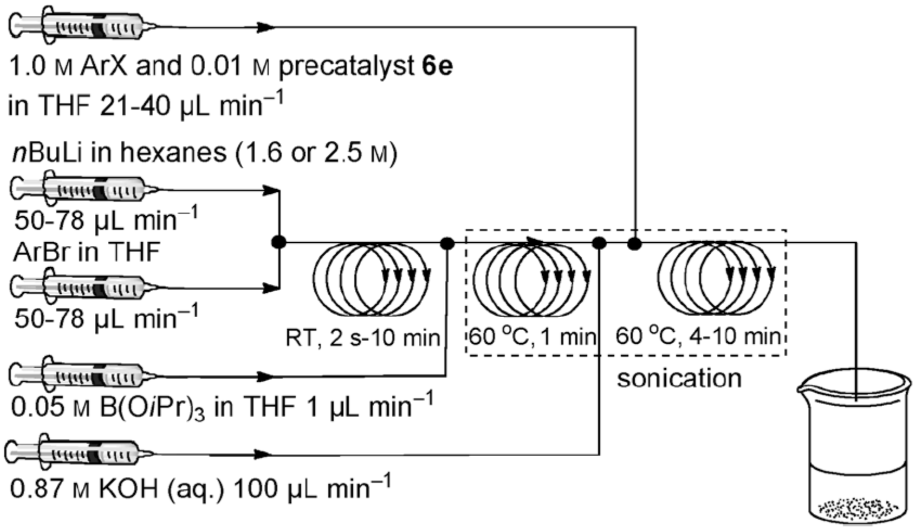
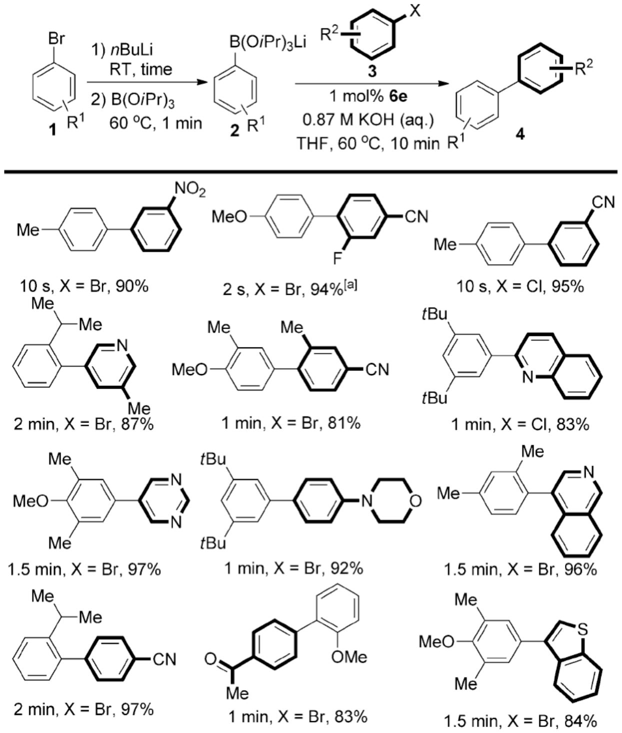


Figure 3. Continuous-flow setup for the lithiation/borylation/Suzuki–Miyaura cross-coupling sequence of two aryl halides.



Reactive Intermediates in Flow

Diazomethane, CH_2N_2/Arndt-Eistert homologation (diazald, KOH)

Pinho, V. D.; Gutmann, B.; Kappe, C. O. *Rsc Adv.* **2014**, *4*, 37419.

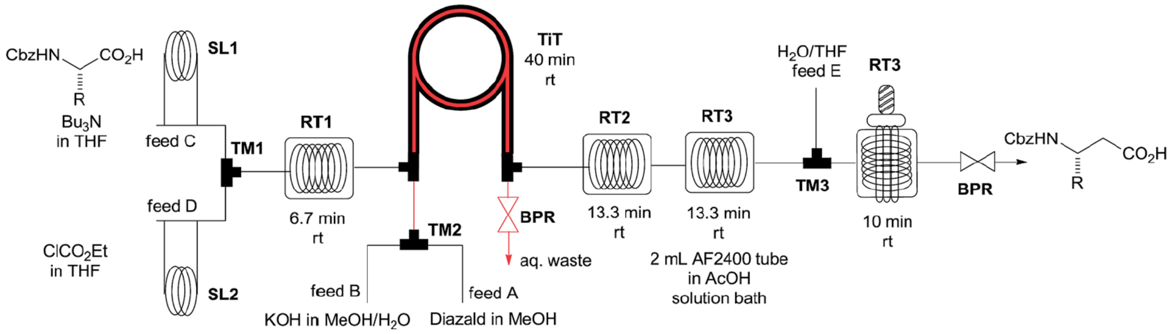


Fig. 1 Flow set-up for the continuous four-step Arndt–Eistert homologation of α-amino acids.

Diazomethane, CH_2N_2 (diazald, KOH)

Maurya, R. A.; Park, C. P.; Lee, J. H.; Kim, D. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5952.
Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590.

Ethyl diazoacetate (EtOOCCHN$_2$) / E+ trapping

Muller, S. T. R.; Smith, D.; Hellier, P.; Wirth, T. *Synlett* **2014**, *25*, 871.
Maurya, R. A.; Min, K. I.; Kim, D. P. *Green Chem.* **2014**, *16*, 116.

Diazoketone (from TMSCHN$_2$ + RC(O)Cl)

Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320.
Lévesque, E. et al. One day...

Aryl- vinyldiazomethane (cyclopropanation)

Roda, N. M.; Tran, D. N.; Battilocchio, C.; Labes, R.; Ingham, R. J.; Hawkins, J. M.; Ley, S. V. *Org. Biomol. Chem.* **2015**, *13*, 2550. (cyclopropanation)
Tran, D. N.; Battilocchio, C.; Lou, S. B.; Hawkins, J. M.; Ley, S. V. *Chem. Sci.* **2015**, *6*, 1120. (cross coupling)
Poh, J. S.; Tran, D. N.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Angew. Chem. Int. Ed.* **2015**, *54*, 7920. (allene synthesis)
Lévesque, E. et al. One day...

Diazene (HN=NH) (from $F_3CC(O)NOC(O)CF_3$ + NH_2OH) - in situ Alkene Reduction

Kleinke, A. S.; Jamison, T. F. *Org. Lett.* **2013**, *15*, 710.

Reactive Intermediates in Flow

Aryldiazonium salts (ArNH$_2$ to ArN$_2$X)

Chernyak, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12466.

CuCF$_3$

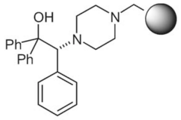
Mazloomi, Z.; Bansode, A.; Benavente, P.; Lishchynskyi, A.; Urakawa, A.; Grushin, V. V. *Org. Process Res. Dev.* **2014**, *18*, 1020.

$^{-}$CCl$_3$

Jensen, A. B.; Lindhardt, A. T. *J. Org. Chem.* **2014**, *79*, 1174.

XCH$_2$Li

Degennaro, L.; Fanelli, F.; Giovine, A.; Luisi, R. *Adv. Synth. Catal.* **2015**, *357*, 21.
Broom, T.; Hughes, M.; Szczepankiewicz, B. G.; Ace, K.; Hagger, B.; Lacking, G.; Chima, R.; Marchbank, G.; Alford, G.; Evans, P.; Cunningham, C.; Roberts, J. C.; Perni, R. B.; Berry, M.; Rutter, A.; Watson, S. A. *Org. Process Res. Dev.* **2014**, *18*, 1354. (Bromomethyltrifluoroborate)



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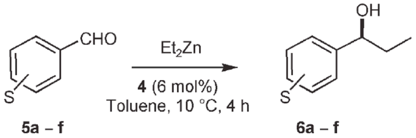
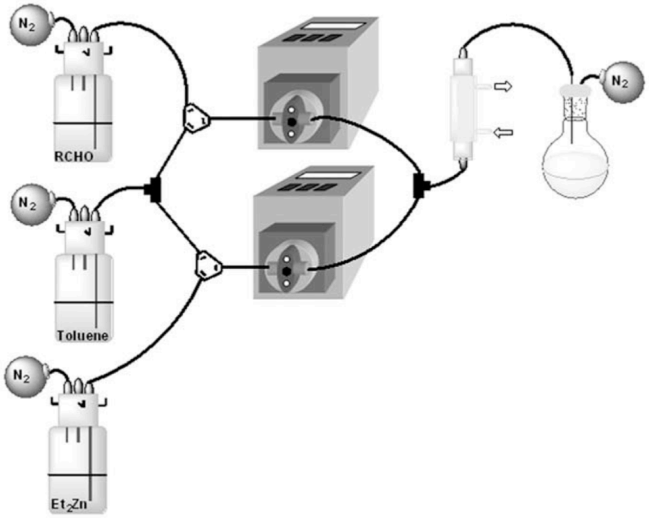
Pericas, M. A.; Herrerias, C. I.; Sola, L. *Adv. Synth. Catal.* **2008**, *350*, 927.

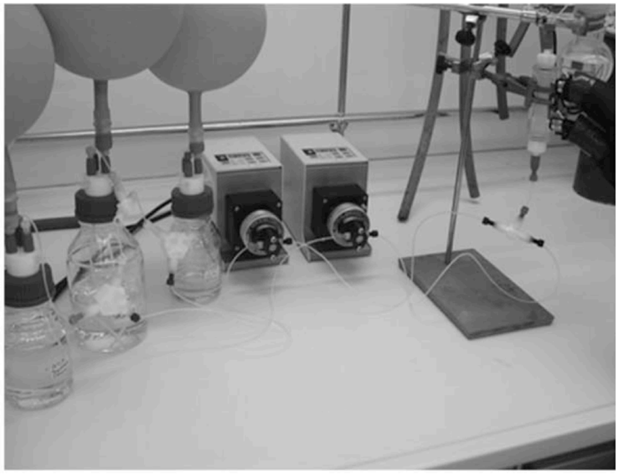
Table 2. Batch catalytic enantioselective ethylation of aldehydes **5a–f**.



Substrate	Conv.[a] [%]	Select.[a] [%]	*ee*[a] [%]
benzaldehyde (**5a**)	99	>99	93
2-fluorobenzaldehyde (**5b**)	99	99	91
4-fluorobenzaldehyde (**5c**)	87	98	92
2-(trifluoromethyl)benzaldehyde (**5d**)	71	76	78
4-(trifluoromethyl)benzaldehyde (**5e**)	98	99	90
4-cyanobenzaldehyde (**5f**)	>99	>99	89

[a] Determined by GC with a Cyclodex-β column. The only by-product was the corresponding benzyl alcohol, and the configuration of the major product enantiomer was (*S*).





Heterogenous Reactions

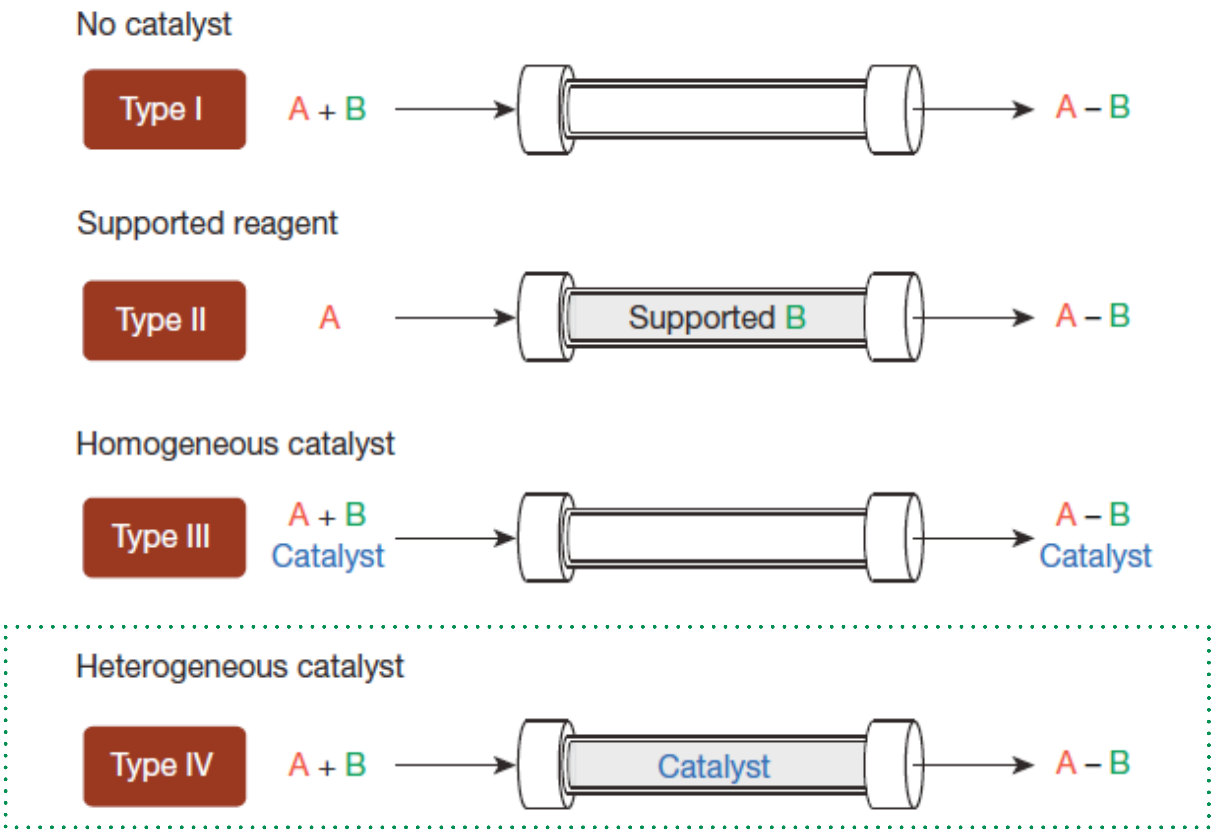
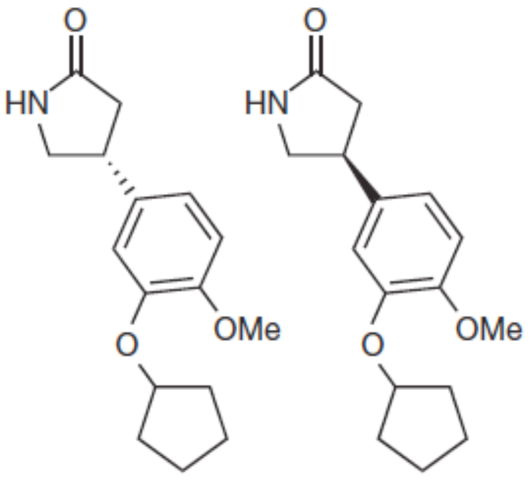


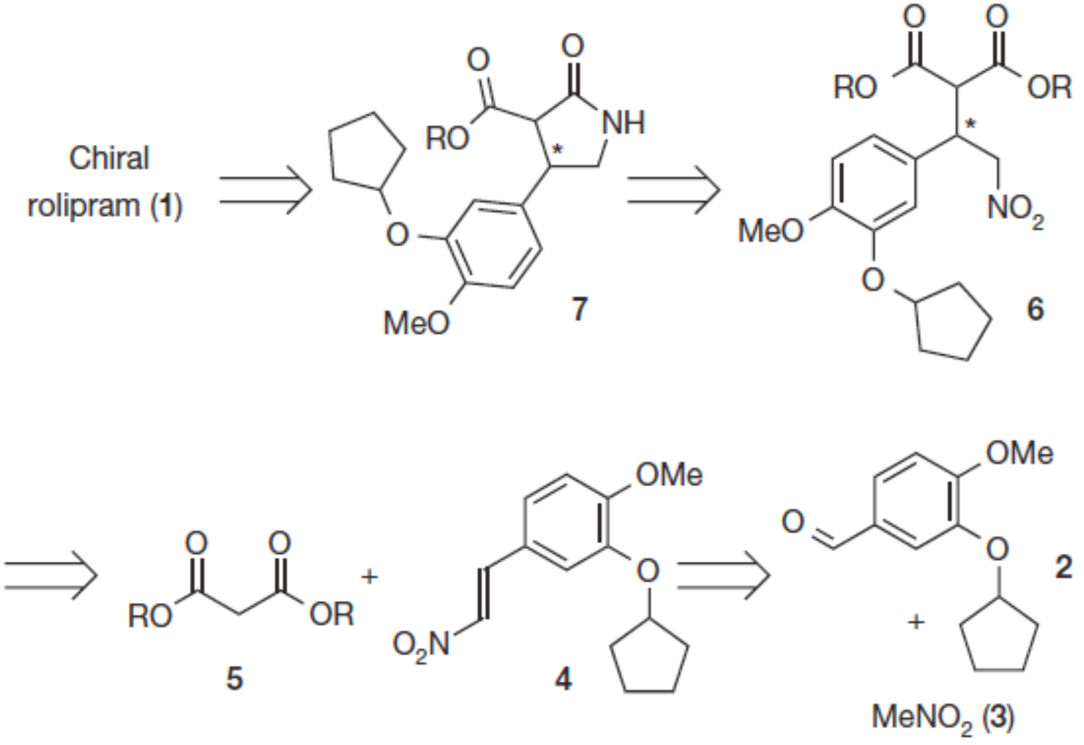
Figure 1 | The four types of continuous-flow systems. The continuous-flow systems so far reported can be divided into types I–IV, as illustrated, using substrates A and B. See main text for details. Type IV is regarded as the best method for continuous-flow synthesis.

Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

Kobayashi's Rolipram Synthesis

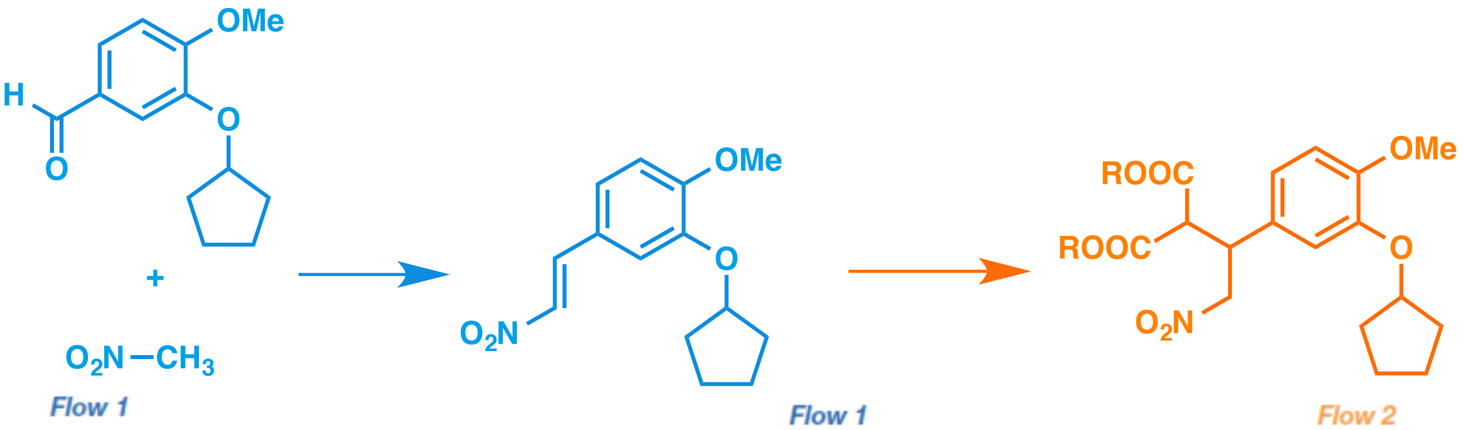


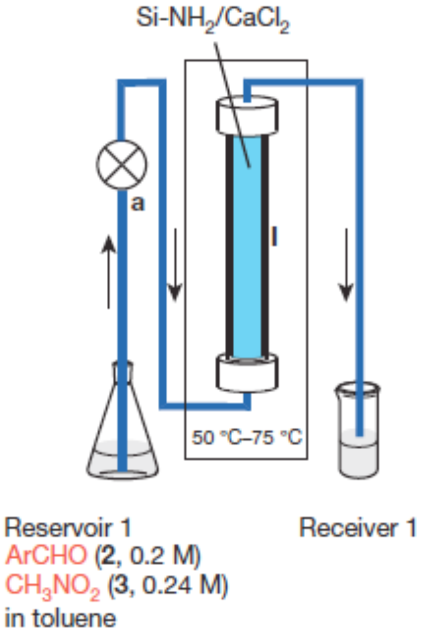
(*R*)-Rolipram (*S*)-Rolipram



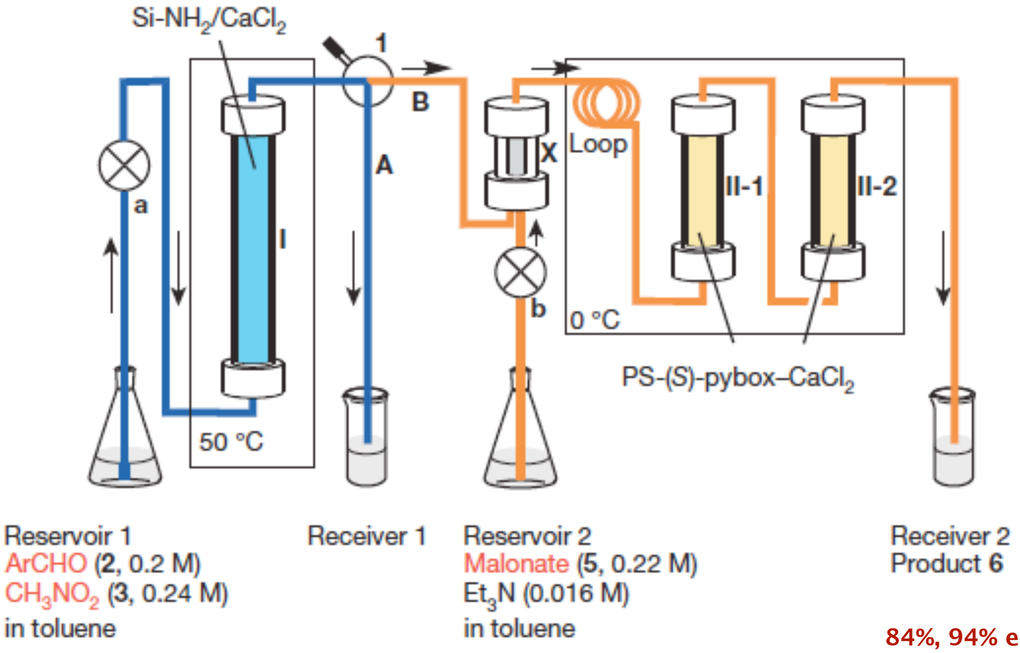
Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

Kobayashi's Rolipram Synthesis





Stage 1: Synthesis of nitroalkenes



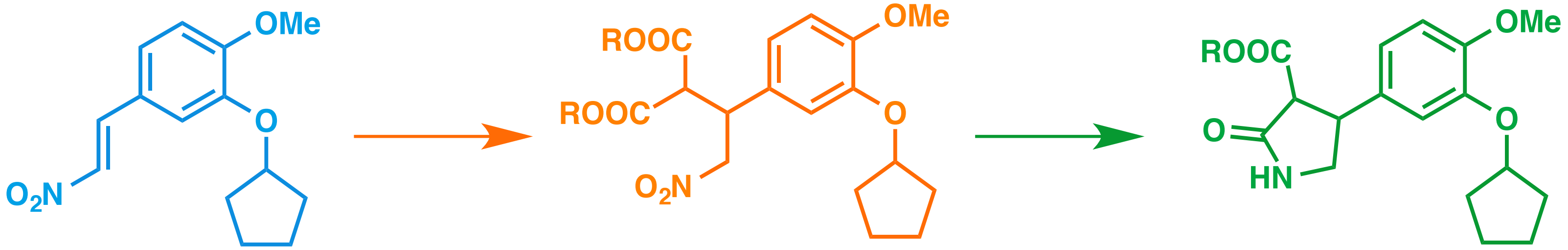
84%, 94% ee

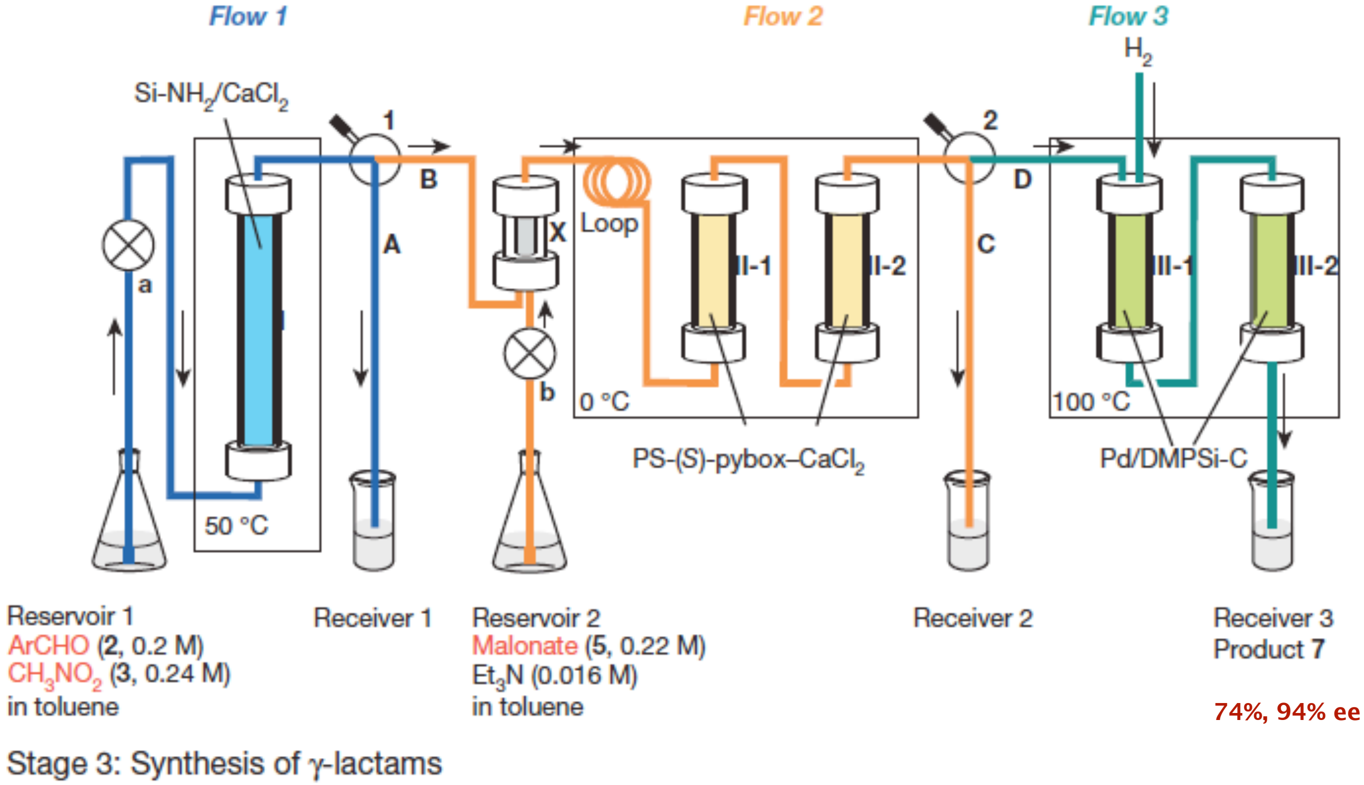
Stage 2: Synthesis of γ-nitro esters

>90%, stable > 1 week at 75 °C

Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

Kobayashi’s Rolipram Synthesis



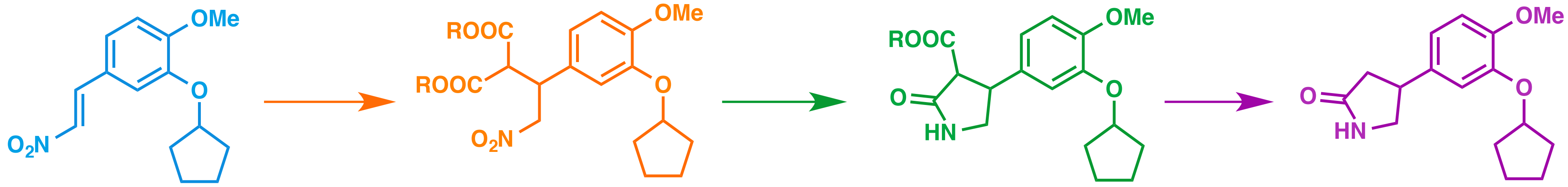


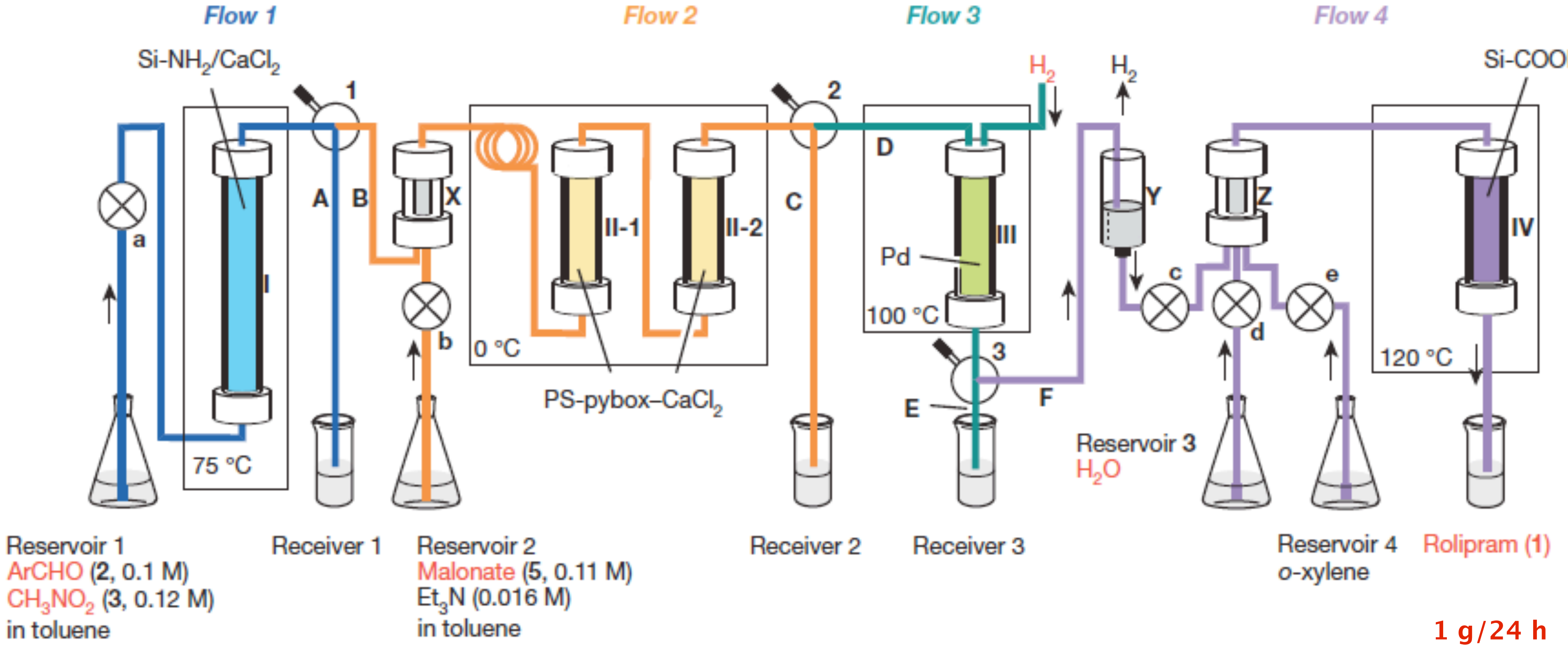
74%, 94% ee

Stage 3: Synthesis of γ-lactams

Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

Kobayashi’s Rolipram Synthesis





1 g/24 h

Stage 4: Synthesis of (*R*)- and (*S*)-rolipram

Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

Summary Flow Chemistry

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- ★ Enhanced heat and mass transfer
- ★ Reduced reaction volumes
- ★ Sealed system (minimizing contamination by oxygen and water)
- ★ Use of extreme temperature and pressure
- ★ Flash chemistry (short reaction time, high pressure/high temperature)
- ★ Excellent mixing
- ★ Safer processes

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- ★ Formation of precipitates can be a problem
- ★ Usually requires that the reagents/subtrate/reaction product/by-products are soluble
- ★ Liquid-liquid heterogenous mixtures are ok but liquid-solid usually not