Introduction to Flow Chemistry

Eric Alexy
Literature Meeting
December 14th, 2018

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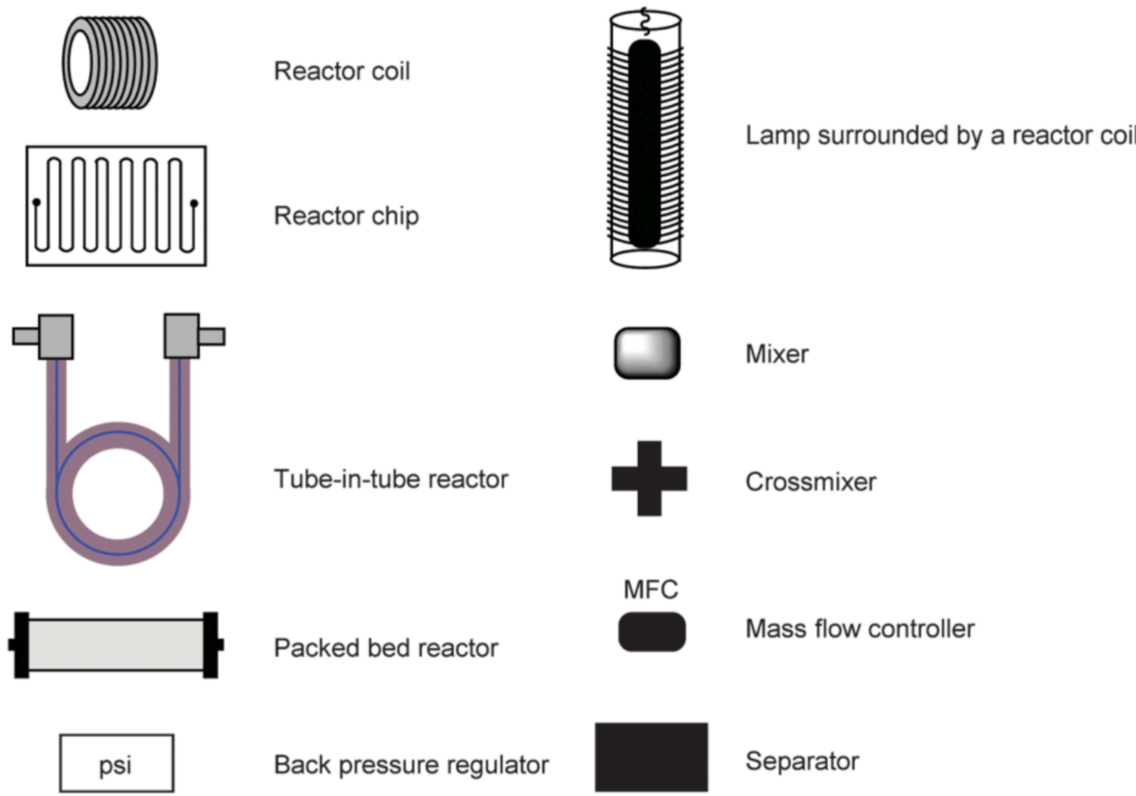
Overview

I. flow chemistry basics and common techniques
- types of reactors
- continuous extraction and other purification methods

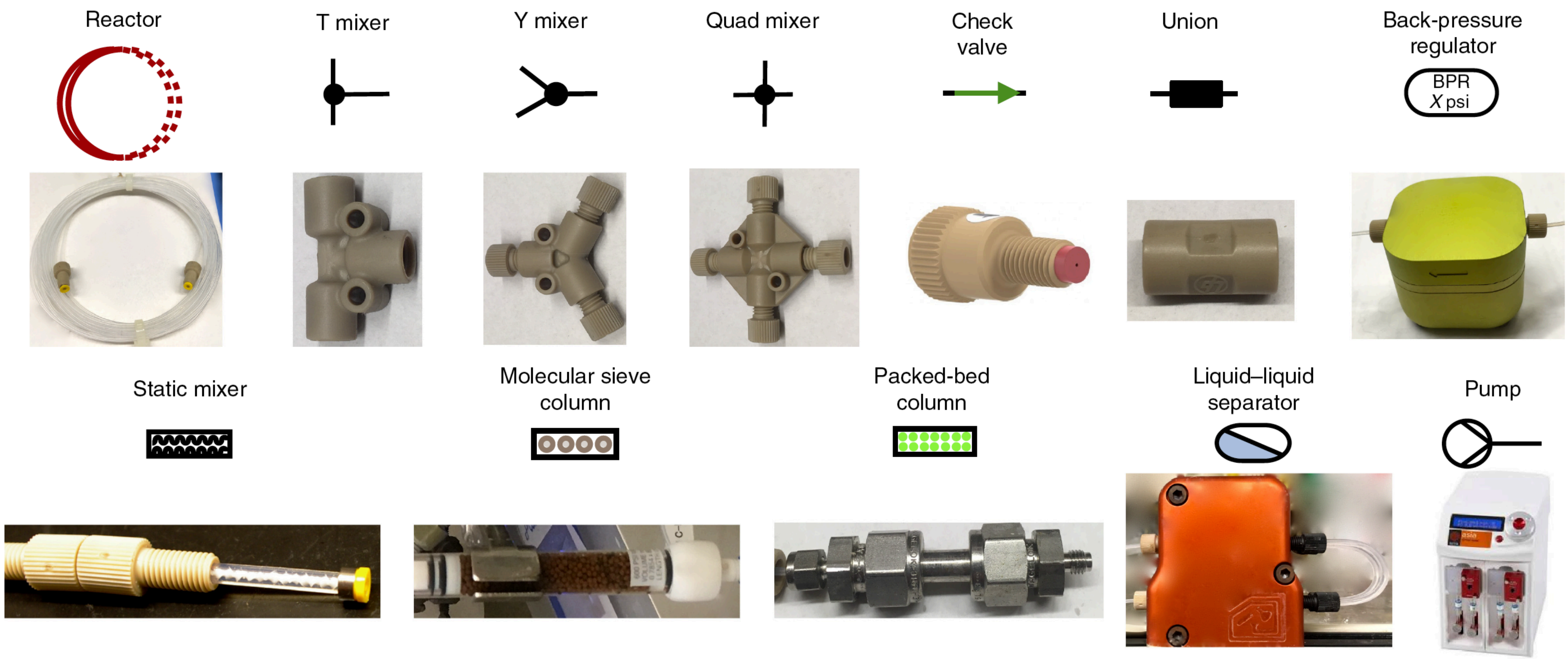
II. selected examples of flow synthetic methodology

III. application of flow chemistry toward API/natural product synthesis
- one-step processes
- multi-step continuous processes

Overview

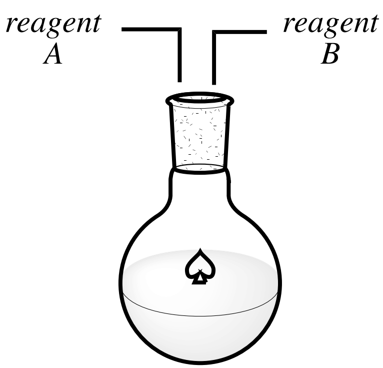

Reactor coil
Reactor chip
Tube-in-tube reactor
Packed bed reactor
psi
Back pressure regulator
Lamp surrounded by a reactor coil
Mixer
Crossmixer
MFC
Mass flow controller
Separator

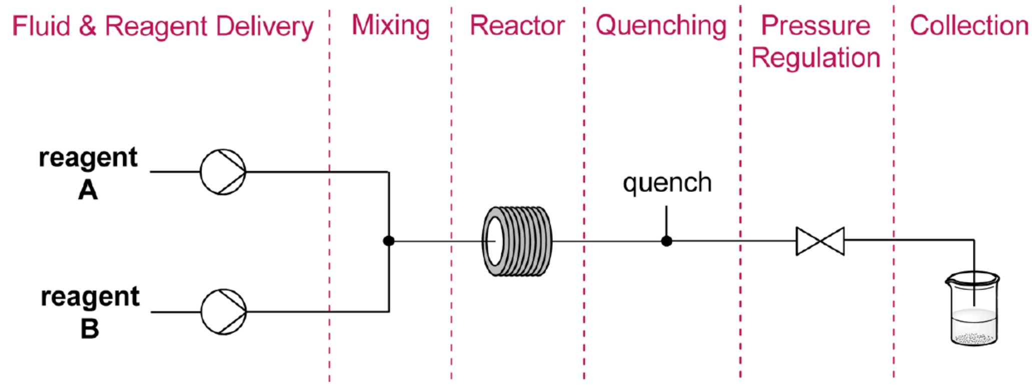
Overview



Jamison, *Nat. Protocols* **2017**, *12*, 2423–2446.

Batch vs. Flow

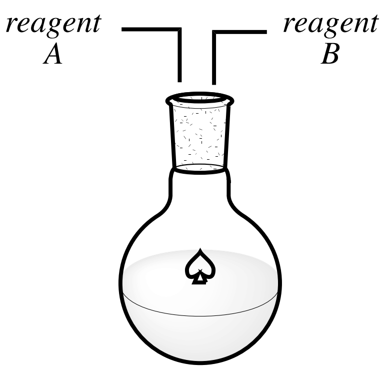


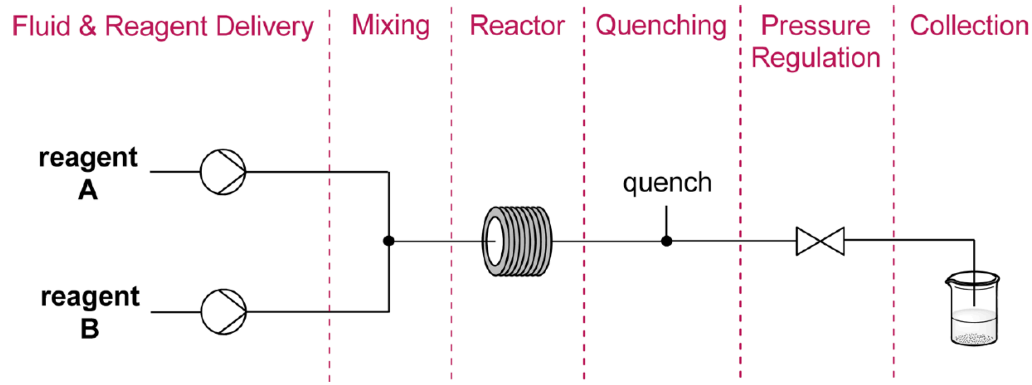


key advantages of flow
-optimal heat transfer due to high surface area
-accelerated mixing/micromixing
-easy use of high pressure: heating solvents above their boiling point
-continuous setup requires minimal intervention once initiated
-increased performance of multiphasic reactions

Plutschack, Pieber, Gilmore, Seeberger *Chem. Rev.* **2017**, *117*, 11796–11893.

Batch vs. Flow





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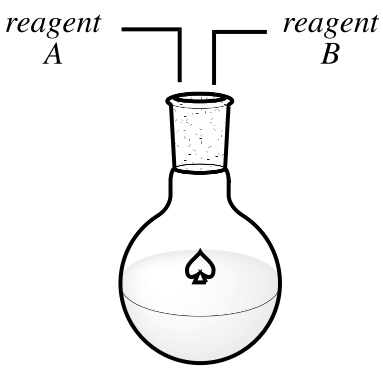
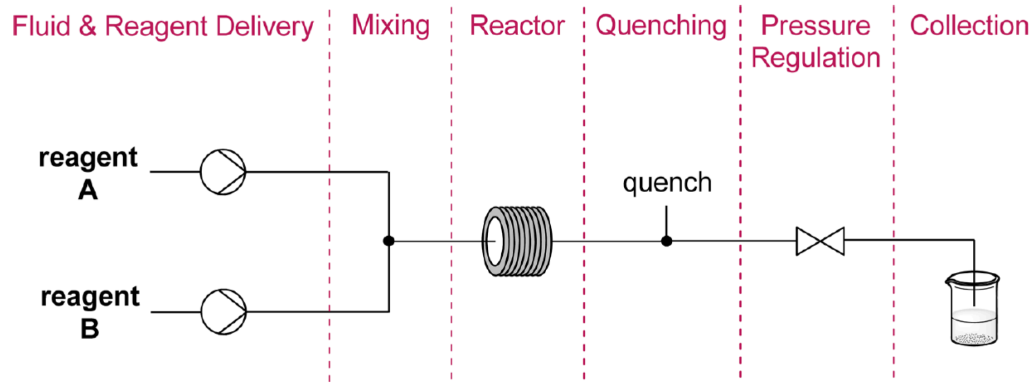
both involve the same fundamental operations

Plutschack, Pieber, Gilmore, Seeberger *Chem. Rev.* **2017**, *117*, 11796–11893.

Batch vs. Flow





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-easy use of high p
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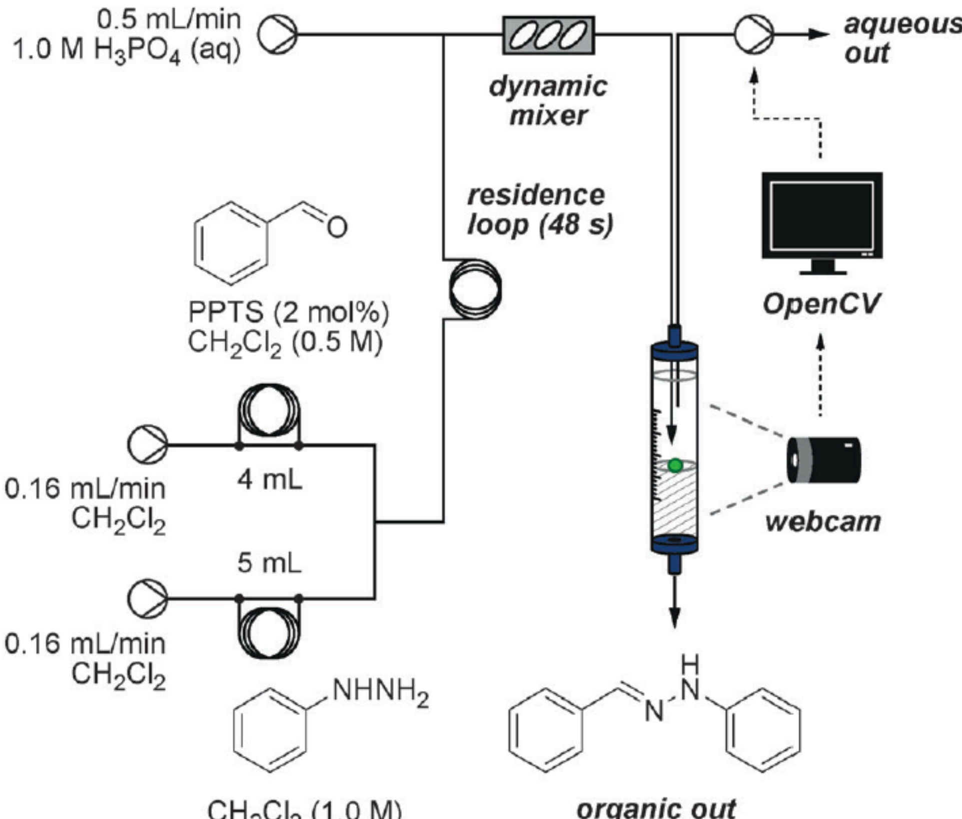
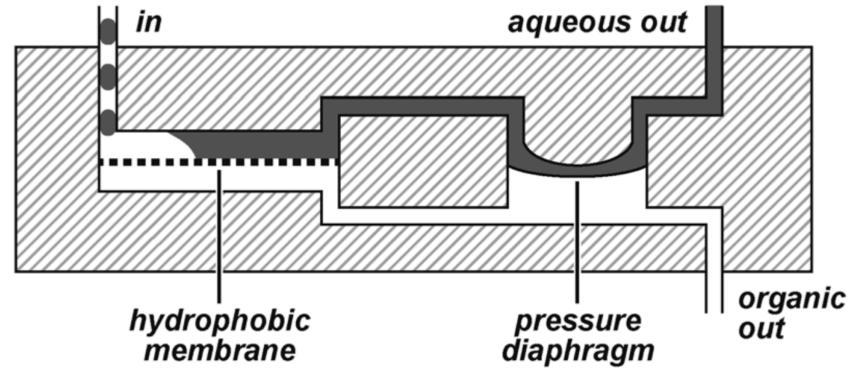
"A machine-assisted approach gives people more time to think plan, and make discoveries."
-Steve Ley

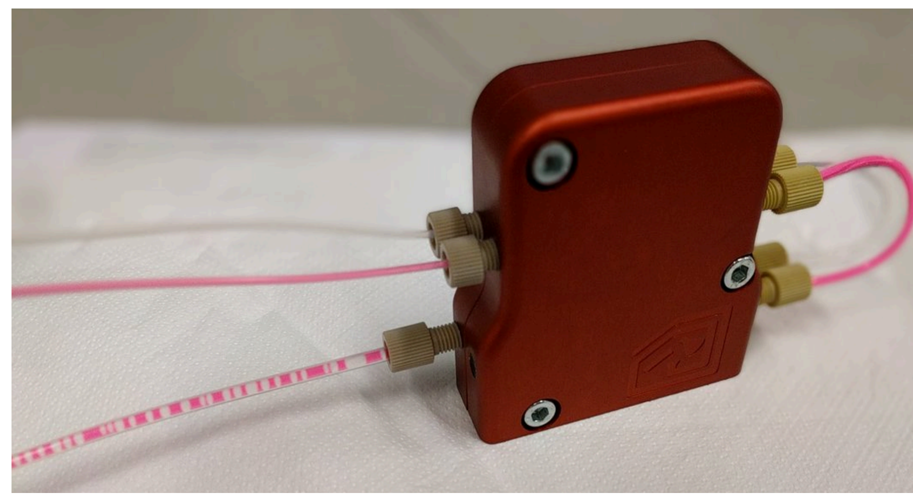
both involve the same fundamental operations

Plutschack, Pieber, Gilmore, Seeberger *Chem. Rev.* **2017**, *117*, 11796–11893.

Liquid–Liquid Extraction



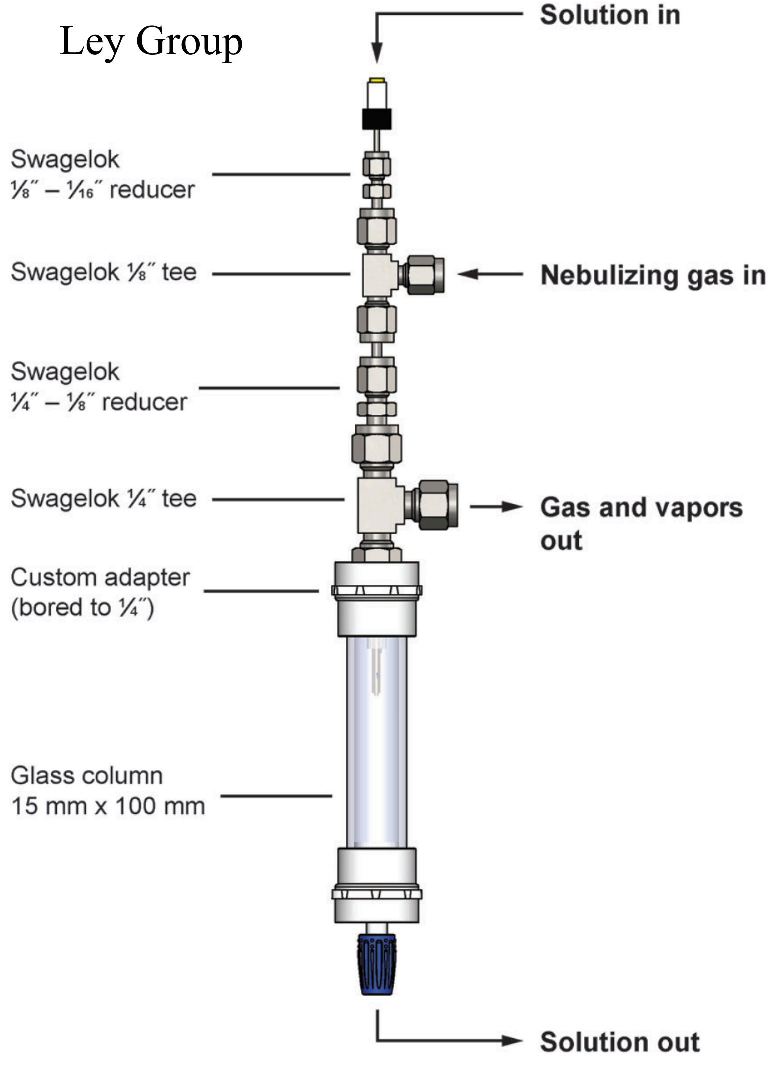




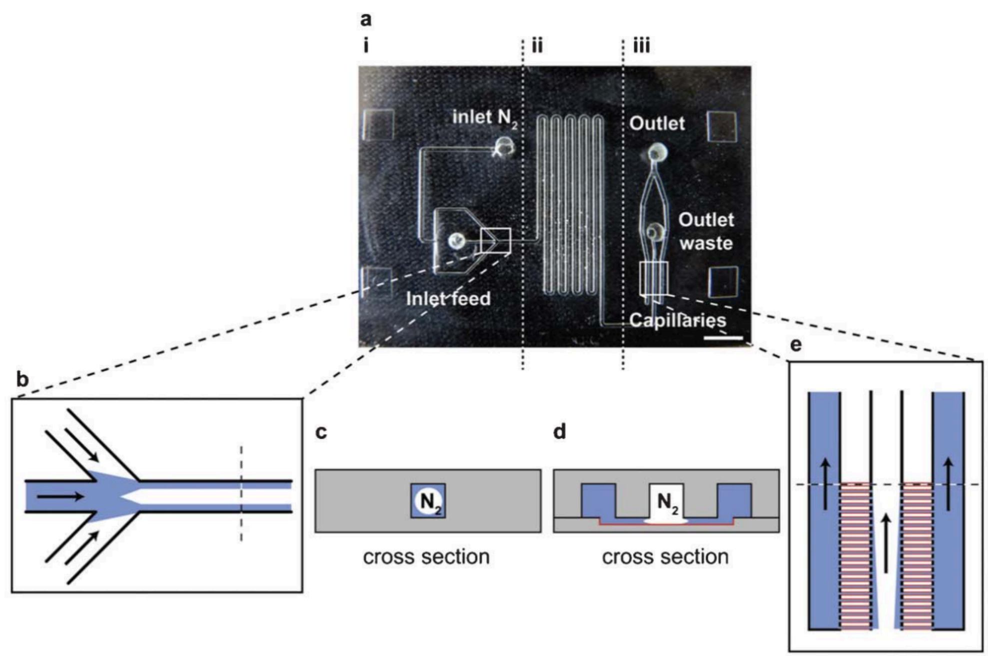
Hu, O'Brien, Ley *Org. Lett.* **2012**, *14*, 4246–4249.
Ley, Fitzpatrick, Ingham, Myers *Angew. Chem., Int. Ed.* **2015**, *54*, 3449–3464.

In-Line Solvent Removal/Swap

Ley Group

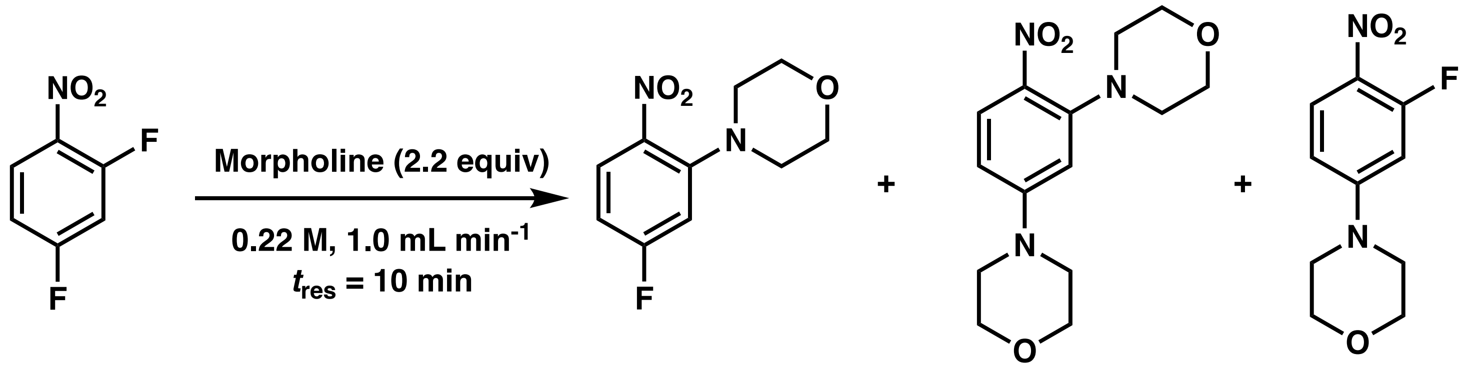


Dittrich Group



Ley, Fitzpatrick, Ingham, Myers *Angew. Chem., Int. Ed* **2015**, *54*, 3449–3464.
Cvetkovic, Lade, Marra, Arima, Rinaldi, Dittrich *RSC Adv.* **2012**, *2*, 11117–11122.

Simulated Moving-Bed (SMB) Chromatography



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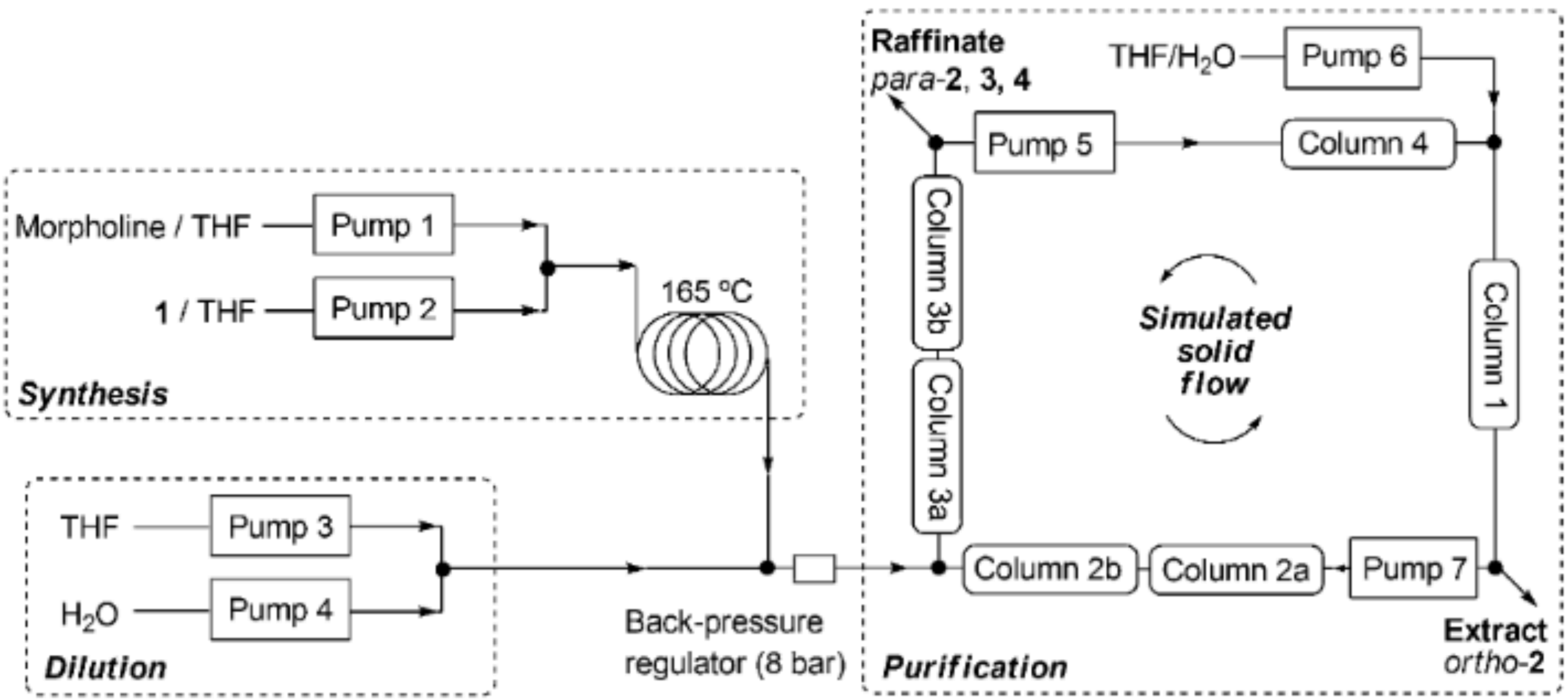
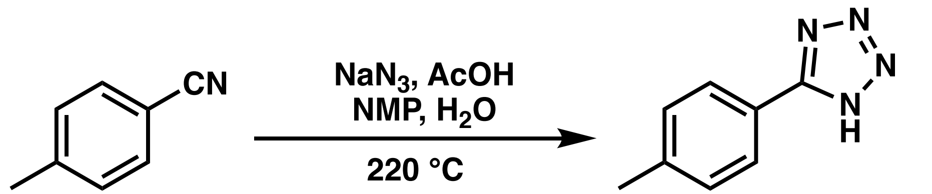


Seeberger, *Angew. Chem., Int. Ed.* **2012**, *51*, 7028–7030.

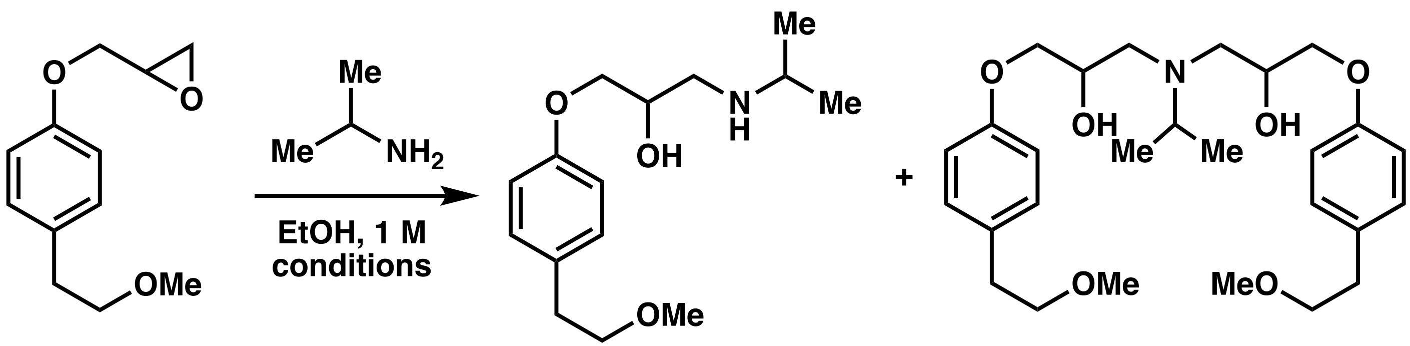
Microwave-to-Flow Paradigm

-paradigm states that reactions optimized in MW conditions easily translate to flow



MW: 5 min, 98% yield
flow: 10 min, 96% yield

-in situ formation of toxic hydrazoic acid (HN_3)

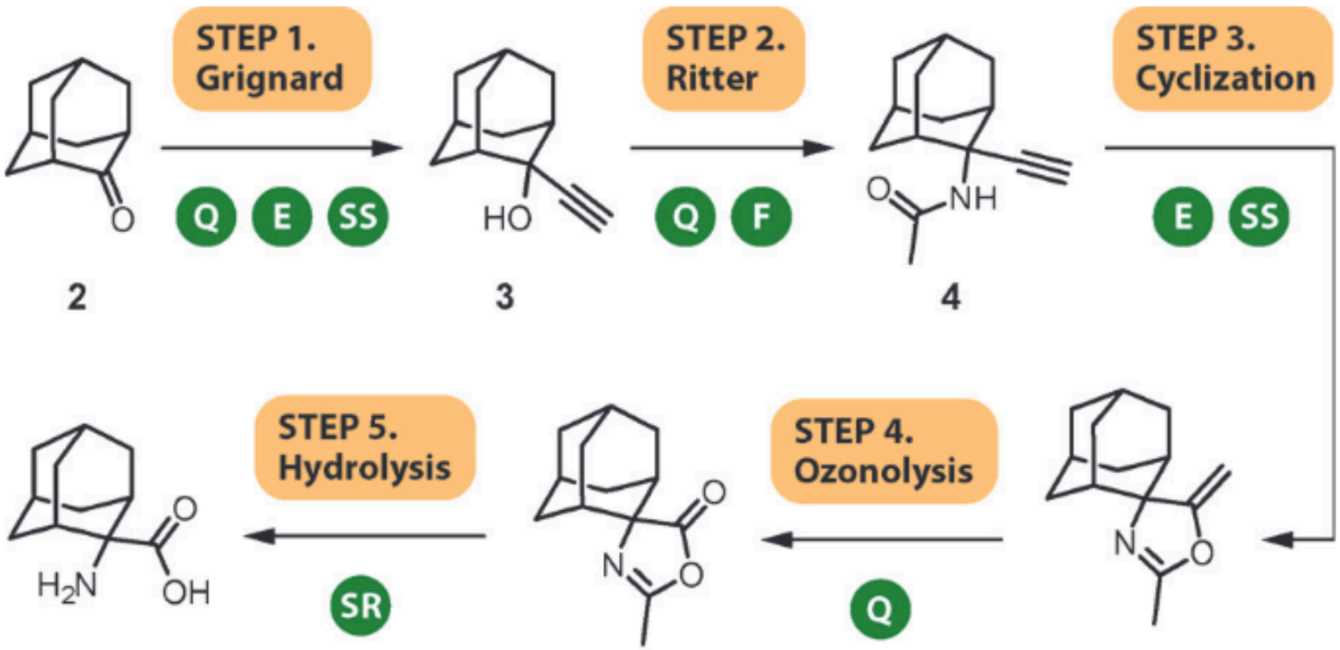


A **B**

entry	conditions (psi)	amine equiv	temp °C	time	yield A	yield B
1	batch MW (100)	1.2	150	30 min	69	28
2	flow (500)	4.0	240	15 s	91	6

Jensen, Jamison, *Org. Process Res. Dev.* **2010**, *14*, 432–440.
Kappe, *Angew. Chem. Int., Ed.* **2010**, *49*, 7101–7105.
Kappe, *Chem. Eur. J.* **2011**, *17*, 11956–11968.

Integrated Operations



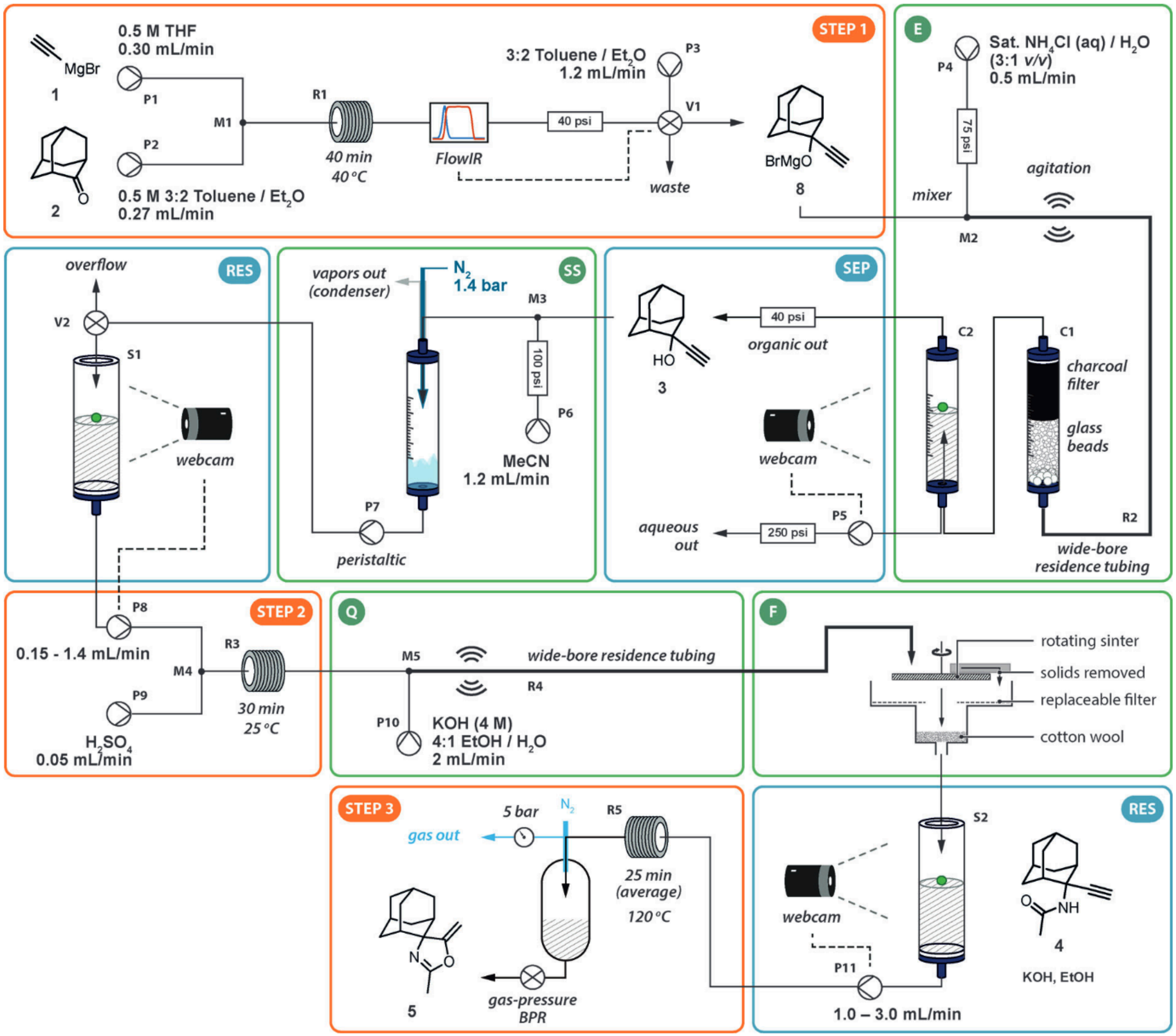
Q = quench
E = extraction

SS = solvent switch
F = filtration

SR = solvent removal

Ley, *Angew. Chem., Int. Ed* **2015**, *54*, 144–148.

Integrated Operations



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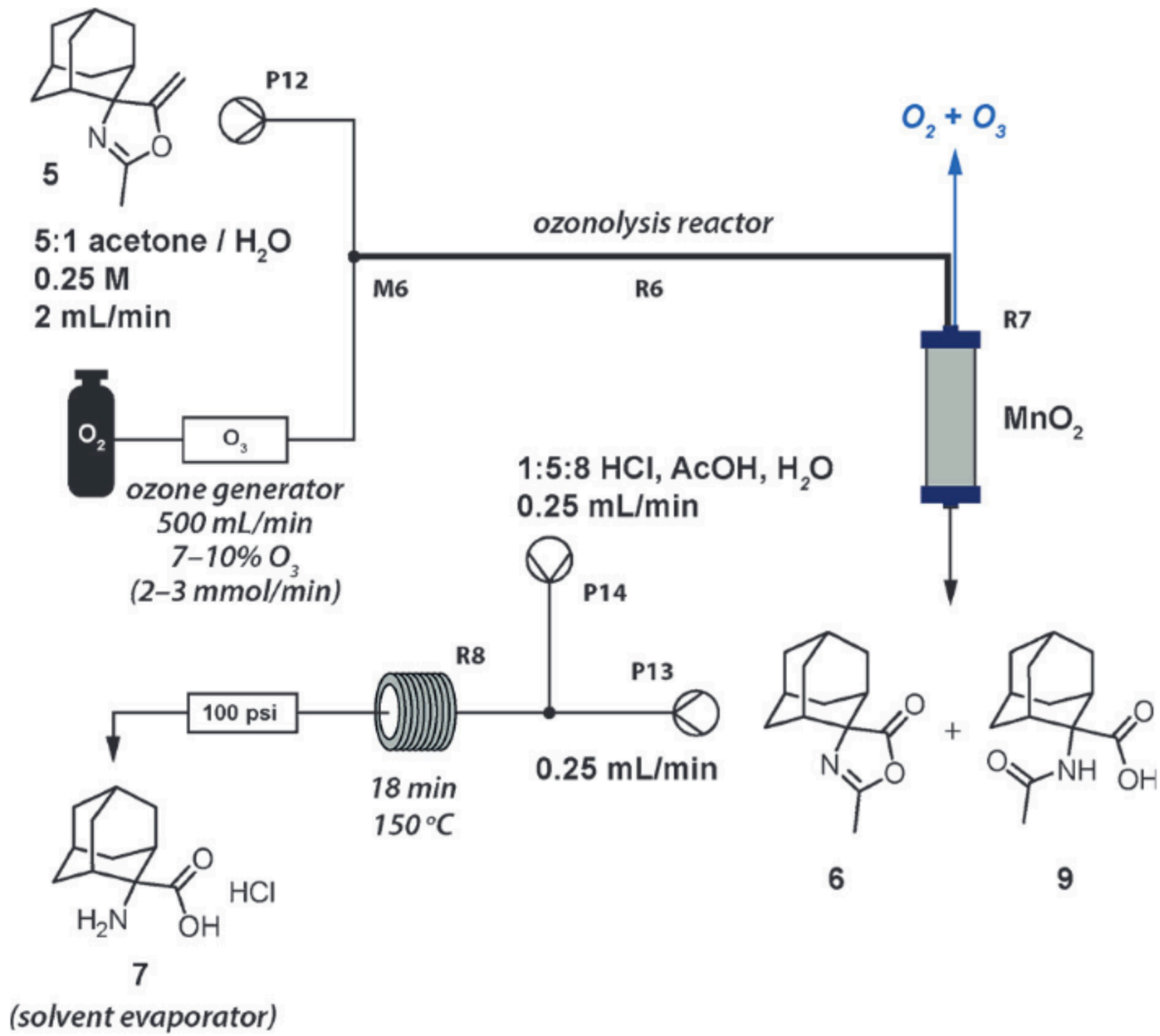

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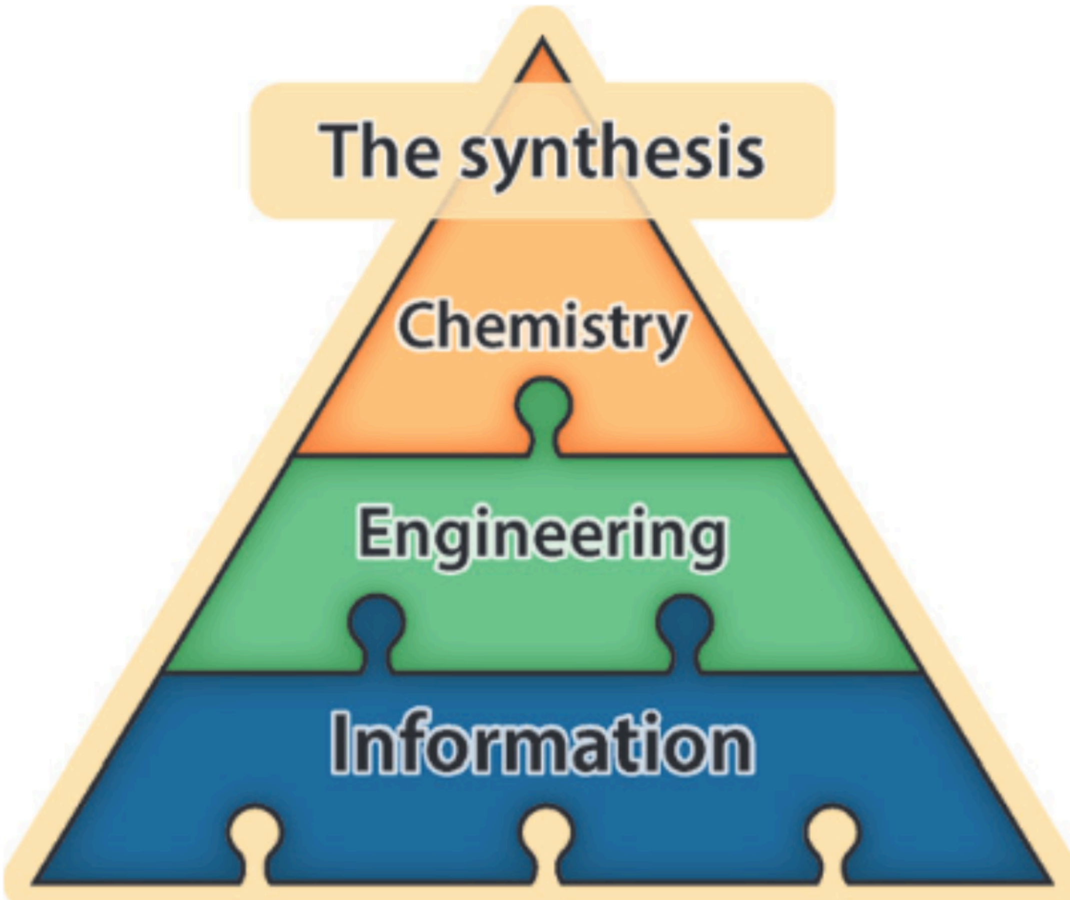
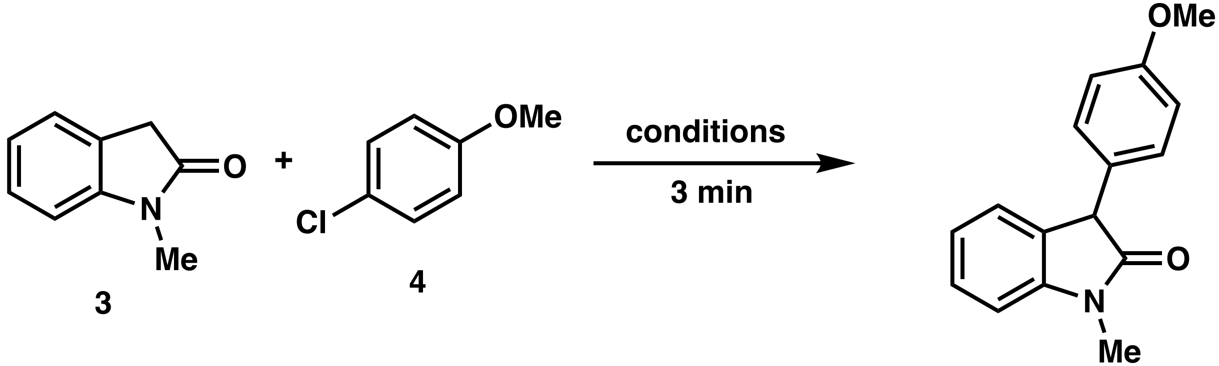
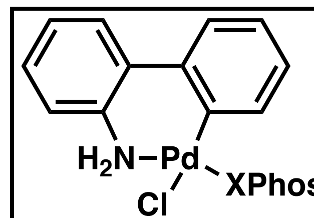


Ley, *Angew. Chem., Int. Ed* **2015**, *54*, 144–148.

Packed-Bed Reactor



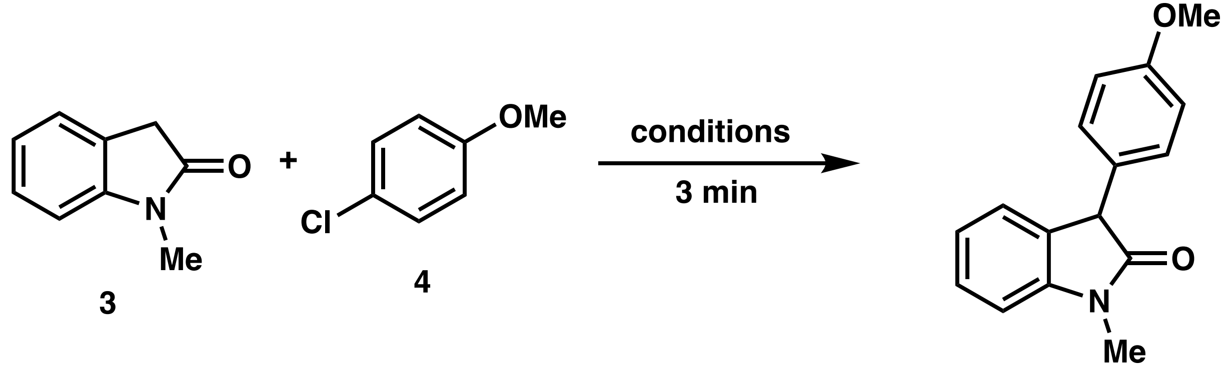
entry	Pd Source (1 mol %)	Base	Solvent	Yield
1	$Pd(dba)_2$	KHMDS	THF/Tol	<5
2	$Pd(dba)_2$	LiMHDS	THF/Tol	12
3	2	LiHMDS	THF/Tol	5
4	2	2.0 M KOH *with TBAB	Tol/H_2O	91



2

Buchwald, *Angew. Chem., Int. Ed.* **2011**, *50*, 6396–6400.

Packed-Bed Reactor



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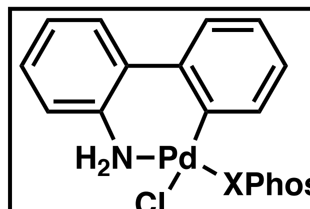
rapid/efficient mixing is crucial for high yields!



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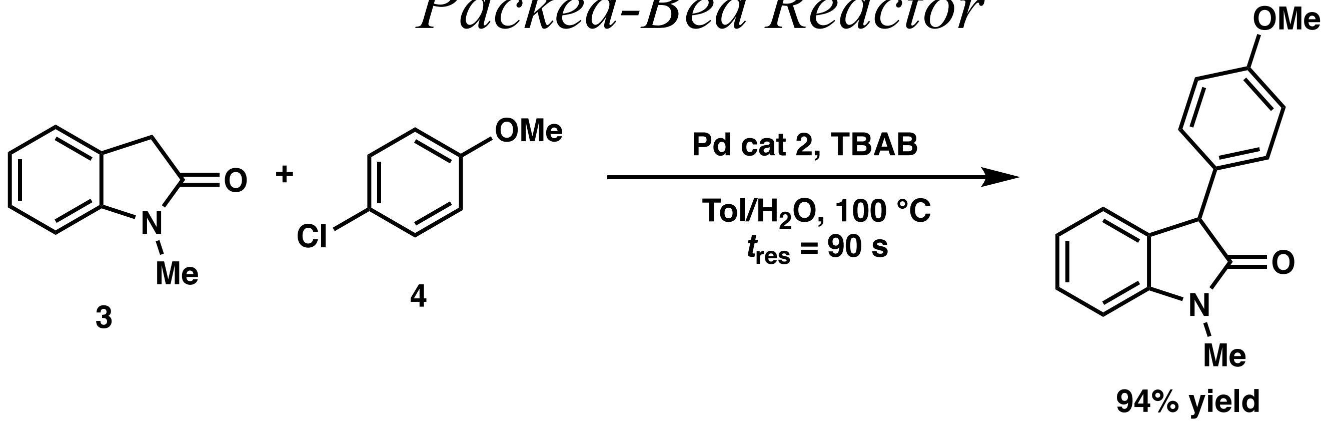
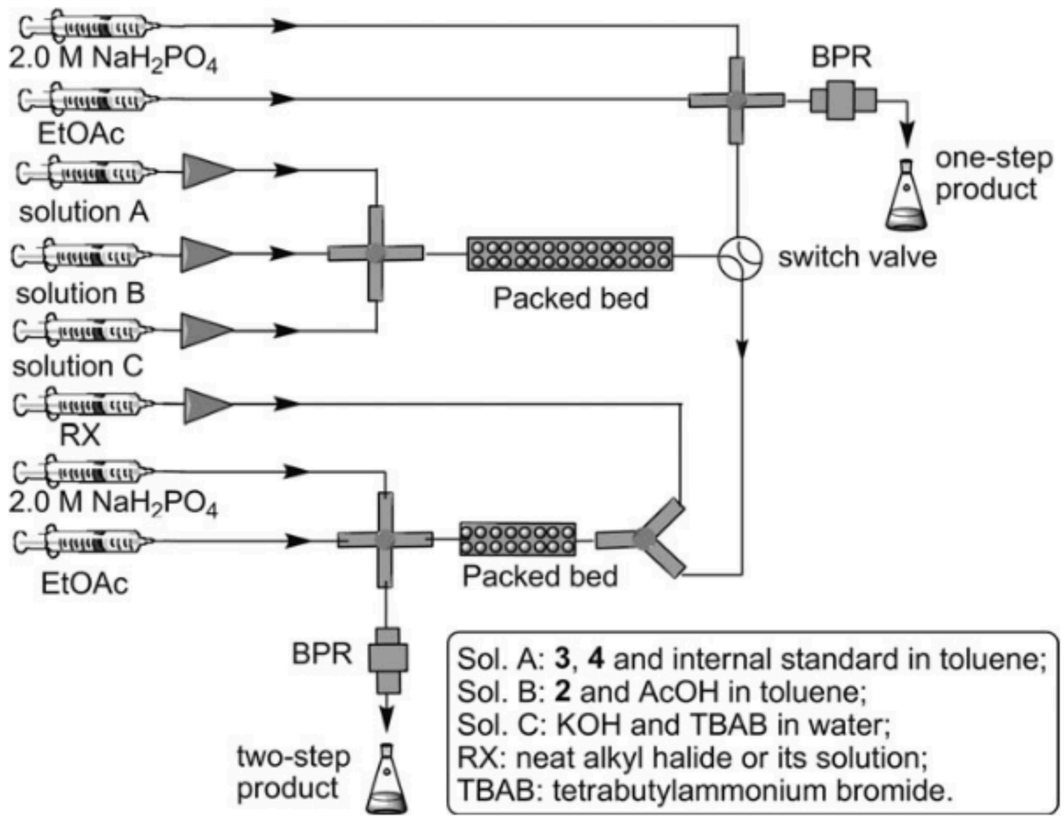
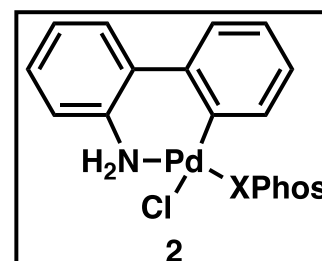
Packed-Bed Reactor

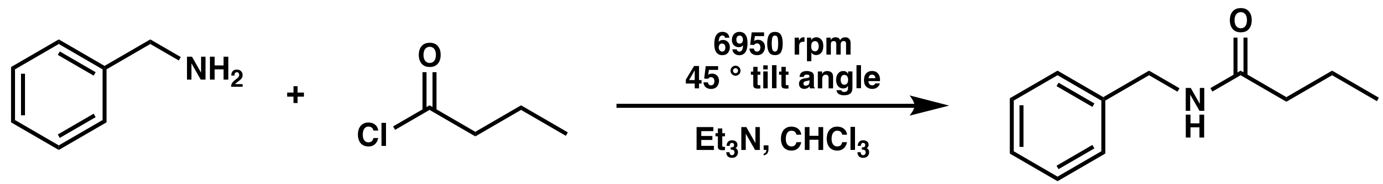






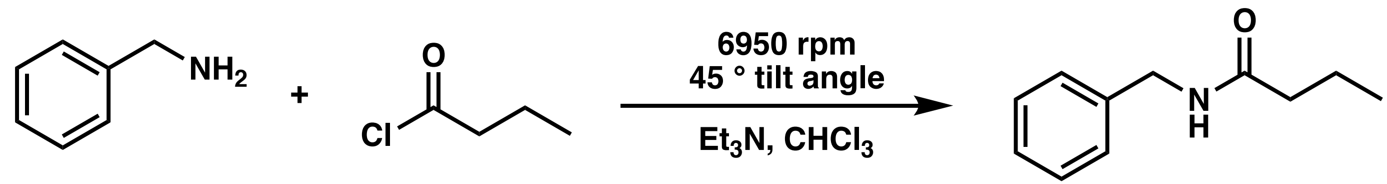
Buchwald, *Angew. Chem., Int. Ed.* **2011**, *50*, 6396–6400.

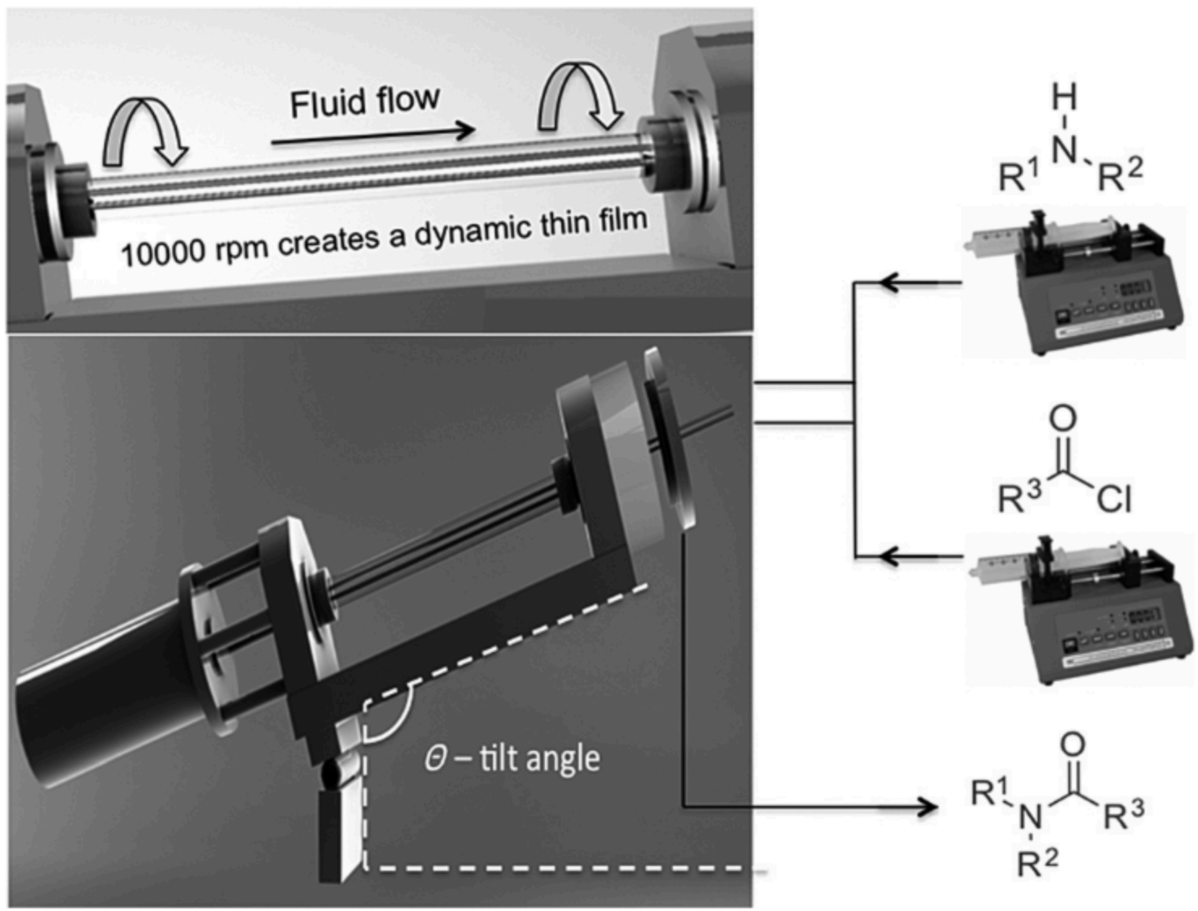
Rapid Vortex Fluidics



Raston, *Chem. Eur. J.* **2015**, *21*, 10660–10665.

Rapid Vortex Fluidics





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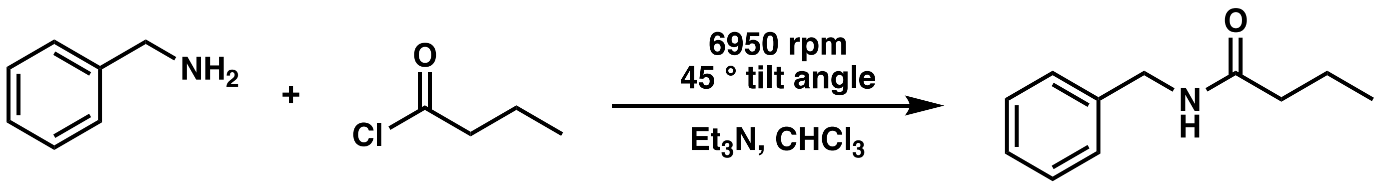

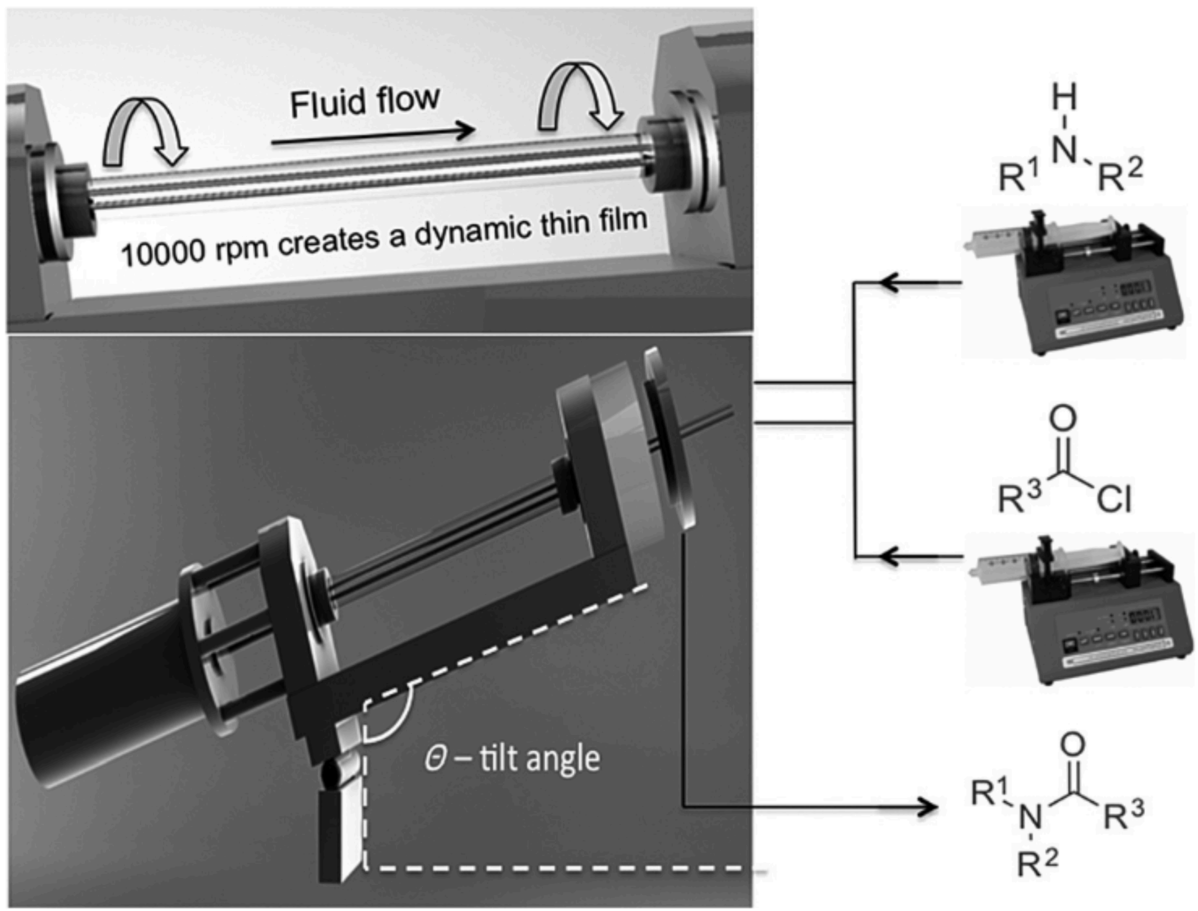

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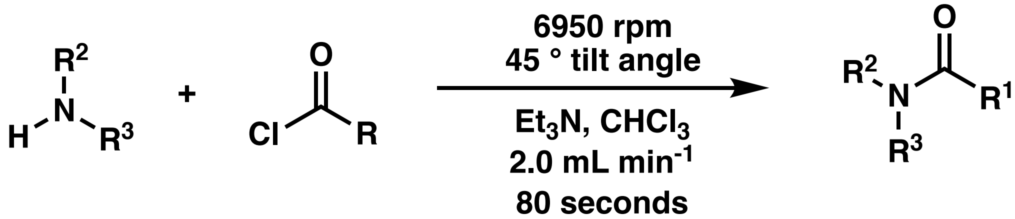
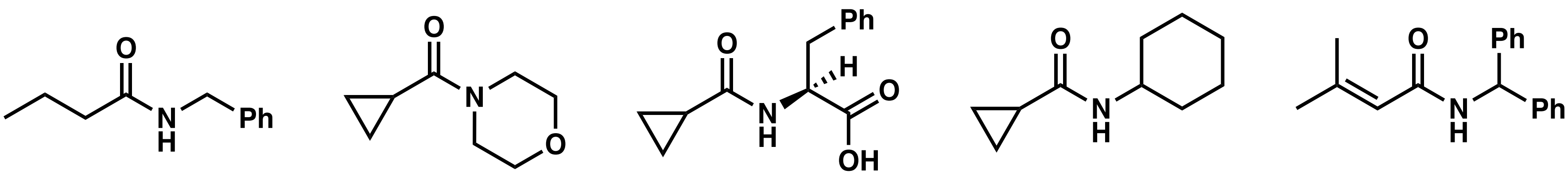
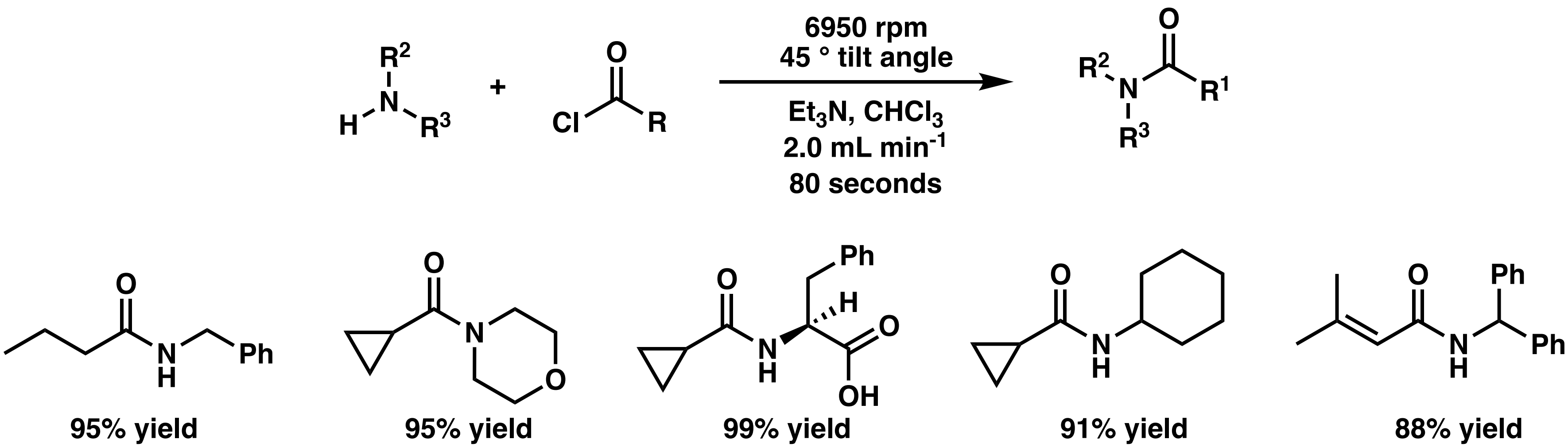


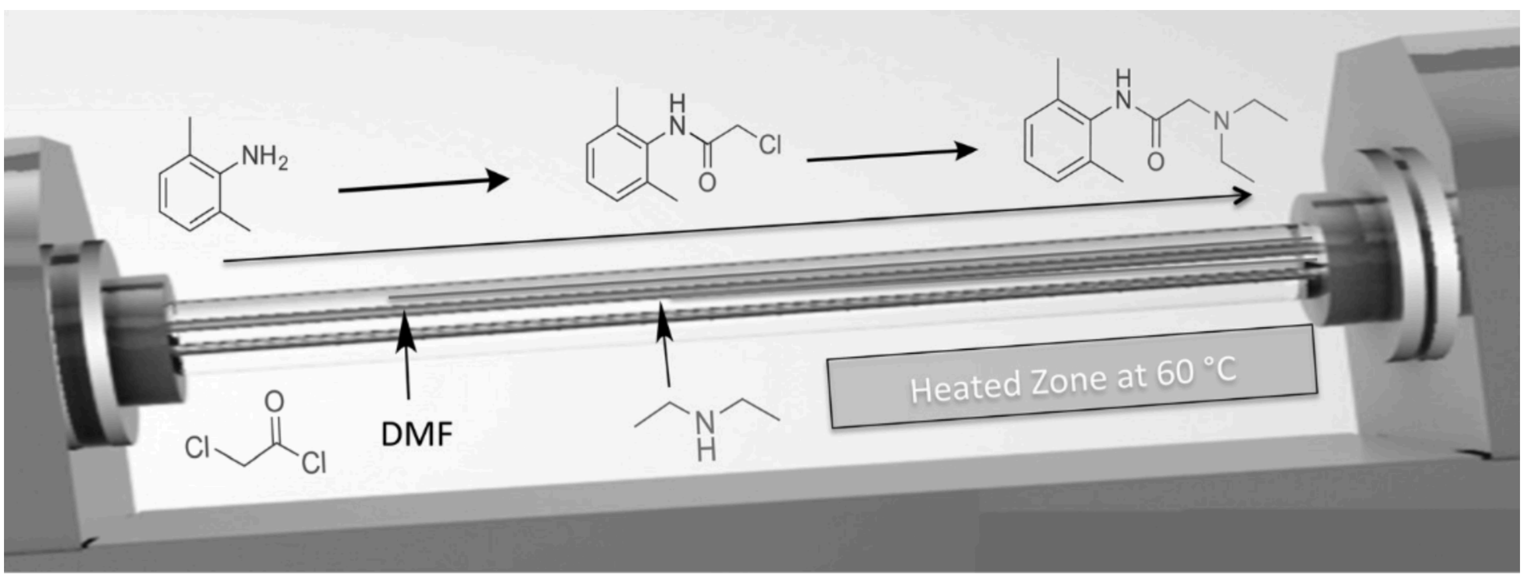


95% yield **95% yield** **99% yield** **91% yield** **88% yield**

Raston, *Chem. Eur. J.* **2015**, *21*, 10660–10665.

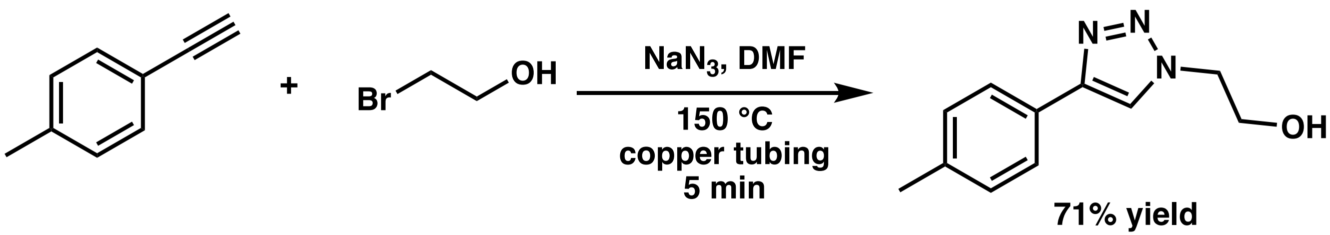
Rapid Vortex Fluidics

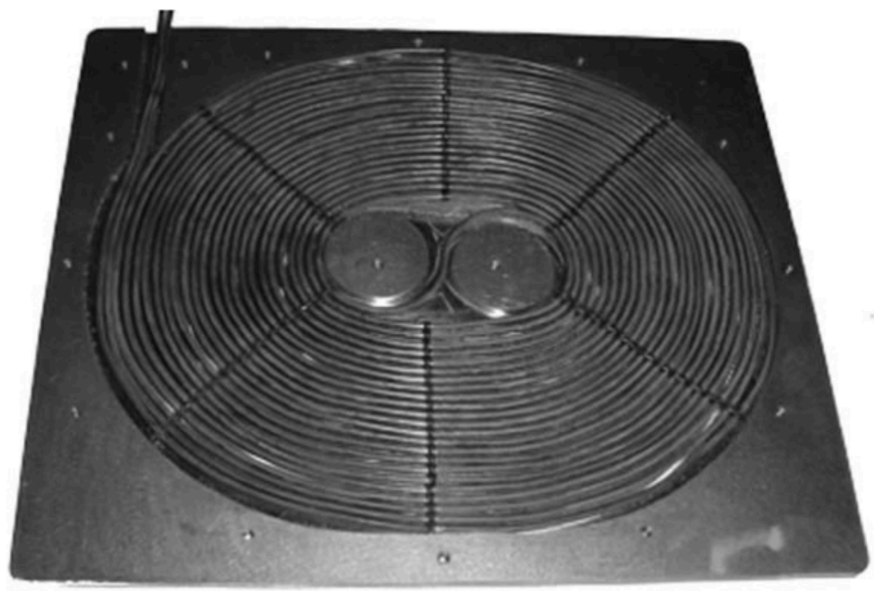




Raston, *Chem. Eur. J.* **2015**, *21*, 10660–10665.

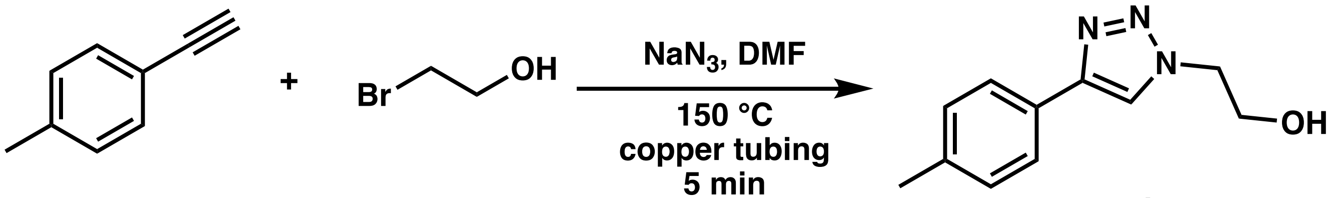
Copper-Tube Reactor



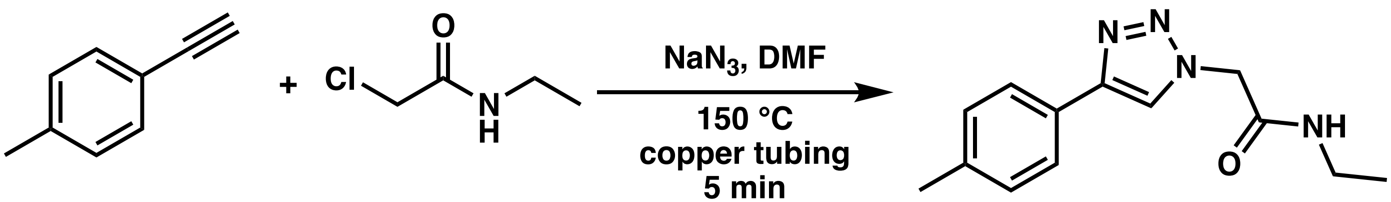


Sach, *Adv. Synth. Catal.* **2009**, *351*, 849–854.

Copper-Tube Reactor



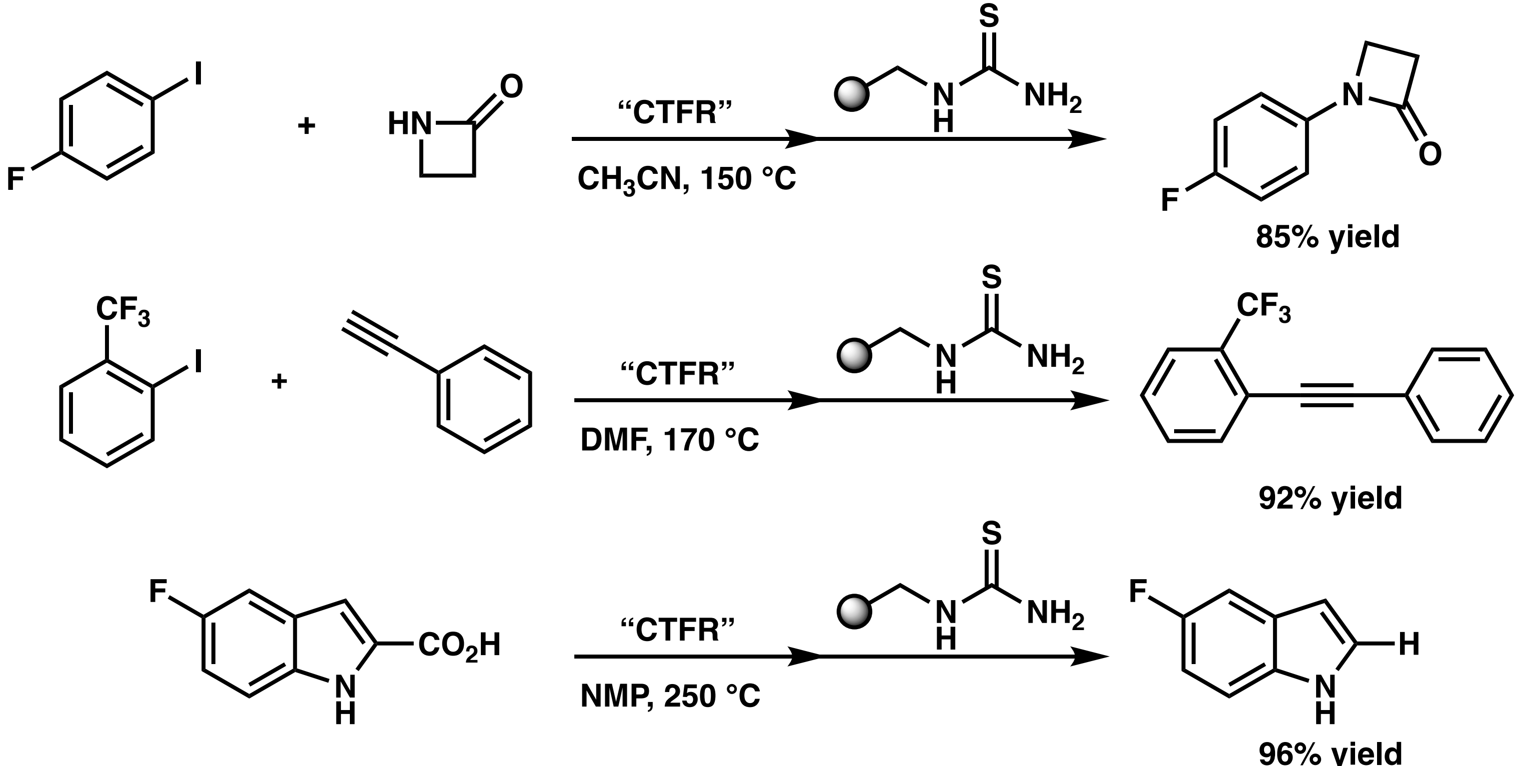
30 different triazoles prepared in a couple hours

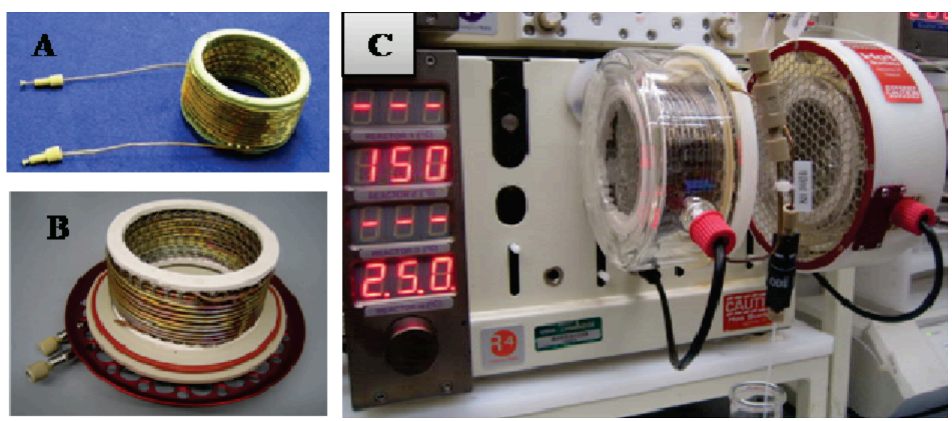


time	output
12 min	115 mg
1 hour	575 mg
1 day	13.8 g

Sach, *Adv. Synth. Catal.* **2009**, *351*, 849–854.

Copper-Tube Reactor

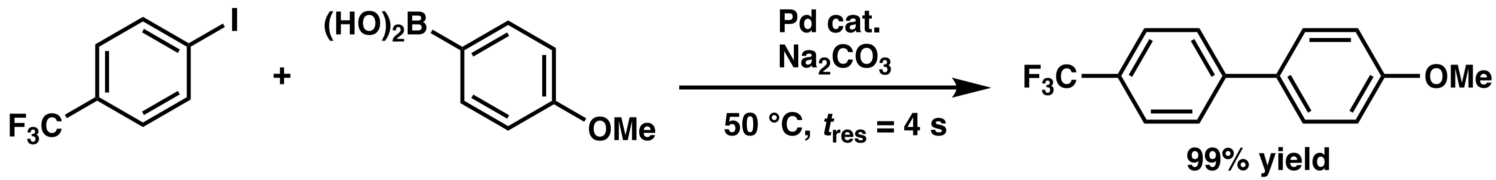




Jamison, Patel, Minolfi *Org. Lett.* **2011**, *13*, 280–283.

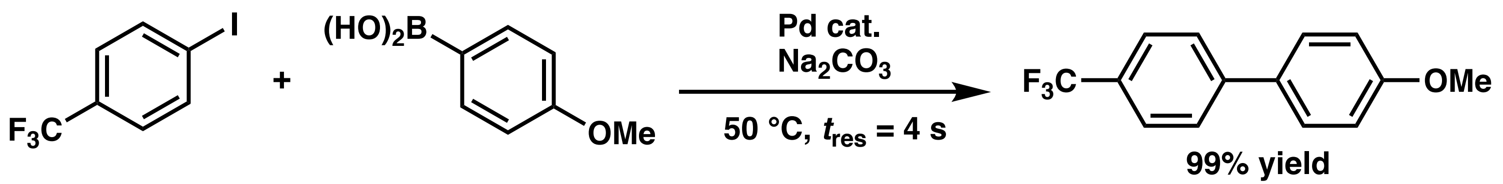
"CTFR" = copper tube flow reactor

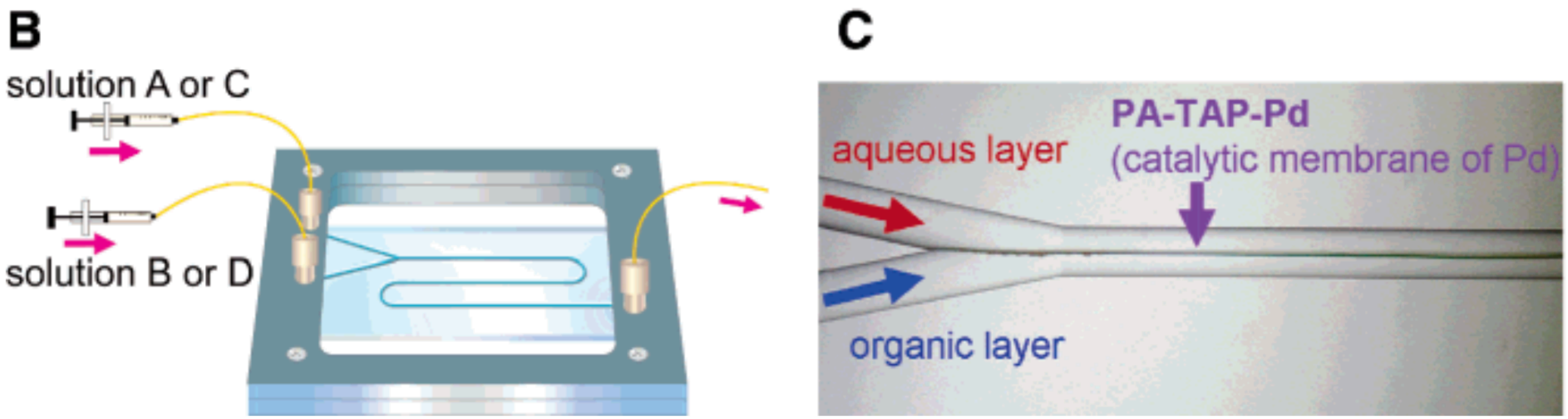
Cross-Coupling in Flow



Uozumi, *J. Am. Chem. Soc.* **2006**, *128*, 15994–15995.

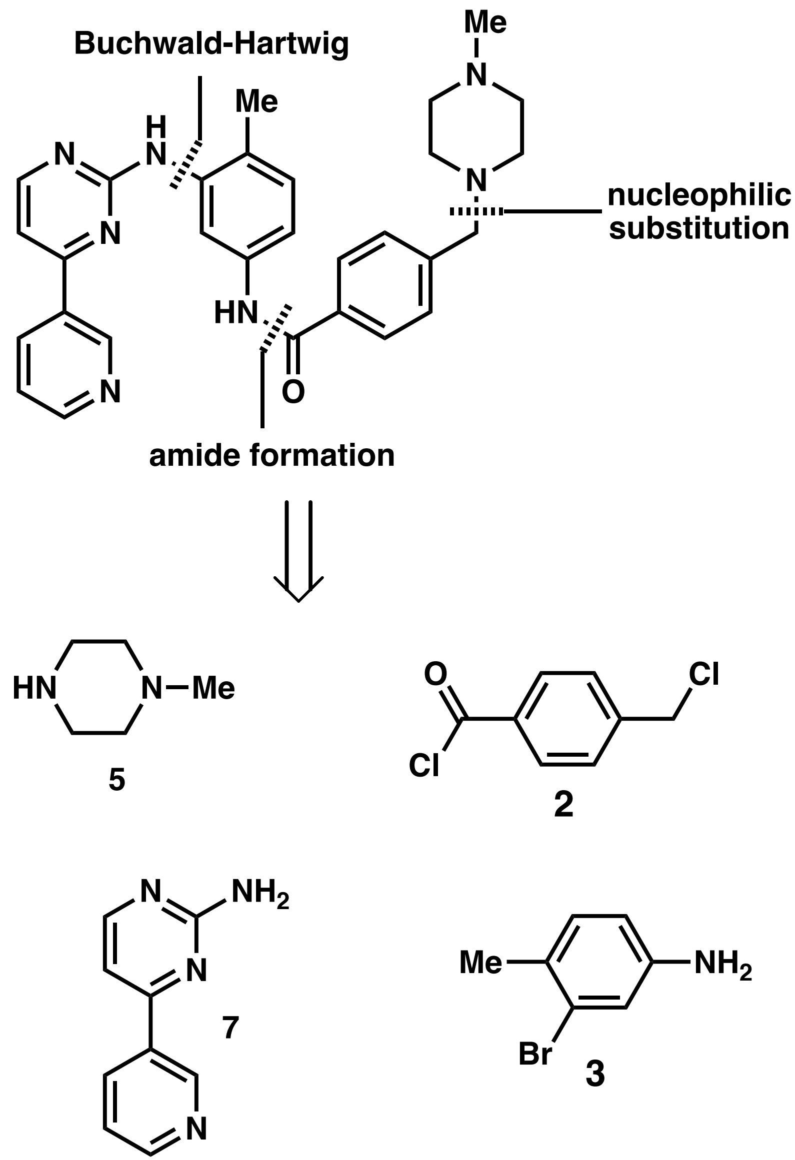
Cross-Coupling in Flow





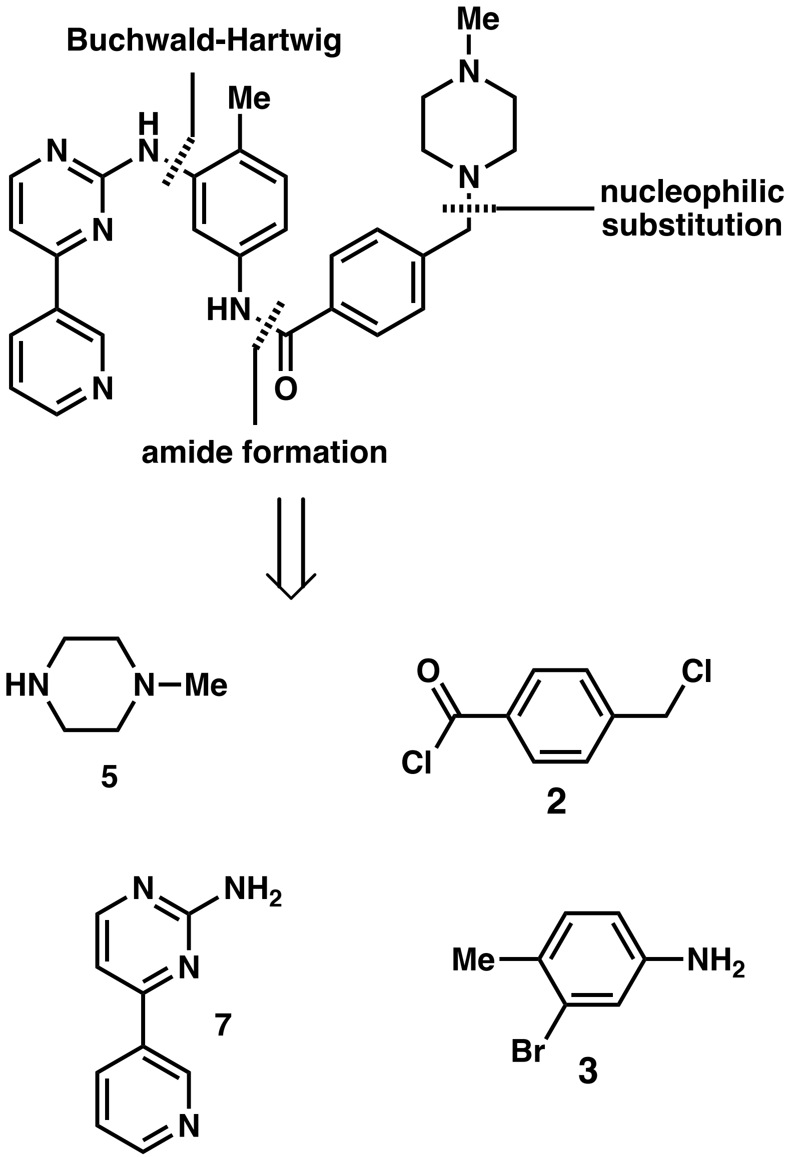
Uozumi, *J. Am. Chem. Soc.* **2006**, *128*, 15994–15995.

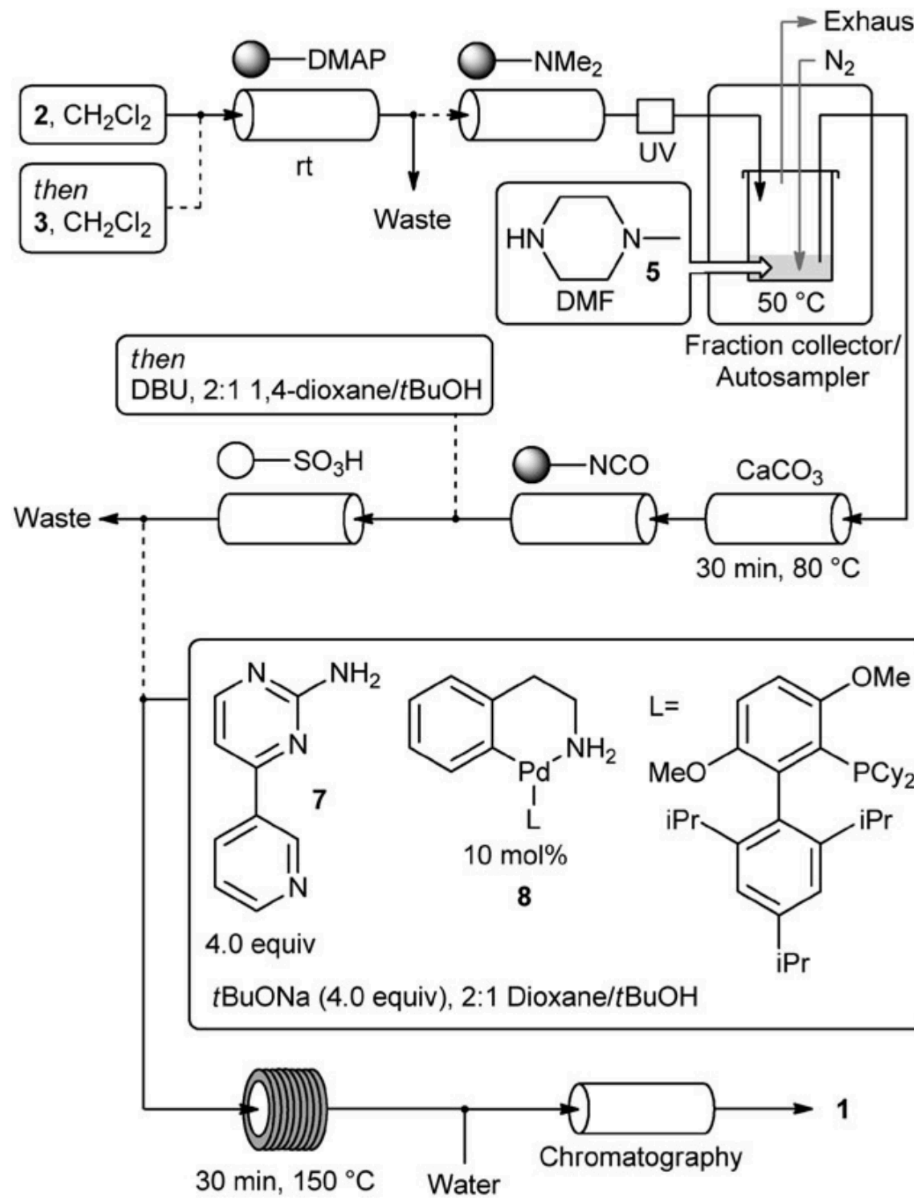
Cross-Coupling in Flow: Synthesis of Imatinib



Ley, *Chem. Commun.* **2010**, *46*, 2450–2452.

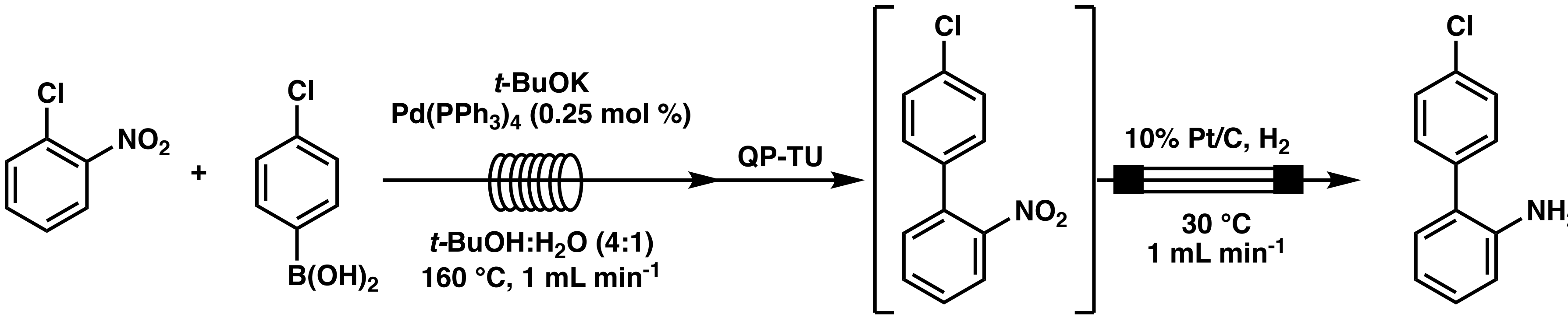
Cross-Coupling in Flow: Synthesis of Imatinib





Ley, *Chem. Commun.* **2010**, *46*, 2450–2452.

Continuous Flow Hydrogenation (H-Cube)



intermediate for
Boscalid, a funicide
made on >1000 tons/year

Kappe, *Adv. Synth. Catal.* **2010**, *352*, 3089–3097.

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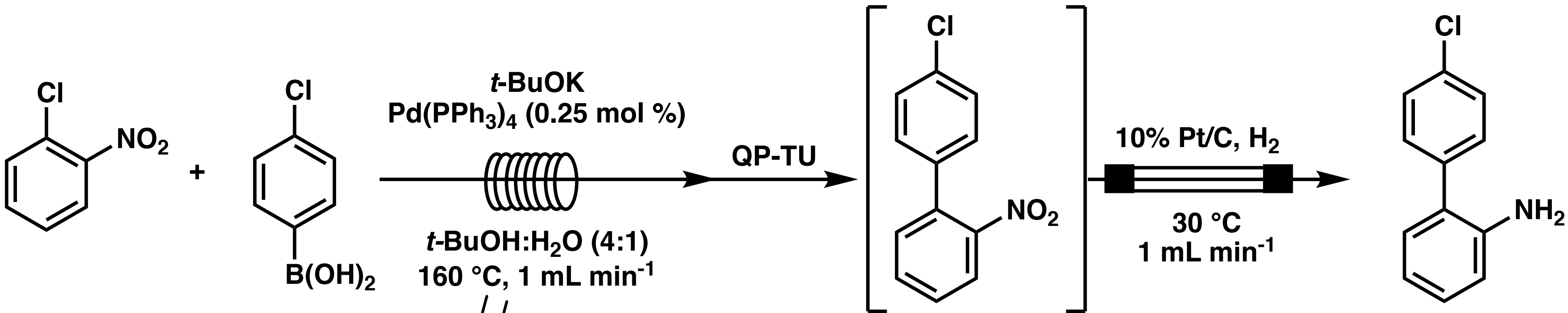

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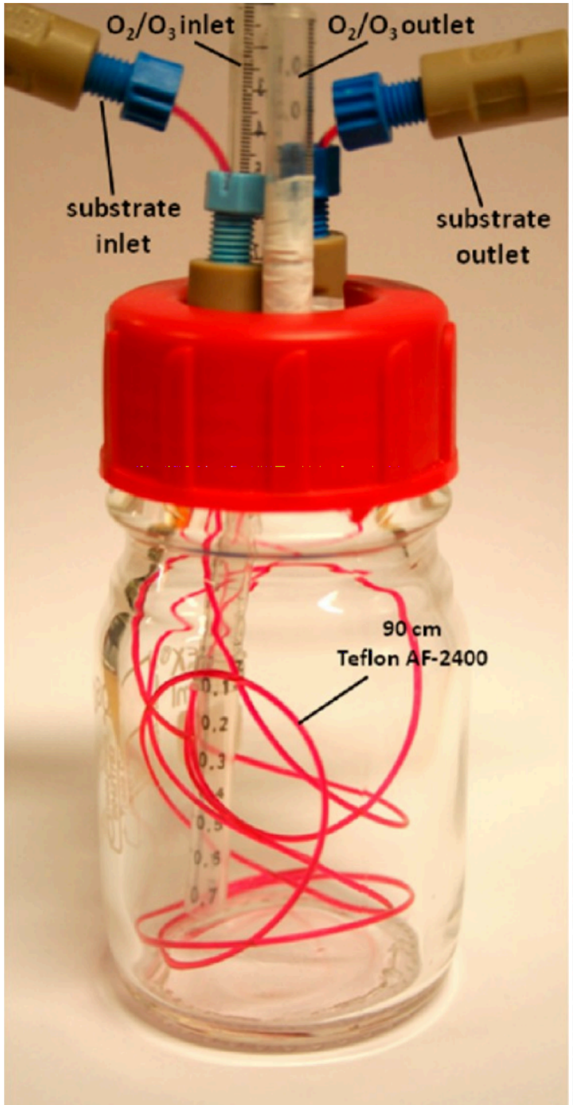
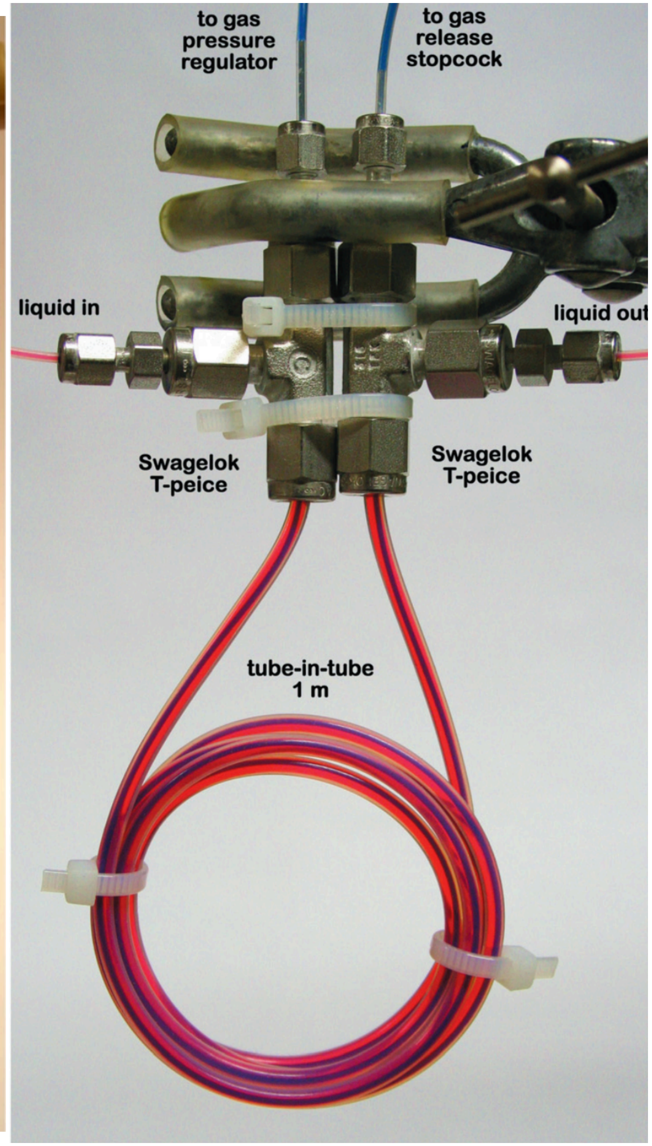
ThalesNano X-Cube

ThalesNano H-Cube

Kappe, *Adv. Synth. Catal.* **2010**, *352*, 3089–3097.

Gas-Liquid Transformations with Tube-in-Tube Reactor

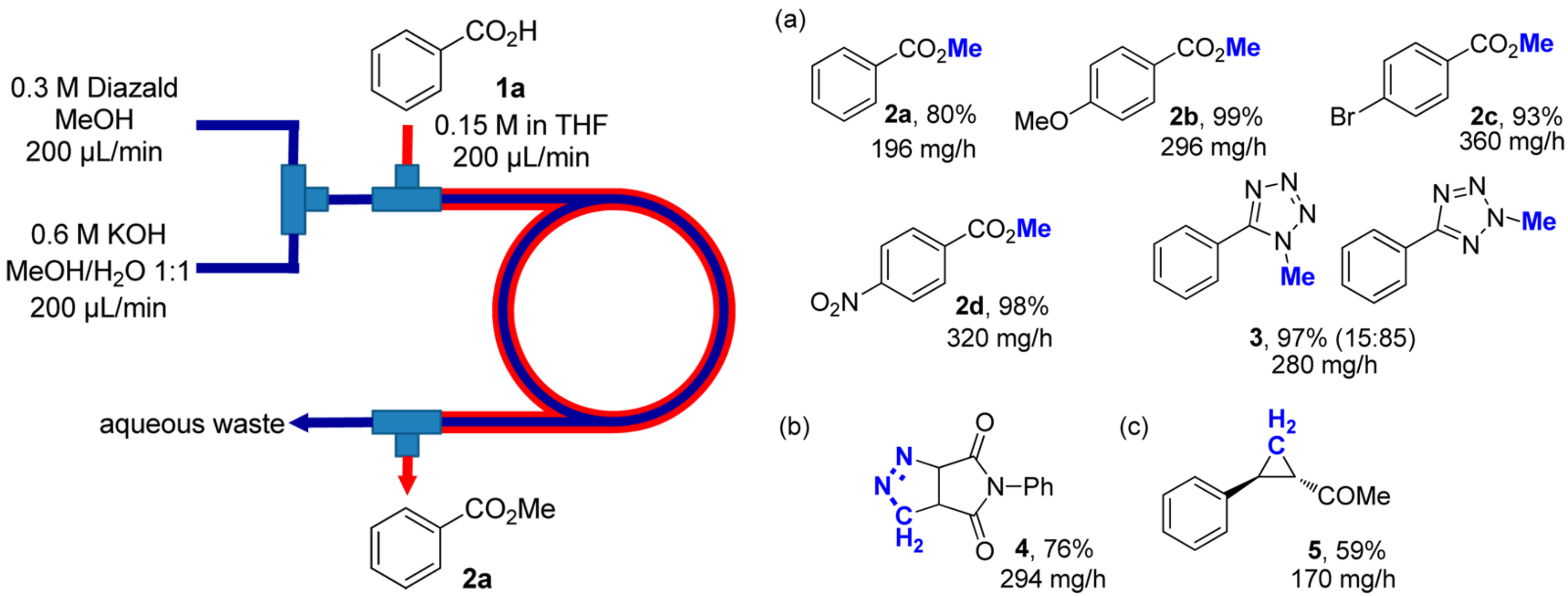




- CO_2 carboxylation of Grignards
- CO methoxycarboxylation
- Me_2NH/CO dimethylaminocarbonylation
- ethylene Heck-vinylation
- CO/H_2 hydroformylation
- NH_3 Paal-Knorr
- O_2 Wacker Oxidation

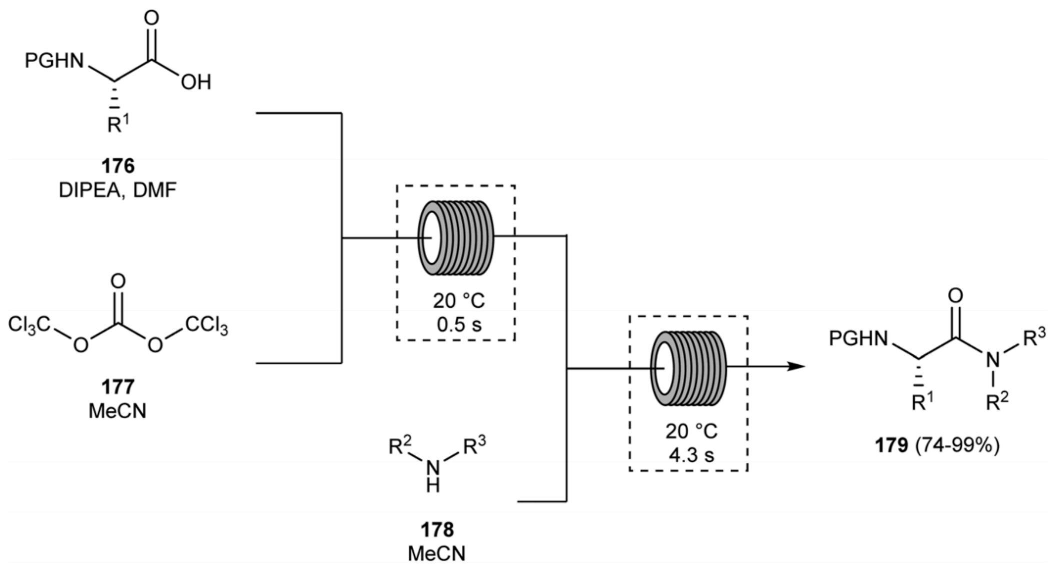
Ley, *Acc. Chem. Res.* **2015**, *48*, 349–362.

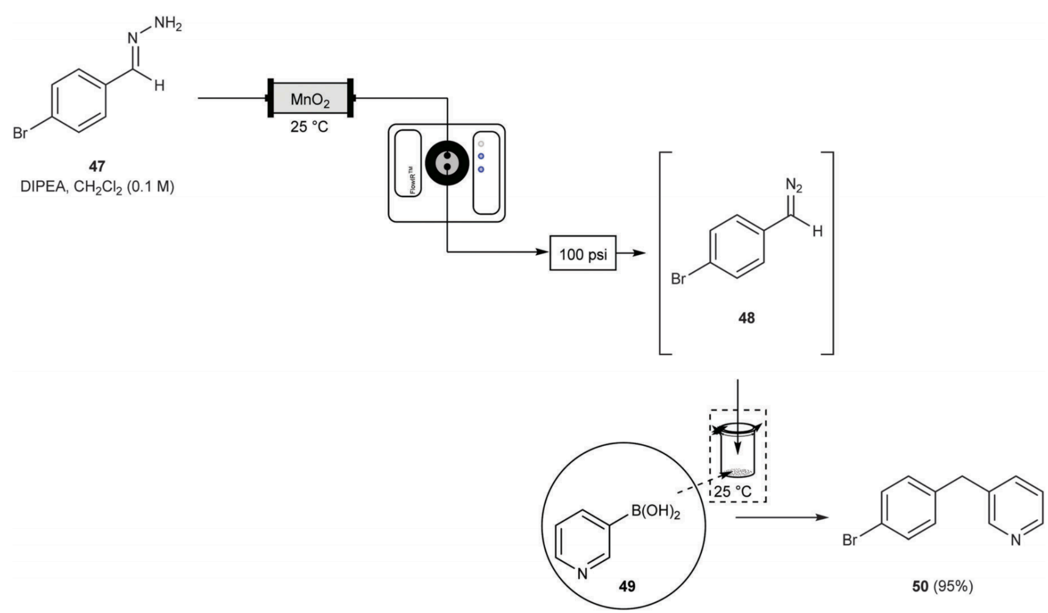
Taming Hazardous Reagents Using Flow



Kappe, *Org. Lett.* **2013**, *15*, 5590–5593.

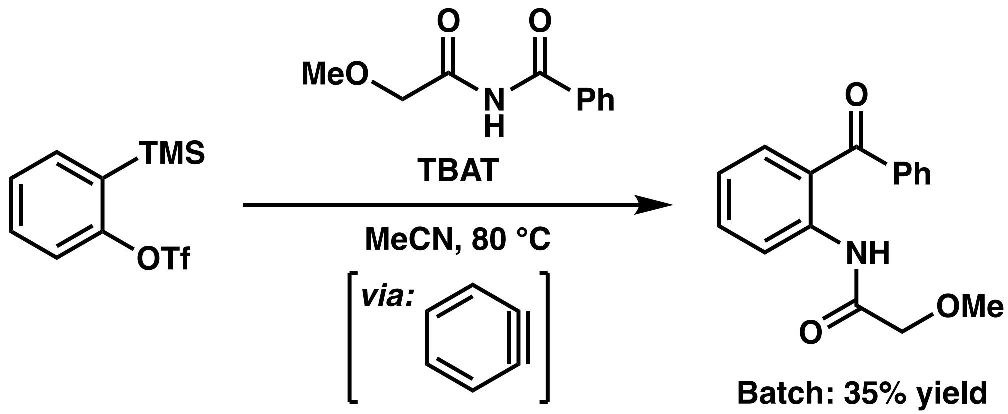
Taming Hazardous Reagents Using Flow





Ley, Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.

Generation/Reaction of Arynes in Flow

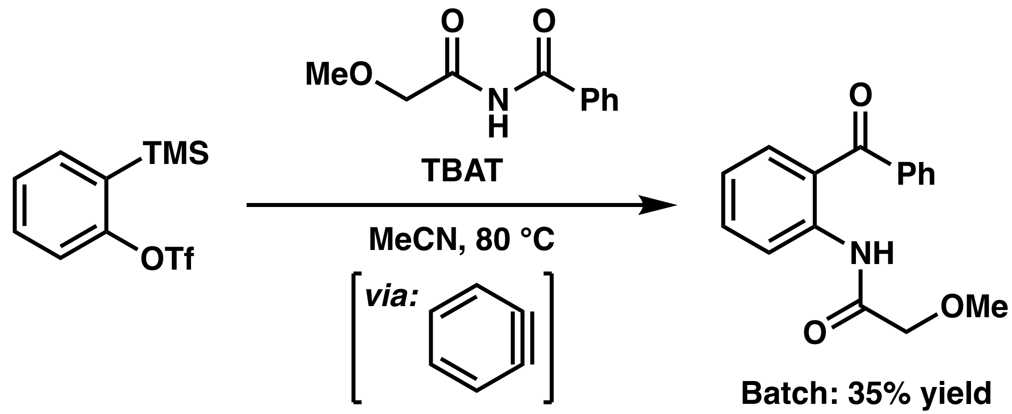


Batch: 35% yield
Flow: 52% yield

–increased mass/heat transfer in flow allows for highly reactive intermediates to react with higher selectivity

Herestsch, Christman *Org. Lett.* **2018**, *20*, 7611–7664.

Generation/Reaction of Arynes in Flow



Batch: 35% yield
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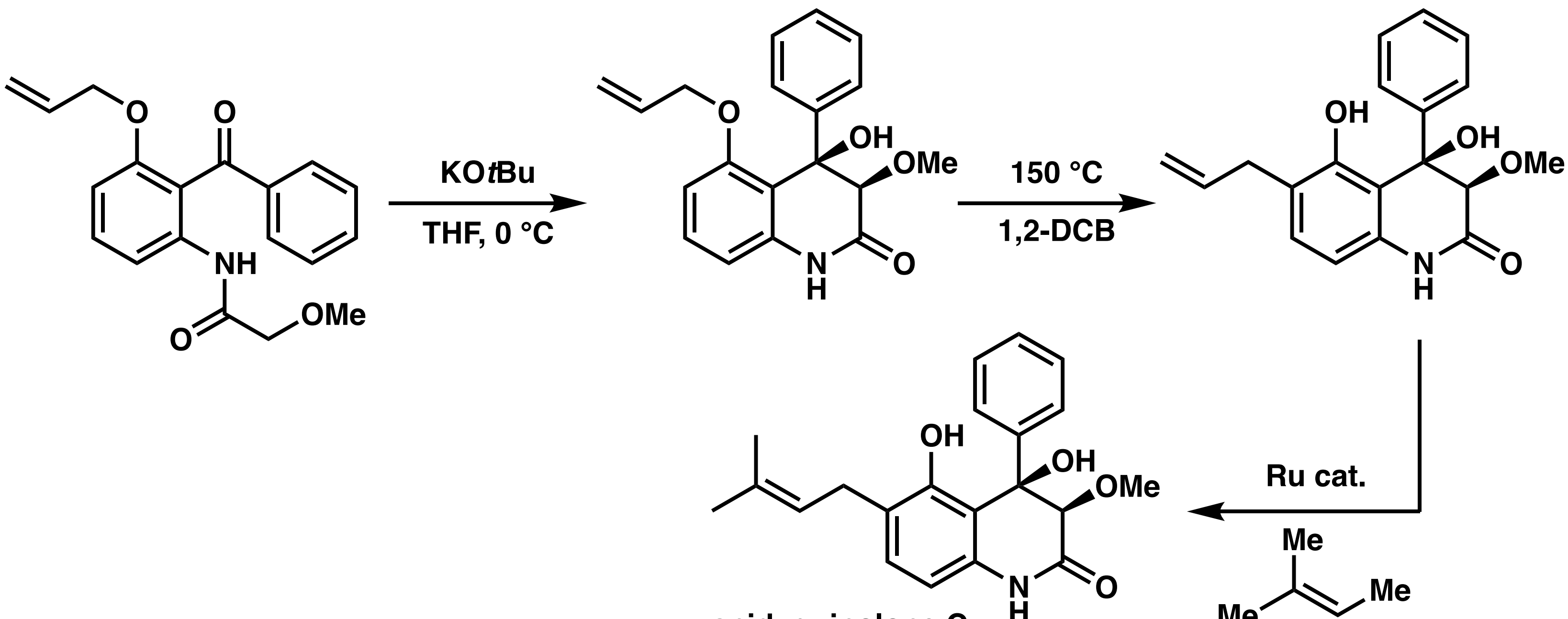
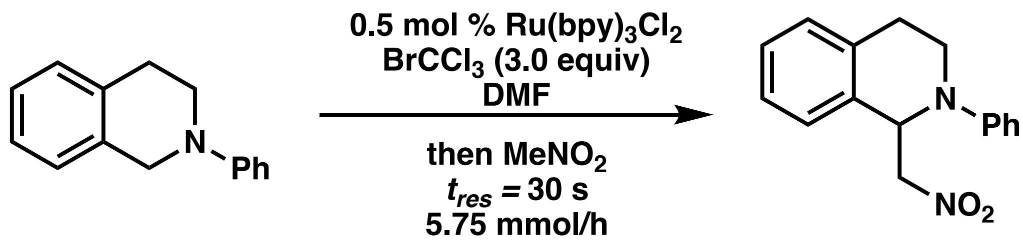
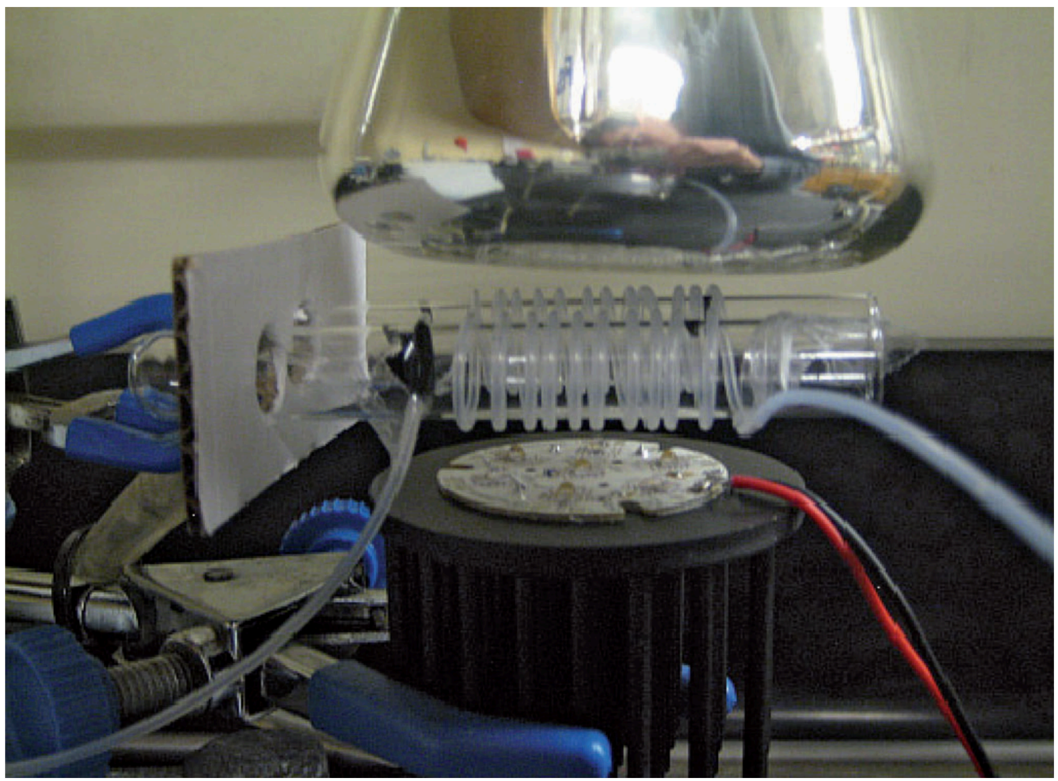


aniduquinolone C

Herestsch, Christman, *Org. Lett.* **2018**, *20*, 7611–7664.

Flow Photochemistry





Stephenson, *Isr. J. Chem.* **2014**, *54*, 351–360.

Flow Photochemistry

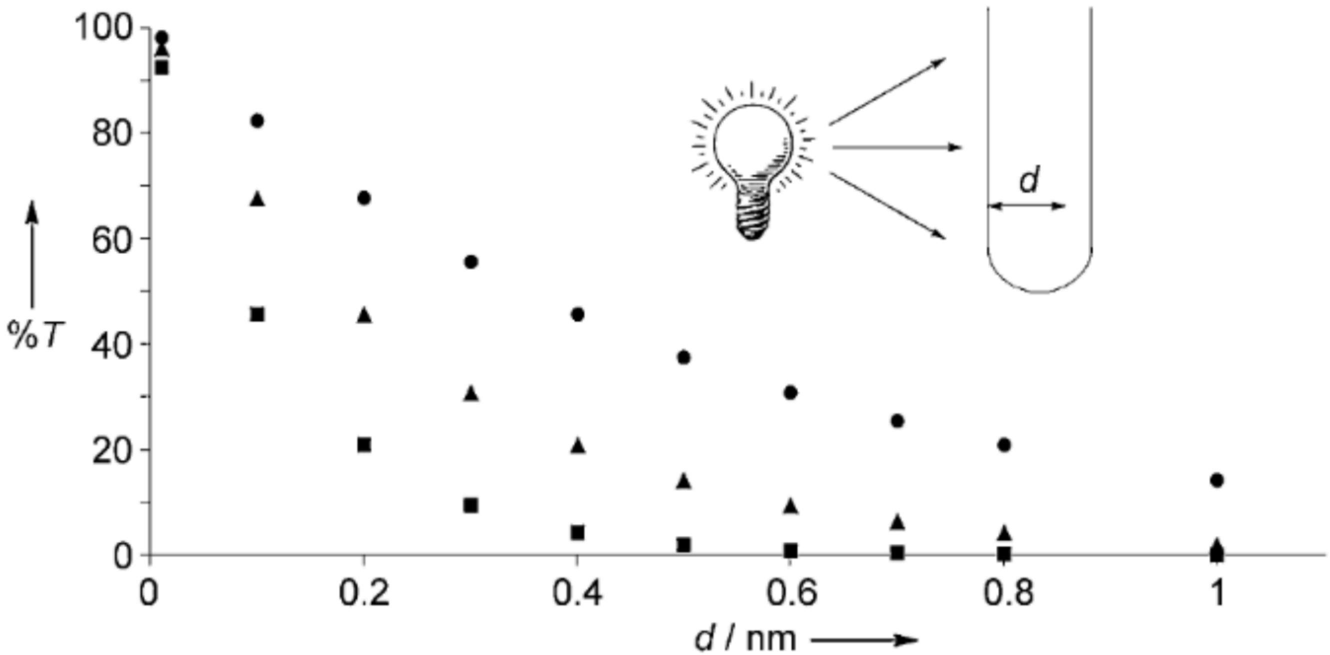
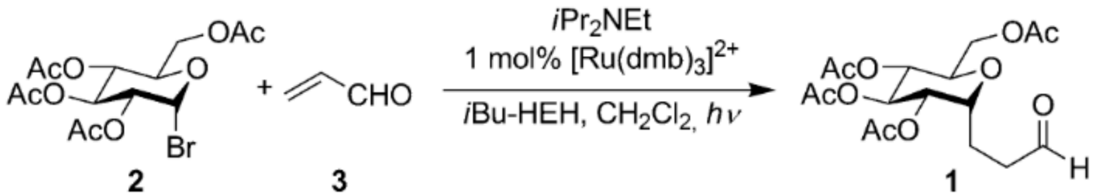


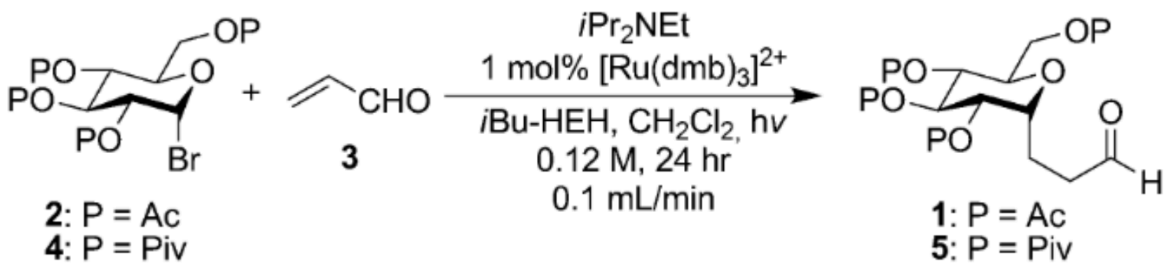
Figure 1. The percent transmittance versus distance from the wall (d) as calculated from the Beer–Lambert law. ● 0.5 mM $[Ru(dmb)_3]^{2+}$, ▲ 1 mM $[Ru(dmb)_3]^{2+}$, ■ 2 mM $[Ru(dmb)_3]^{2+}$.

Gagne, *Angew. Chem. Int., Ed.* **2012**, *51*, 4140–4143.

Flow Photochemistry



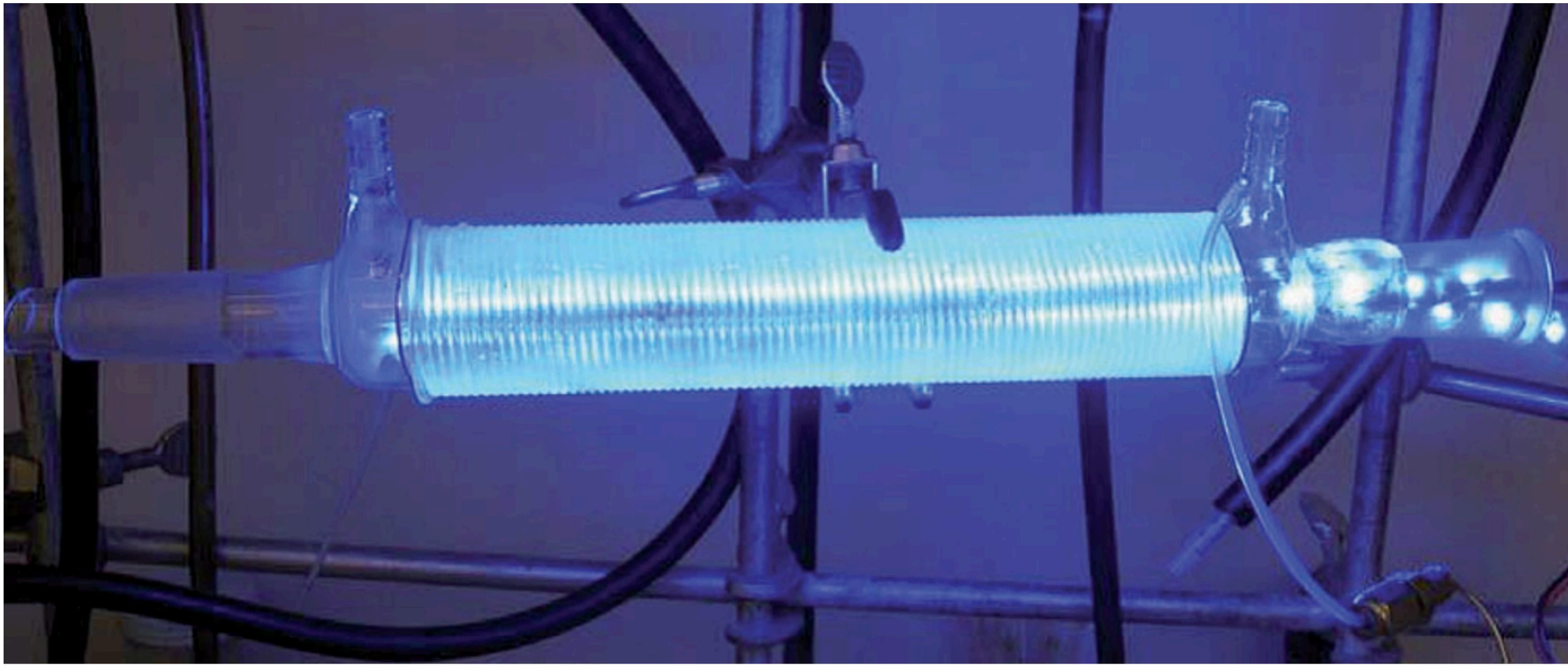
	t [h]	**2** mmol	Conv. [%]	TOF [h^{-1}]
25 mL flask	24	2.43	85	3.5
5 mm NMR tube	1	0.06	73	70



85% yield
5.5 g

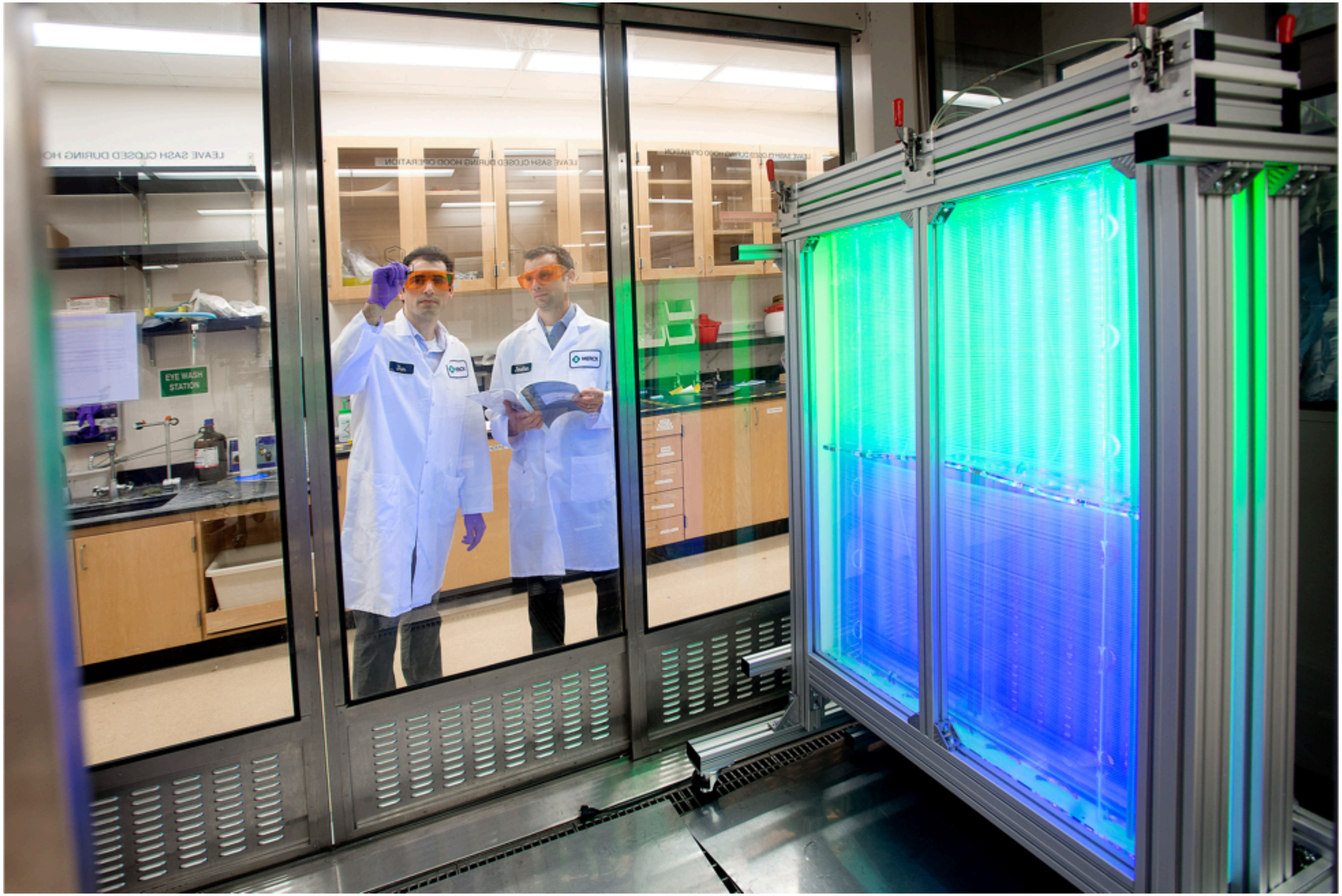
Gagne, *Angew. Chem. Int., Ed.* **2012**, *51*, 4140–4143.

Flow Photochemistry



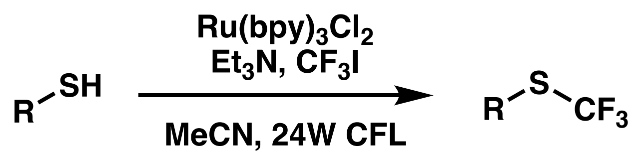
Gagne, *Angew. Chem. Int., Ed.* **2012**, *51*, 4140–4143.

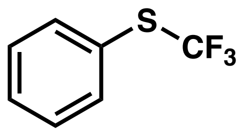
Flow Photochemistry



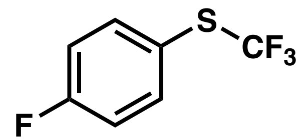
Edubs

Flow Photochemistry

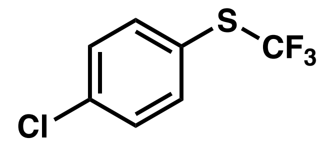




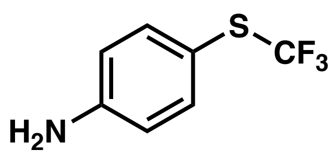
Batch: 30 min, 95% yield
Flow: 1 min, 98% yield



Batch: 2 h, 65% yield
Flow: 1 min, 91% yield

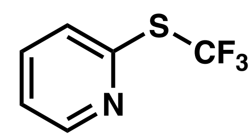


Batch: 1 h, 78% yield
Flow: 1 min, 96% yield



Batch: 1.5 h, 88% yield
Flow: 1 min, 73% yield

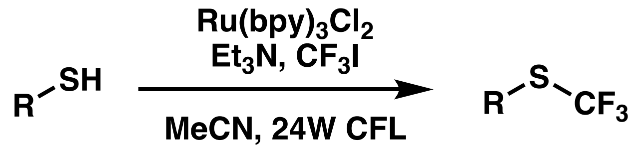
Batch: 2.5 h, 41% yield
Flow: 30 min, 59% yield

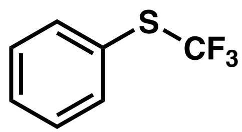


Batch: 1 h, 91% yield
Flow: 1 min, 91% yield

Noel, *Chem. Sci.* **2014**, *5*, 4768–4773.

Flow Photochemistry





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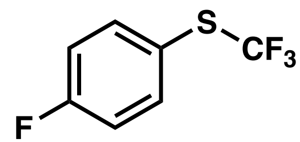
Flow: 1 min, 98% yield



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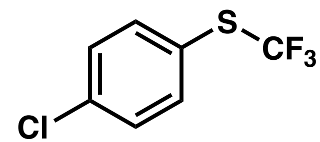

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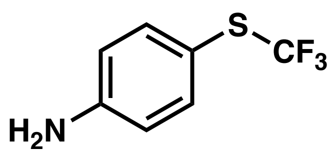

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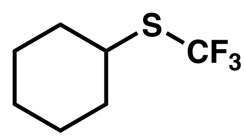
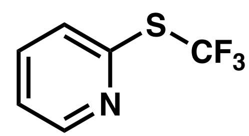


Batch: 2.5 h, 41% yield
Flow: 30 min, 59% yield

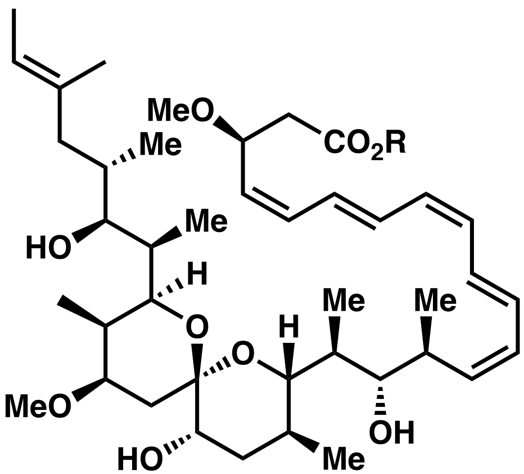


Batch: 1 h, 91% yield
Flow: 1 min, 91% yield

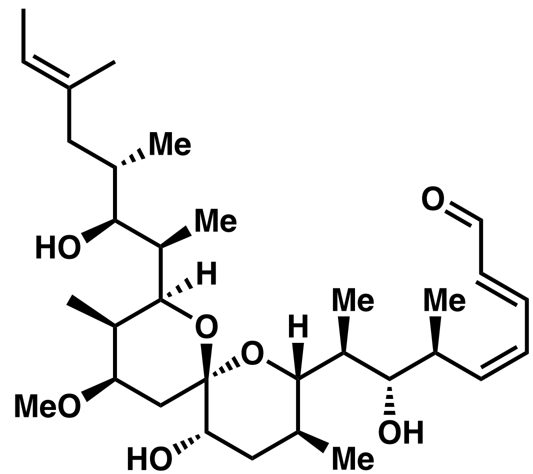
–segmented gas-liquid flow
–flow requires only 1.1 equiv of CF_3I (batch uses 4 equiv)

Noel, *Chem. Sci.* **2014**, *5*, 4768–4773.

Natural Product Total Synthesis Using Flow: Spirocyclic Polyketides



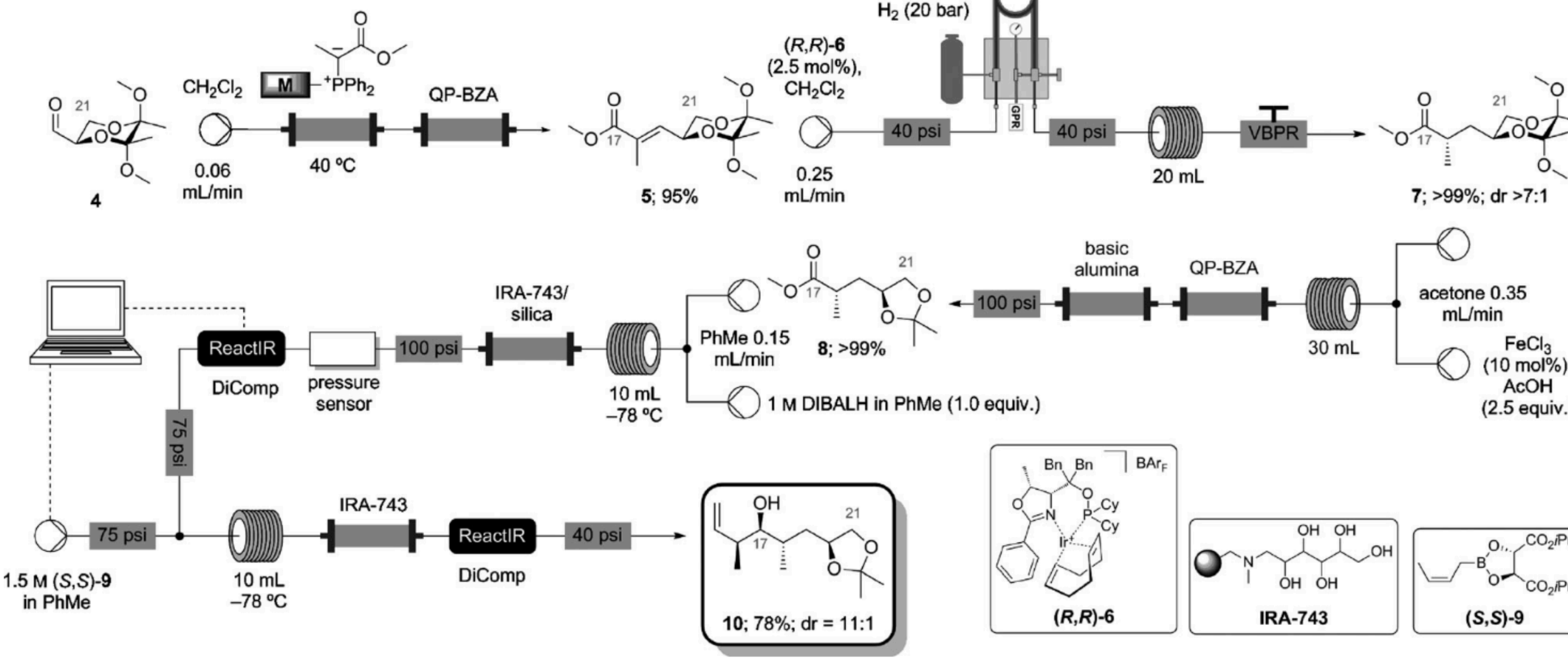
spirangien A (R = H)
spirangien A methyl ester (R = Me)



spirodienal A

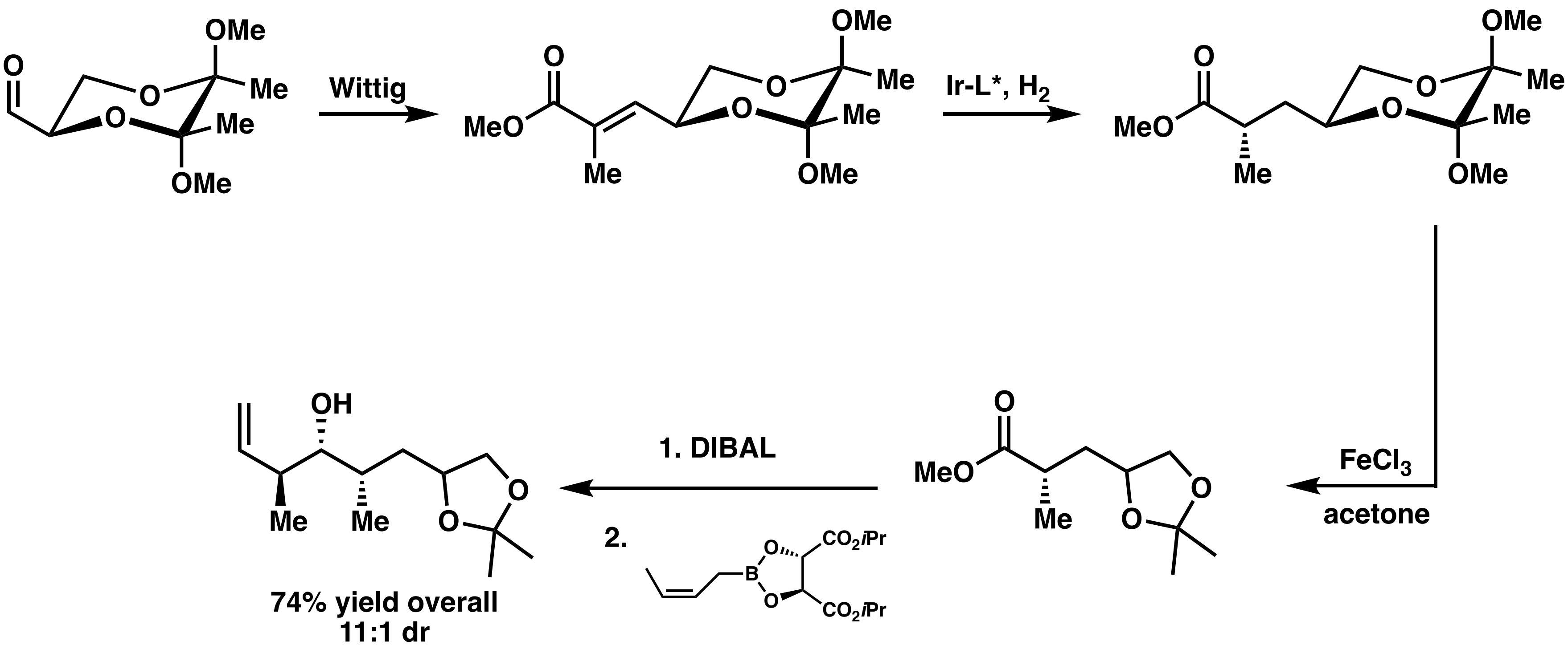
Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

Natural Product Total Synthesis Using Flow: Spirocyclic Polyketides

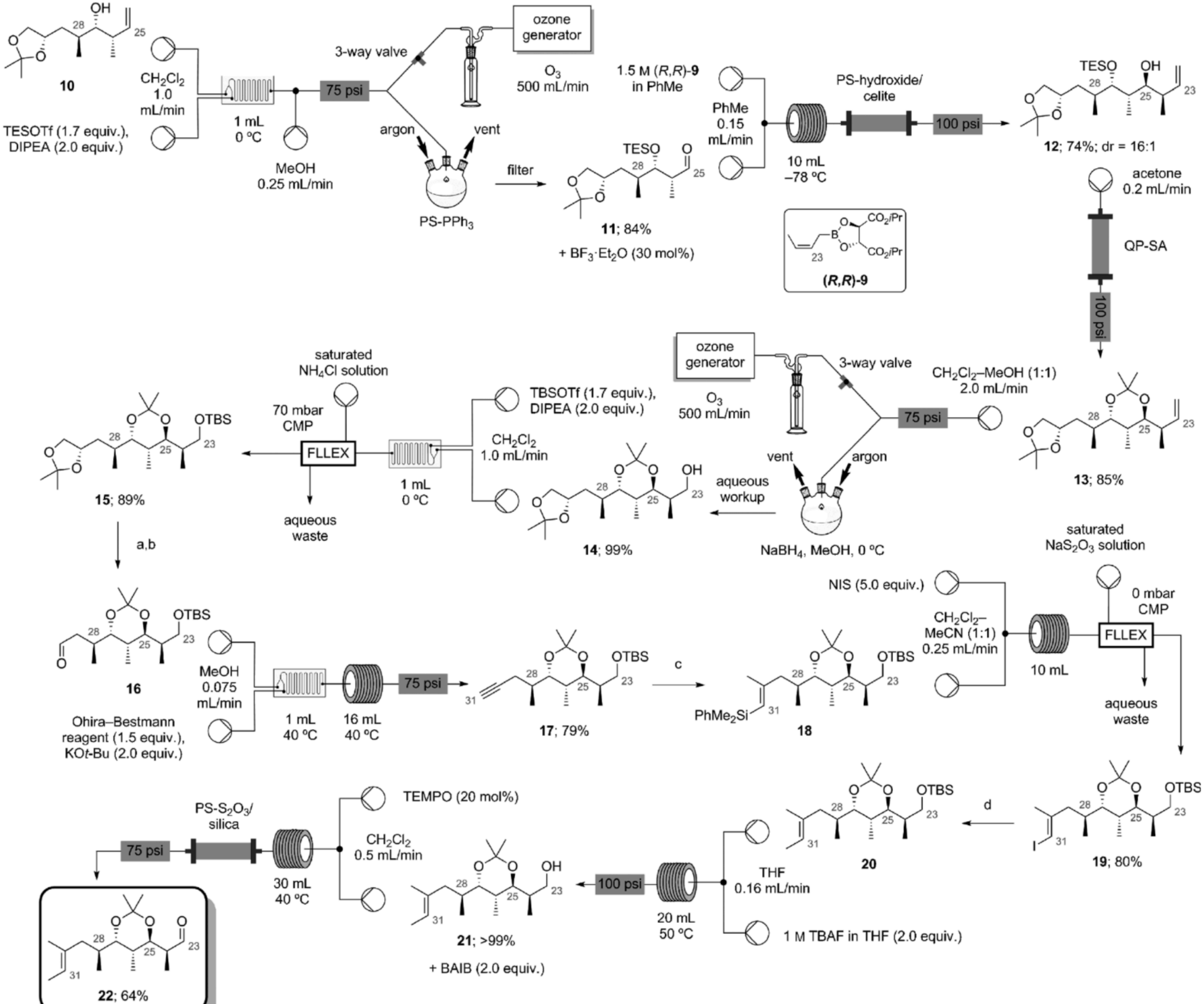


Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

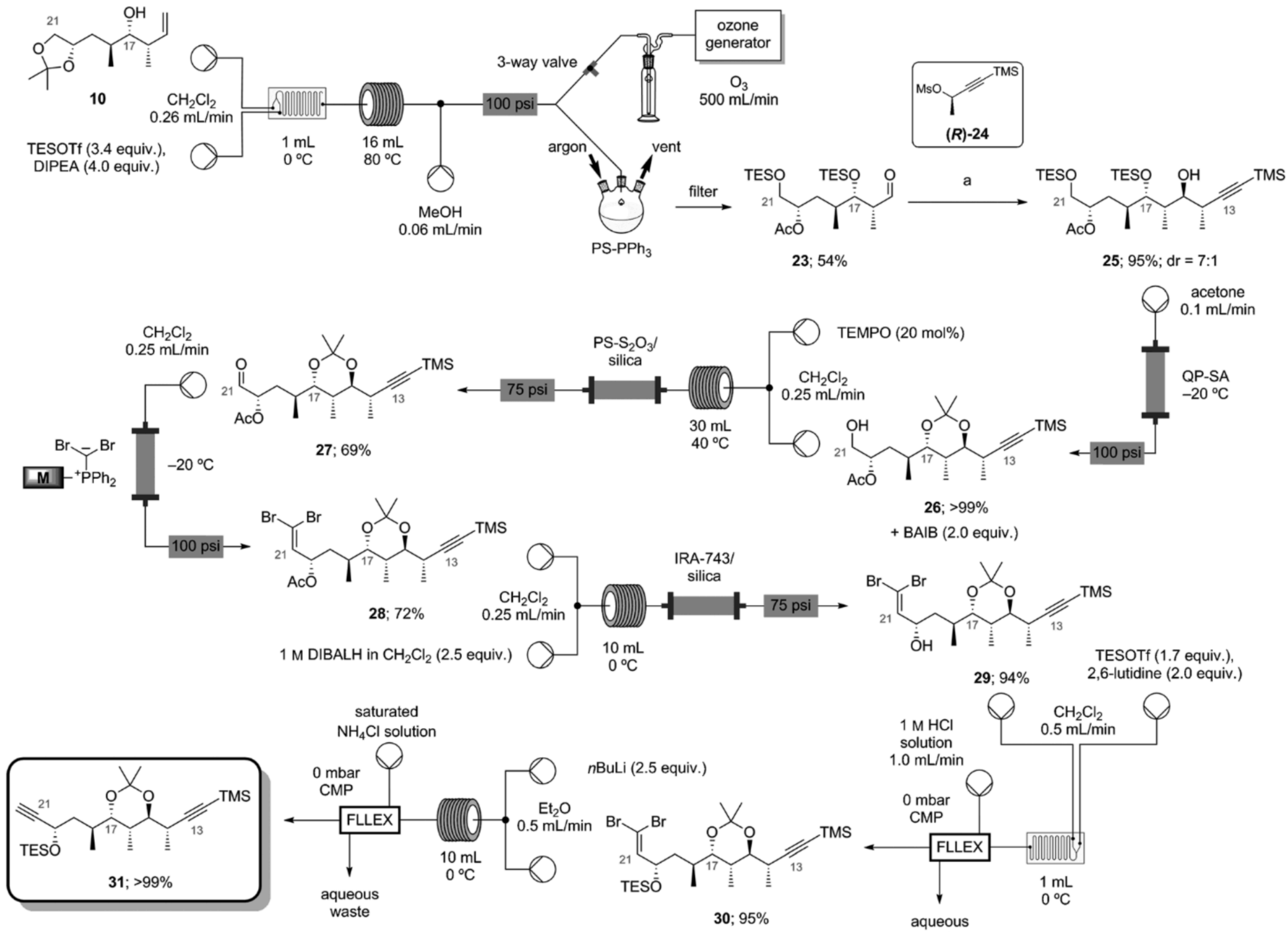
Natural Product Total Synthesis Using Flow: Spirocyclic Polyketides



Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

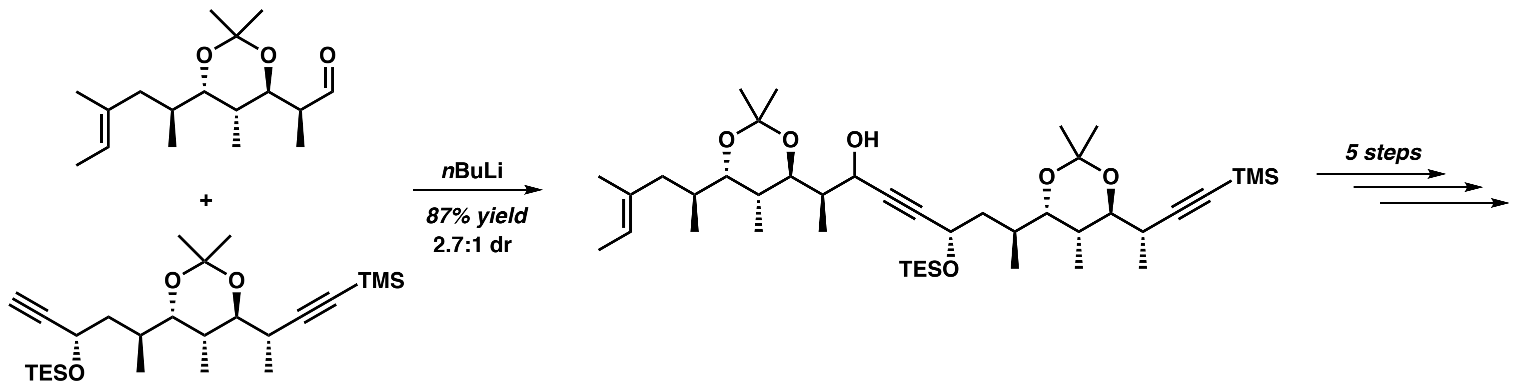


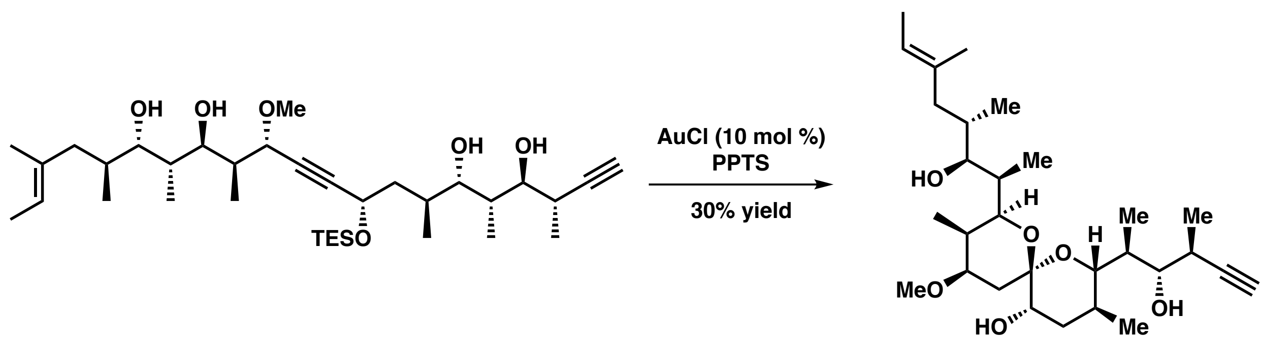
Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.



Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

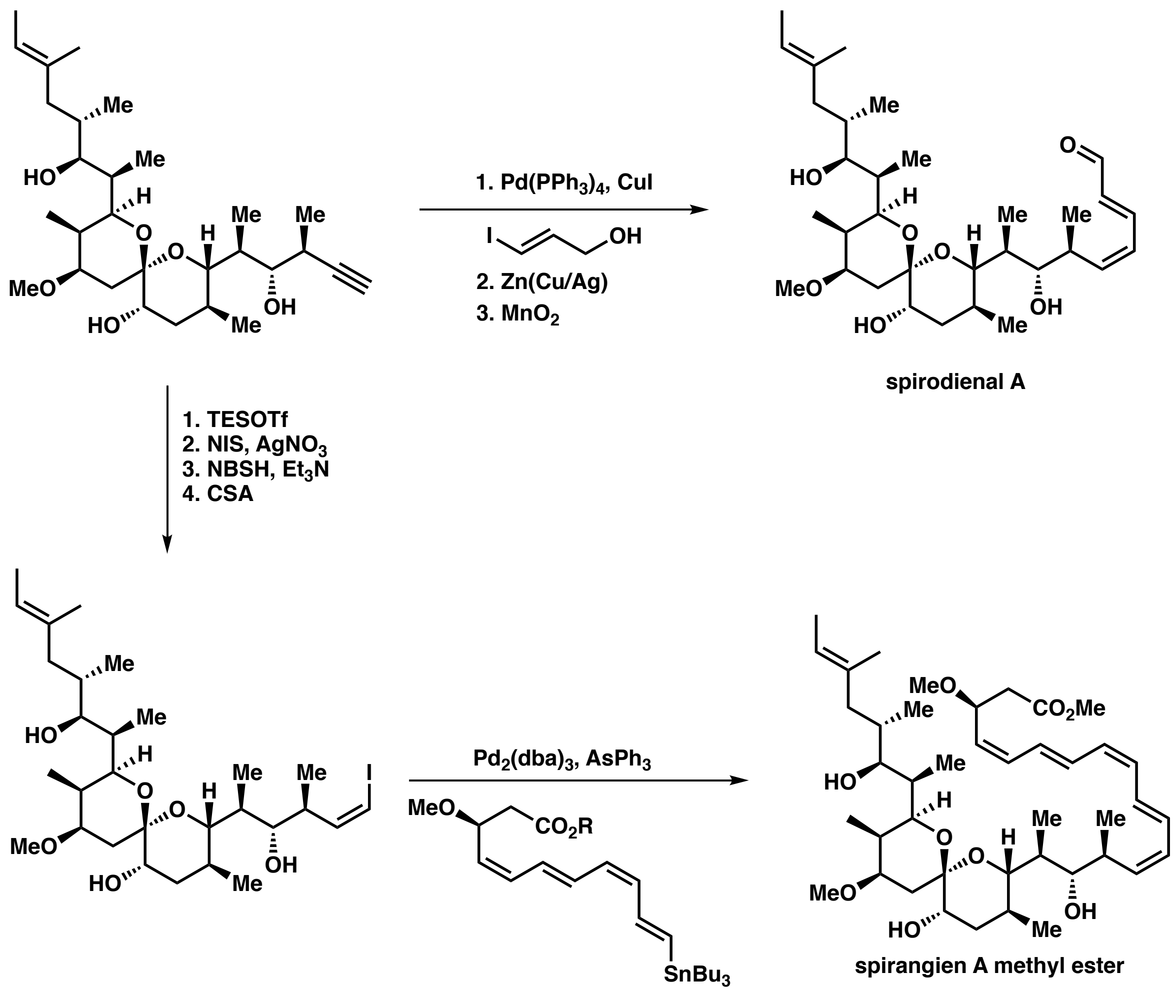
Natural Product Total Synthesis Using Flow: Spirocyclic Polyketides





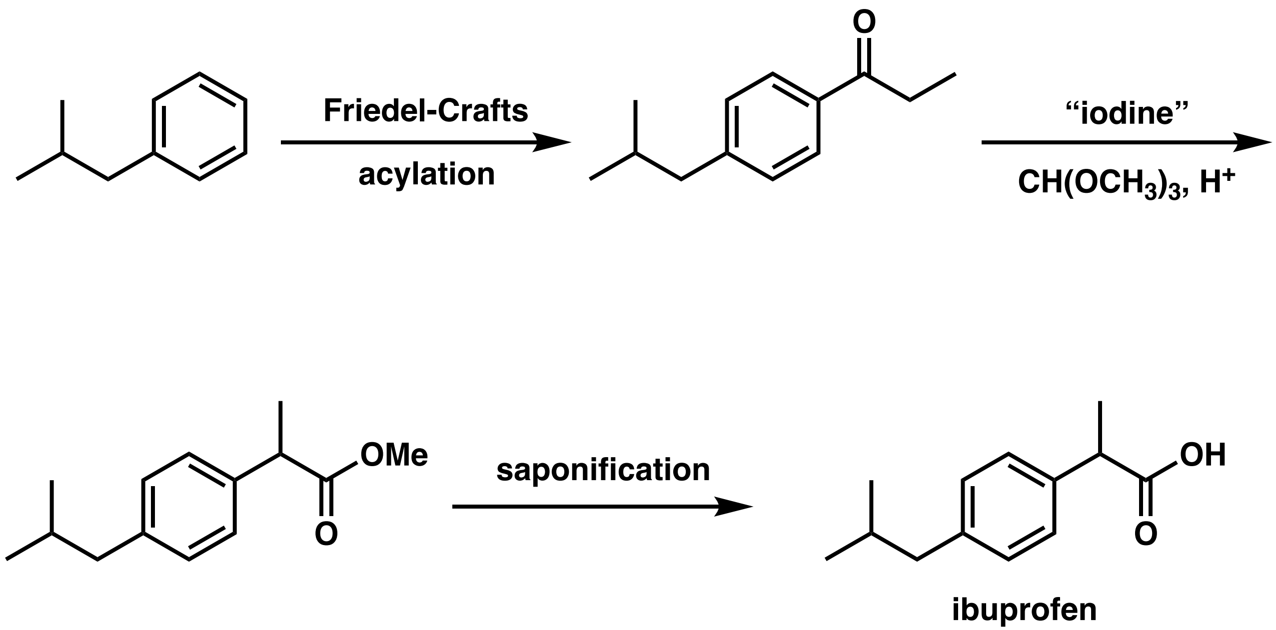
Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

Natural Product Total Synthesis Using Flow: Spirocyclic Polyketides



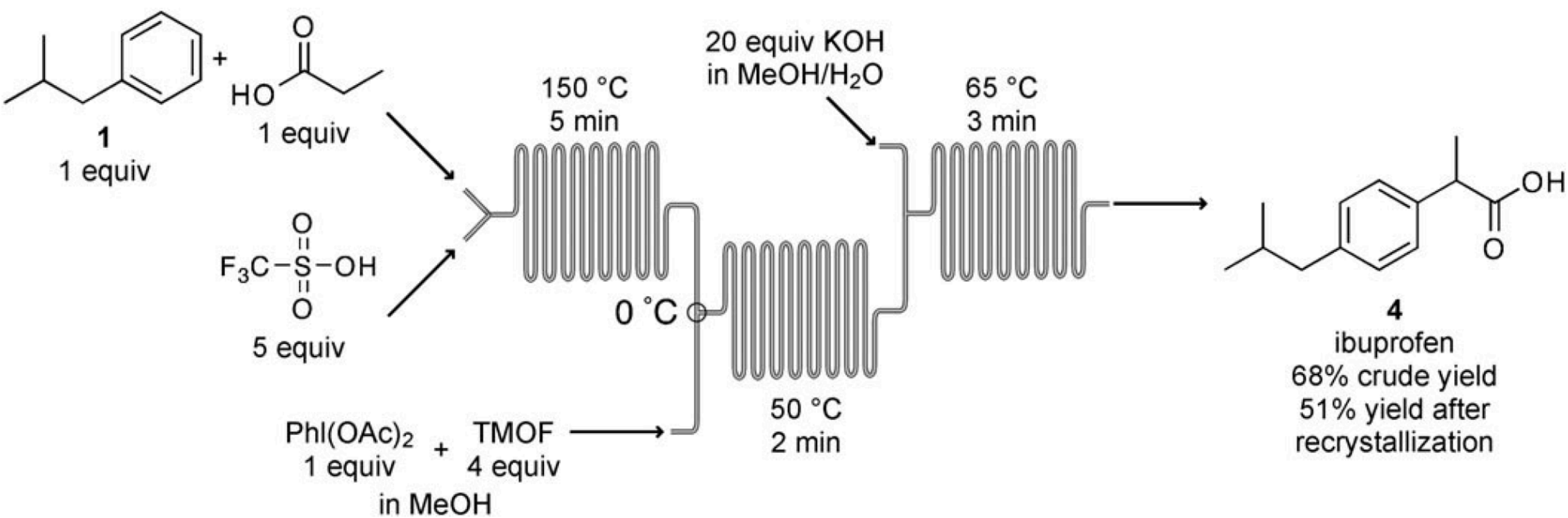
Ley, *Angew. Chem. Int., Ed.* **2014**, *53*, 4915–4920.

Continuous Flow Synthesis of Ibuprofen



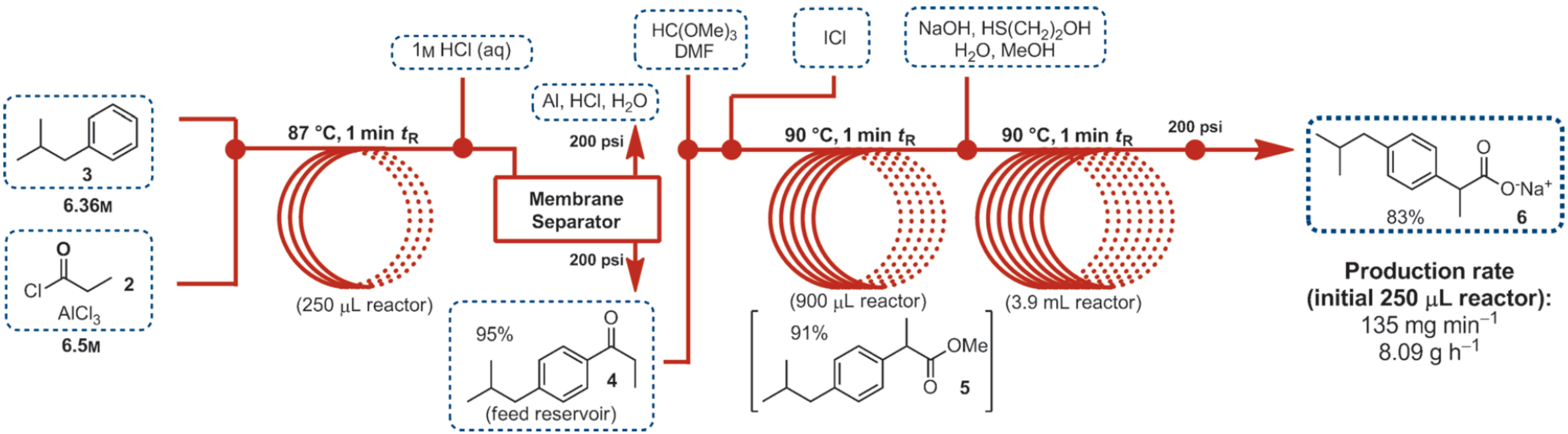
McQuade, *Angew. Chem. Int., Ed.* **2009**, *48*, 8547–8550.

Continuous Flow Synthesis of Ibuprofen



McQuade, *Angew. Chem. Int., Ed.* **2009**, *48*, 8547–8550.

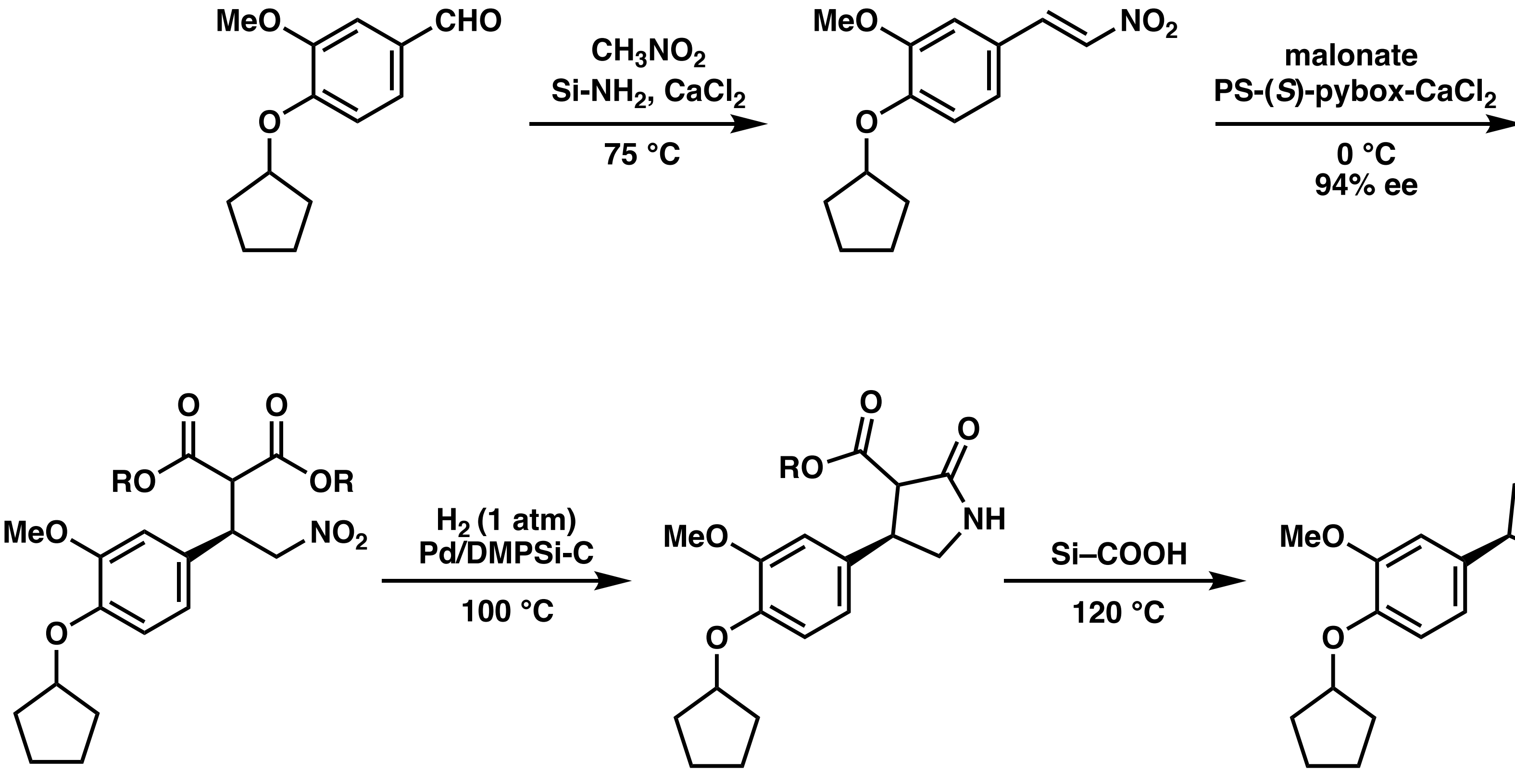
Continuous Flow Synthesis of Ibuprofen



–initial Friedel-Crafts performed neat
–total 3 min of retention time
–ICl is heated and pumped in neat, as solutions of ICl slowly decompose
–total size of reactor setup is approximately half a fume hood

Jamison, *Angew. Chem. Int., Ed.* **2015**, *54*, 983–987.

Continuous Flow Synthesis of Rolipram

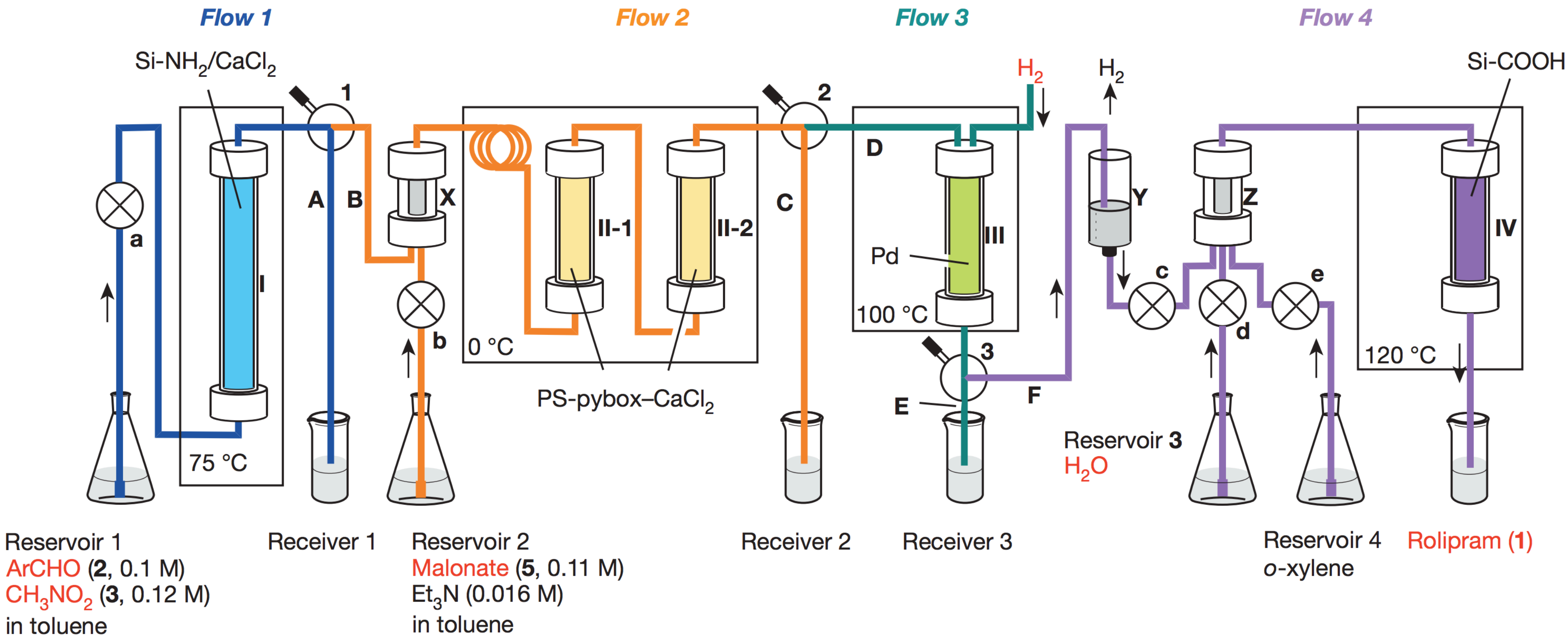


(*R*)-Rolipram
50% yield over 4 steps

PS = polymer supported
DMPSi-C = dimethylpolysilane

Kobayashi, *Nature* **2015**, *520*, 329–332.

Continuous Flow Synthesis of Rolipram

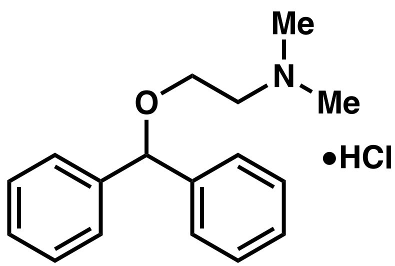


Kobayashi, *Nature* **2015**, *520*, 329–332.

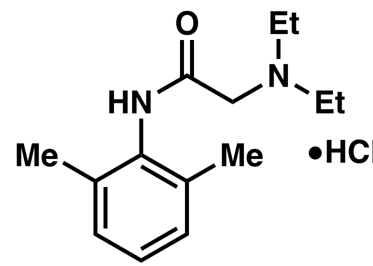
End-to-End Continuous Manufacturing

Jamison, Jensen, Myerson, *Science* **2016**, *352*, 61–67.

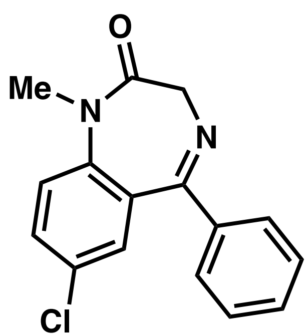
End-to-End Continuous Manufacturing



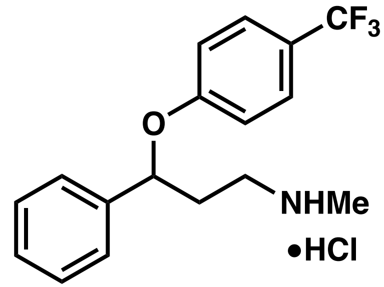
Diphenhydramine hydrochloride (Benadryl)



Lidocaine hydrochloride



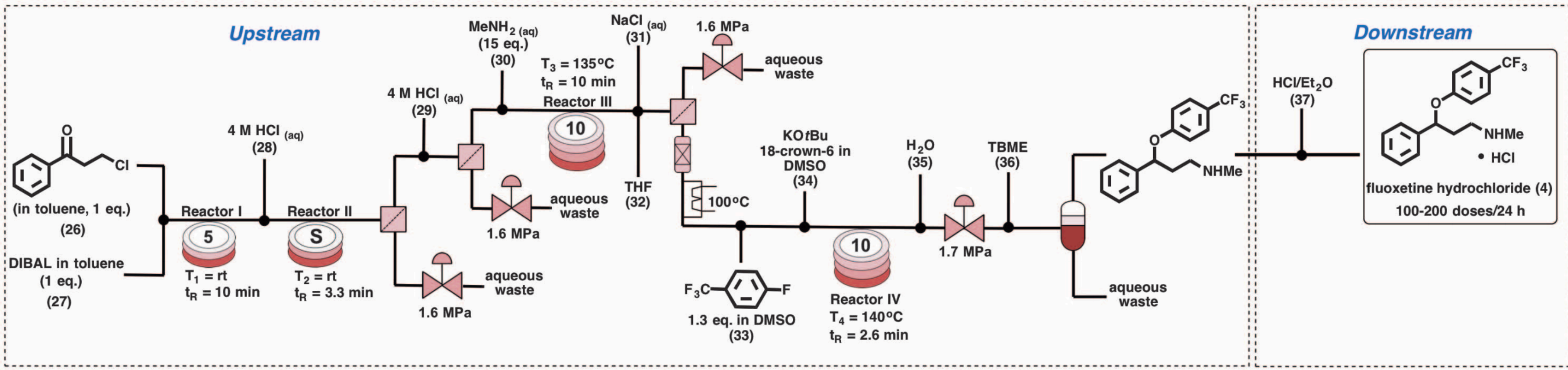
Diazepam (Valium)



Fluoxetine hydrochloride (Prozac)

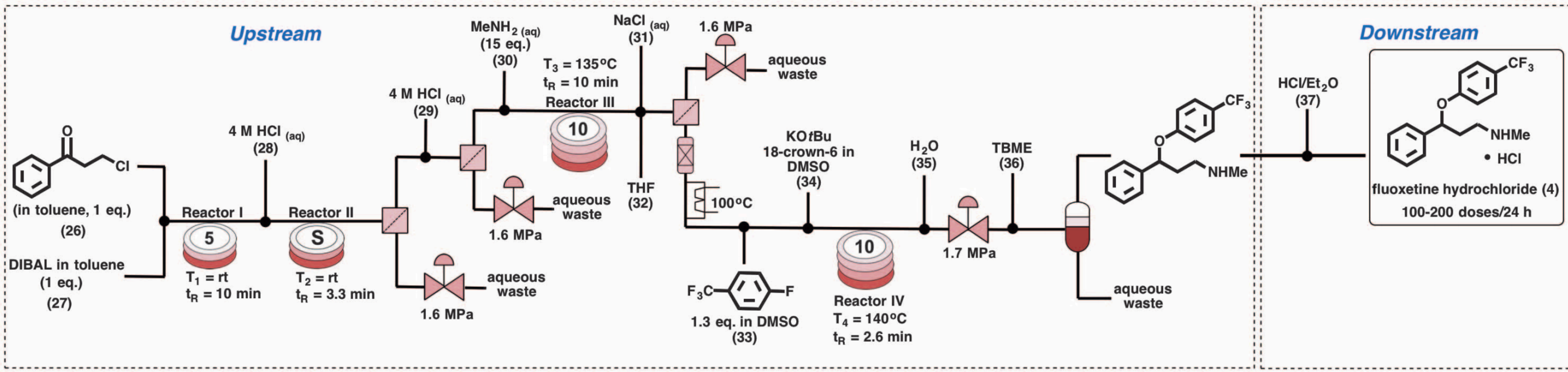
Jamison, Jensen, Myerson, *Science* **2016**, *352*, 61–67.

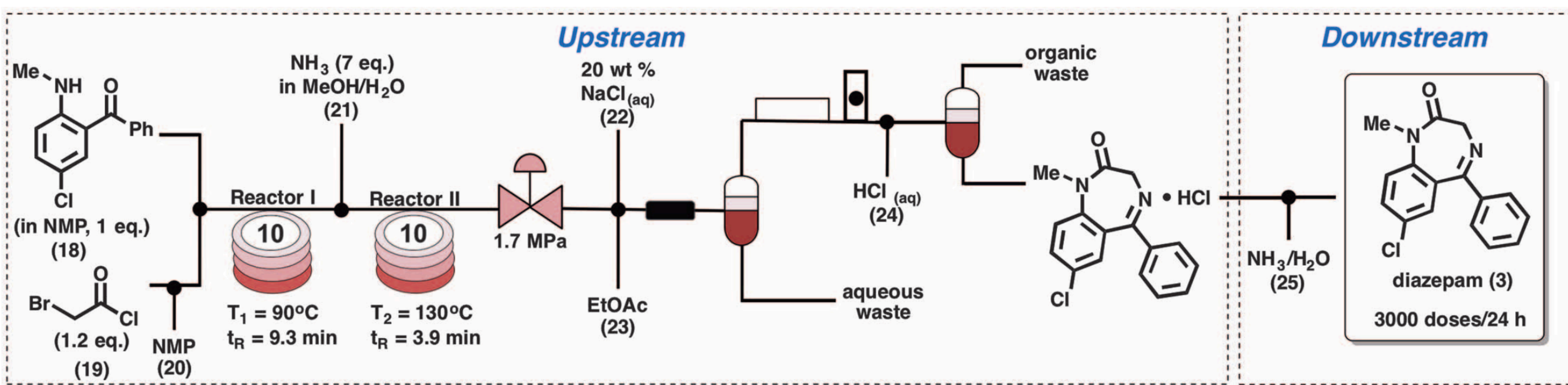
End-to-End Continuous Manufacturing



Jamison, Jensen, Myerson, *Science* **2016**, *352*, 61–67.

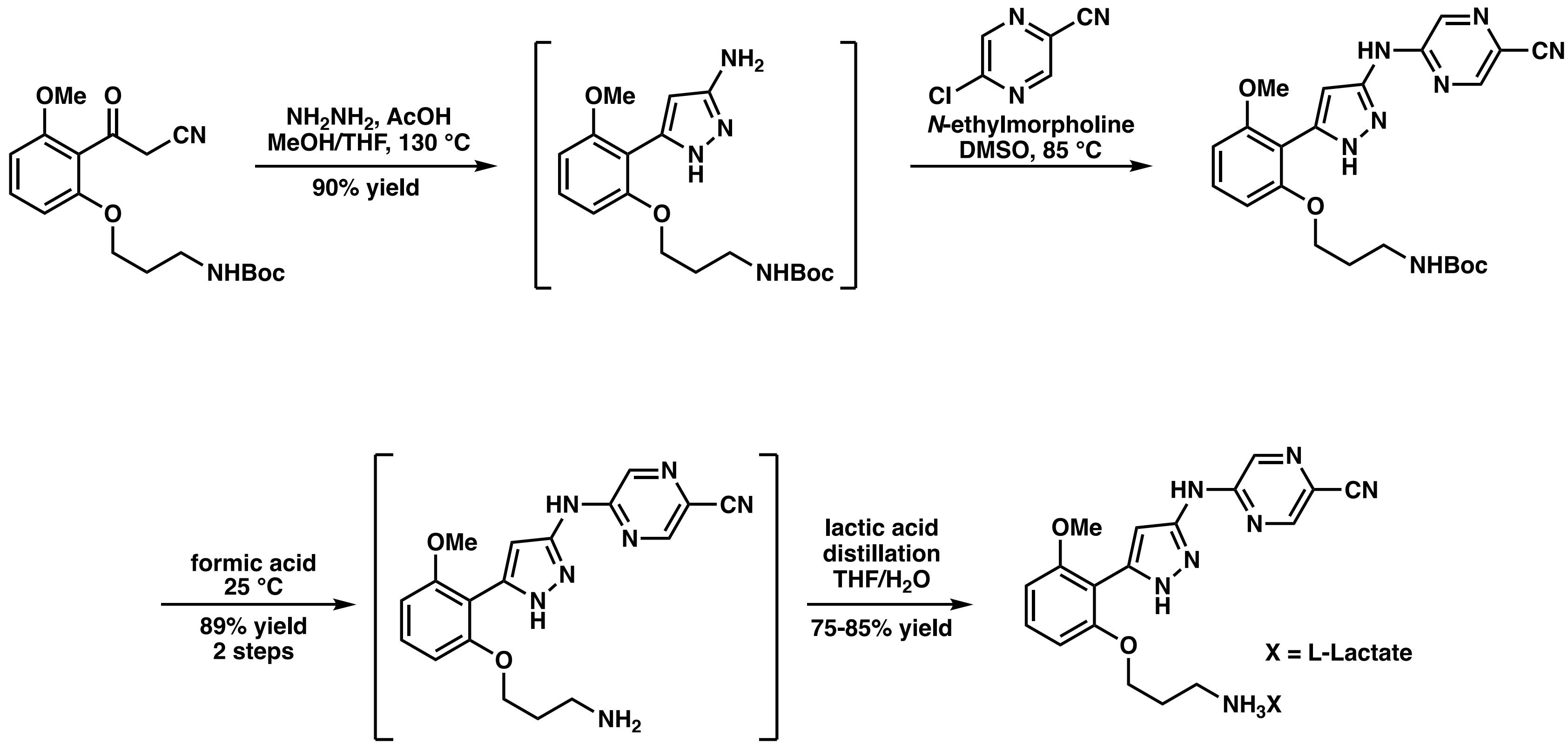
End-to-End Continuous Manufacturing





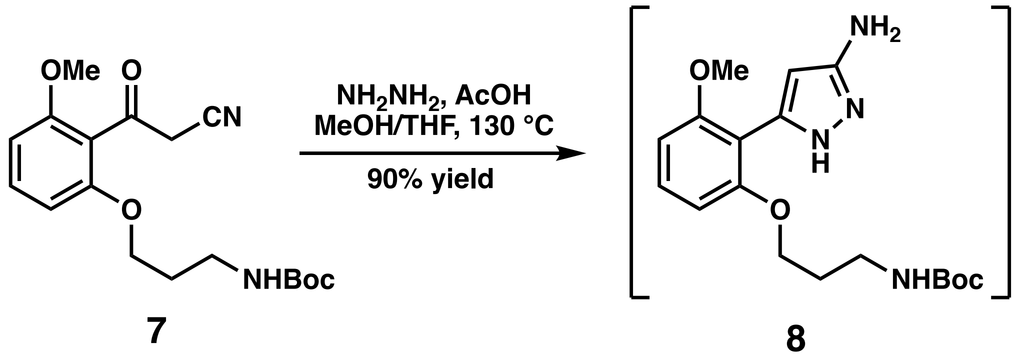
Jamison, Jensen, Myerson, *Science* **2016**, *352*, 61–67.

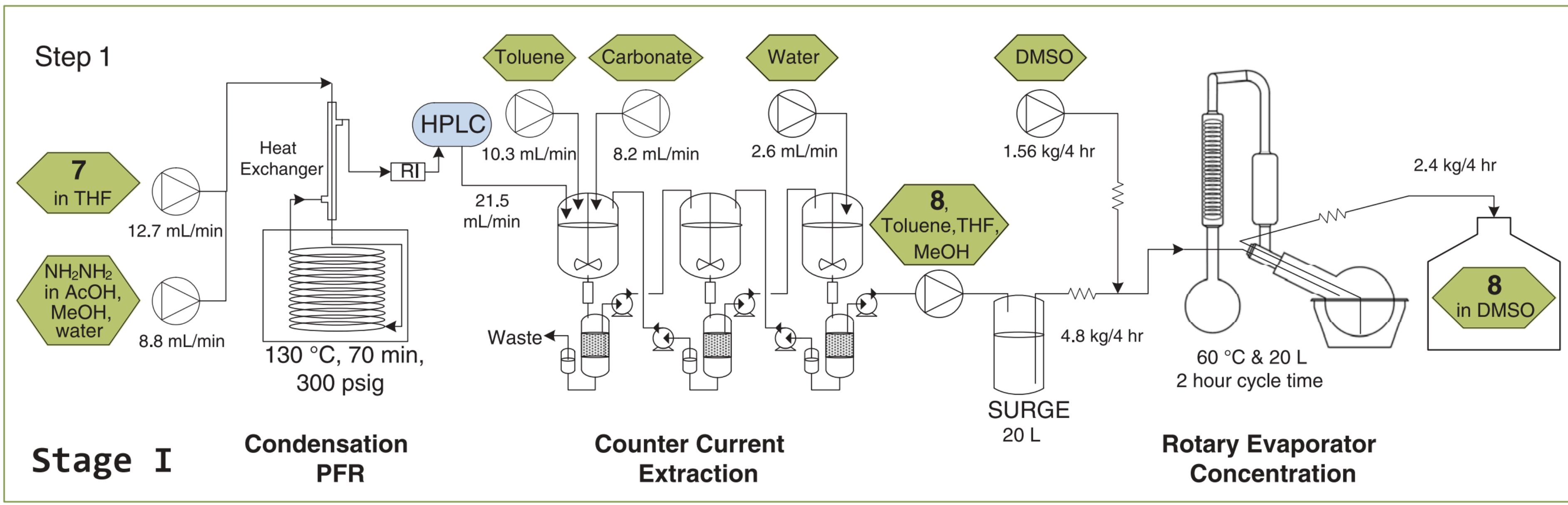
Kilogram-scale Continuous Flow Synthesis



Cole, *Science* **2017**, *356*, 1144–1150.

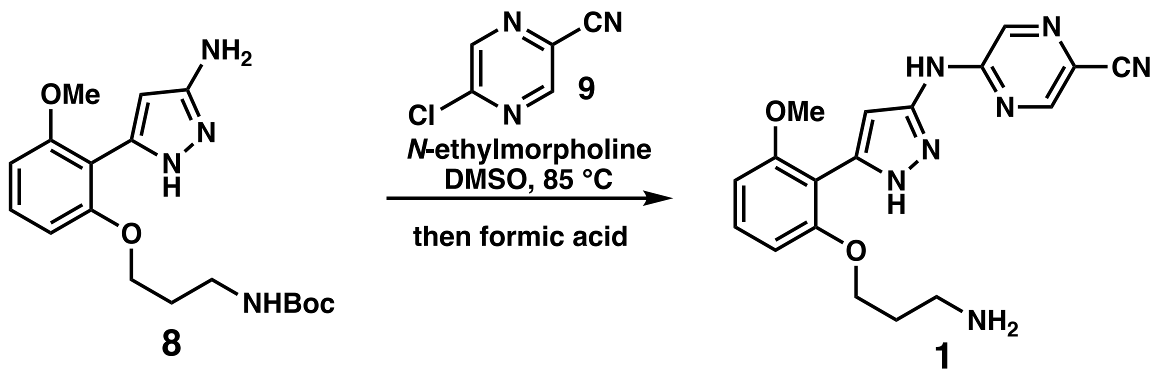
Kilogram-scale Continuous Flow Synthesis

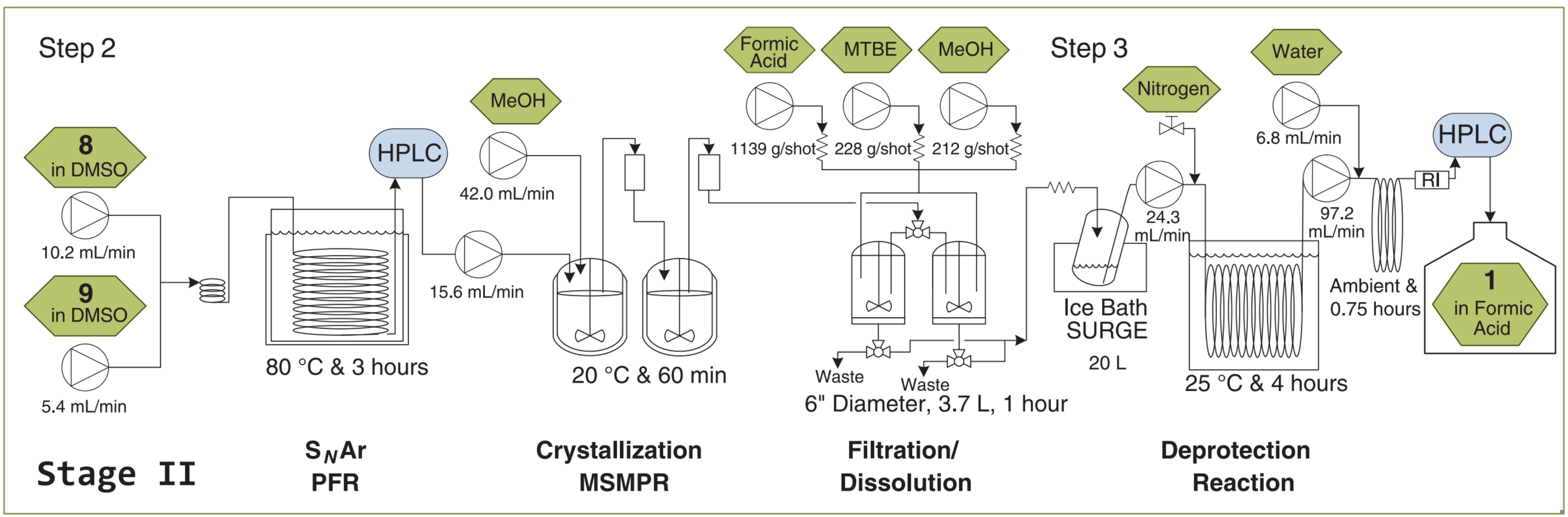




Cole, *Science* **2017**, *356*, 1144–1150.

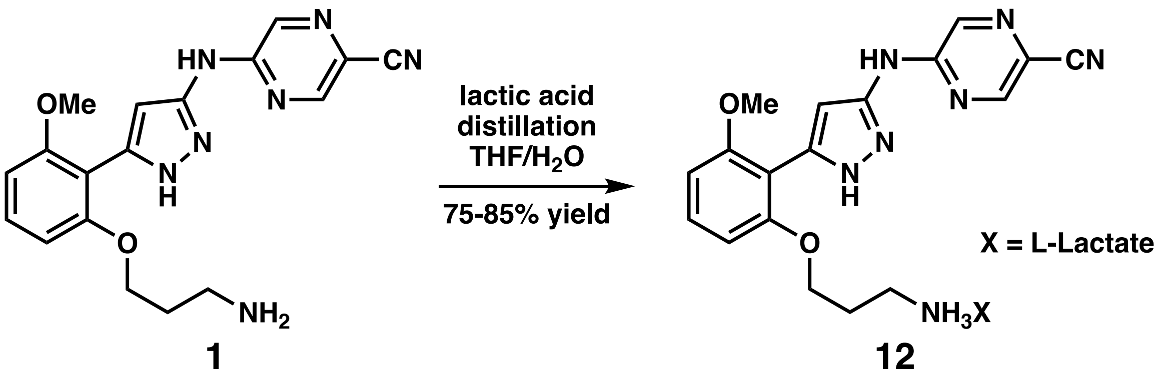
Kilogram-scale Continuous Flow Synthesis

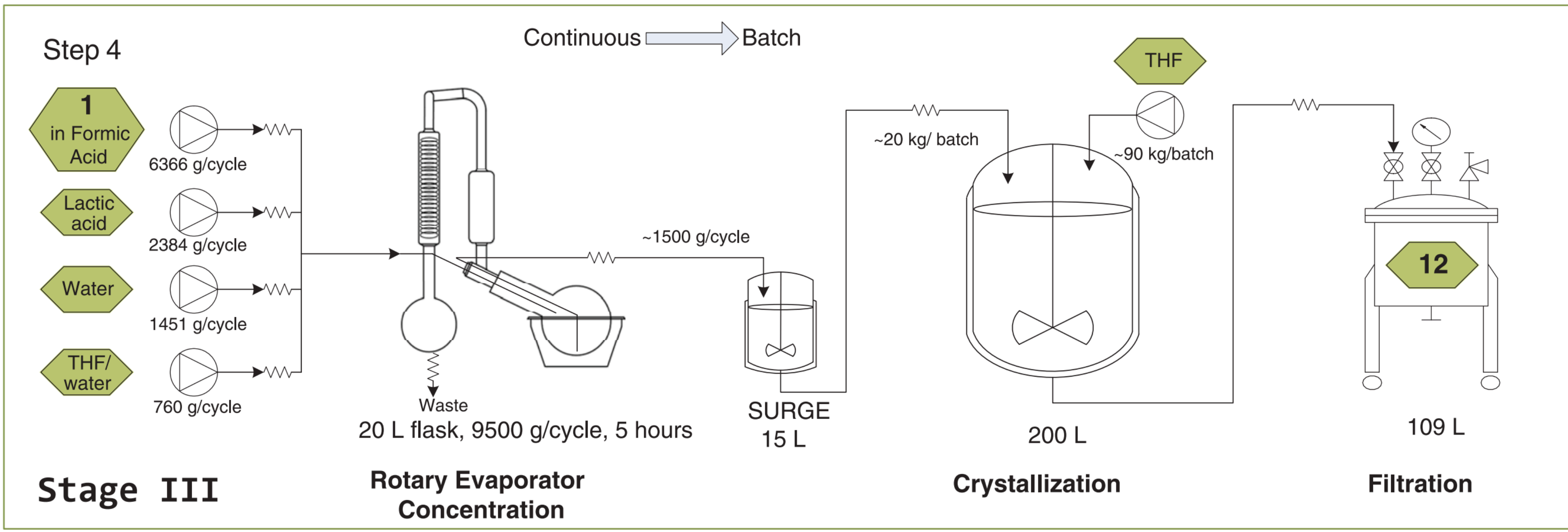




Cole, *Science* **2017**, *356*, 1144–1150.

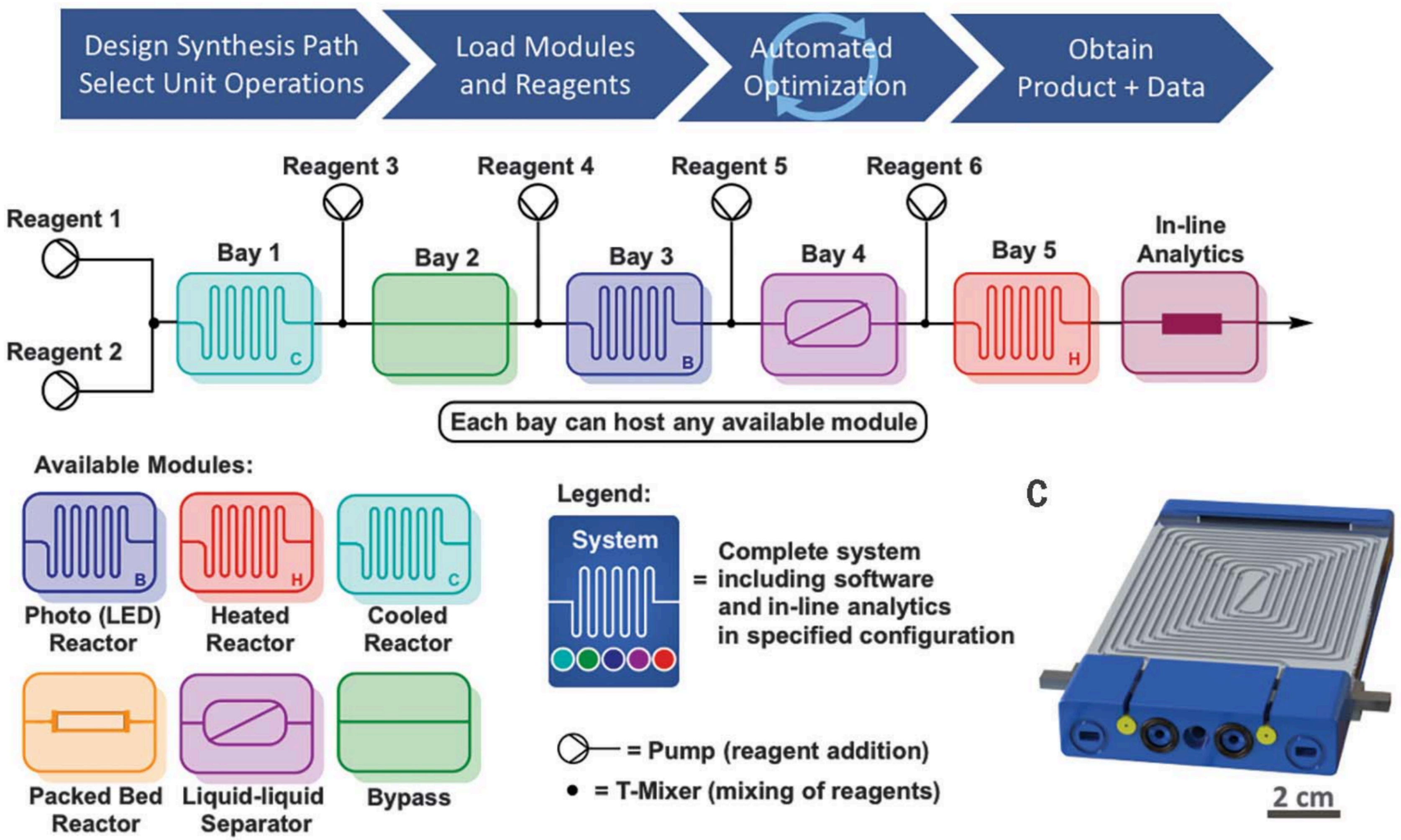
Kilogram-scale Continuous Flow Synthesis





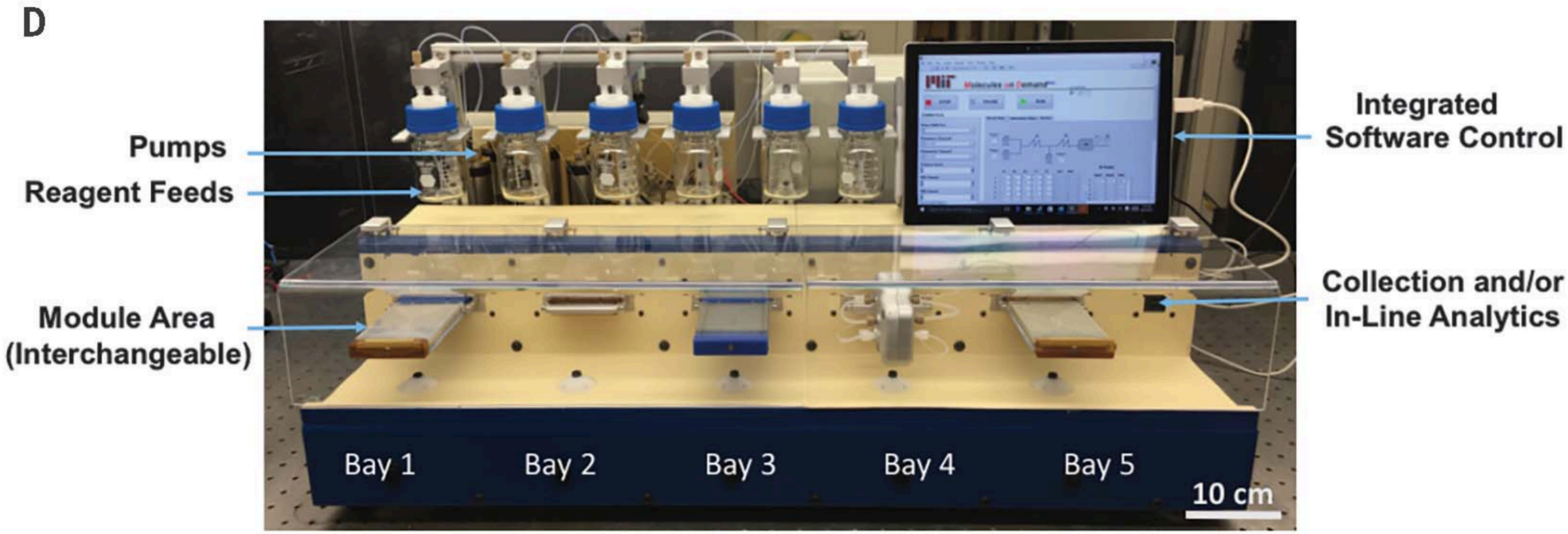
Cole, *Science* **2017**, *356*, 1144–1150.

Automated Reaction Optimization



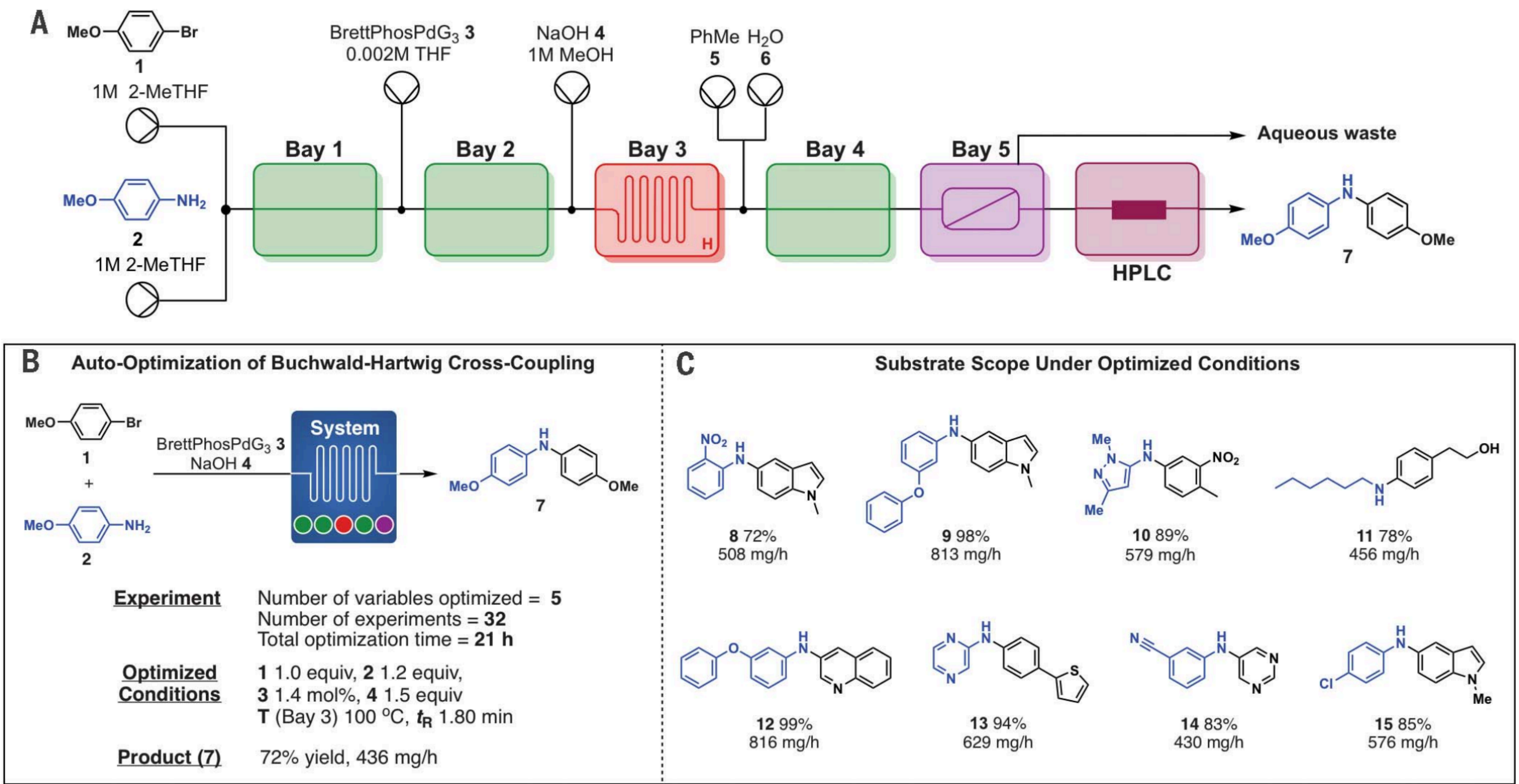
Jensen, Jamison, *Science* **2018**, *361*, 1220–1225.

Automated Reaction Optimization



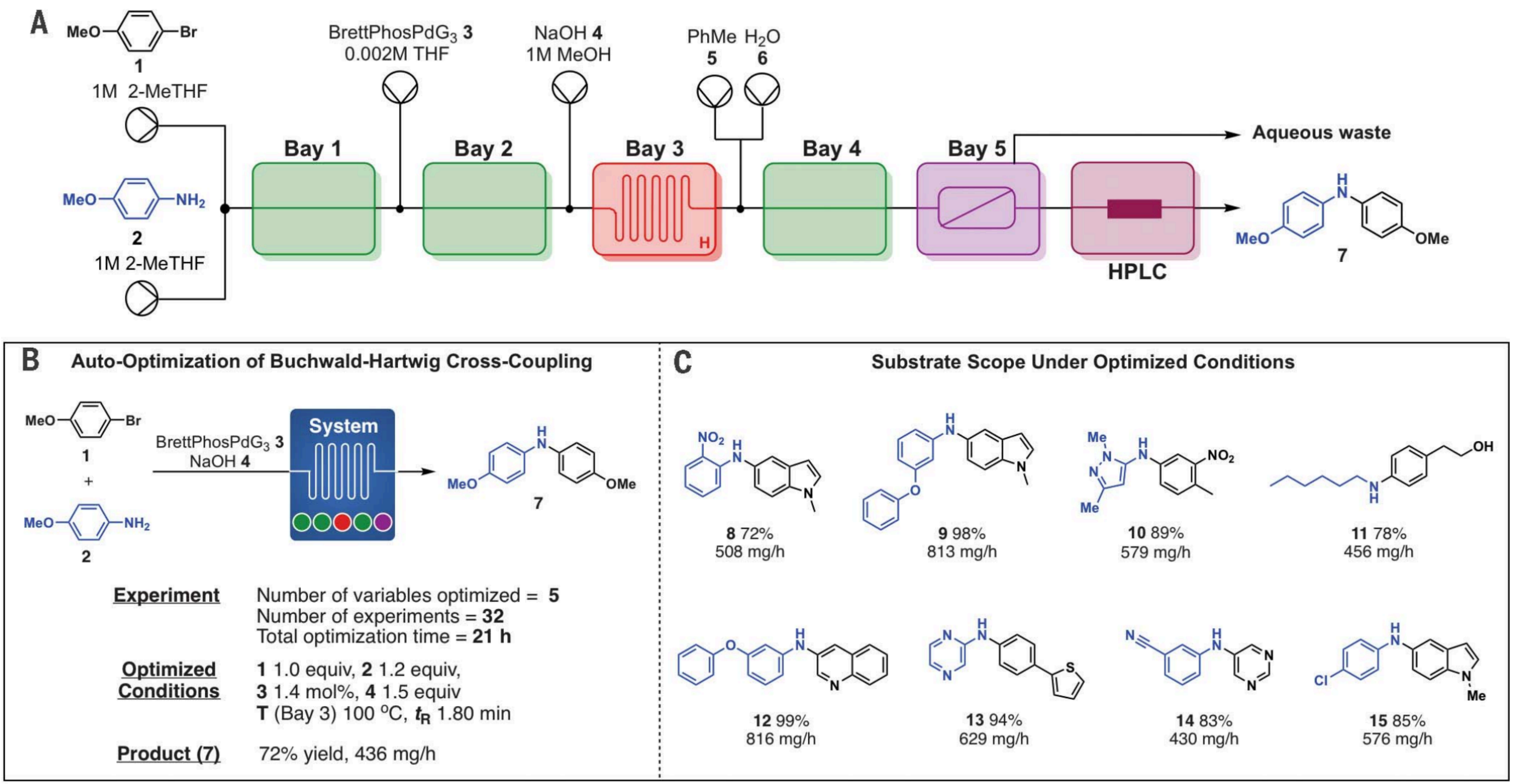
Jensen, Jamison, *Science* **2018**, *361*, 1220–1225.

Automated Reaction Optimization



Jensen, Jamison, *Science* **2018**, *361*, 1220–1225.

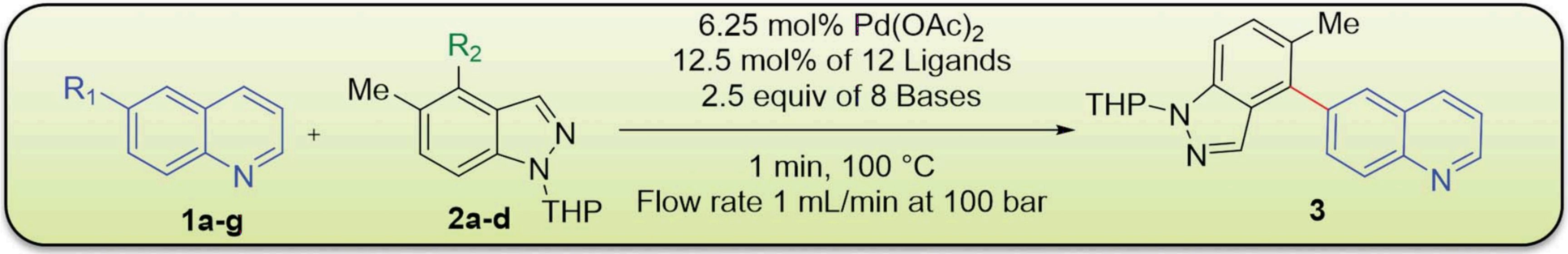
Automated Reaction Optimization



also applied to:
HWE olefination, reductive amination, Suzuki-Miyaura coupling, S_NAr, photoredox cyanation, ketene-alkene [2+2]

Jensen, Jamison, *Science* **2018**, *361*, 1220–1225.

Automated Reaction Optimization



1a-g
- **1a** R_1 = Cl
- **1b** R_1 = Br
- **1c** R_1 = OTf
- **1d** R_1 = I
- **1e** R_1 = $B(OH)_2$
- **1f** R_1 = Bpin
- **1g** R_1 = BF_3K

2a-d
- **2a** R_2 = $B(OH)_2$
- **2b** R_2 = Bpin
- **2c** R_2 = BF_3K
- **2d** R_2 = Br

Ligands:
- **L_1** $P(t\text{Bu})_3$
- **L_2** PPh_3
- **L_3** AmPhos
- **L_4** $P(Cy)_3$
- **L_5** $P(o\text{-Tol})_3$
- **L_6** CataCXium A
- **L_7** SPhos
- **L_8** dtbpf
- **L_9** XPhos
- **L_{10}** dppf
- **L_{11}** Xantphos
- **L_{12}** None

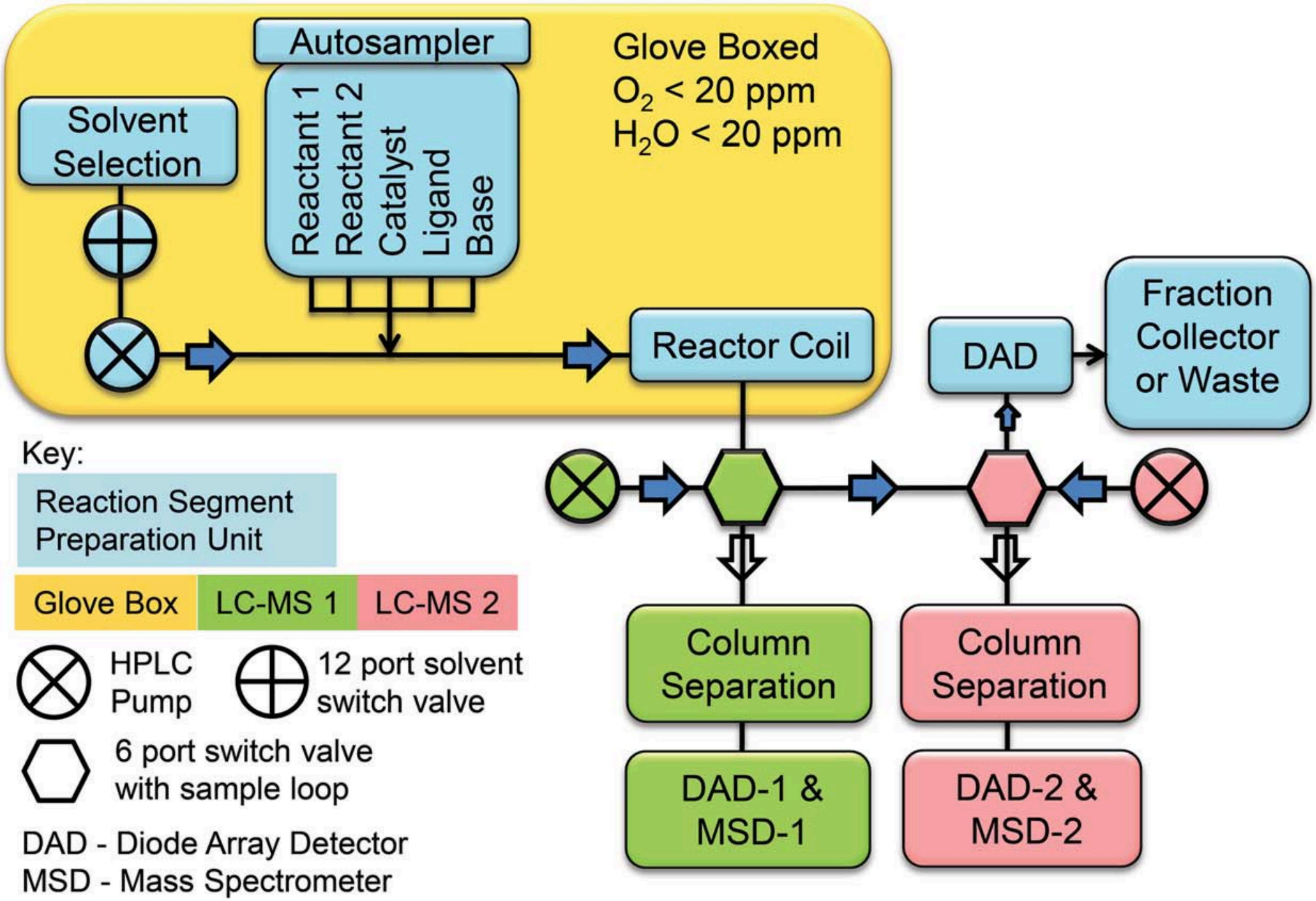
Bases:
- **B_1** None
- **B_2** Et_3N
- **B_3** LiO*t*Bu
- **B_4** CsF
- **B_5** K_3PO_4
- **B_6** KOH
- **B_7** $NaHCO_3$
- **B_8** NaOH

Solvents:
- **S_1** MeOH/H_2O 9:1
- **S_2** THF/H_2O 9:1
- **S_3** MeCN/H_2O 9:1
- **S_4** DMF/H_2O 9:1

–segmented flow
–run through ~1500 reaction combinations over 24 hours
–optimization scale is 0.05 mg each reaction

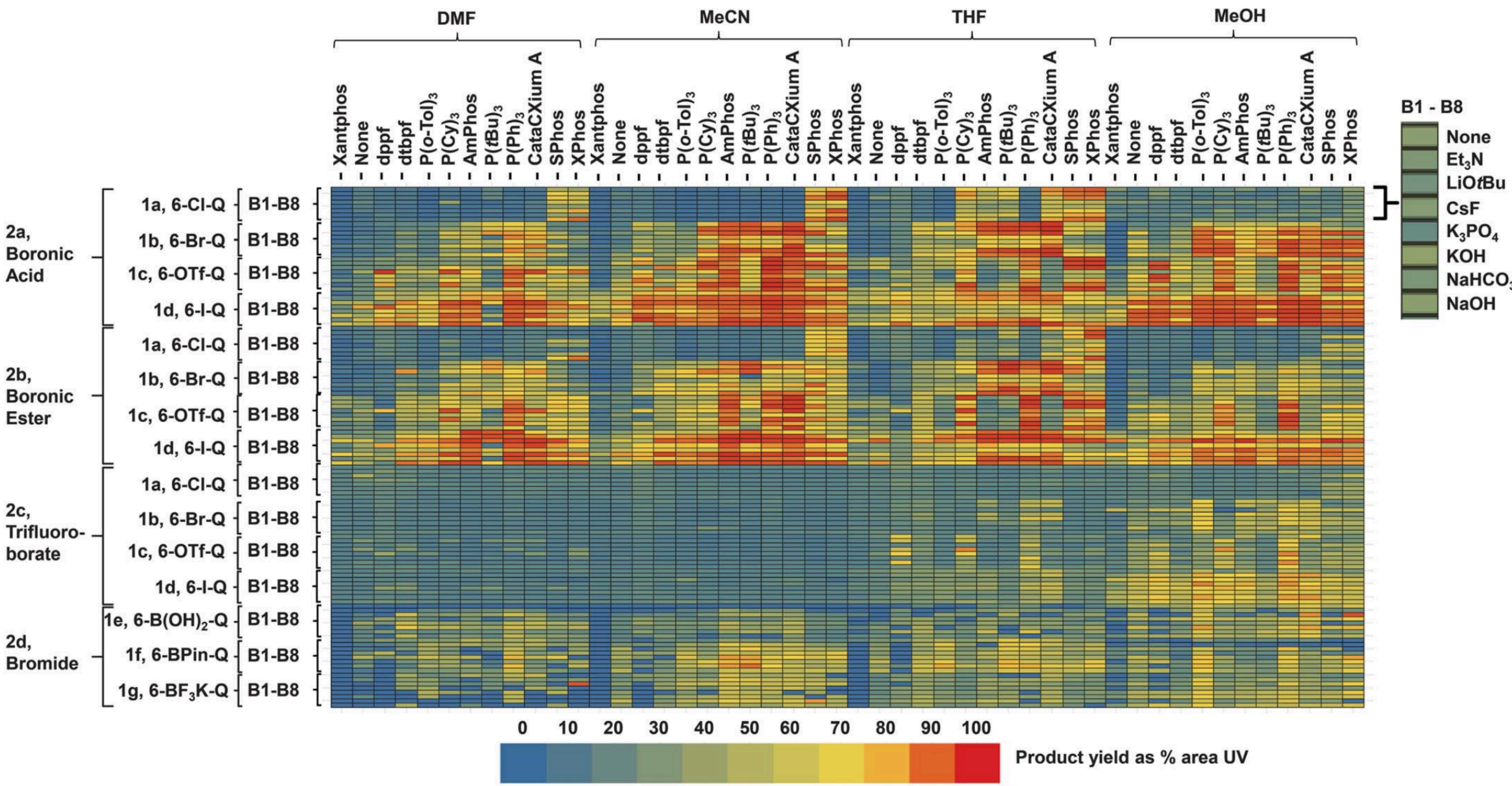
Perera, Richardson, Sach, *Science* **2018**, *359*, 429–434.

Automated Reaction Optimization



Perera, Richardson, Sach, *Science* **2018**, *359*, 429–434.

Automated Reaction Optimization



Perera, Richardson, Sach, *Science* **2018**, *359*, 429–434.