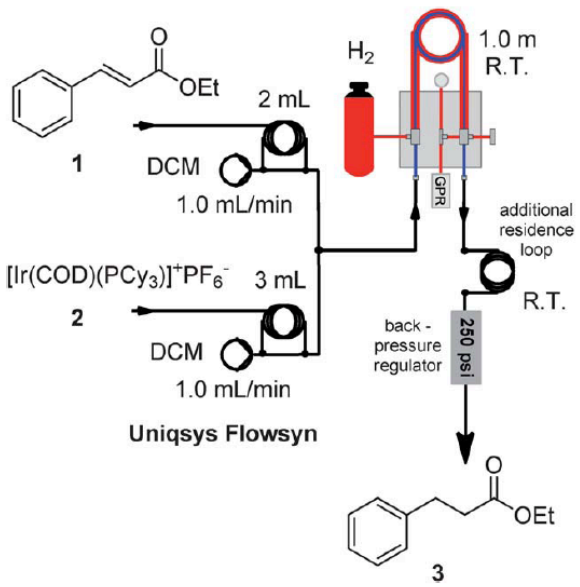
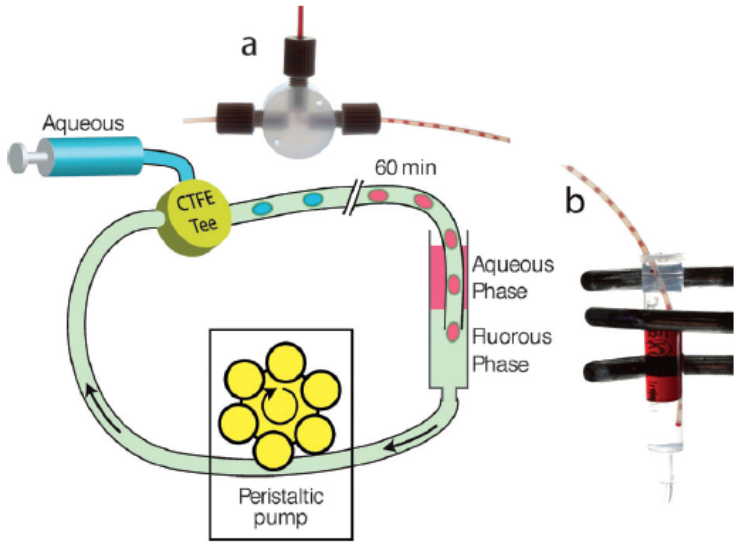
Catalysis in Continuous Flow

Robert J Comito

MacMillan Group Meeting April 11, 2012

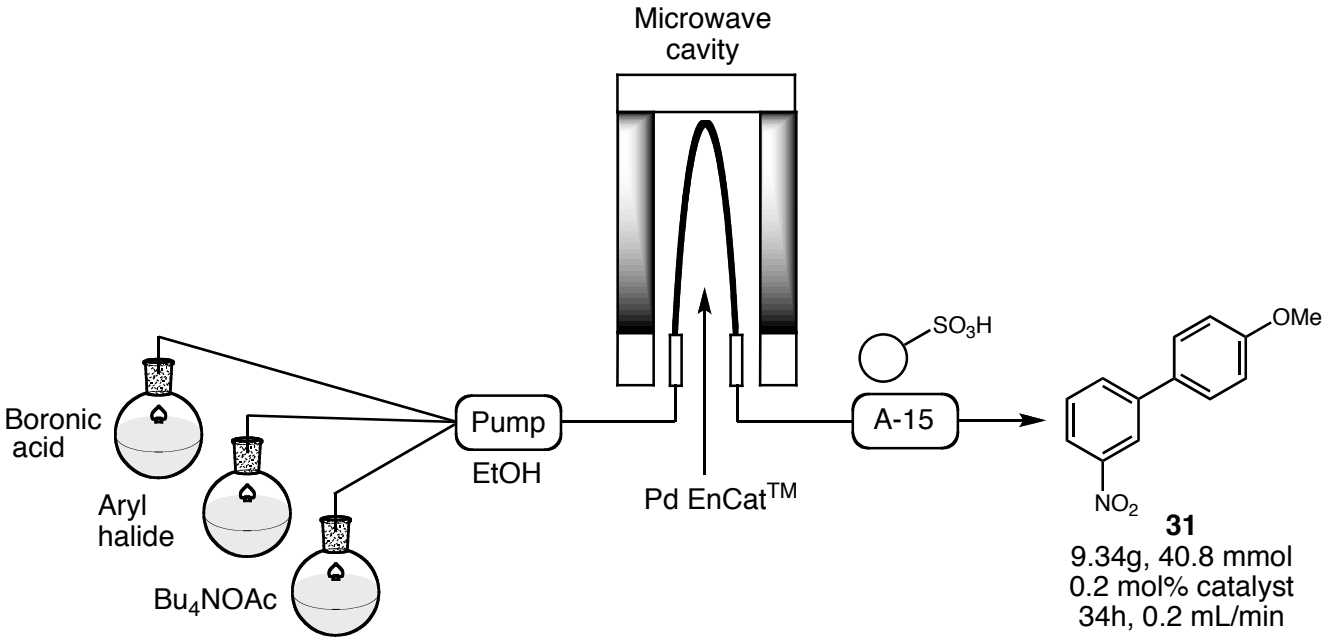




Images: Ley, S. et al. *Org. Lett*. **2003**, *5*, 4665. Jensen, K. et al. *Chem. Sci.* **2011**, *2*, 287.

Introduction to Continuous Flow

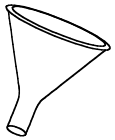
- Continuous input of starting material and output of product
- Microreactor—a device where a small portion of the overall material is undergoing reaction at a given time
- Programmable conditions

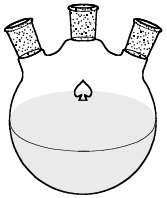


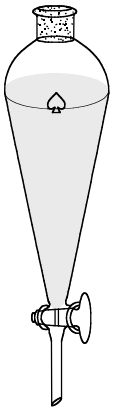
Microreactors in Organic Synthesis and Catalysis. Wirth, T. ed.; Wiley-VCH: Weinheim, **2008**, 103.

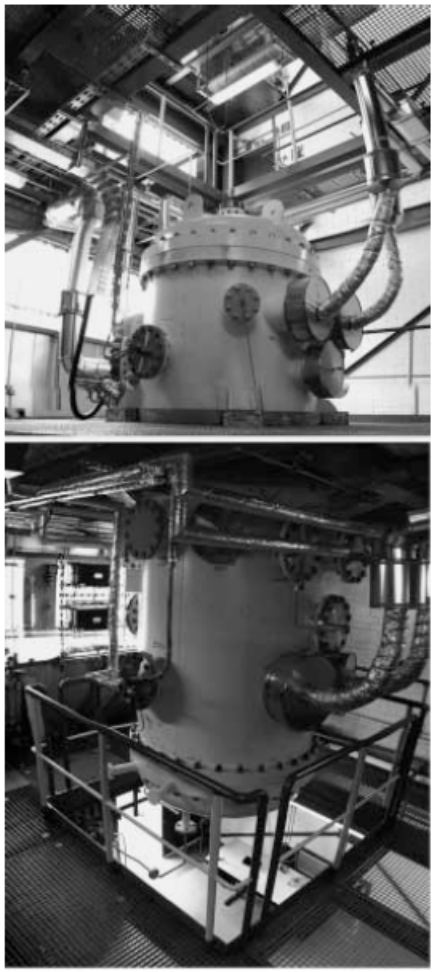
Comparison with Batch Chemistry

- Batch chemistry
  - economy of scale
  - homogenous product
  - conventional glassware
  - established procedures





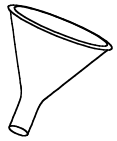


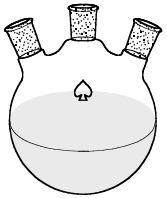


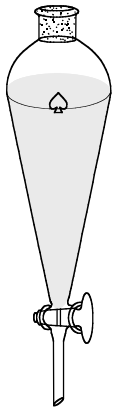
Jahnisch. K.; Hessel, V.; Lowe, H. Baerns, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 406-446.

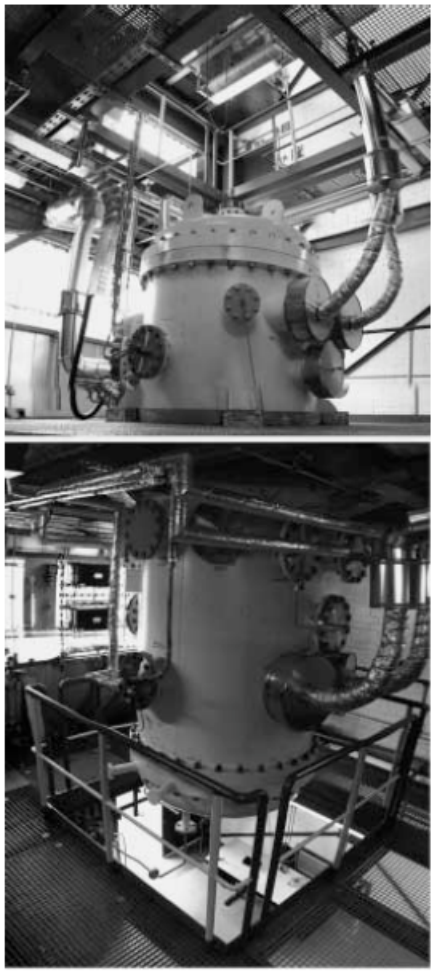
Comparison with Batch Chemistry

- Batch chemistry
  - batch-dependent output
  - lack of scalability
  - safety hazards
  - stop and go synthesis





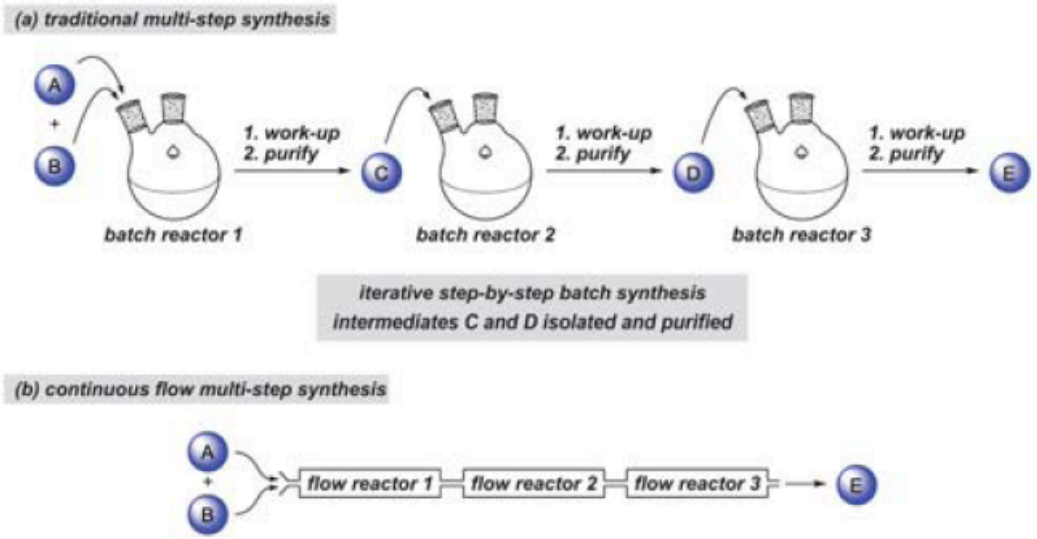




Jahnisch. K.; Hessel, V.; Lowe, H. Baerns, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 406-446.

Comparison with Batch Chemistry

- Continuous Flow
  - Shorter time from input to application
  - Cascading steps enables rapid generation of chemical complexity
  - Scalability through numbering up or longer run of continuous process
  - Reproducibility



Webb, D.; Jamison, T. *Chem. Sci.* **2010**, *1*, 675-680.

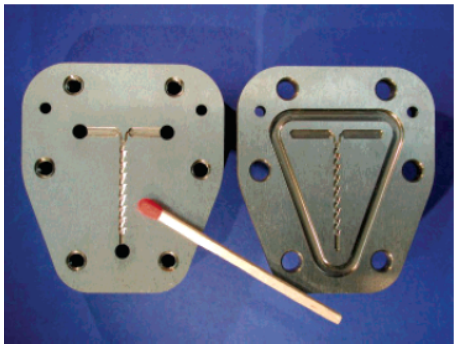
Comparison with Batch Chemistry

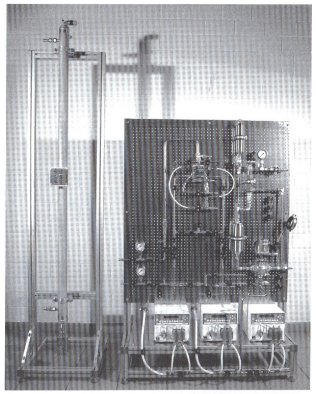
- Process Intensification
  - Hazardous conditions and intermediates are only present in small quantities
  - Point-of-source, point-of-use, and as needed
  - Lower space, inventory, and transportation requirements
  - Lower capital investment

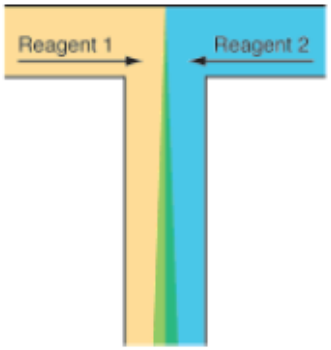
LeViness, S. et al. *Improved Fischer-Tropsch Economics enabled by Microchannel Technology.* Velocys: **2011**.
Charpentier, J.-C. *Chem. Eng. J.* **2007**, *134*. 84-92.

Microreactors

- Enhanced physical and chemical control of reaction conditions
  - Large internal and interphasic surface to volume ratio
  - More efficient mass and thermal transfer
  - Precise stoichiometry and residence time
  - Immediate use of unstable or hazardous intermediates



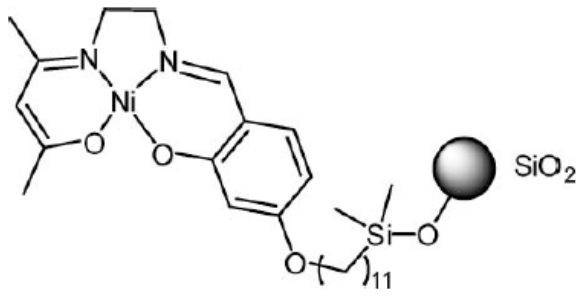


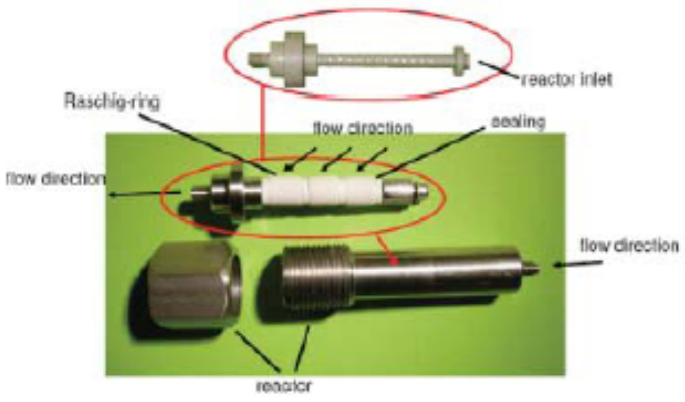


Microreactors in Organic Synthesis and Catalysis. Wirth, T. ed.; Wiley-VCH: Weinheim, **2008**.
Mason, B.; Price, K.; Steinbacher, J.; Bogdan, A.; McQuade, D.. *Chem. Rev.* **2007**, *107*. 2300-2318
Also 2007 group meeting by Joe Carpenter "Microreactors and Microfluidic Cells in Organic Synthesis" .

Heterogeneous Catalysis

- Advantages of heterogenous catalysis in flow
  - Faster relative reaction rates due to larger ratio of contact area to reaction volume, meaning a more efficient use of catalysts
  - Facile recoverability and reuse of catalyst and exclusion from product
  - Incorporation into multistep processes

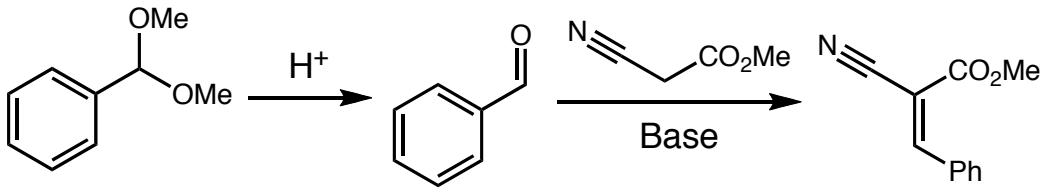


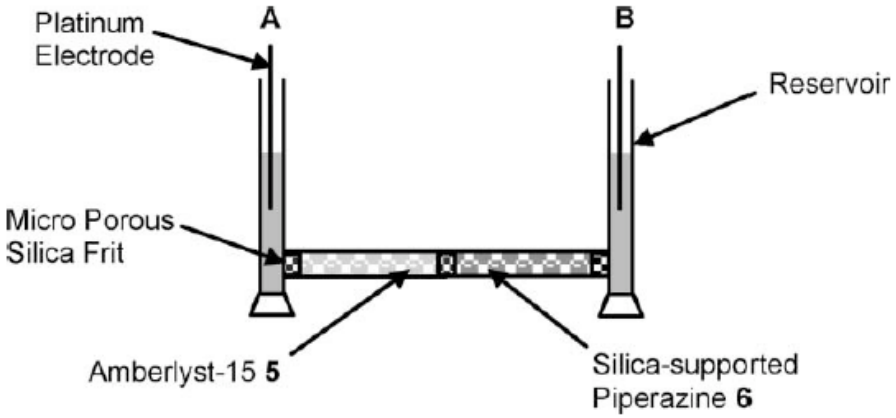


Frost, C.; Mutton, L. *Green Chem*. **2010**, *12*, 1687-1703.

α,β-Unsaturated Ester Synthesis

- Acid- and base- catalyzed synthesis of α,β-unsaturated esters
  - Two mutually incompatible catalytic conditions spatially separated but run simultaneously
  - Commercially available Amberlyst-15 resin as acid catalyst
  - Piperazine supported on silica as base catalyst

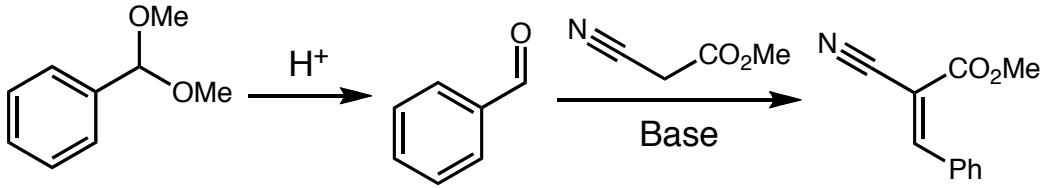


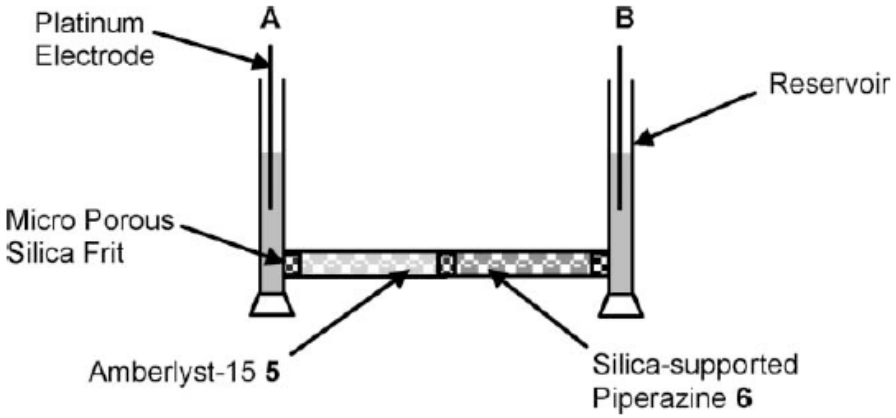


Wiles, C.; Watts, P.; Haswell, S. *Lab. Chip*. **2007**, *7*, 322-330.

α,β-Unsaturated Ester Synthesis

- Catalyst integrity
  - 20 substrates prepared by recycling the catalyst
  - >200 turnovers per equivalent of catalyst
  - Yield > 99%
  - Purity > 99.9%

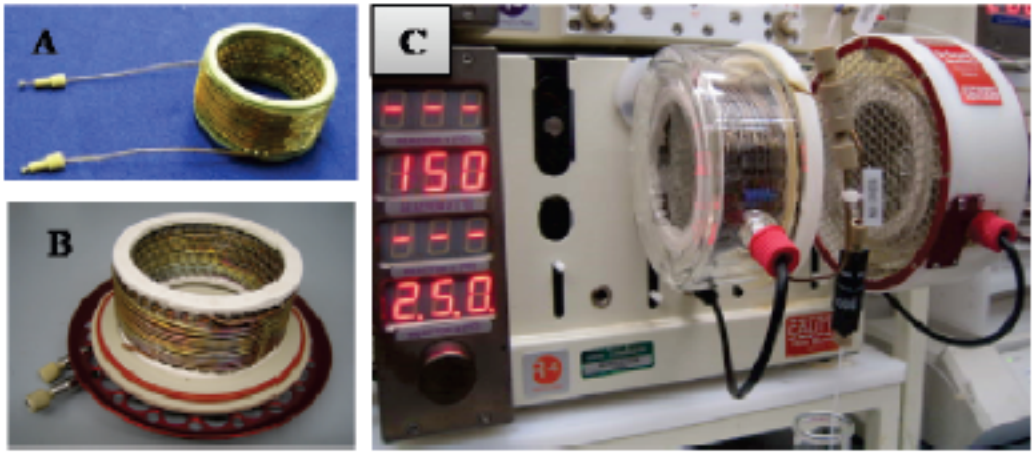




Wiles, C.; Watts, P.; Haswell, S. *Lab. Chip*. **2007**, *7*, 322-330.

CTFRs

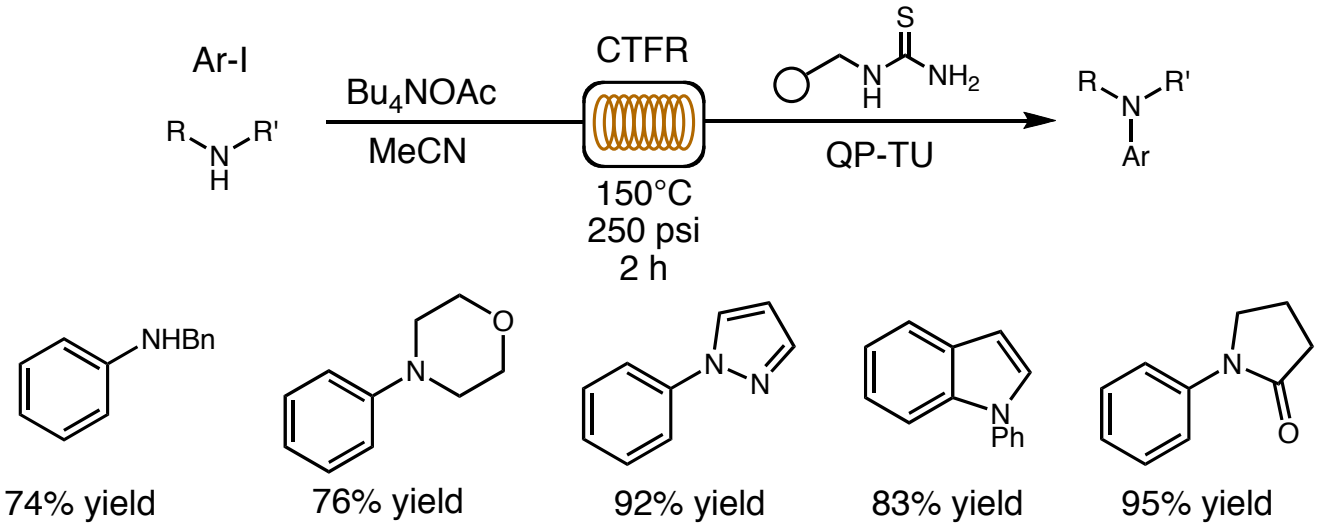
- Copper tube flow reactors (CTFR)
  - Prepared from commercially available 1.0 mm id copper tubes
  - Flow and temperature control by Vapourtec R4 module
  - Leached copper efficiently scavenged by Quadrapure Thiourea resin (QP-TU) (Sigma-Aldrich)



Zhang, Y.; Jamison, T.; Patel, S.; Mainolfi, N. *Org. Lett.* **2011**, *13*, 280-283.

CTFRs

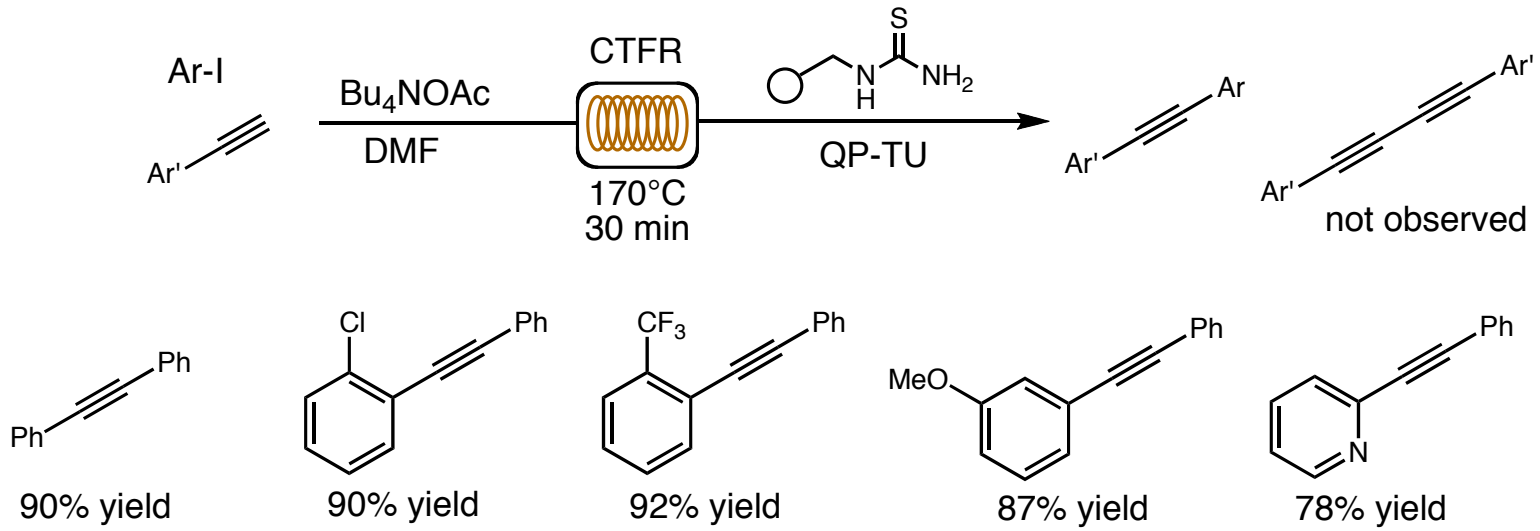
- Ullman condensations in CTFR
  - No added ligand or metal
  - Backpressure regulator allows high pressure and temperature



Zhang, Y.; Jamison, T.; Patel, S.; Mainolfi, N. *Org. Lett.* **2011**, *13*, 280-283.

CTFRs

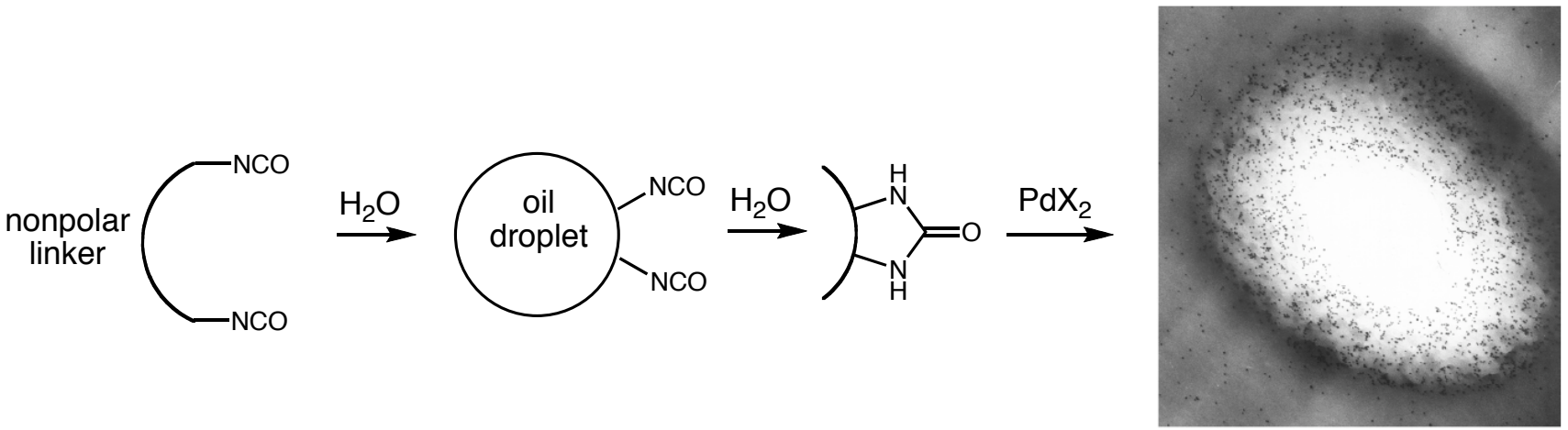
- Sonogashira coupling in CTFR
  - Glaser-Hay products not observed in flow



Zhang, Y.; Jamison, T.; Patel, S.; Mainolfi, N. *Org. Lett.* **2011**, *13*, 280-283.

Pd EnCat

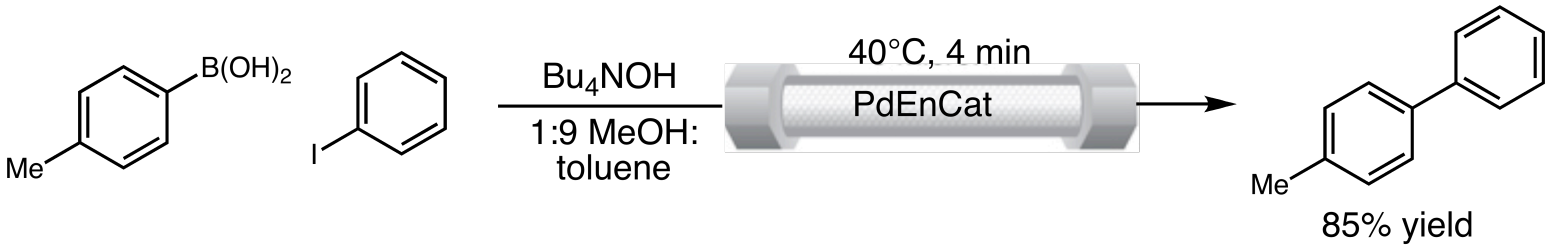
- Polyurea microcapsule polymers loaded with Pd(II) salt
- Several forms Commercially available (Sigma Aldrich)
    - Pd EnCat 30 and 40
    - Pd EnCat TPP 30 – Pd(II)•PPh_3
    - Pd EnCat TOTP 30 – Pd(II) •P(*o*-tolyl)$_3$



Frost, C.; Mutton, L. *Green Chem*. **2010**, *12*, 1687-1703.
Ramarao, C.; Ley, S.; Smith, S.; Shirly, I.; De Almeida, N. *Chem. Commun*. **2002**, 1132-1133.

Pd EnCat

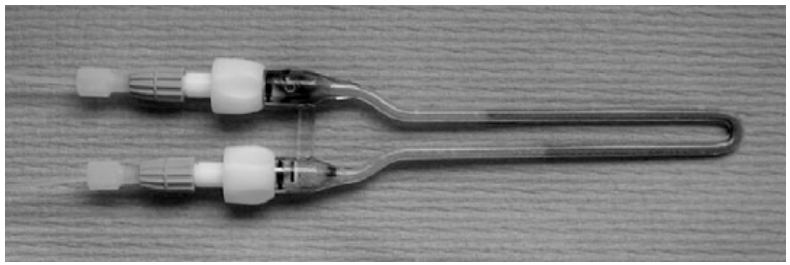
- Suzuki coupling
  - Pd EnCat conveniently packed in HPLC columns
  - Short residence time (4 min)
  - Mild conditions (40°C)
  - Catalyst recycled 4 times with minimal loss in efficiency

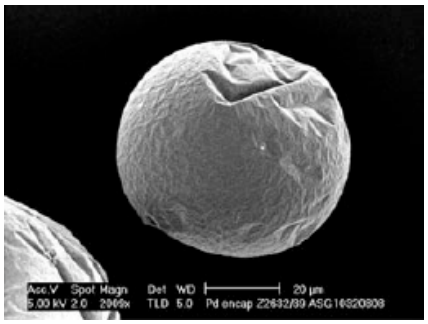


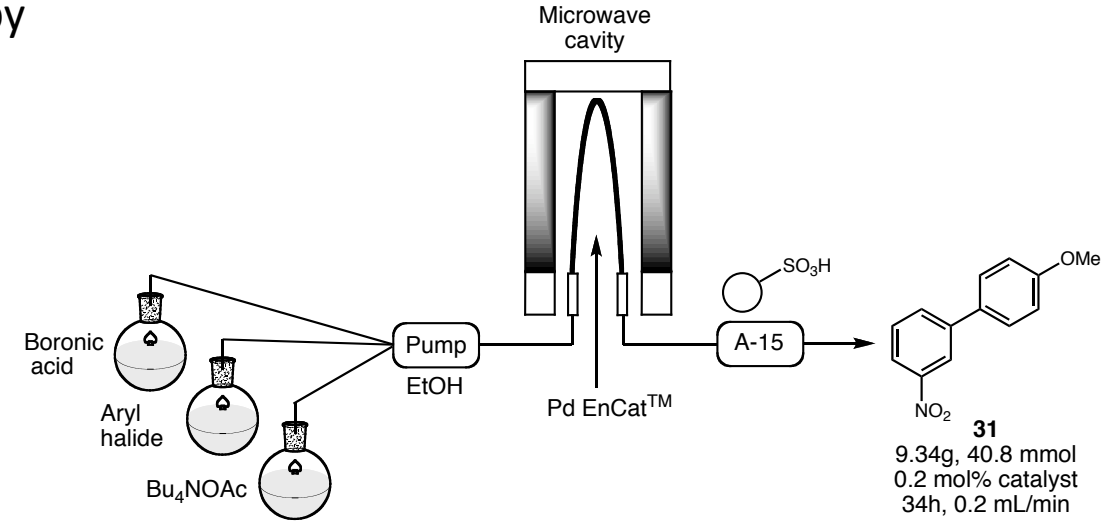
Lee, C.; Holmes, A.; Ley, S.; McConvey, I.; Al-Duri, B.; Leeke, G.; Santos, R.; Seville, J. *Chem. Commun.* **2005**, 2175-2177.

Pd EnCat

- Microwave-heated Suzuki couplings
  - 65s residence time in microwave cavity
  - In-line scavenging of base and excess boronic acids
  - Clean products isolated by evaporation of solvent

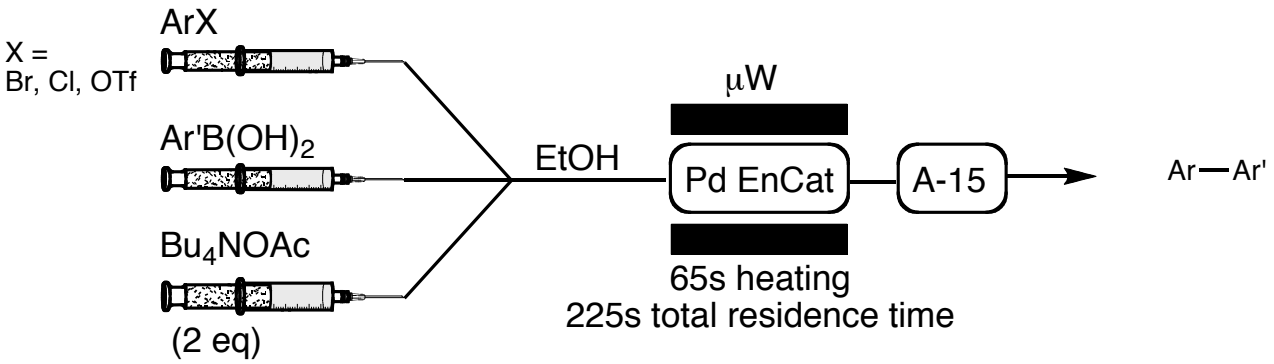


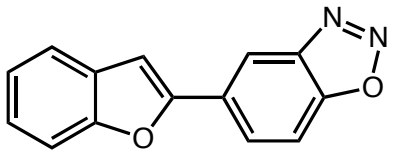




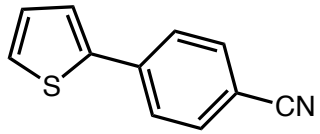
Baxendale, I.; Griffiths-Jones, C.; Ley, S.; Tranmer, G. *Chem. Eur. J*. **2006**, *12*, 4407-4416.

Pd EnCat

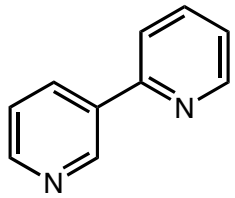




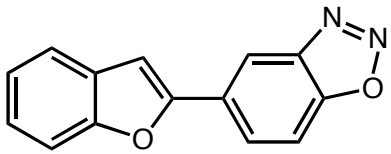
81% yield
98% purity



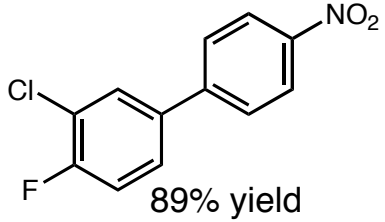
76% yield
98% purity



95% yield
82% purity



97% yield
91% purity
(from ArOTf)

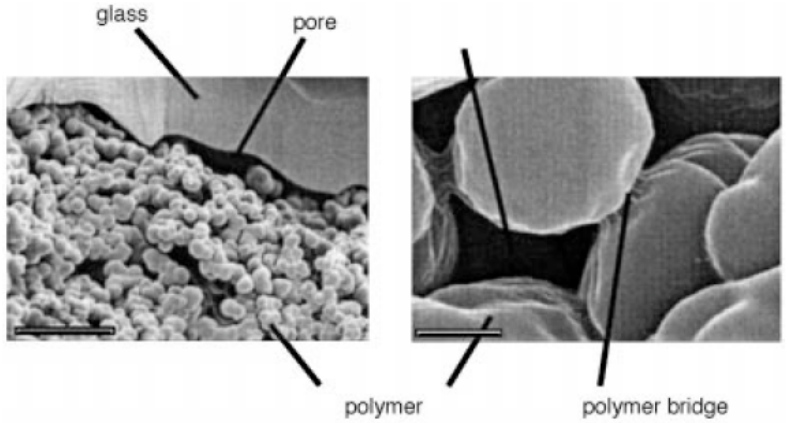


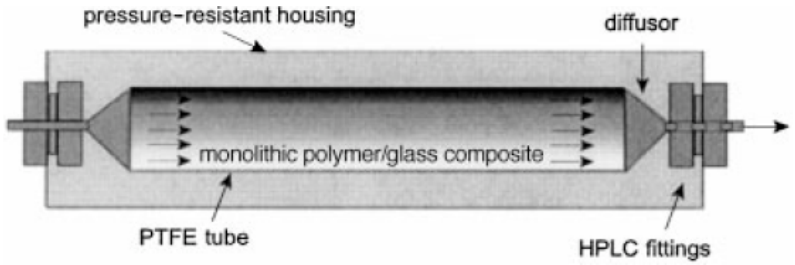
89% yield
98% purity
(from ArCl)

Baxendale, I.; Griffiths-Jones, C.; Ley, S.; Tranmer, G. *Chem. Eur. J*. **2006**, *12*, 4407-4416.

PASSflow

- PASSflow (polymer-assisted solution phase synthesis)
  - Monolithic polymer-glass composite produced by crosslinking polymer beads and their container
  - Efficient flow between beads gives high contact area with supported reagents and low pressure drops
  - Contact with walls of container minimize bypass
  - Few problems associated with polymer swelling

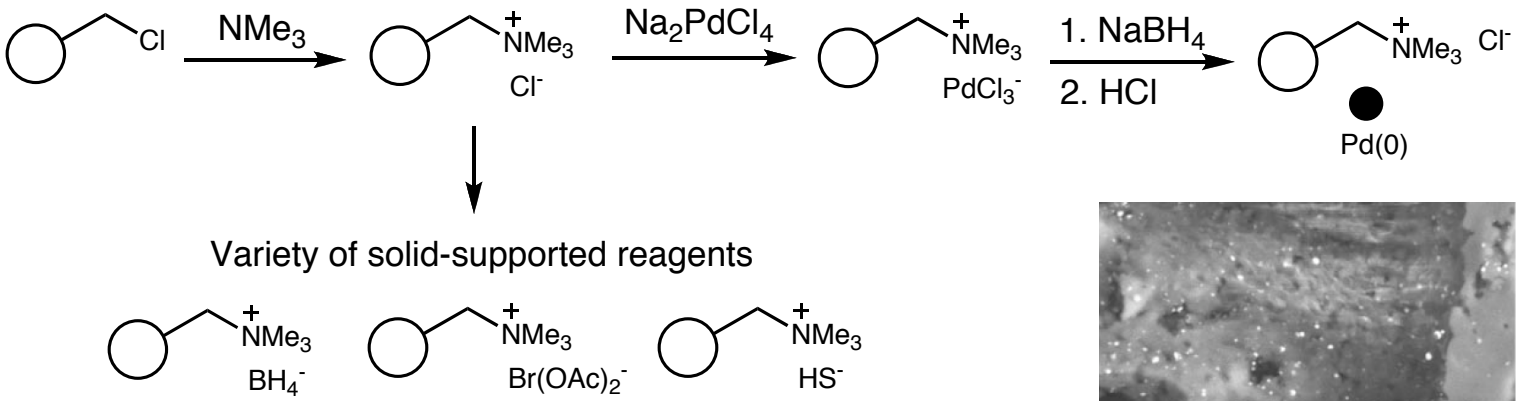




Kirshning, A.; Altwicker, C.; Drager, G.; Harders, J.; Hoffman, N.; Hoffman, U.; Schonfeld, H.; Solodenko, W.; Kunz, U *Angew. Chem. Int. Ed.* **2001**, *40*, 3995-3998.

PASSflow

- Copolymer of styrene, polyvinylchlorobenzene, and divinylbenzene
  - Anionic reagents supported by counterion exchange
  - Reduction of ionically bound $PdCl_3^-$ gives 7-10 nm Pd particles



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Frost, C.; Mutton, L. *Green Chem*. **2010**, *12*, 1687-1703.

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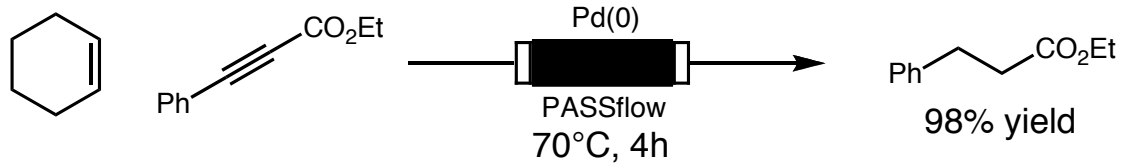
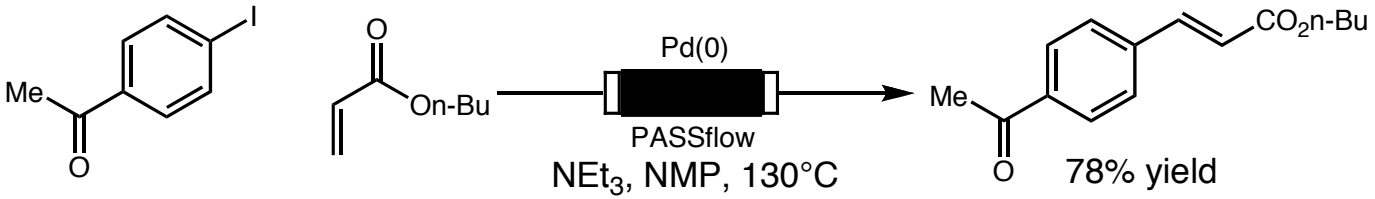
PASSflow

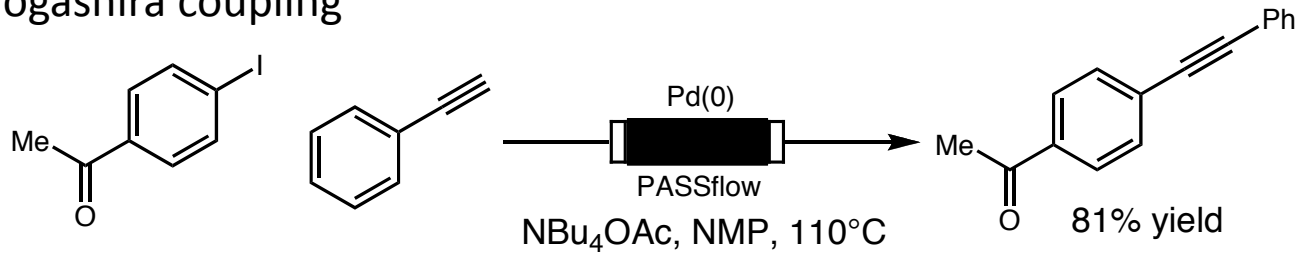
- Transfer hydrogenation



- Heck coupling



- Sonogashira coupling



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Frost, C.; Mutton, L. *Green Chem*. **2010**, *12*, 1687-1703.
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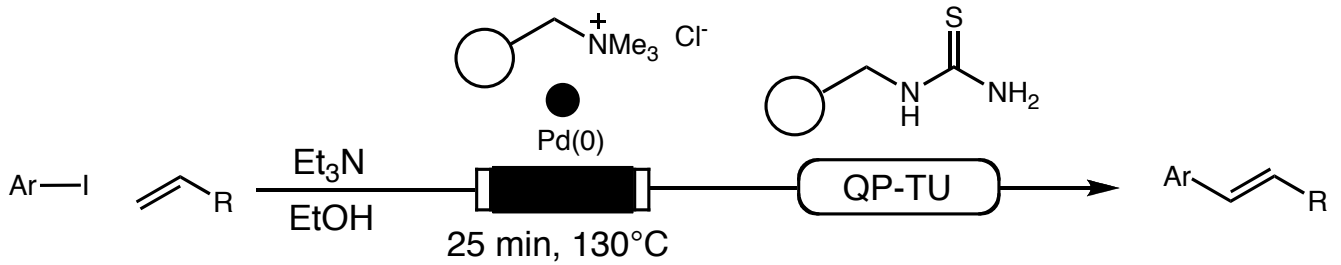
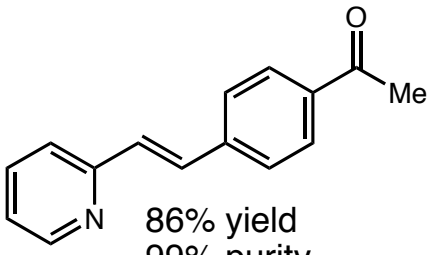
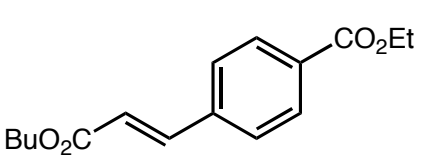
PASSflow

- Ligand-free Heck reaction
  - High temperature in EtOH
  - Pd impurities effectively scavenged by Quadrapure thiourea column
  - Catalyst recycled up to 20 times

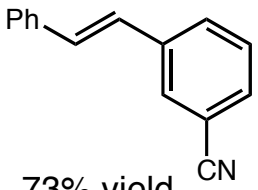




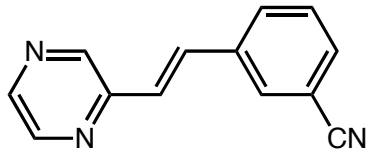
86% yield
99% purity



87% yield
95% purity



73% yield
99% purity

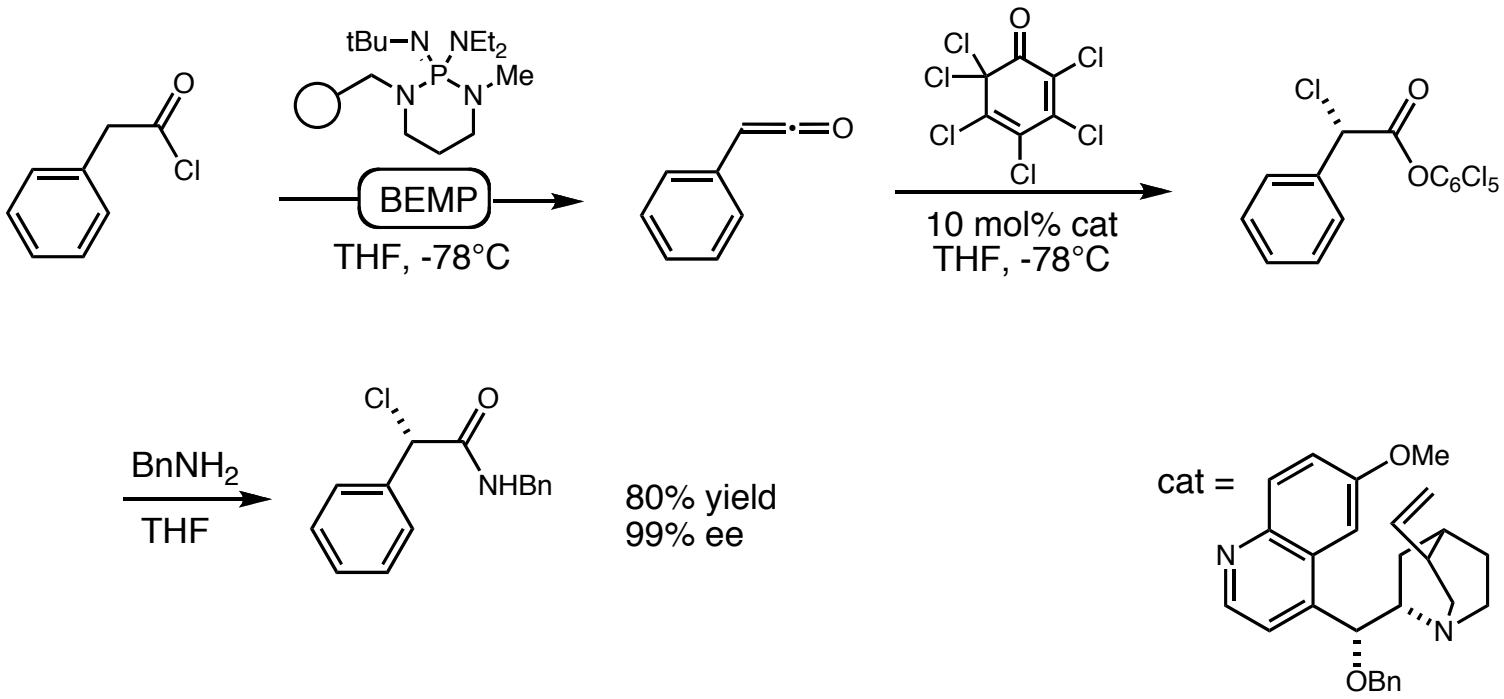


78% yield
99% purity

Nikbin, N.; Ladlow, M.; Ley, S. *Org. Proc. Res. Dev.* **2007**, *11*, 458-462.

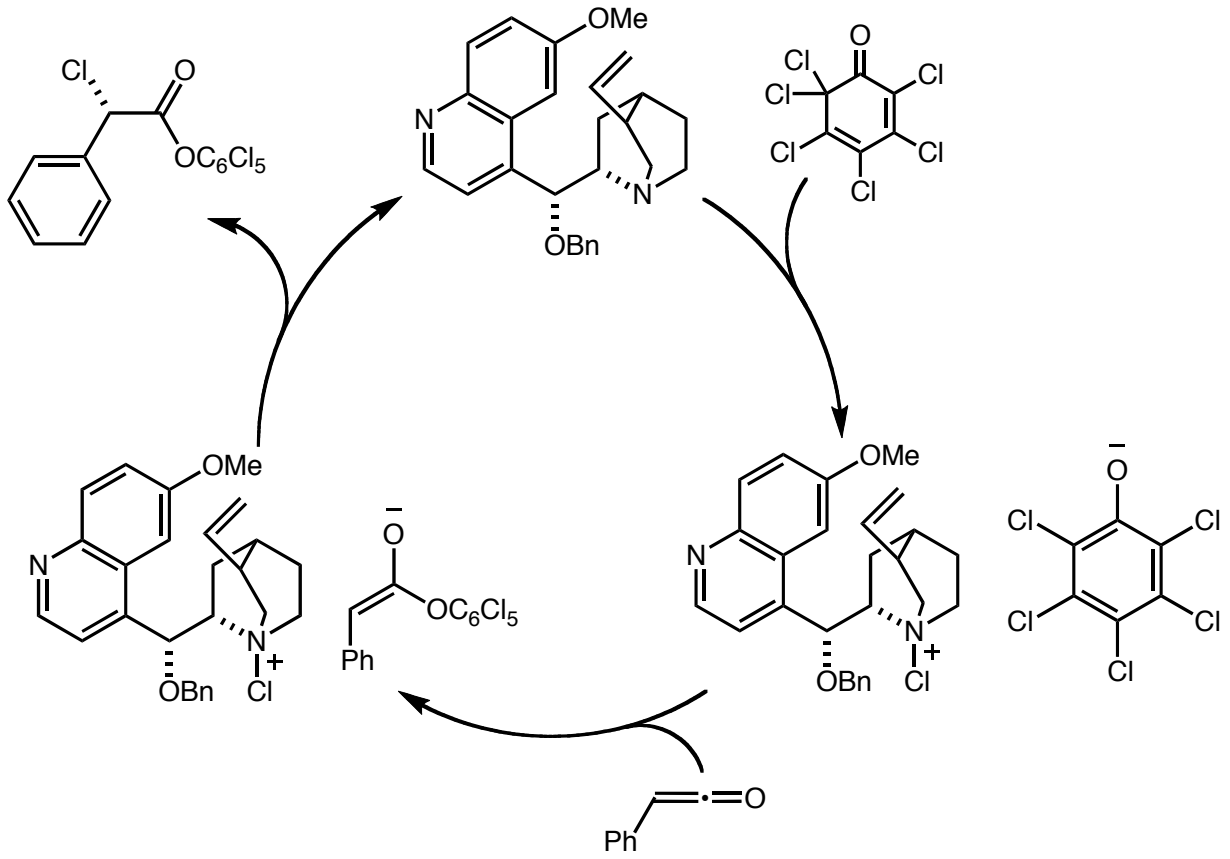
Alpha-Chlorination

- Lectka's organocatalytic asymmetric alpha-chlorination reaction



Wack, H.; Taggi, A.; Hafez, A.; Drury, W.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532.

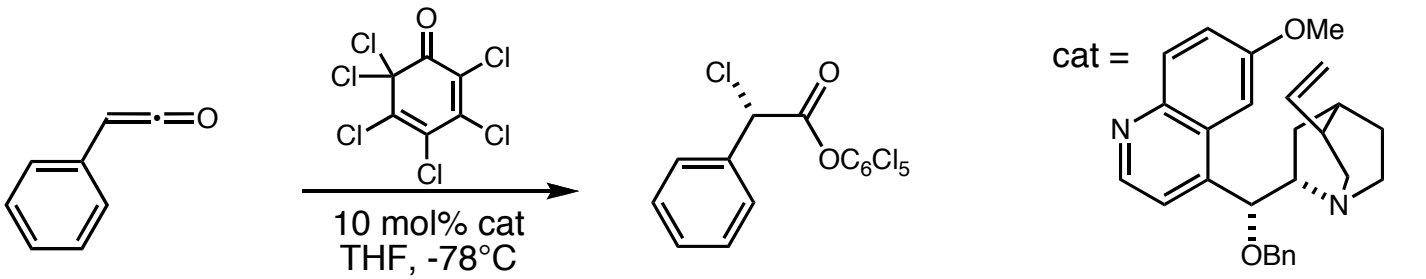
Chlorination Mechanism



Wack, H.; Taggi, A.; Hafez, A.; Drury, W.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532.

Alpha-Chlorination

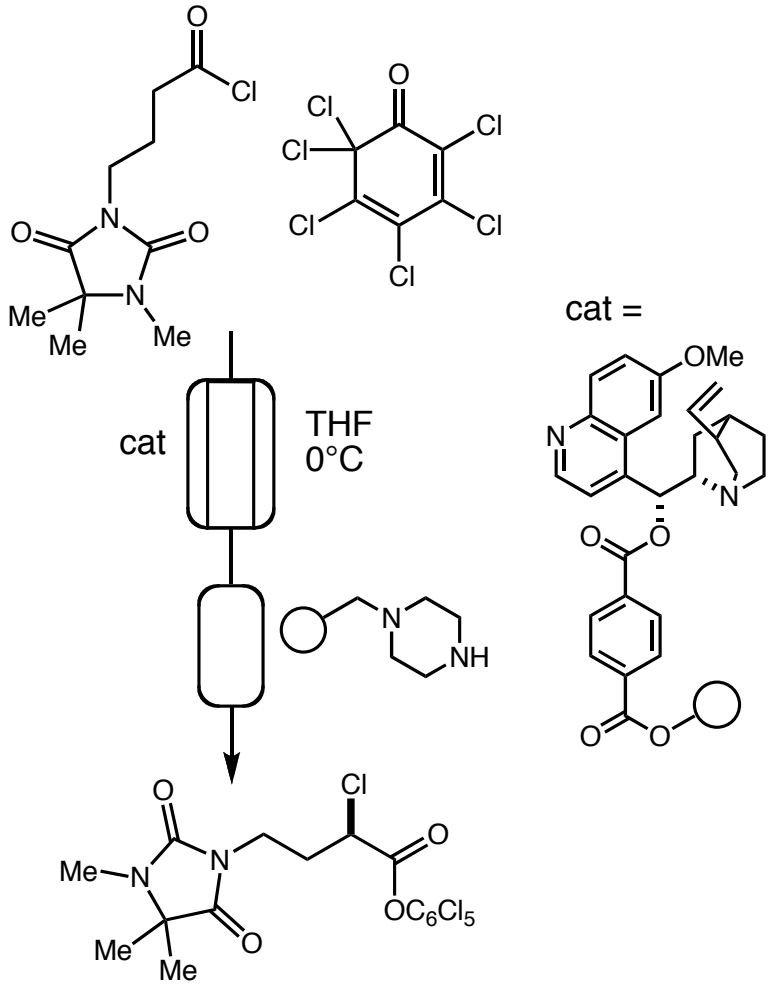
- Motivations for developing a continous flow reaction
  - Reaction needs cryogenic temperatures to avoid side reactions with highly reactive intermediates
  - Flow would allow immediate consumption of reactive ketene and pentachlorophenyl ester
  - Integration into a multistep synthesis
  - Highly selective reaction with easily scavenged byproducts ideal for flow



Wack, H.; Taggi, A.; Hafez, A.; Drury, W.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532.

Flow Synthesis of BMS-275291

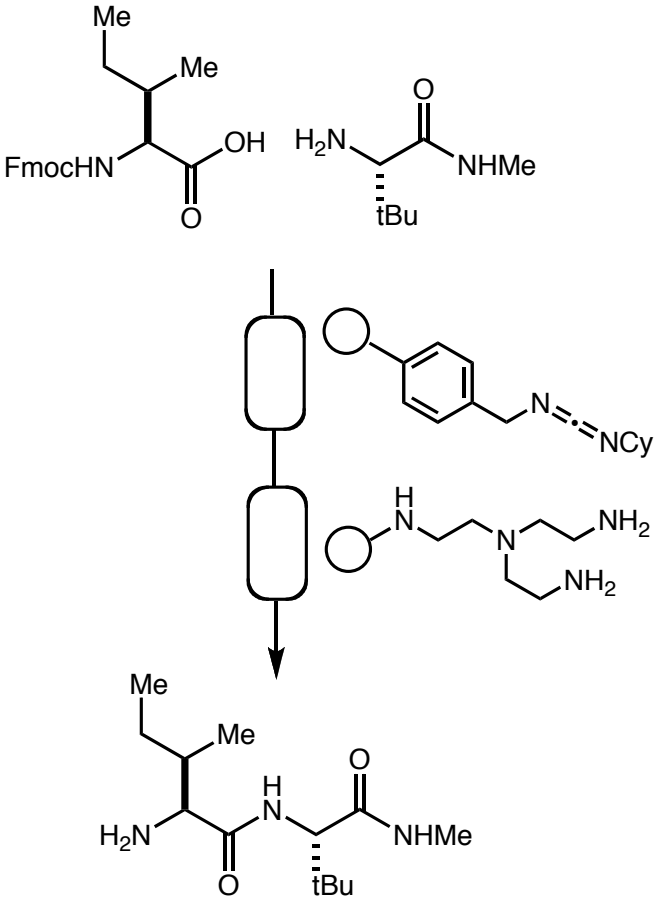
- Wang-resin bound cinchona alkaloid catalyst
  - Ketene formation and alpha-chlorination without exogenous base in the same step
  - Jacketed column and ice bath
  - Piperazine resin scavenges excess acyl chloride to give a high purity intermediate

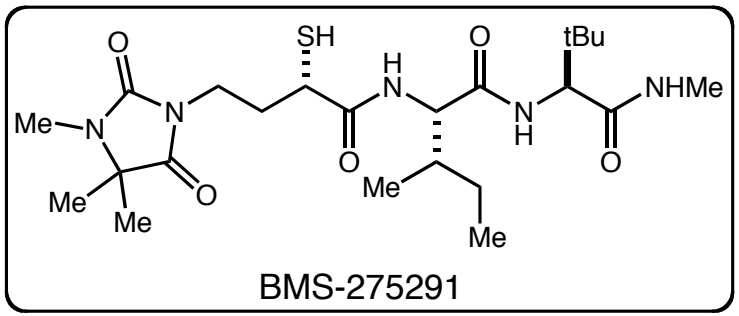


France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Org. Lett.* **2005**, *7*, 3009-3012.

Flow Synthesis of BMS-275291

- Solid-phase synthesis of dipeptide fragment in flow

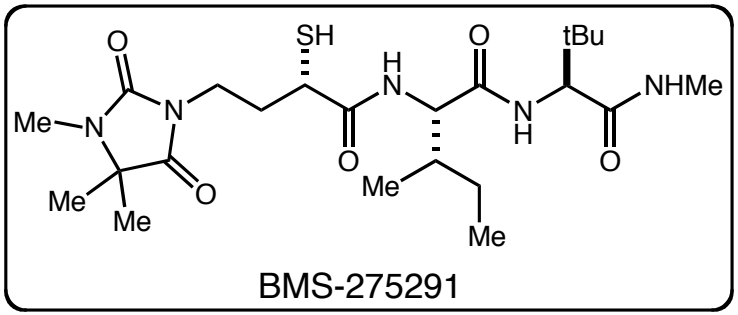


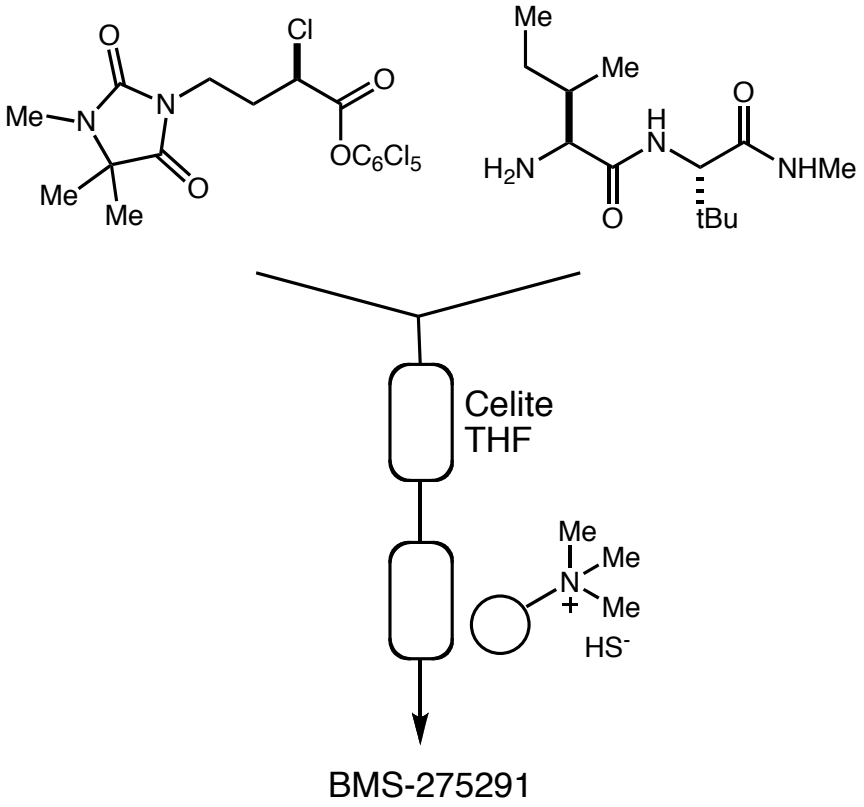


France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Org. Lett.* **2005**, *7*, 3009-3012.

Flow Synthesis of BMS-275291

- Product prepared in 15h
  - 34% yield
  - 83% diasteromeric excess
  - 55 mg product
  - Cinchona alkaloid catalyst cleanly recyclable

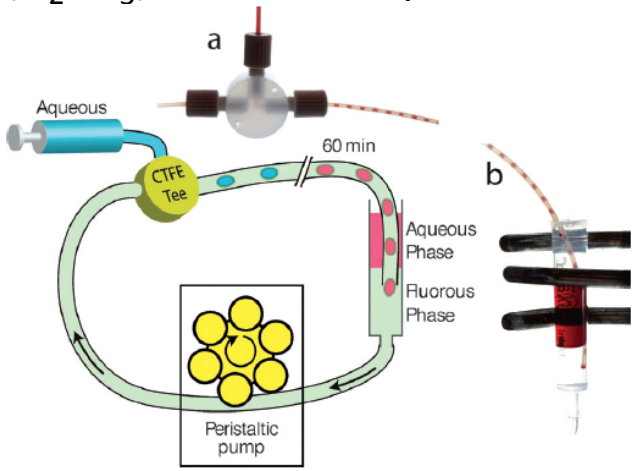




France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Org. Lett.* **2005**, *7*, 3009-3012.

Multiphase Catalysis in Flow

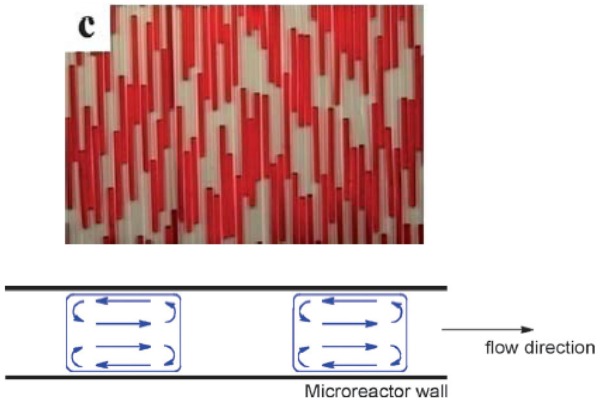
- Microreactors can promote efficient mixing of phases
- Facile separation of phases at the end of reaction
  - Gaseous or aqueous reagents can be conveniently used in excess
  - Continuous extraction of byproducts
  - Recycling of catalysts and expensive solvents (florous solvents, ionic liquids)
- Dangerous gases (H_2, O_3) can be both produced and consumed continuously



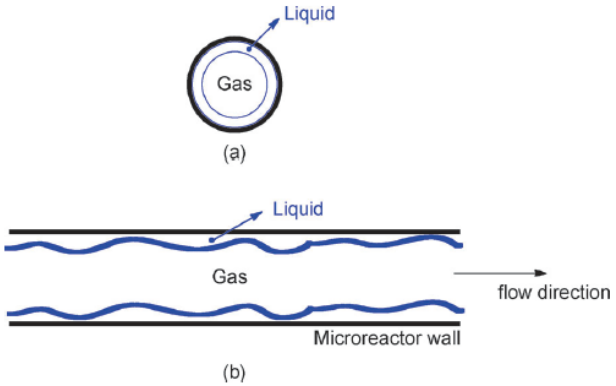
Noel, T.; Buchwald, S. *Chem. Soc. Rev.* **2011**, *40*, 5010-5029.

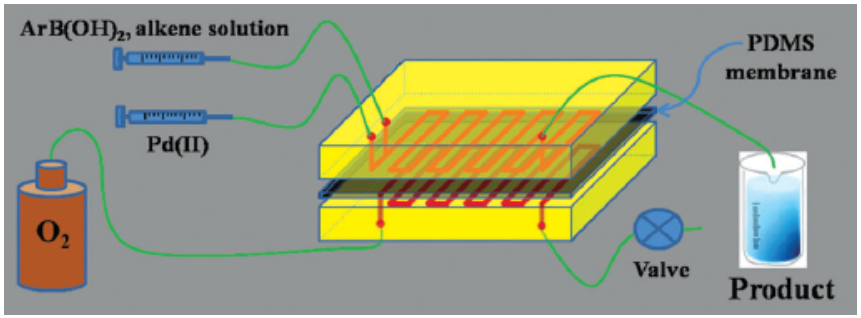
Multiphase Catalysis in Flow

Segmented Flow



Annular Flow



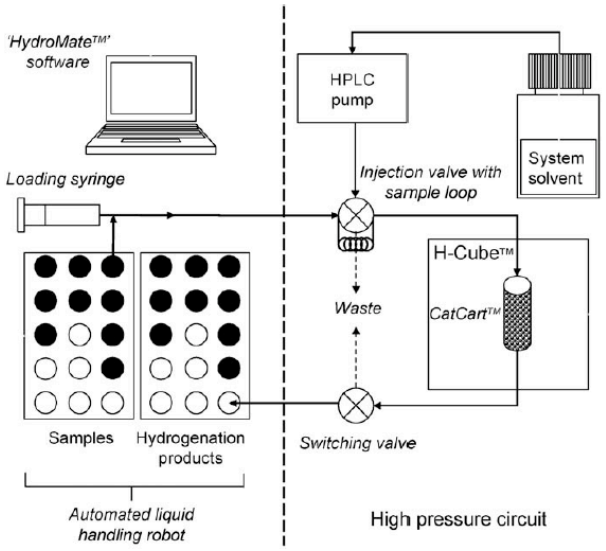


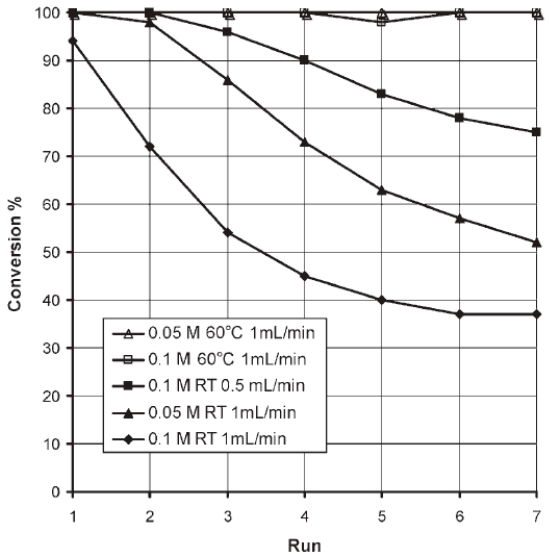
Semipermeable Membranes

Noel, T.; Buchwald, S. *Chem. Soc. Rev.* **2011**, *40*, 5010-5029.

H-Cube Hydrogenations

- H_2 produced continuously by hydrolysis of H_2O
- When combined with a solid-supported catalyst cartridge (Pd/C), hydrogenation can be carried out in flow
- Automated fraction collection, followed by offline analysis, allows for rapid optimization of catalytic conditions

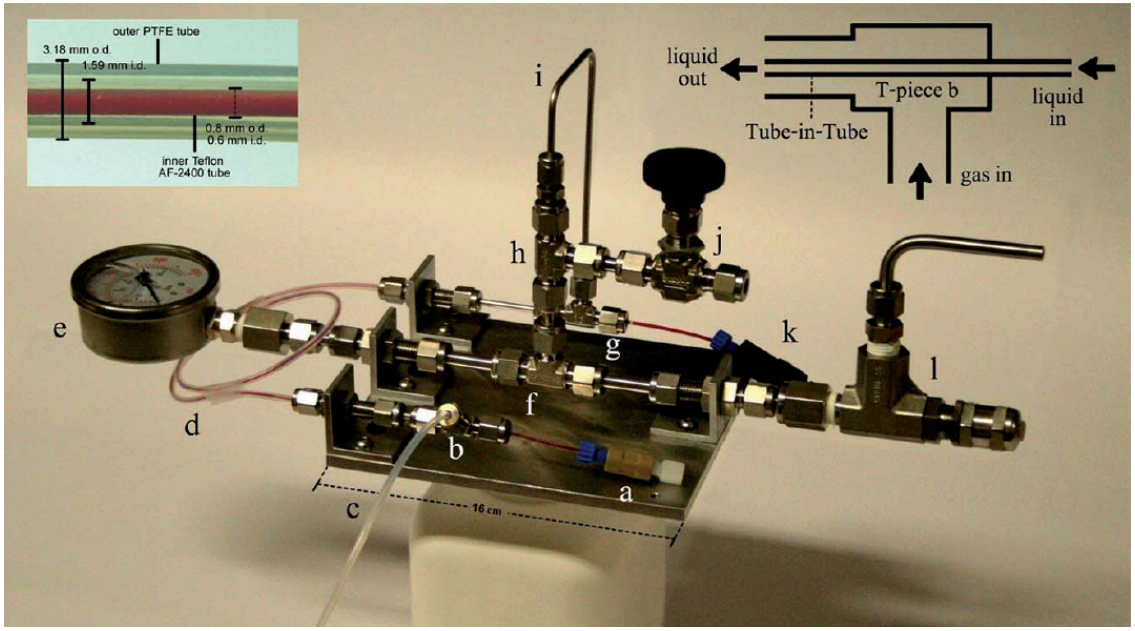




Knudsen, K.; Holden, J.; Ley, S.; Ladlow, M.; *Adv. Synth. Catal*. **2007**, *349*, 535-538.

Tube-in-Tube Hydrogenations

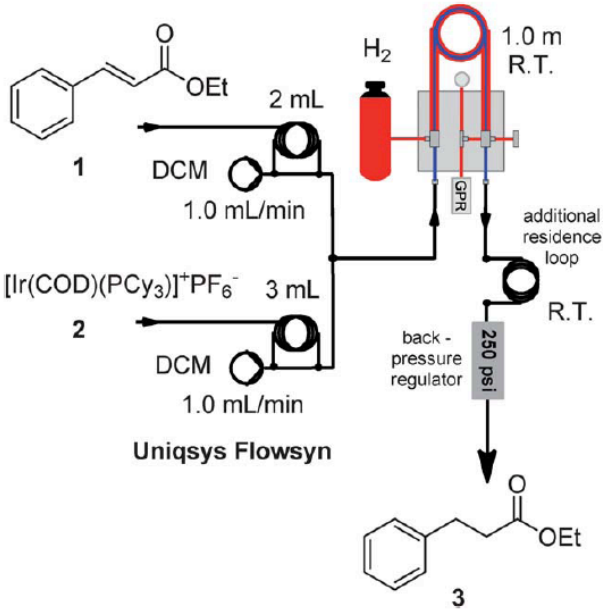
- Semipermeable Teflon AF-2400 tube separates reaction phase from gas phase allowing efficient transfer of H_2 to the reaction
  - Also applied for ozonolysis in flow

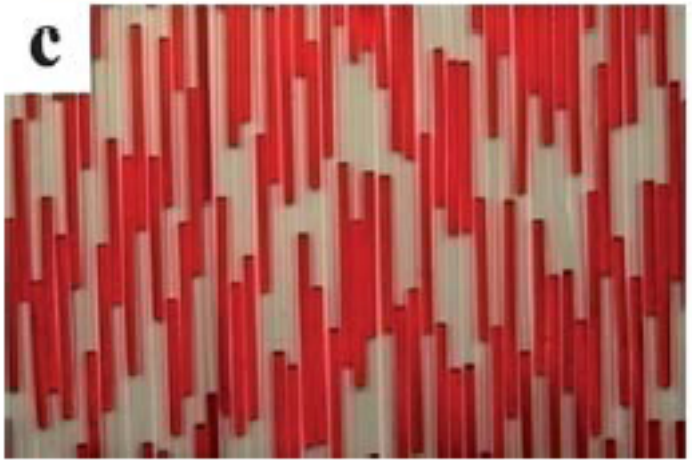


O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I.; Ley, S. *Chem. Sci*. **2011**, *2*, 1250.

Tube-in-Tube Hydrogenations

- Catalyst and substrate are combined then allowed to absorb H_2
- Additional residence time optimized for hydrogenation to run to completion
- In-line quantification of H_2-consumption by "bubble counting" the offgassed H_2 after the back pressure regulator

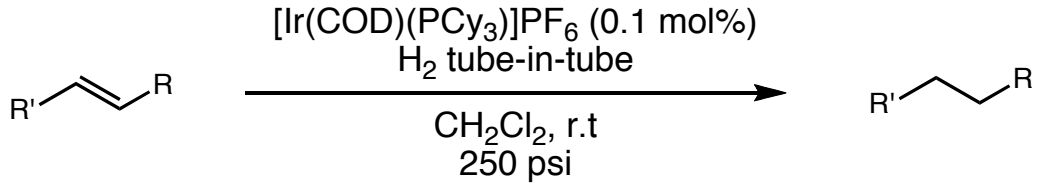




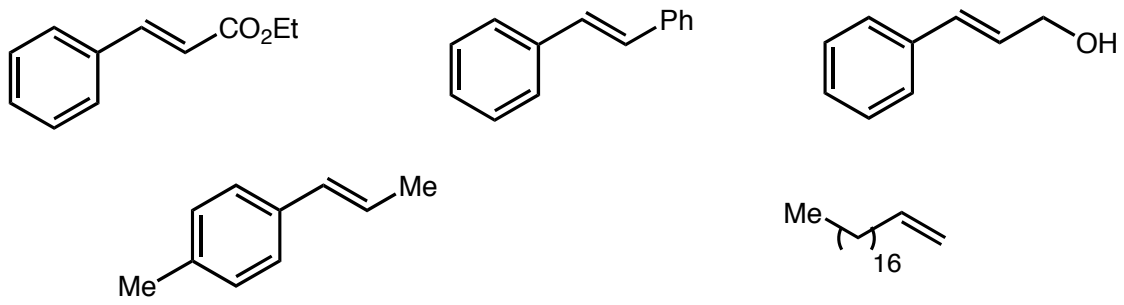
O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I.; Ley, S. *Chem. Sci*. **2011**, *2*, 1250.

Tube-in-Tube Hydrogenations

- Quantitative conversions via homogenous hydrogenation



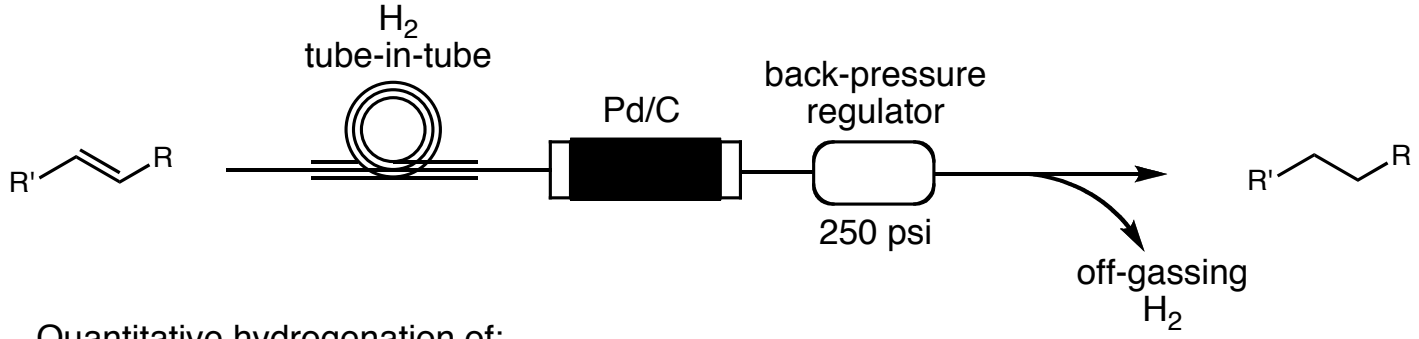
Quantitative hydrogenation of:



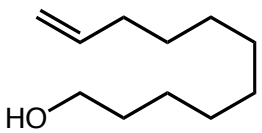
O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I.; Ley, S. *Chem. Sci*. **2011**, *2*, 1250.

Tube-in-Tube Hydrogenations

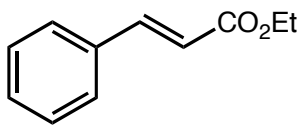
- Sequential hydrogen absorption, heterogenous catalysis, and offgassing



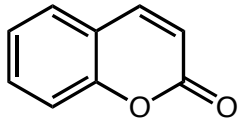
Quantitative hydrogenation of:



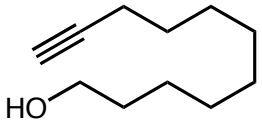
130 min



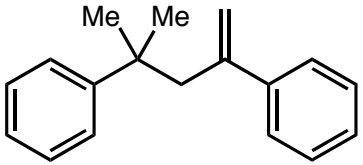
360 min



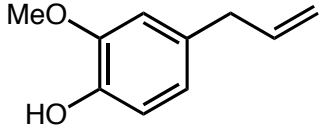
120 min



250 min



110 min

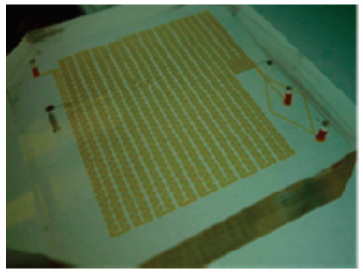


120 min

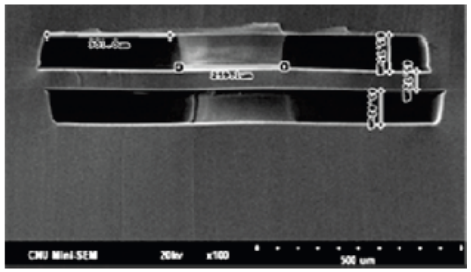
O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I.; Ley, S. *Chem. Sci*. **2011**, *2*, 1250.

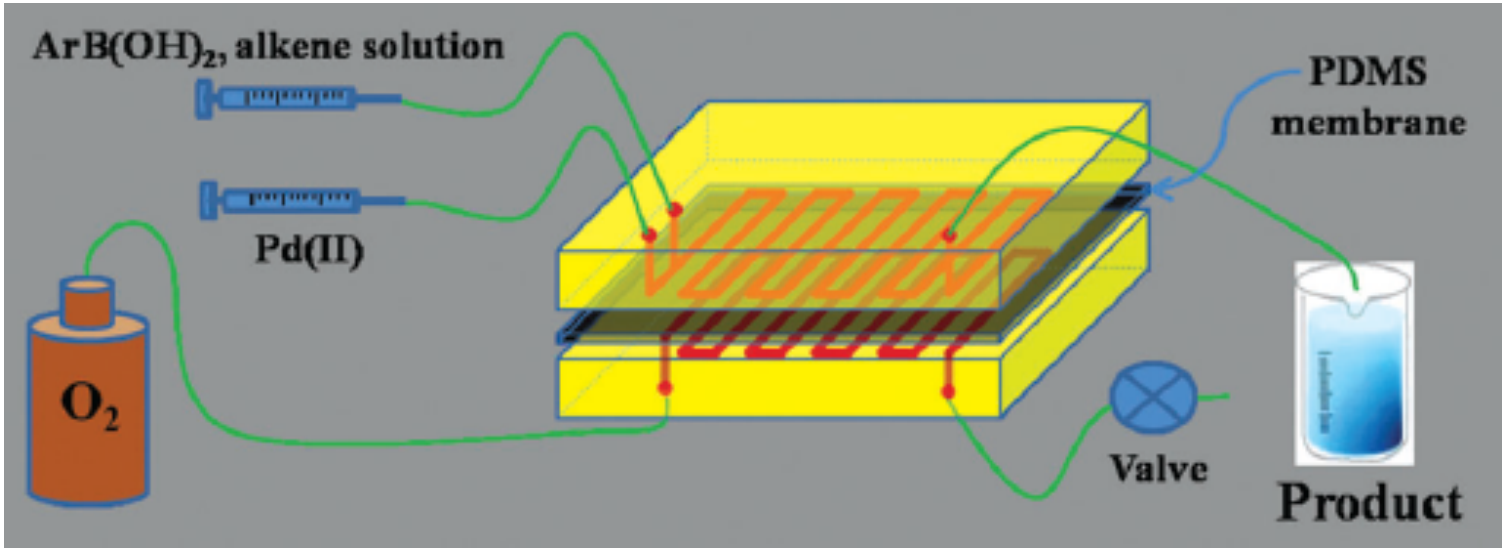
Oxidative Heck in Flow

- Dual channel reactor separated by polydimethylsiloxane (PDMS) membrane allows absorption



b)

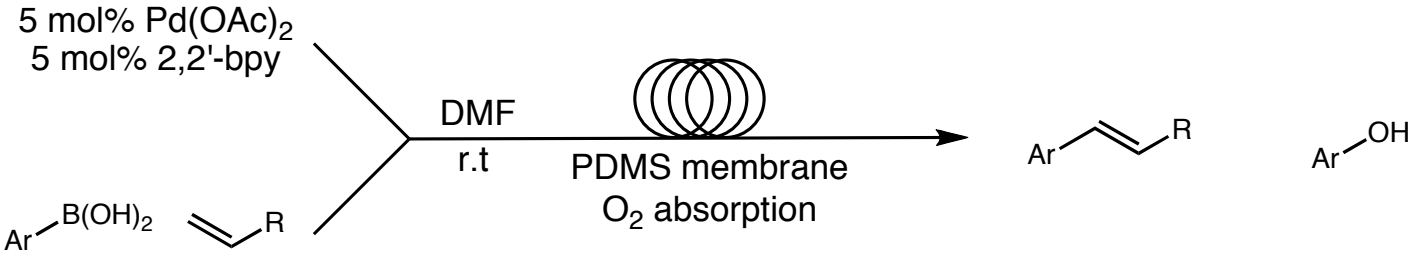


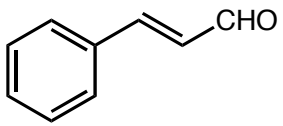


Park, C.; Kim, D.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10102-10106.

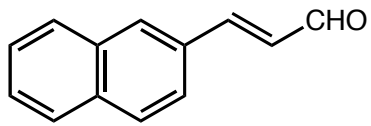
Oxidative Heck in Flow

- Continuous absorption of oxygen and optimization of residence time allows efficient oxidative Heck coupling, with selectivity over alcohol byproduct

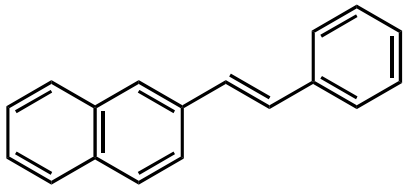




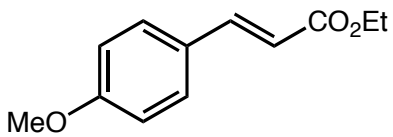
80% yield
8% alcohol



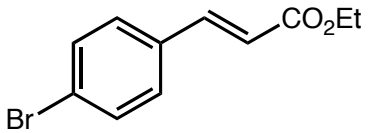
77% yield
10% alcohol



80% yield
10% alcohol



79% yield
7% alcohol

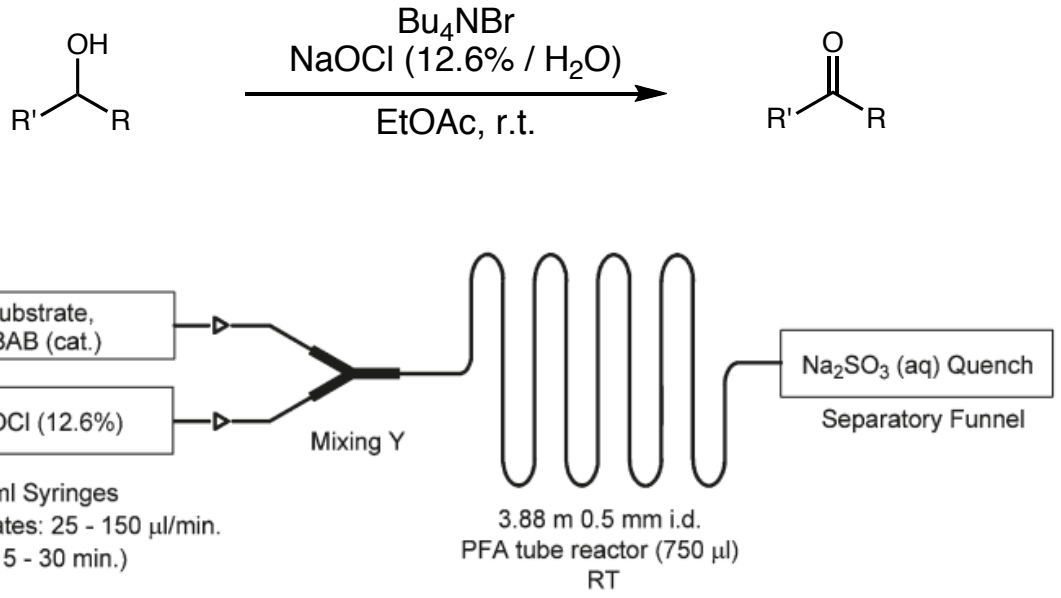


85% yield
7% alcohol

Park, C.; Kim, D.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10102-10106.

Steven's Oxidation in Flow

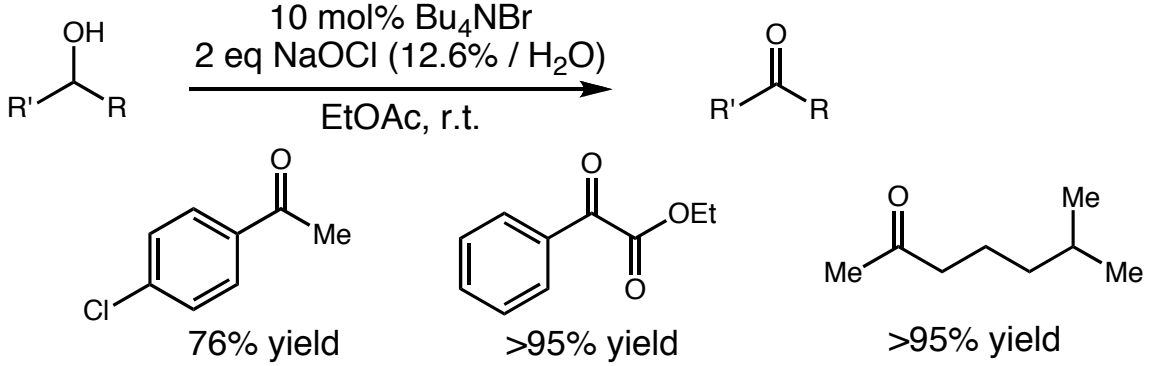
- Phase-transfer catalyzed NaOCl oxidation



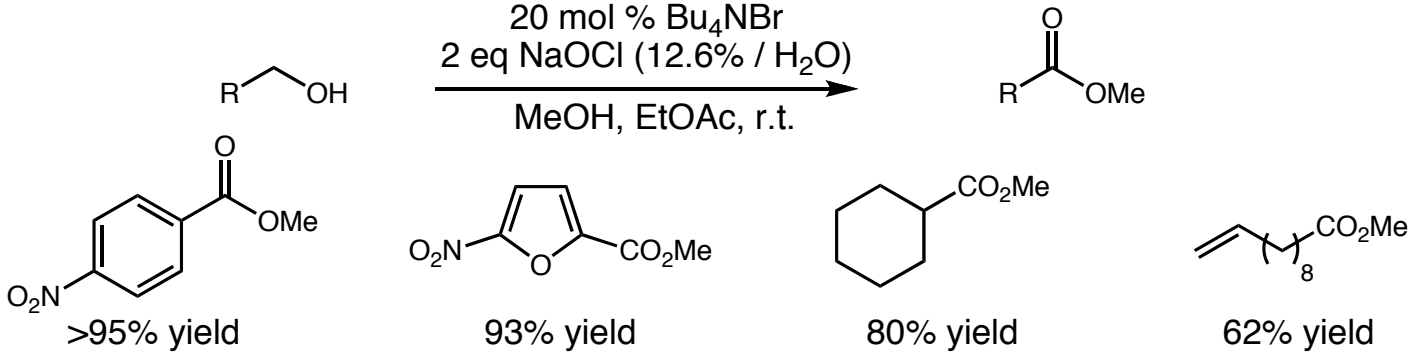
Leduc, A.; Jamison, T.; *Org. Proc. Res. Dev*. **2012.** In press.

Steven's Oxidation in Flow

- Ketones



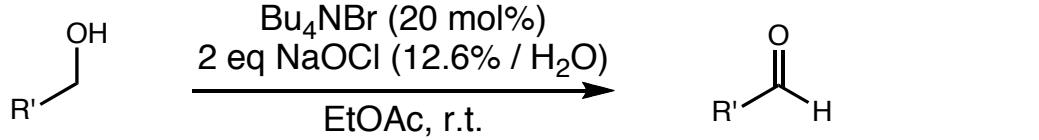
- Esters

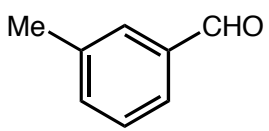


Leduc, A.; Jamison, T.; *Org. Proc. Res. Dev*. **2012.** In press.

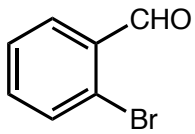
Steven's Oxidation in Flow

- Aldehydes
  - Overoxidation minimized by controlled mixing and residence time

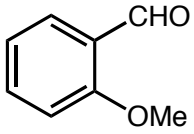




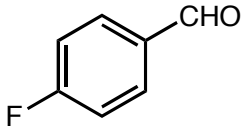
95% yield



95% yield



93% yield

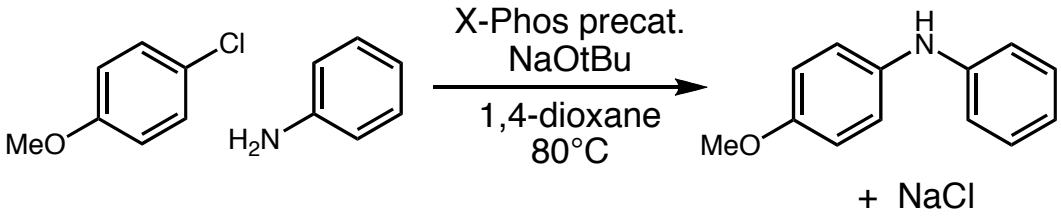


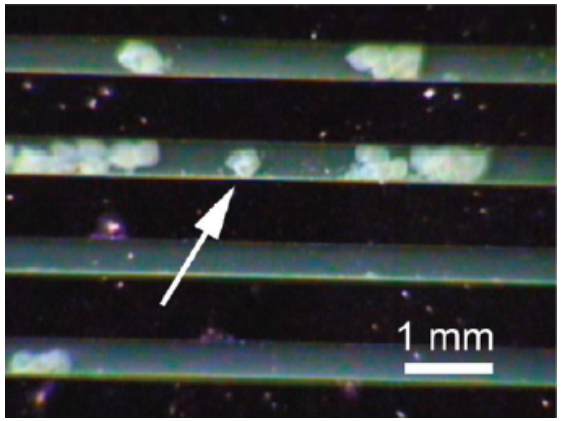
95% yield

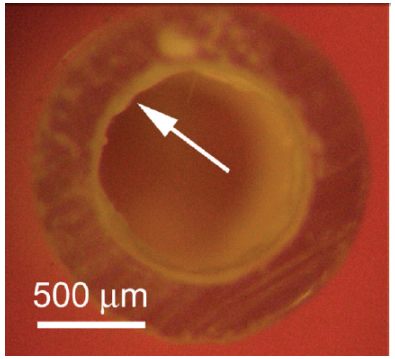
Leduc, A.; Jamison, T.; *Org. Proc. Res. Dev*. **2012.** In press.

Clogging in C—N Cross Couplings

- Buchwald-Hartwig cross couplings often involve inorganic bases and produce insoluble byproducts
- Standard conditions in flow generate clogs (NaCl in the image)



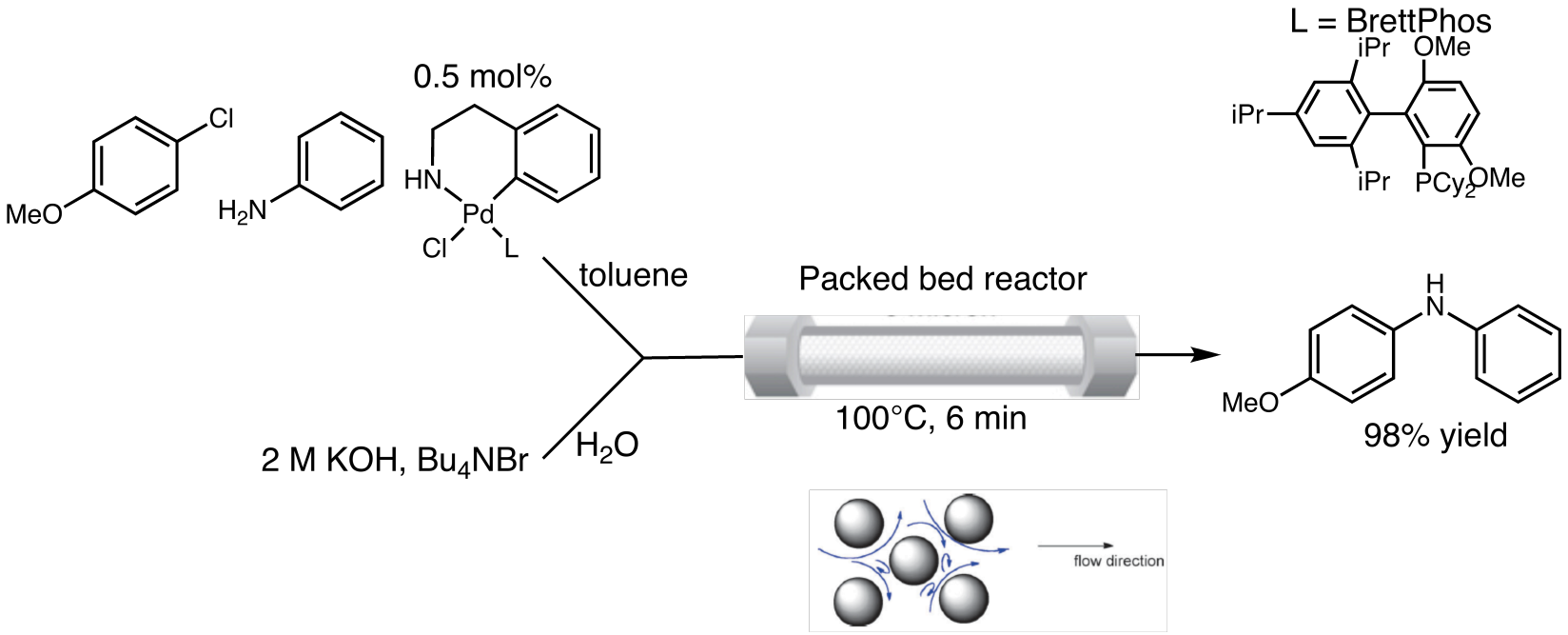




Hartman, R.; Naber, J.; Zaborenko, N.; Buchwald, S.; Jensen, K. *Org. Proc. Res. Dev.* **2010**, *14*, 1347-1357.

Clogging in C—N Cross Couplings

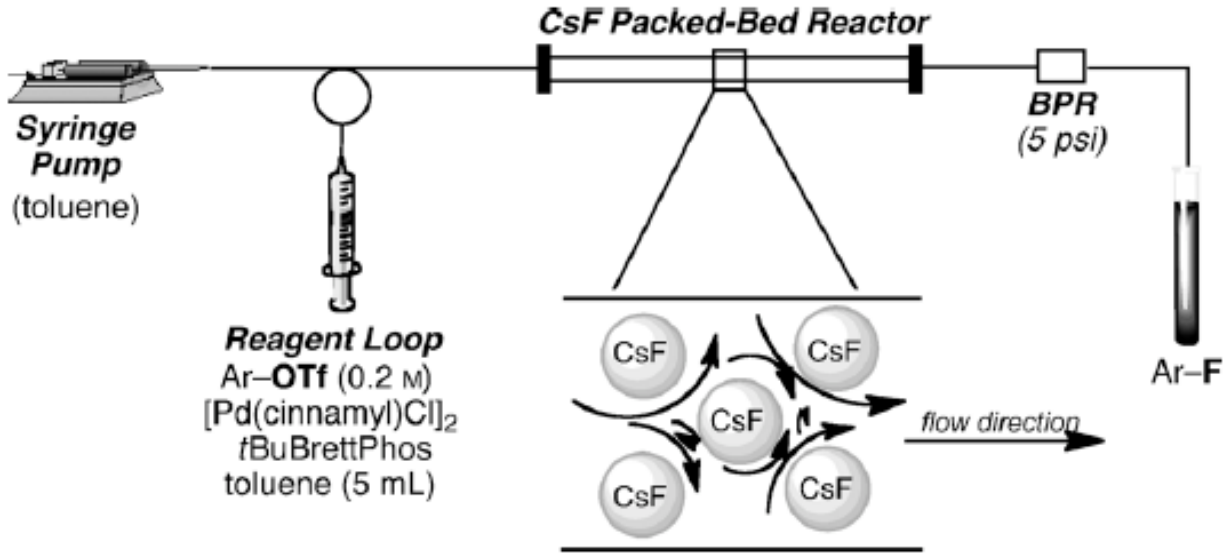
- Phase transfer conditions allows use of aqueous base and continuous extraction of byproducts
- Packed bed reactor consisting of fine stainless steel spheres for efficient mixing of two phases



Naber, J.; Buchwald, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 9469-9474.

Aryl Fluorinations in Flow

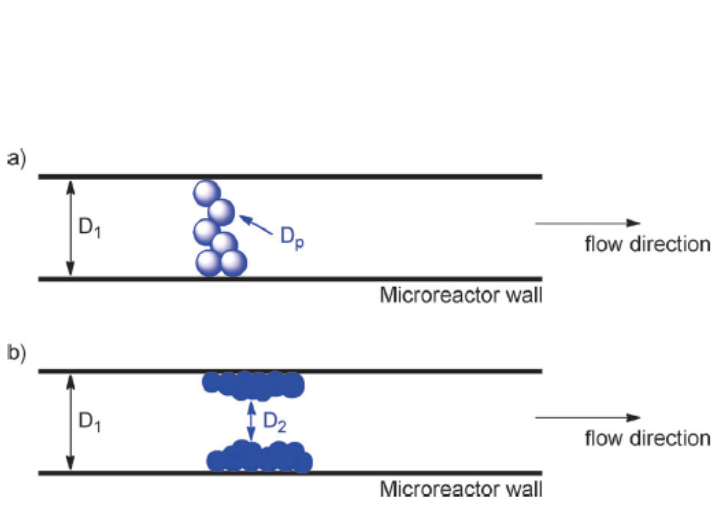
- CsF finely ground and sieved to 45-106µm particles packed in a stainless steel packed bed reactor
- 20 min residence time needed at 120°C
- Yields 60-85%

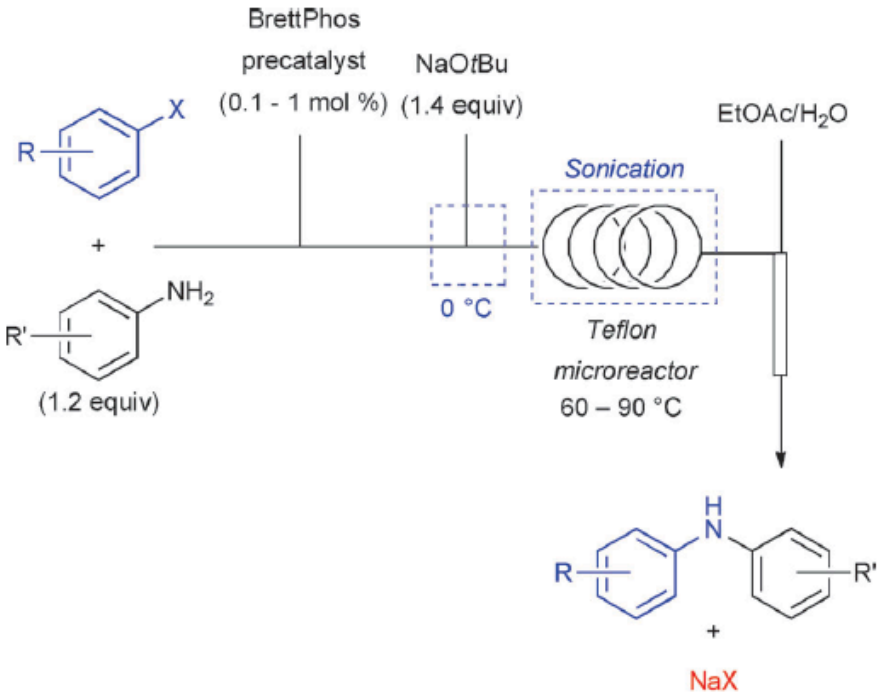


Hartman, R.; Naber, J.; Zaborenko, N.; Buchwald, S.; Jensen, K. *Org. Proc. Res. Dev.* **2010**, *14*, 1347-1357.
Noel, T.; Buchwald, S. *Chem. Soc. Rev.* **2011**, *40*, 5010-5029.

Clogging in C—N Cross Couplings

- Sonication shown to minimize clogging by “bridging”
- Increased flow rate causes abrasive conditions that break up channel deposits
- Rates comparable to batch, with residence times as low as 20 s

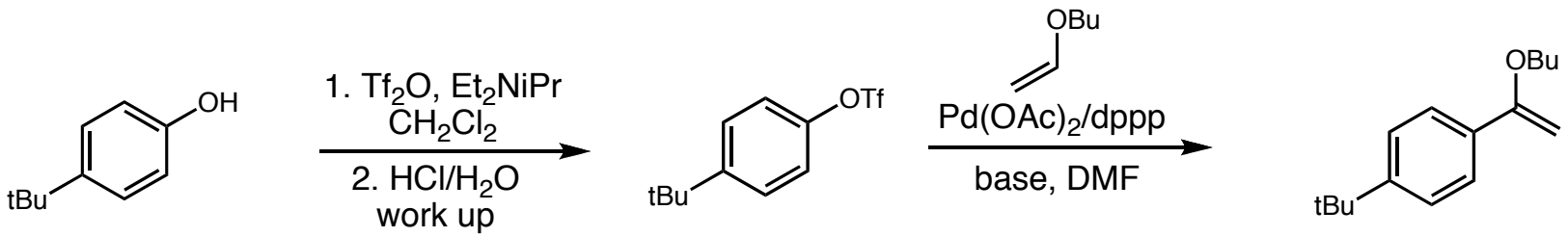




Hartman, R.; Naber, J.; Zaborenko, N.; Buchwald, S.; Jensen, K. *Org. Proc. Res. Dev.* **2010**, *14*, 1347-1357.
Noel, T.; Buchwald, S. *Chem. Soc. Rev.* **2011**, *40*, 5010-5029.

In-Line Microdistillation

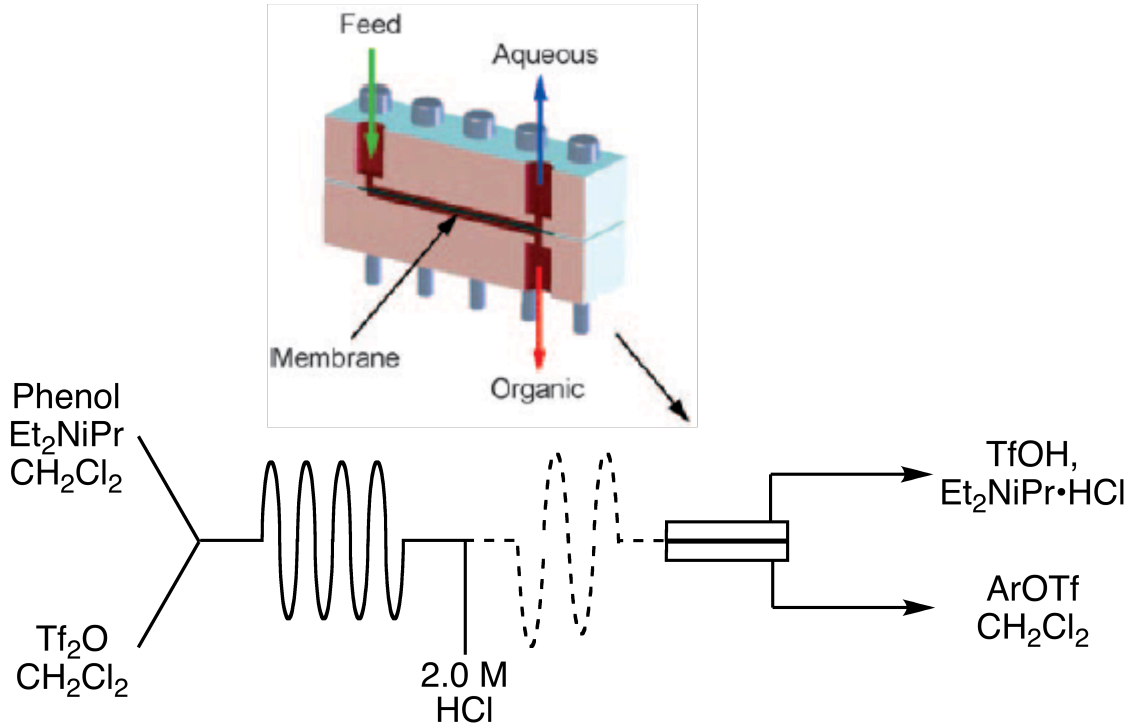
- Sequential formation of aryl triflate and Heck coupling in flow
  - Formation of aryl triflates occurs most efficiently in CH_2Cl_2
  - Byproducts need to be extracted with aqueous workup
  - CH_2Cl_2 detrimental to Pd-catalyzed reaction (needs DMF or toluene and elevated temperatures)



Hartman, R.; Naber, J.; Buchwald, S.; Jensen, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903..

In-Line Microdistillation

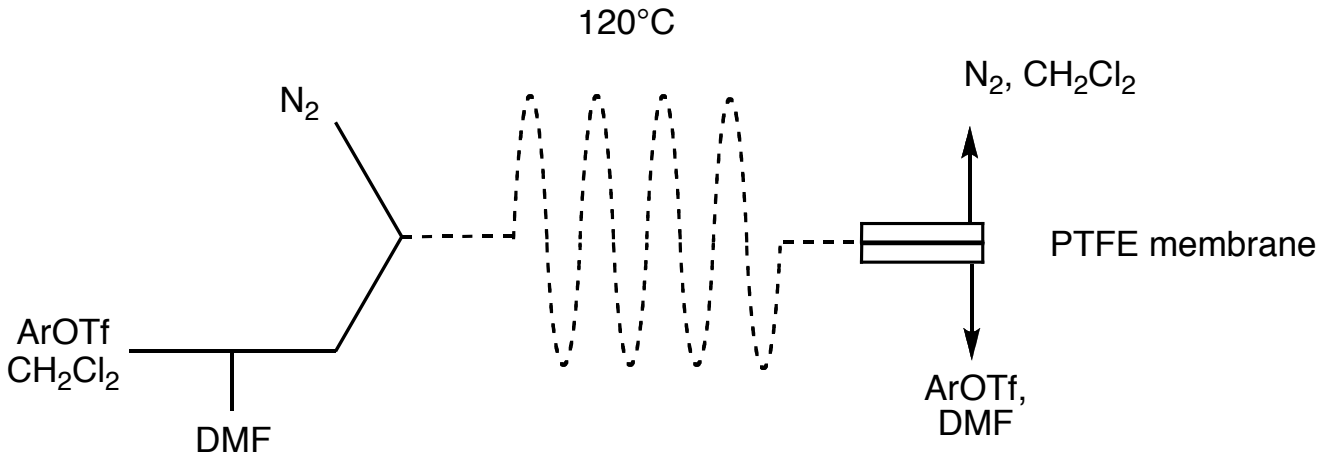
- Triflation followed by HCl/H_2O extraction in segmented flow
  - Two phases effectively separated in flow



Hartman, R.; Naber, J.; Buchwald, S.; Jensen, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903..

In-Line Microdistillation

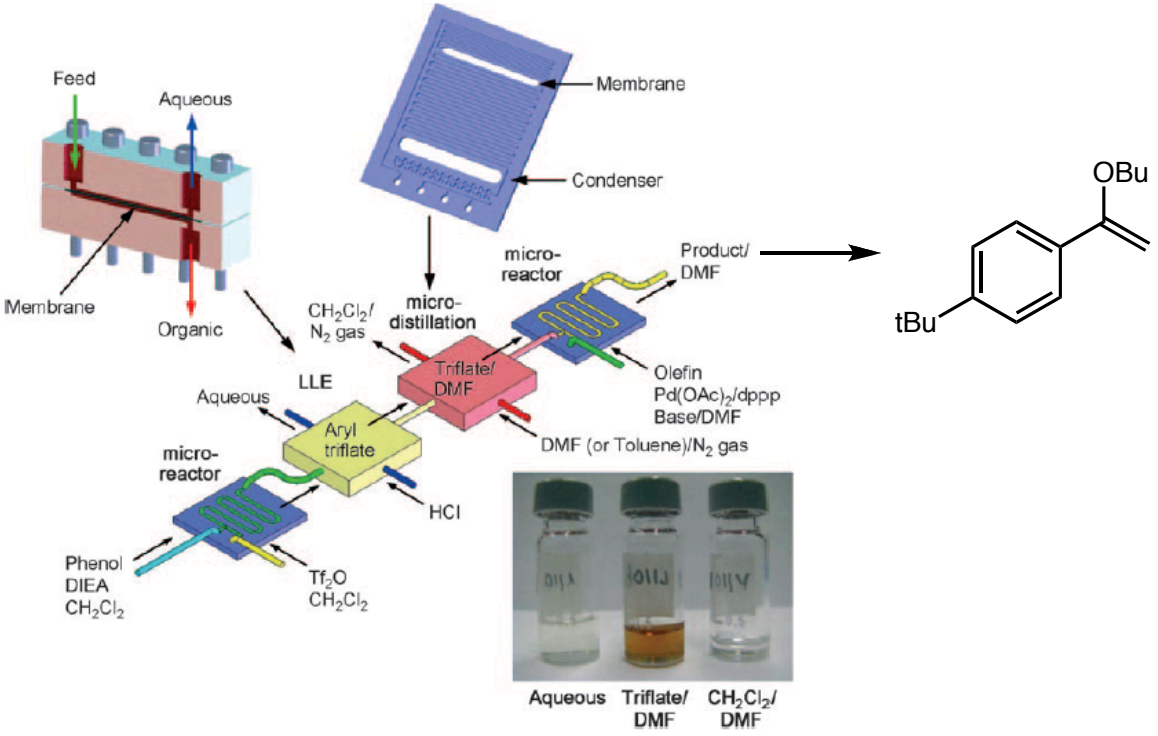
- Dilution with DMF and off distillation of CH_2Cl_2 at elevated temperature
  - Segmentation with N_2 slugs and heating transfers CH_2Cl_2 to vapor phase
  - Separation of vapor and solution phase with semipermeable PTFE membrane



Hartman, R.; Naber, J.; Buchwald, S.; Jensen, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903..

In-Line Microdistillation

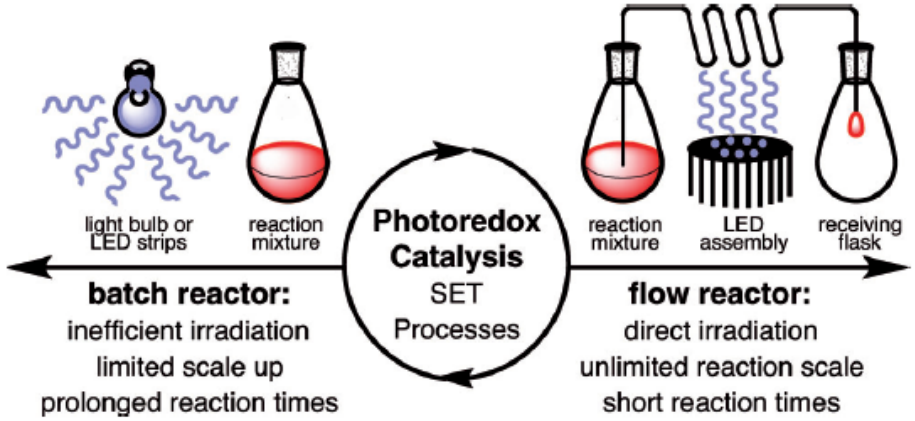
- In line reaction with olefin, $Pd(OAc)_2$/dppp, and base in DMF gives desired product in 69%

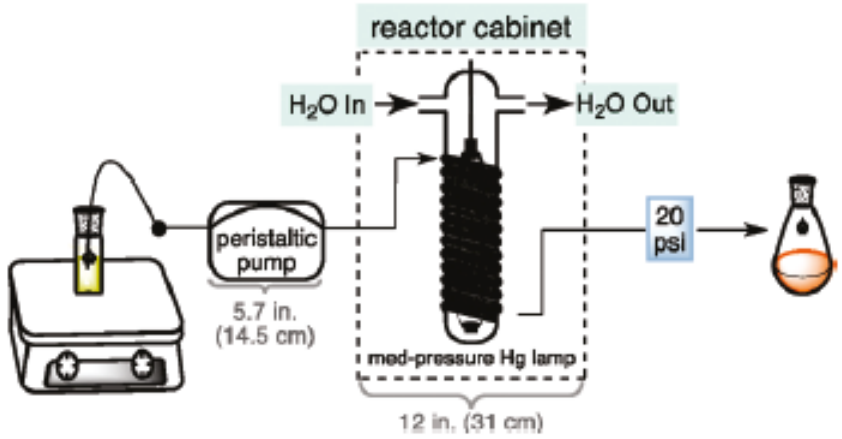


Hartman, R.; Naber, J.; Buchwald, S.; Jensen, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903..

Photochemistry in Flow

- Use of a microreactor with a high surface area increases efficiency of irradiation when penetration depth is short
- Process intensification advantages for large scale
  - Greater energy efficiency when a greater fraction of radiation is absorbed
  - Lower power, space, and thermal dissipation requirements with a smaller photoreactor

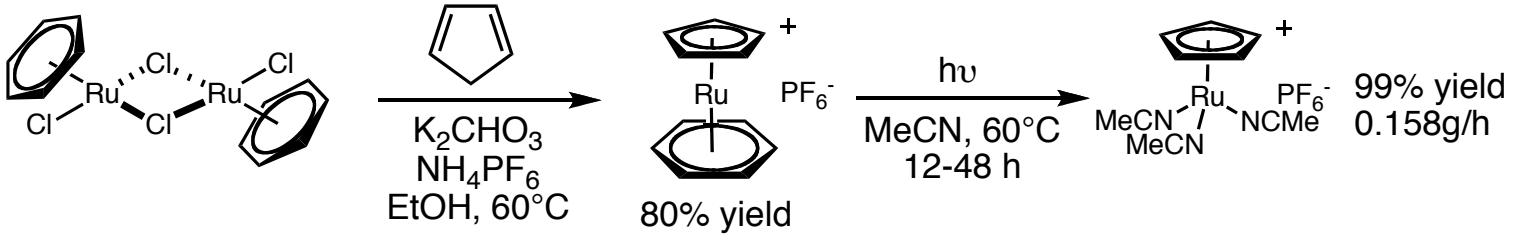


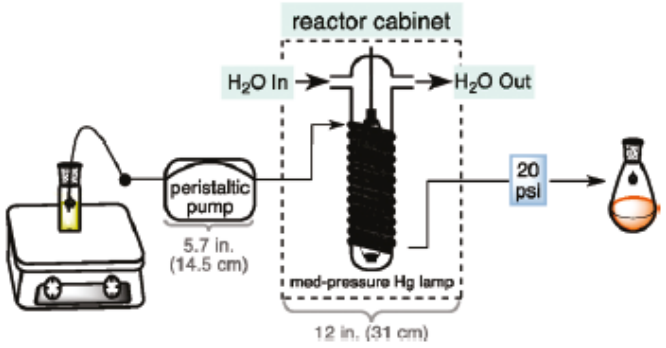


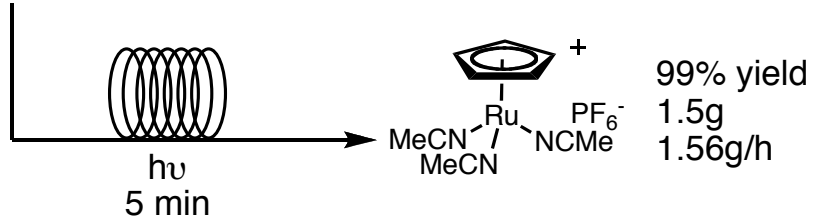
Gutierrez, A.; Jamison, T. *Org. Lett.* **2011**, *13*, 6414-6417.
Tucker, J.; Zhang, Y.; Jamison, T.; Stephenson, C. *Angew. Chem. Int. Ed.* **2012**, *51*, in press.

Photolytic Activation of $CpRu^+$

- $CpRu(MeCN)_3(PF_6)$ is a highly labile Lewis-acidic catalyst
- Generated in batch by photodissociation of a benzene ligand
- More efficient irradiation in flow increases flux of photolysis



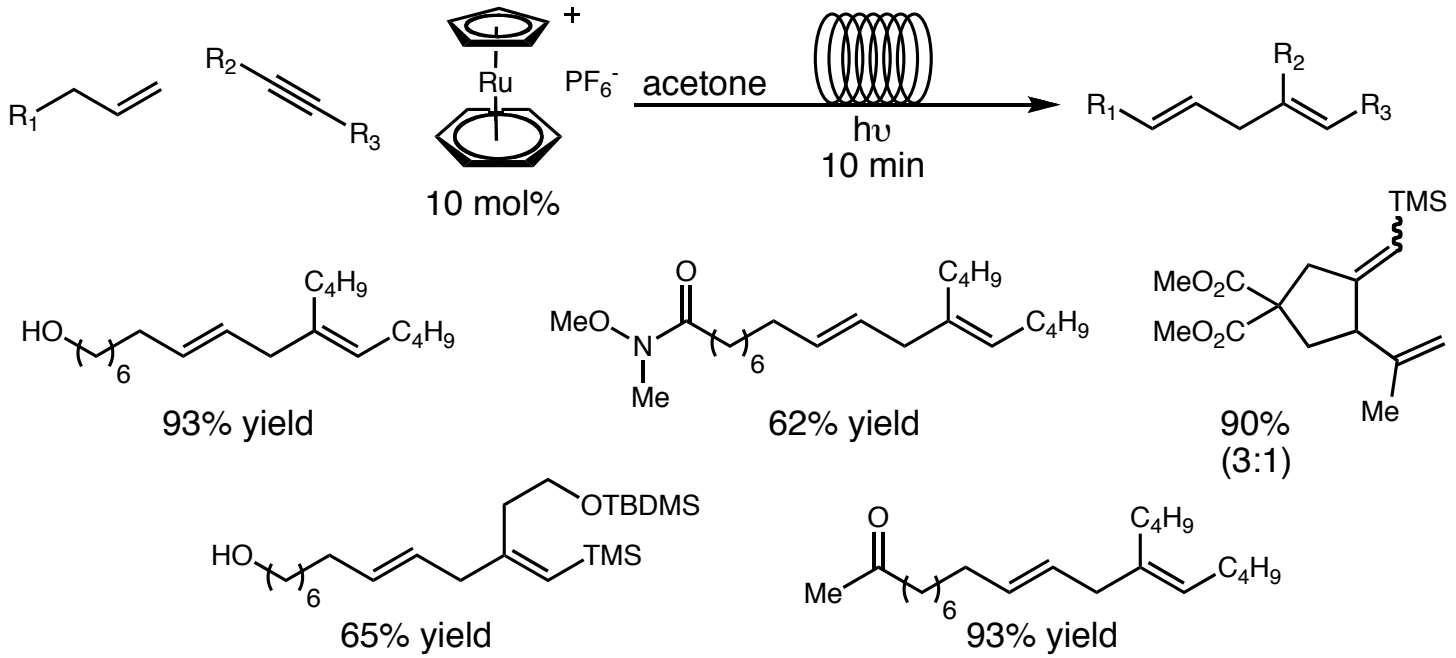




Gutierrez, A.; Jamison, T. *J. Flow. Chem.* **2011**, *1*, 24-27.

Ru-Catalyzed Ene Reaction in Flow

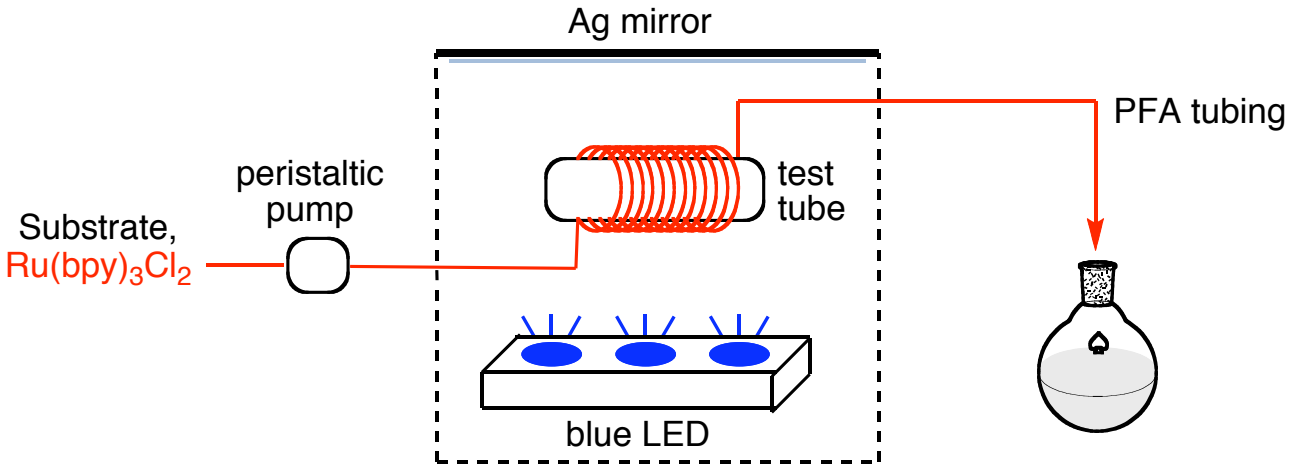
- Photolytic activation of CpRu+ catalyst
- In situ catalytic ene reaction to generate complex dienes



Gutierrez, A.; Jamison, T. *Org. Lett.* **2011**, *13*, 6414-6417.

Photoredox Catalysis in Flow

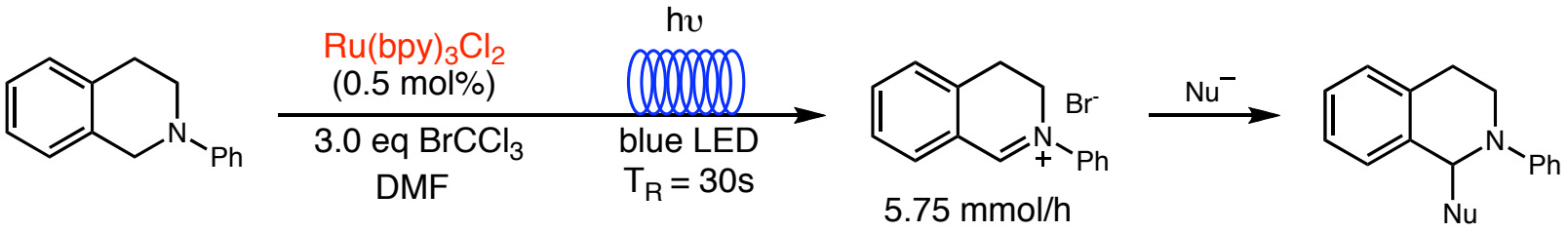
- $Ru(bpy)_3Cl_2$ has a high molar extinction coefficient (13000 $M^{-1}cm^{-1}$) at the wavelength being used (blue LED)
  - At 1 mM concentration 99% of radiation is absorbed in 1.5 mm
- Commercially available perfluoroalkoxy alkane (PFA) tubing
  - Inner diameter of 0.762 mm
  - 90% of incident radiation absorbed

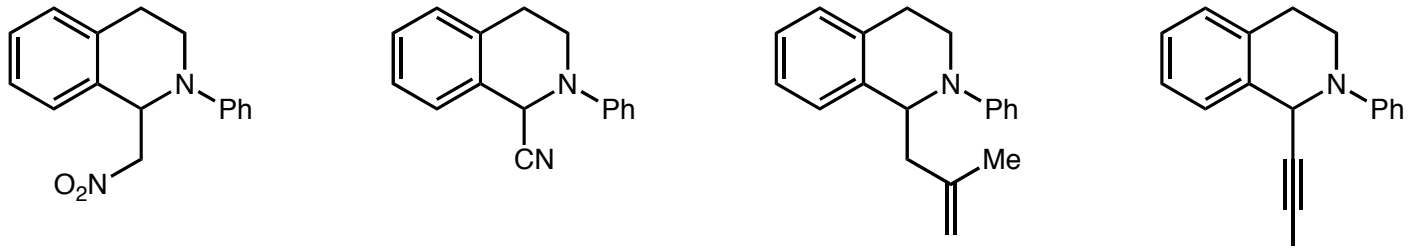


Tucker, J.; Zhang, Y.; Jamison, T.; Stephenson, C. *Angew. Chem. Int. Ed.* **2012**, *51*, in press.

Photoredox Catalysis in Flow

- Benzyl iminium ions generated in flow and trapped offline with nucleophile
- Excess of nucleophiles can be generated under conditions not compatible with photoredox reaction

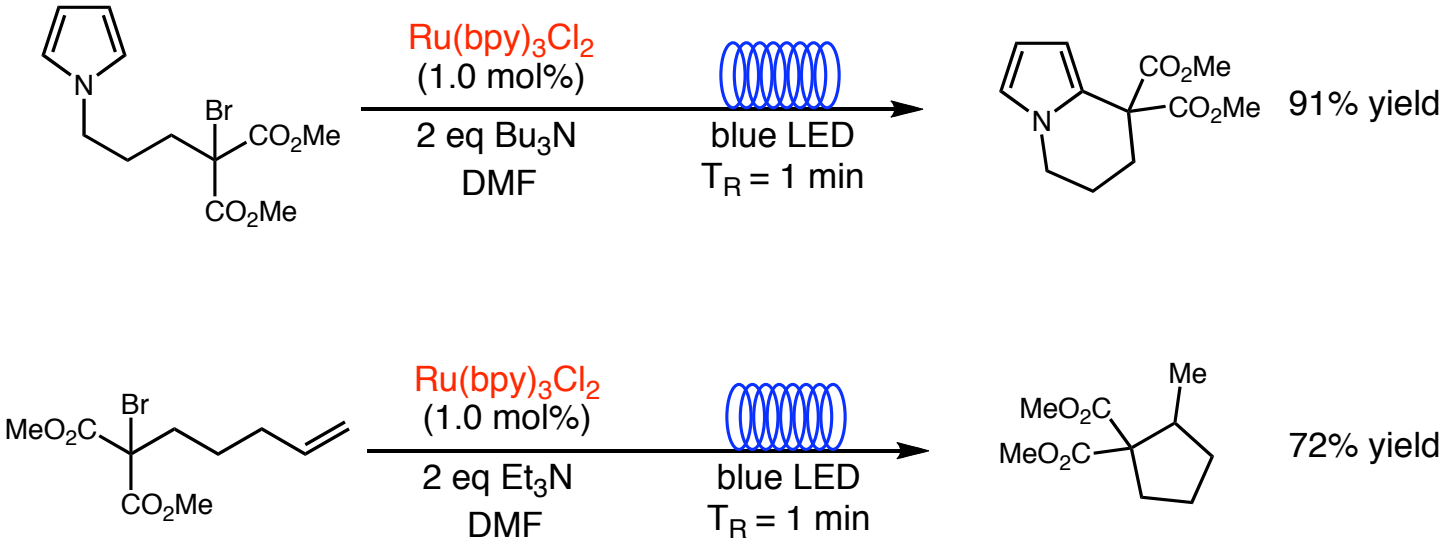




Tucker, J.; Zhang, Y.; Jamison, T.; Stephenson, C. *Angew. Chem. Int. Ed.* **2012**, *51*, in press.

Photoredox Catalysis in Flow

- Efficient source of malonyl radicals



Tucker, J.; Zhang, Y.; Jamison, T.; Stephenson, C. *Angew. Chem. Int. Ed.* **2012**, *51*, in press.