FLUOROUS
Technologies Incorporated

2006 ACS Technical Achievements in Organic Chemistry (TAOC) Award Presentation

Sept. 13, 2006, San Francisco

High-Throughput Organic Synthesis Using Fluorous Technology

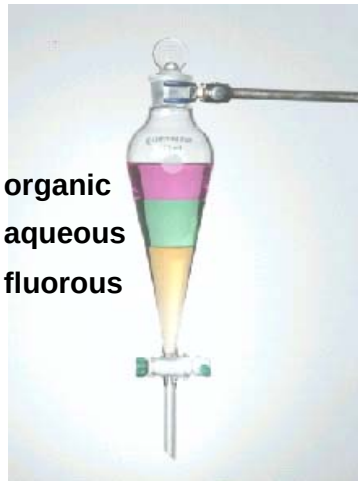
Yimin Lu, Tadamichi Nagashima, Wei Zhang

Presentation Outline

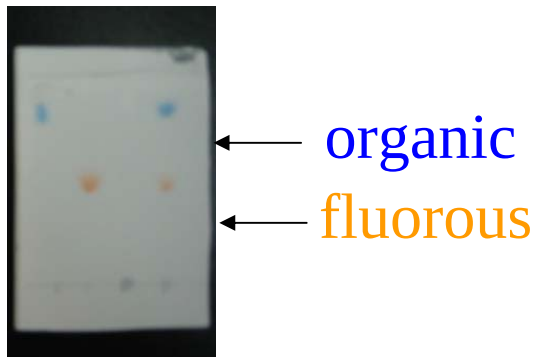
- Fluorous separation techniques
- High-throughput organic synthesis using fluorous technology
  - Fluorous reagents and scavengers
  - Fluorous protecting groups (tags)
  - Fluorous-enhanced Multi-component reaction (MCR)
- Summary

What is Fluorous Chemistry?

- **Fluorous phase is a third phase orthogonal to organic and aqueous phases**



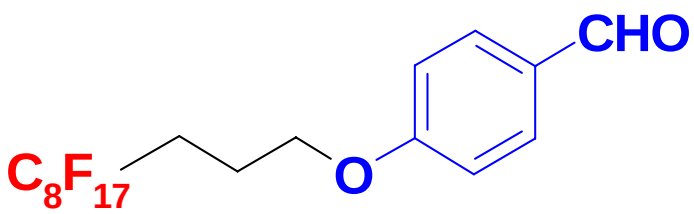
- **Fluorous molecules can be separated from other molecules based on fluorophilicity**



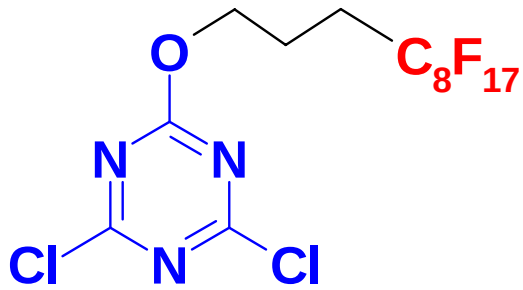
- **Fluorous solid-phase extraction (F-SPE) : a light fluorous technology**

What are Fluorous Molecules?

Fluorous Molecule = **Organic Functional Group** — **Spacer** — **Fluorous Tag**



F-PMB aldehyde
(Amine protecting group)

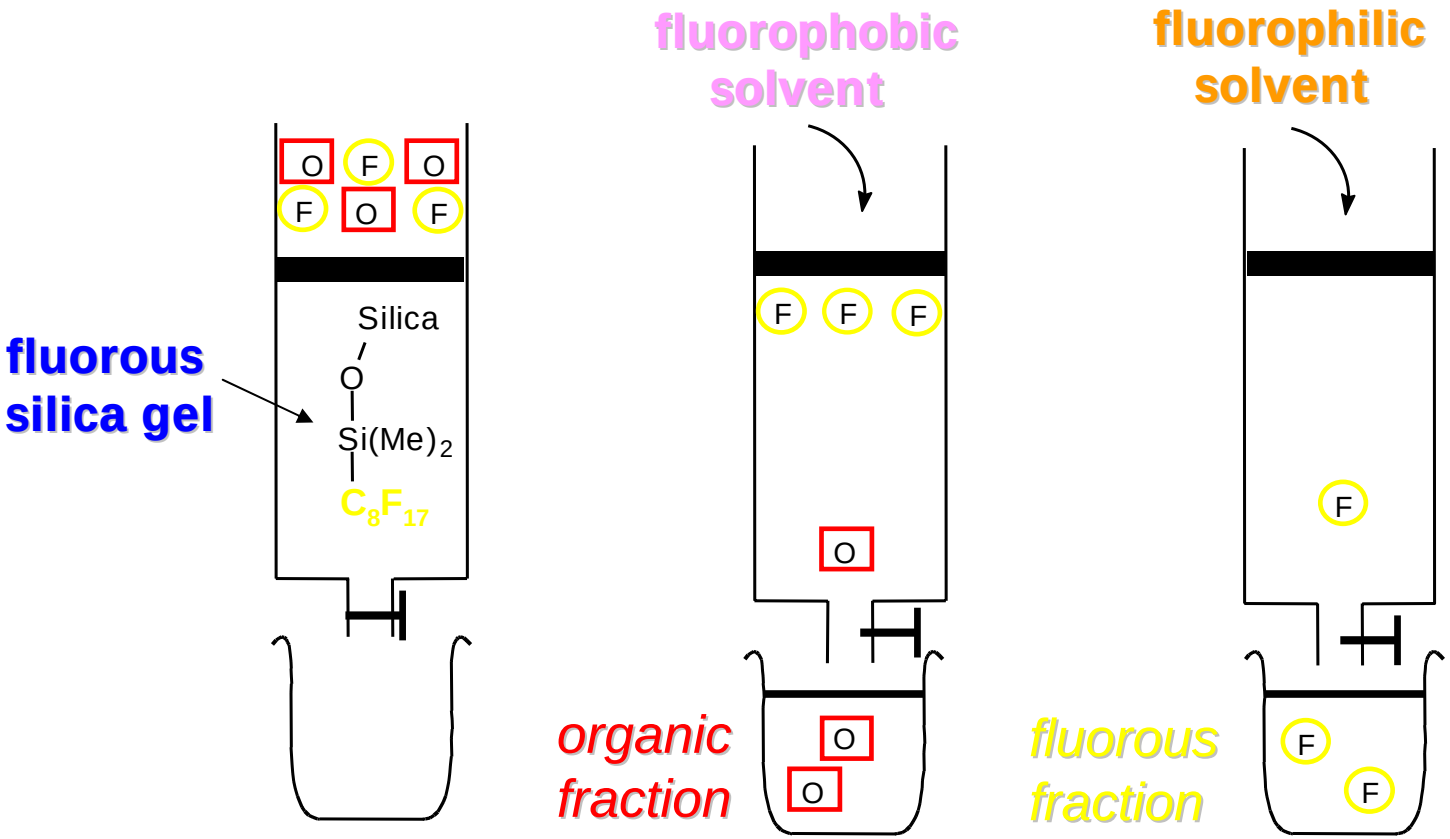


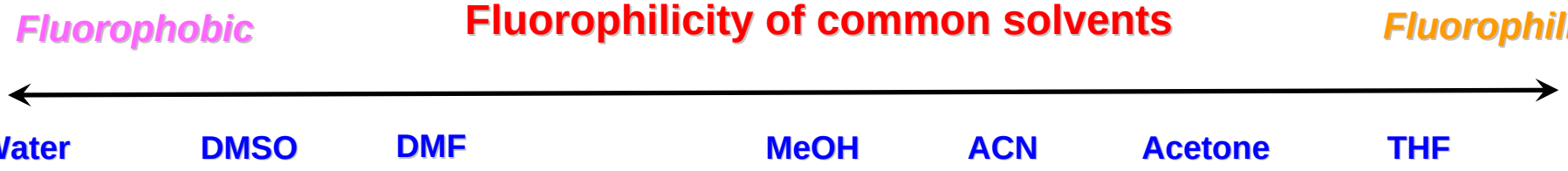
F-DCT
(Amide coupling reagent)

Organic group controls reactivity

Fluorous tag controls separation

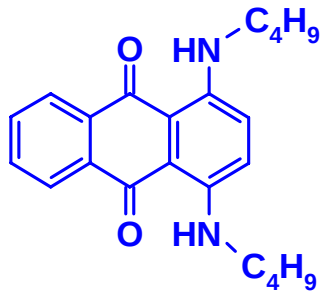
Fluorous Solid-Phase Extraction (F-SPE)



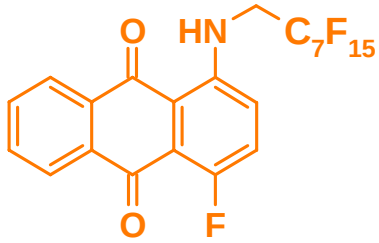


Zhang, W.; Curran, D. P. *Tetrahedron* 2006, *62*, 11837.

Fluorous SPE Demo



organic dye (blue)



fluorous dye (orange)

Left tube: during **fluorophobic** wash (80:20 MeOH:H_2O)

Center tube: end of **fluorophobic** wash

Right tube: end of **fluorophilic** wash (100% MeOH)

Zhang, W. *Tetrahedron*, 2003, *59*, 4475.

Plate-to-Plate F-SPE

- **High-throughput parallel purification**
- **24-, 48-, or 96-channel on standard plate footprint**
- **Plate reusable.**

24-Channel Plates

- **Up to 4 g F-silica gel**
- **40-60 μm silica gel**
- **Up to 300 mg sample purification**
- **Vacuum SPE**

96-Well Plate

- **Up to 1 g of F-silica gel**
- **125-210 μm silica gel**
- **Up to 100 mg sample purification**
- **Gravity SPE**

Zhang, W.; Lu, Y.; Nagashima, T. *J. Comb. Chem.* 2005, *7*, 893.

Automated F-SPE by RapidTrace™

Caliper Life Sciences (formerly Zymark Corp)

Single unit (10 Cartridges)
Single unit (10 Cartridges)

10 units parallel (10x10 cartridges)
10 units parallel (10x10 cartridges)

- **Automatic sample loading, cartridge conditioning, elution and rinsing**
- **Pump-controlled solvent delivery with choices of 8 solvents**
- **10 Cartridges sequential, up to 10 modules parallel**
- **Up to 200 mg sample purification**

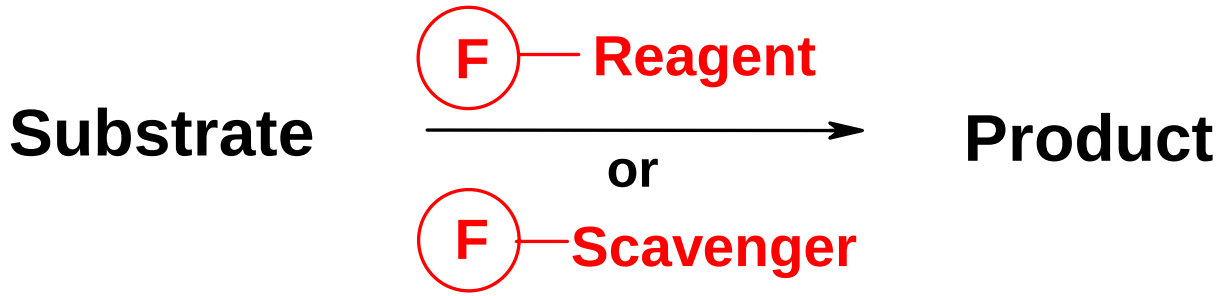
Zhang, W.; Lu, Y. *J. Comb. Chem.* 2006, *8*, 890.

Why use fluorous?

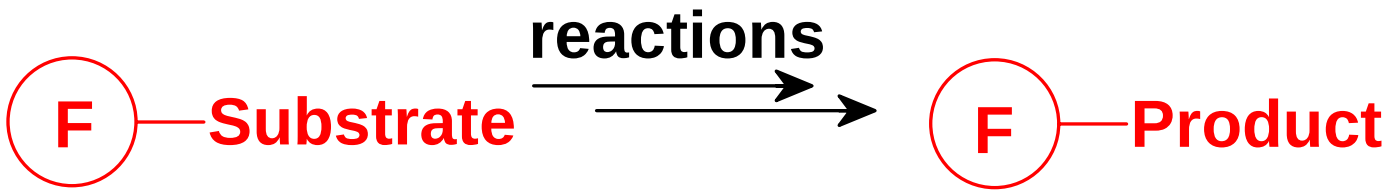
Feature	Benefit
High Chemical Compatibility	Greater chemical diversity Greater synthetic flexibility Readily scaled
Technological Compatibility	Drop-in technology Automation-friendly
High Predictability	Minimal reaction development Minimal purification development
Complete Solution Phase Chemistry	Solution kinetics Reaction monitoring Intermediate purification
Flexibility	SPE, LLE, flash chromatography, HPLC, recrystallization, distillation

Fluorous Synthesis

Fluorous Reagents, Catalysts and Scavengers



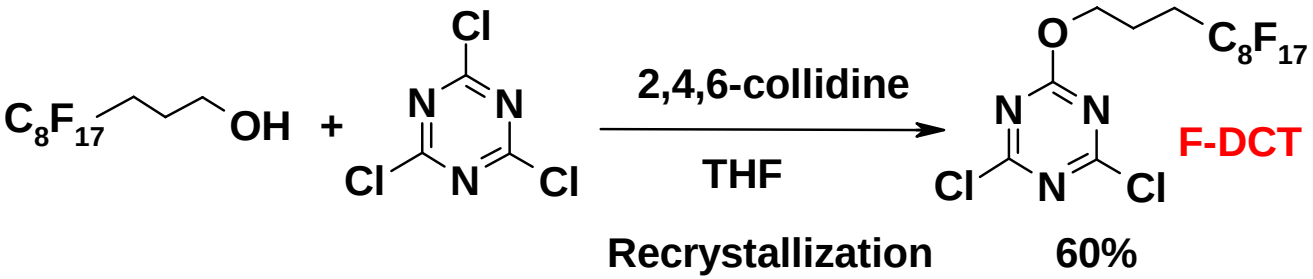
Fluorous Protecting Groups/Tags



Zhang, W. *Chem. Rev.* 2004, *104*, 2531.

Fluorous Dichlorotriazine (F-DCT)

Synthesis of F-DCT



F-DCT as an amide coupling reagent

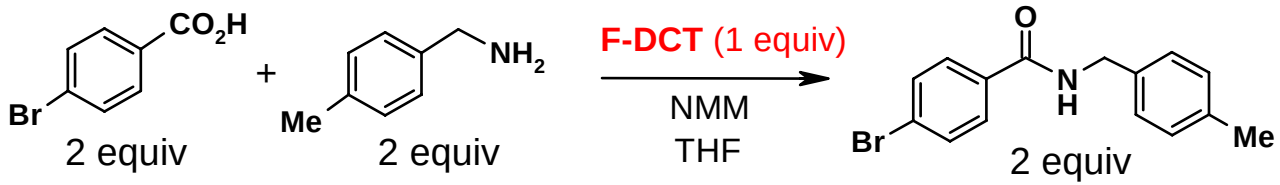
- Activating 2 equivalents of acids
- Good for bulky amines and anilines

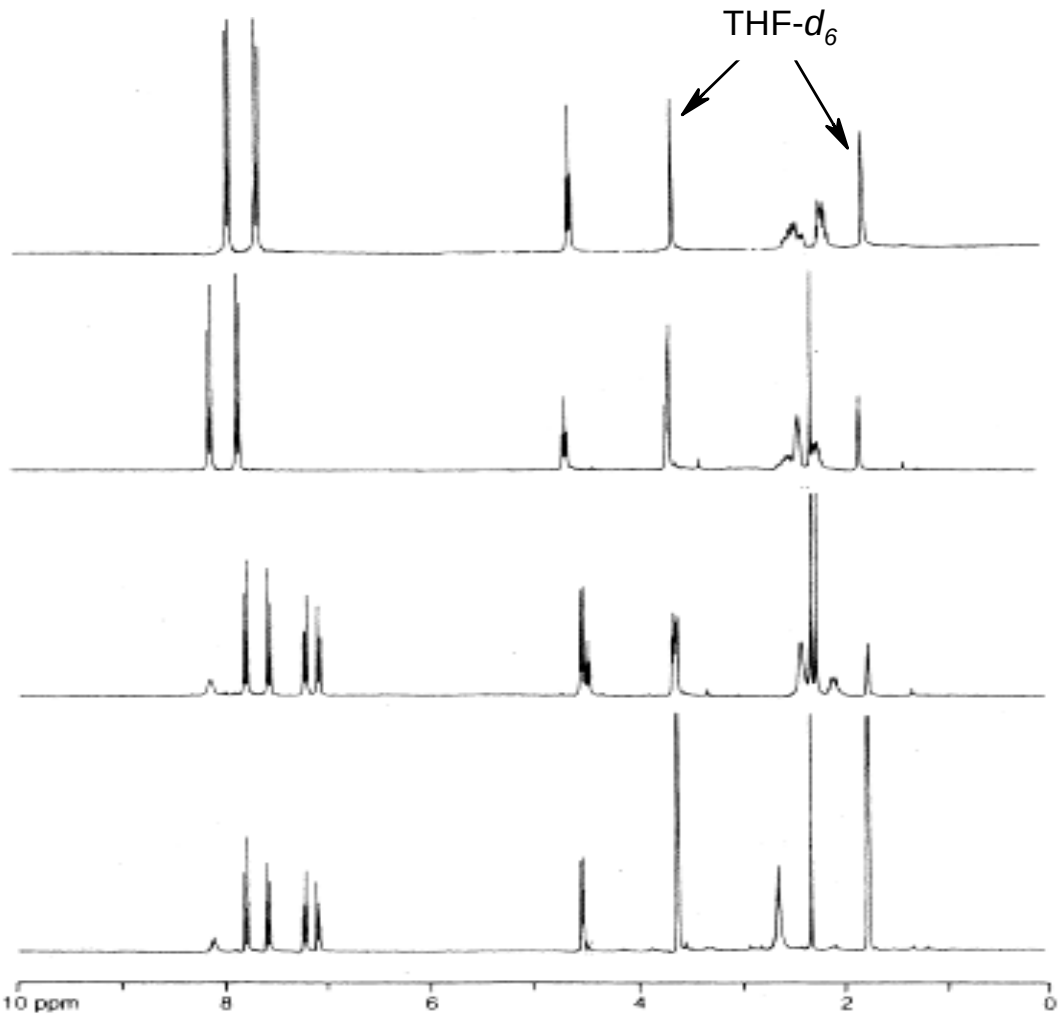
F-DCT as a nucleophile scavenger

- Scavenging up to 2 equivalents of nucleophiles
- Scavenging amines and thiols

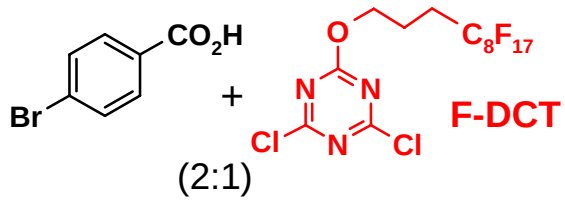
Zhang, W; Lu, Y. *QSAR Comb. Science* 2006, 724 and 728.

Follow the Amide Coupling by ^{1}H NMR



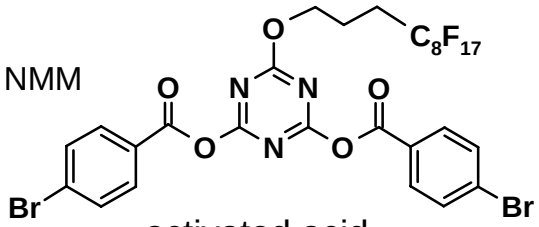


a



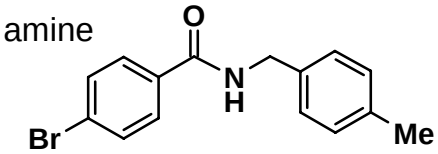
(2:1)

b add NMM



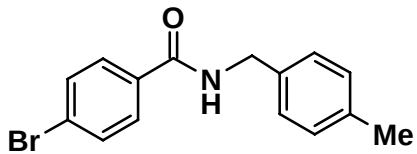
activated acid

c add amine



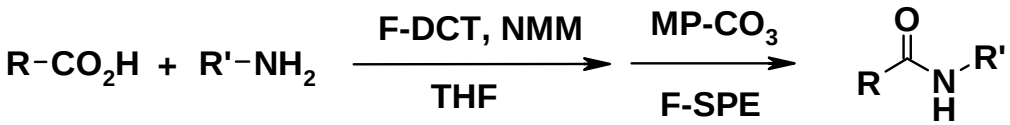
amide product

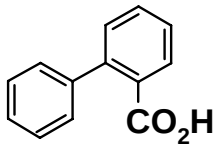
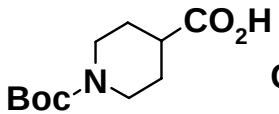
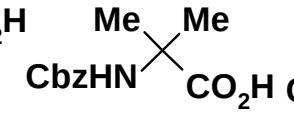
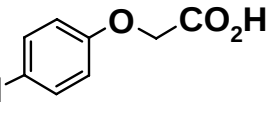
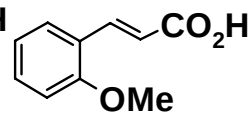
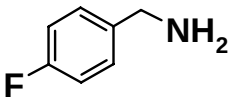
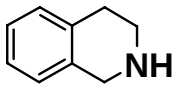
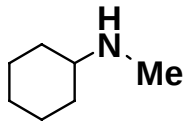
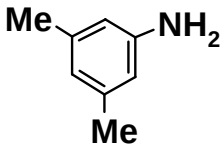
d



after F-SPE

Amide Coupling Promoted by F-DCT



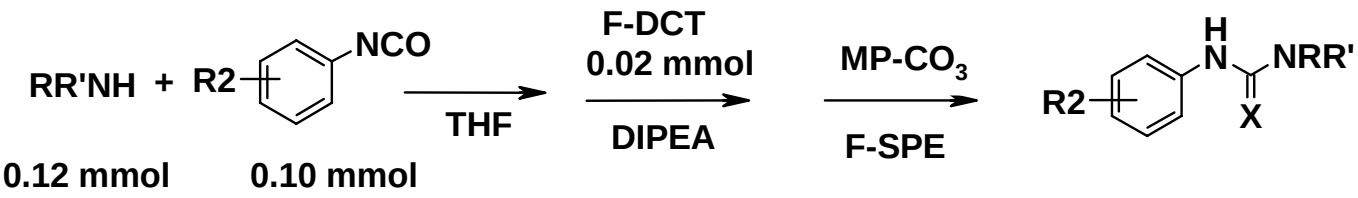
					
	58%(98%)*	56%(96%)	74%(76%)	62%(99%)	79%(91%)
	48%(95%)	62%(95%)	46%(92%)	73%(76%)	79%(94%)
	45%(83%)	56%(79%)	6%(93%)	68%(99%)	89%(91%)
	50%(95%)	55%(99%)	71%(92%)	62%(99%)	75%(98%)

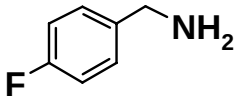
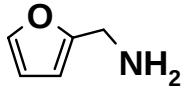
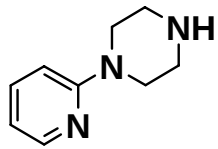
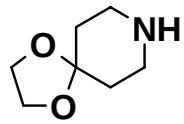
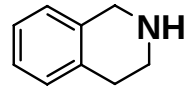
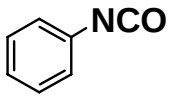
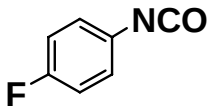
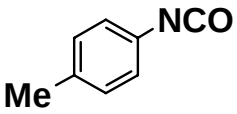
*yield% (purity%), purities were determined by UV210

- 20 Parallel reactions
- Purified by plate-to-plate F-SPE
- MP-CO_3 to free NMM·HCl salt

Zhang, W; Lu, Y. *OSAR Comb. Science* 2006, 25, 724.

F-DCT as an Amine Scavenger



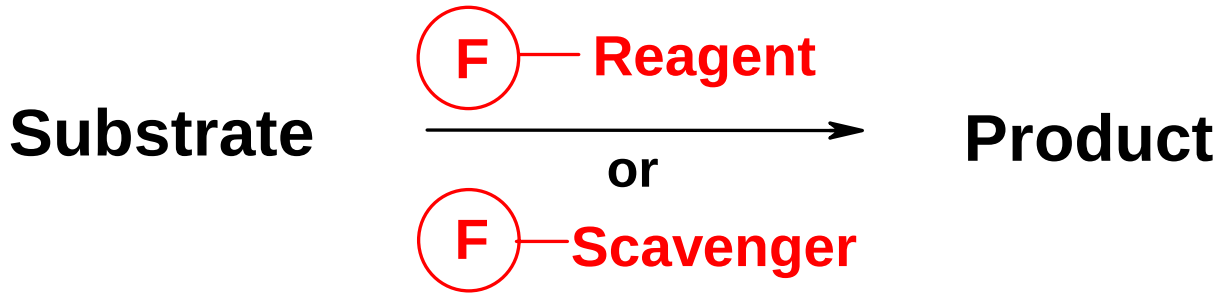
	$BuNH_2$					
	47%(93%)*	63%(94%)	64%(94%)	89%(96%)	92%(90%)	96%(80%)
	67%(96%)	58%(96%)	52%(96%)	63%(95%)	57%(94%)	48%(97%)
	57%(77%)	77%(98%)	87%(90%)	96%(86%)	93%(80%)	79%(87%)

*yield% (purity%), purities were determined by UV254

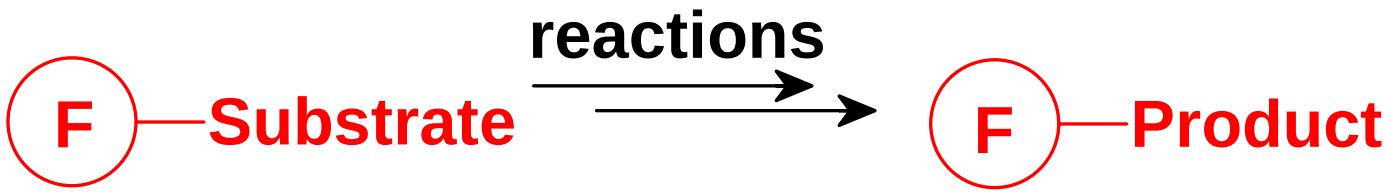
- 18 Parallel reactions
- Purified by RapidTrace automated F-SPE
- MP-CO_3 to free DIPEA·HCl salt

Fluorous Synthesis

Fluorous Reagents, Catalysts and Scavengers

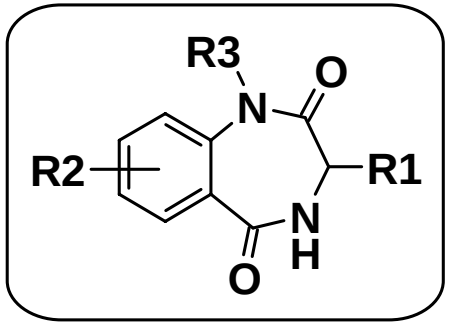


Fluorous Protecting Groups/Tags

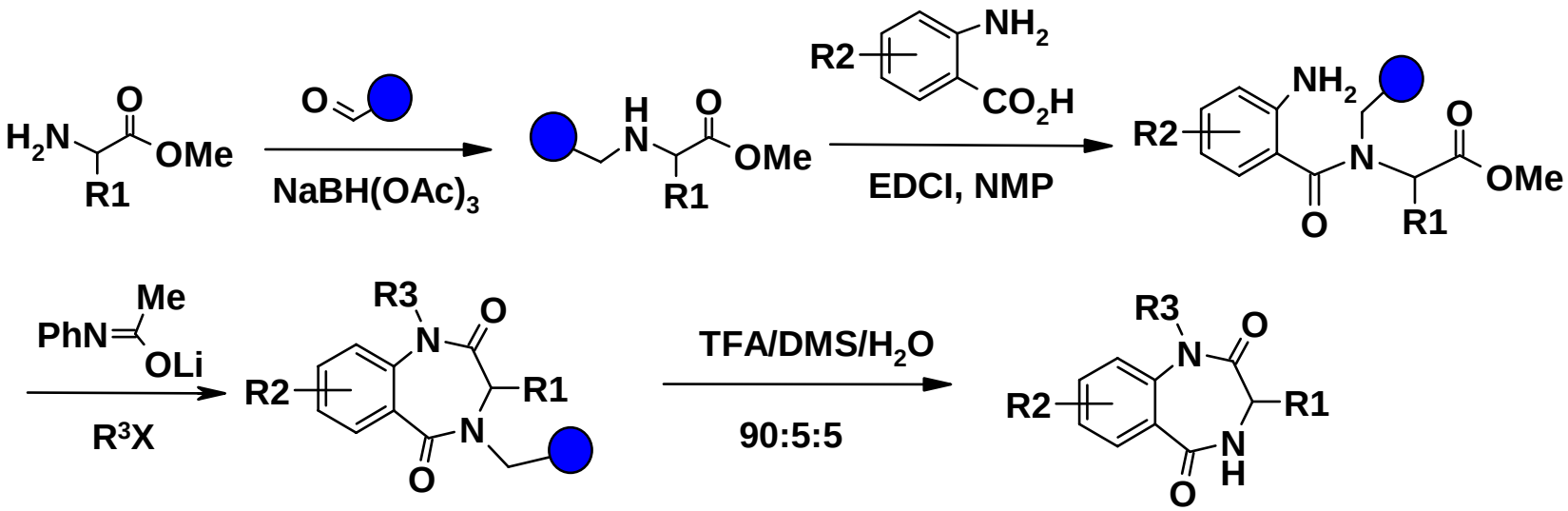


Zhang, W. *Chem. Rev.* 2004, *104*, 2531.

1,4-Benzodiazepine-2,5-dione Library

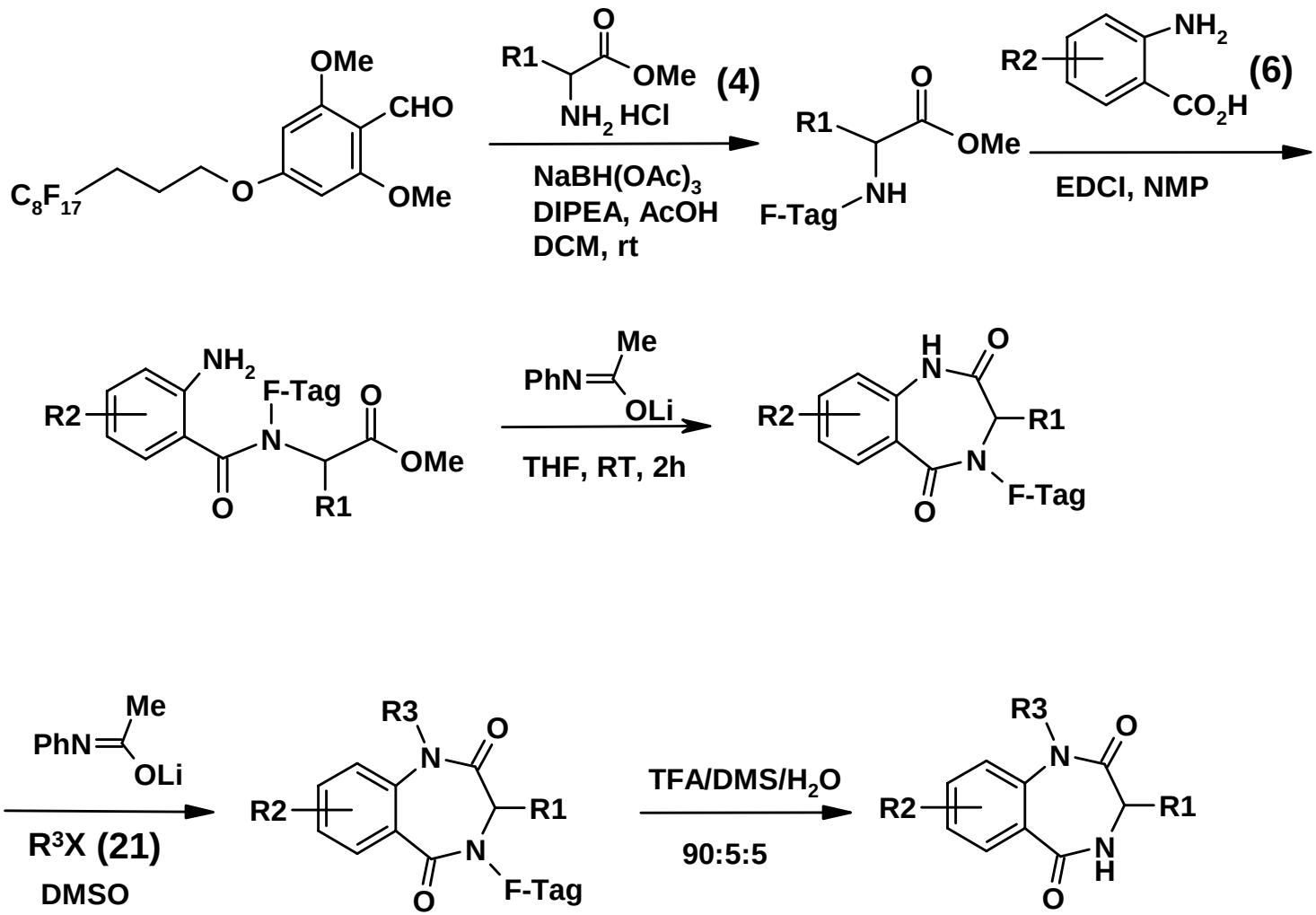


Published Solid-Phase Synthesis

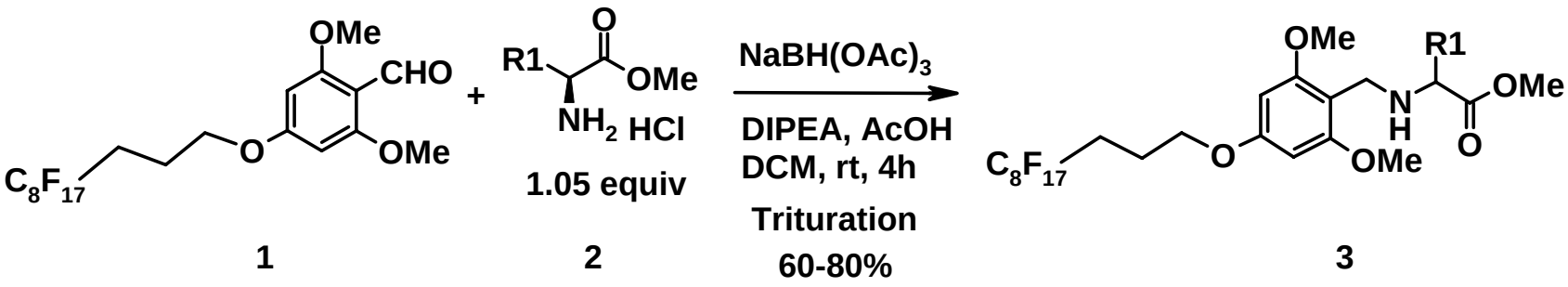


Ellman, J. *et al.* J. Org. Chem. 1997, 62, 1242

Fluorous Approach

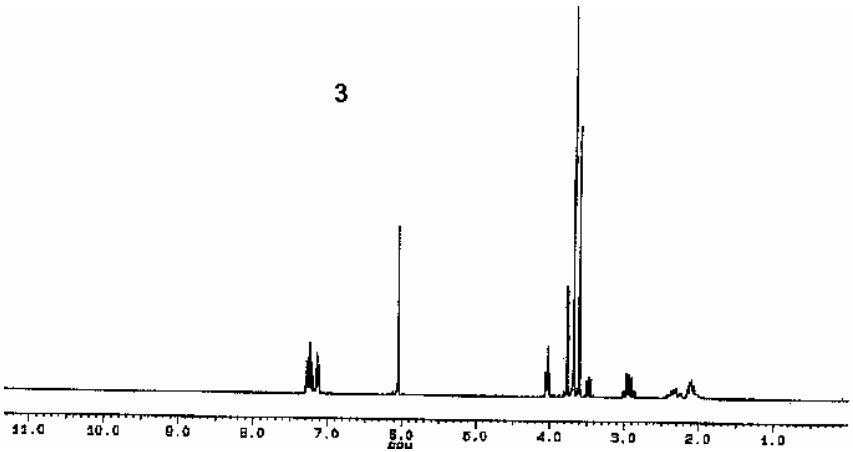


Tagging with Fluorous Benzaldehyde



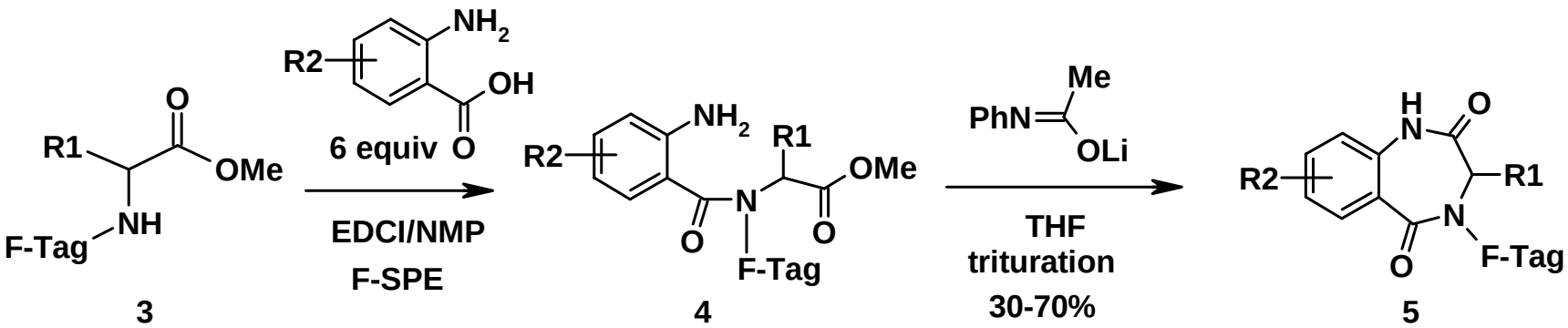
1 2 3

^{1}H NMR of 3

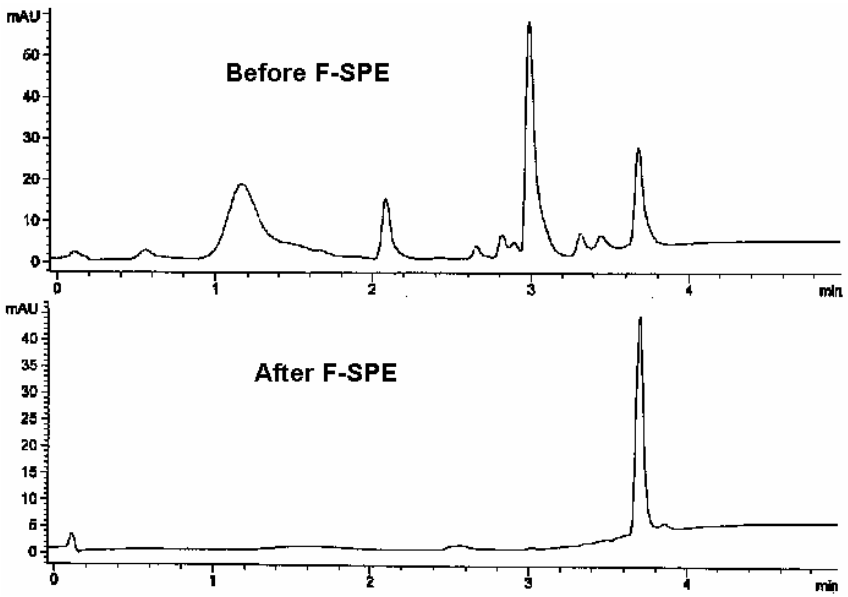


- Tagging by reductive amination
- 4 Reactions at 60 mmol scale
- Reactions monitored by LCMS
- Purified by Si-gel filtration and trituration

Amide Coupling and Cyclization

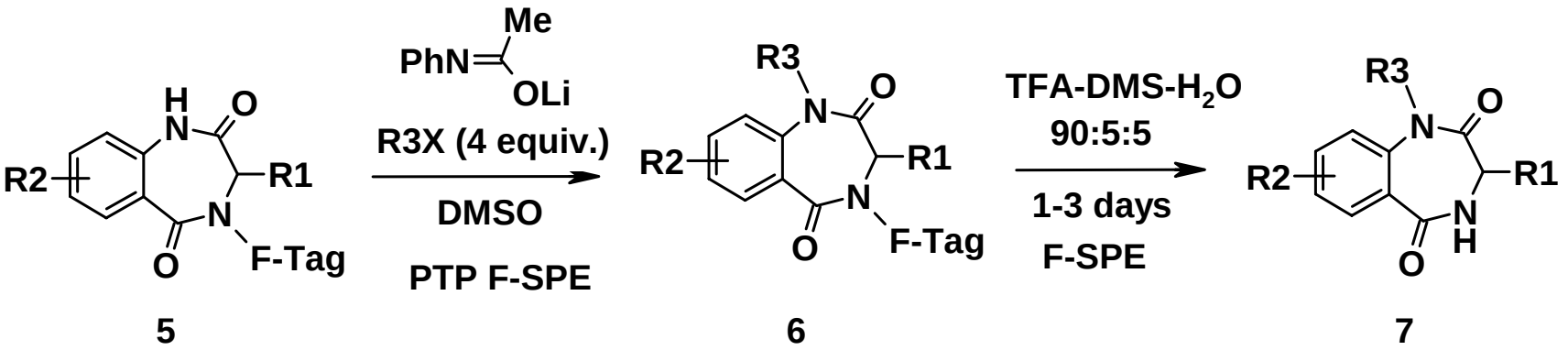


HPLC trace of 4

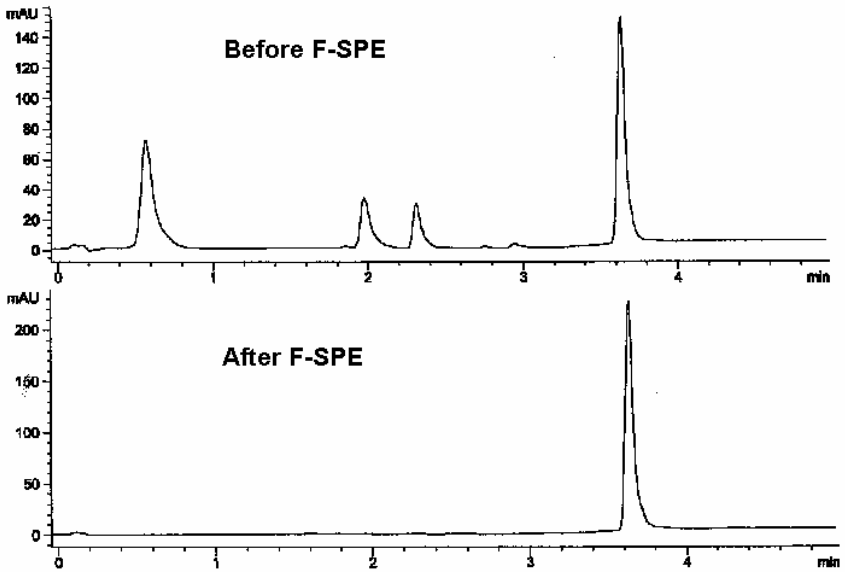


- 24 Amide coupling and cyclization at 6 mmol scale
- Reactions monitored by LCMS
- Compounds 4 purified by F-SPE
- Compounds 5 purified by trituration in MeOH or chromatography

Alkylation and Detagging



HPLC trace of 6



- 504 Alkylation and detagging at 0.1 mmol scale
- Reactions monitored by LCMS
- 96-Well plate-to-plate gravity F-SPE to purify 6
- Parallel F-SPE to purify products 7
- 48 Cartridges for 504 final F-SPEs

Summary of Library Production

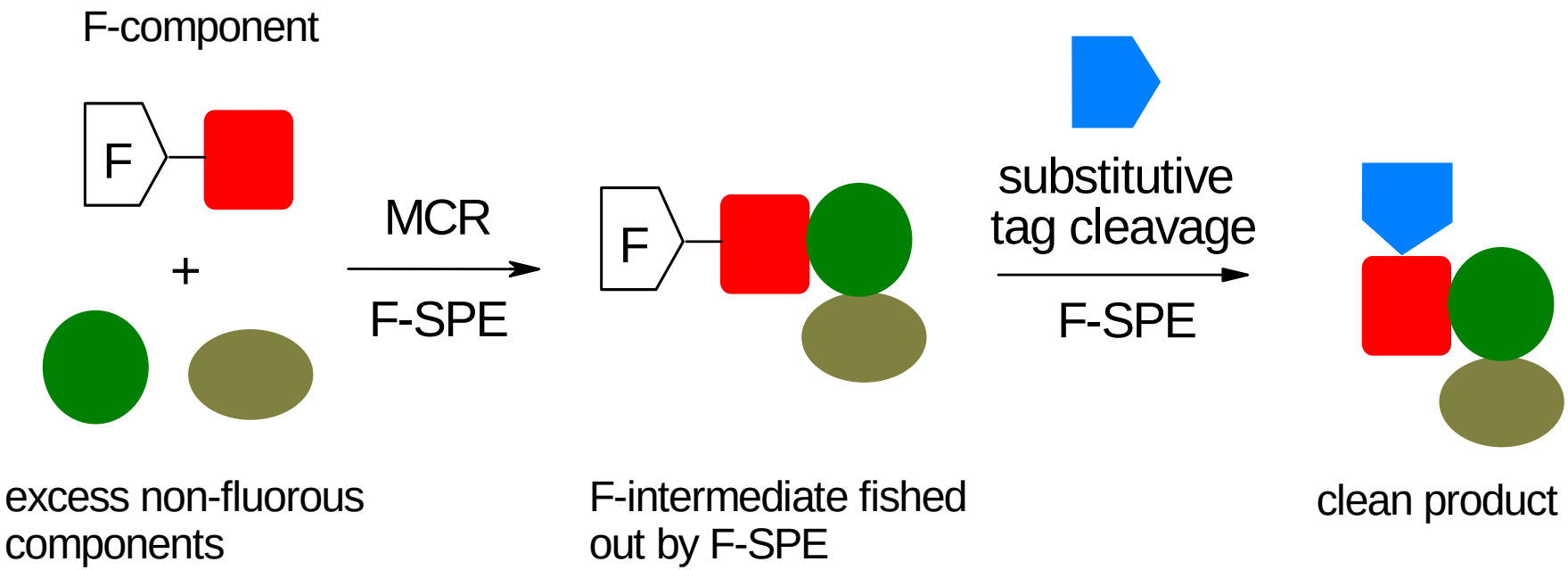
Result of Library Production

AA (R1)	Purification Method	Success Rate*
AA1	F-SPE	82%
AA2	F-SPE	73%
AA3	F-SPE	68%
AA4	F-SPE, HPLC	69%
Total		73%

*>3 mg, >85% purity at UV220, confirmed mass

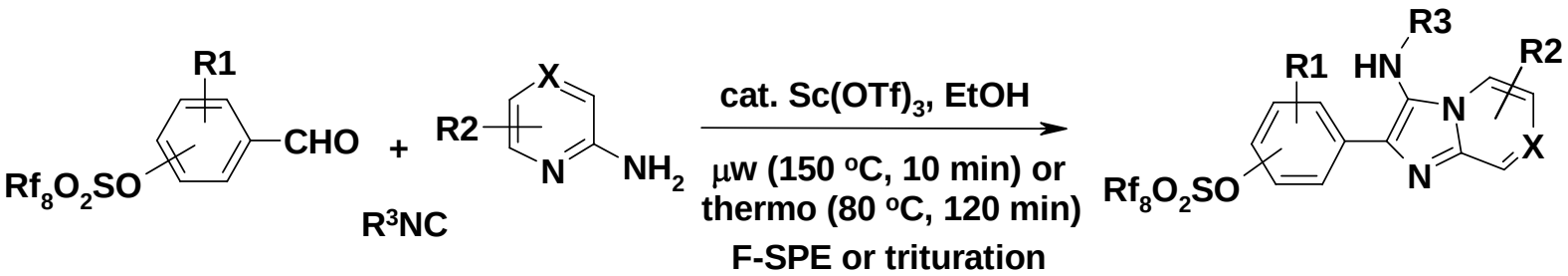
- Adopted SP-chemistry to produce a 504-member library
- Consume less reagents than the reported SP-synthesis
- Monitored reactions by LCMS
- Purified and analyzed intermediates using various methods
- Reaction scales from 0.1 mmol to 60 mmol

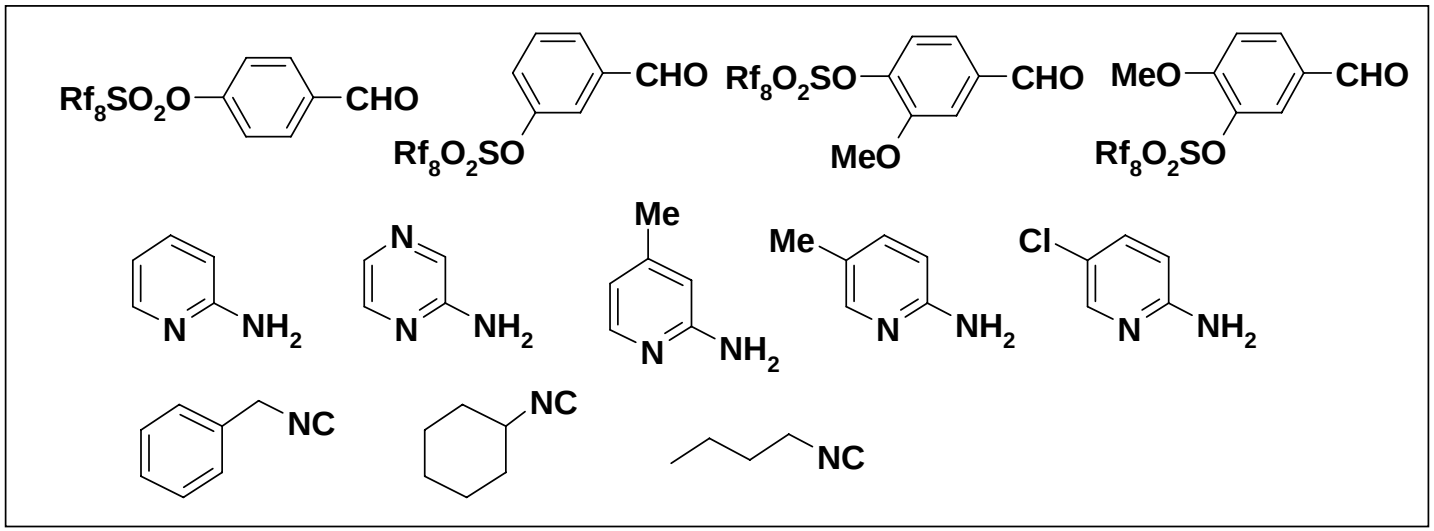
Fluorous-Enhanced Multi-Component Reaction



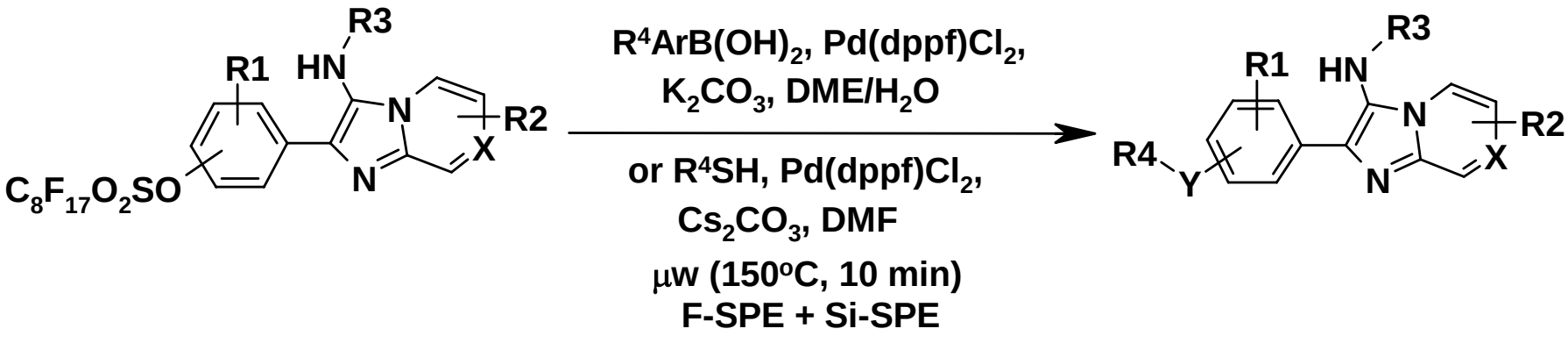
Zhang, W. *Chem. Rev. 2004*, 104, 2531.

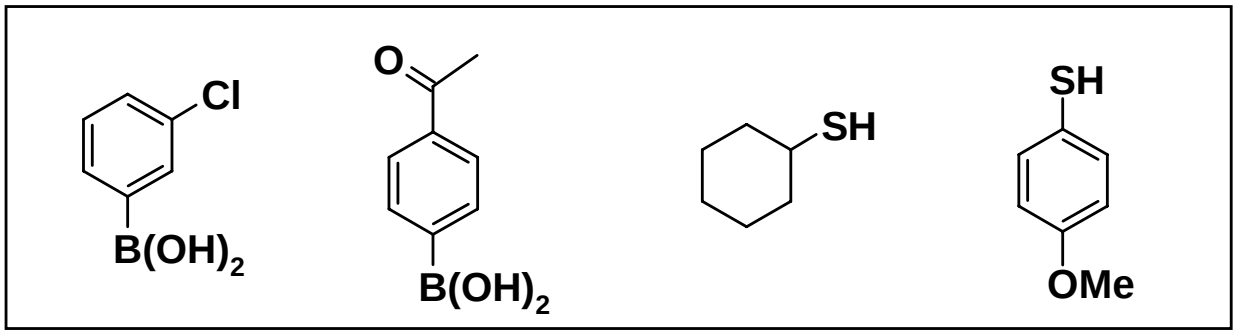
Imidazo[1,2-a]pyridines from Fluorous MCR





Post-MCR Modification and Detagging





Three functions of the fluorous tag:

- OH protecting group
- Phase-tag for intermediate purification
- Activation of phenol for cross-coupling reactions

Lu, Y.; Zhang, W. *QSAR Comb. Sci.* 2004, *23*, 827.

Summary

- Developed plate-to-plate and automated F-SPE for high-throughput purification
- Demonstrated fluorous high-throughput purification with a new fluorous reagent (F-DCT)
- Demonstrated fluorous tagging strategy with a 504-member library synthesis.
- Integrated fluorous technologies with microwave reactions and multi-component reactions in library production

Fluorous technology provides valuable tools for high-throughput organic synthesis

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