FLUOROUS
Technologies Incorporated

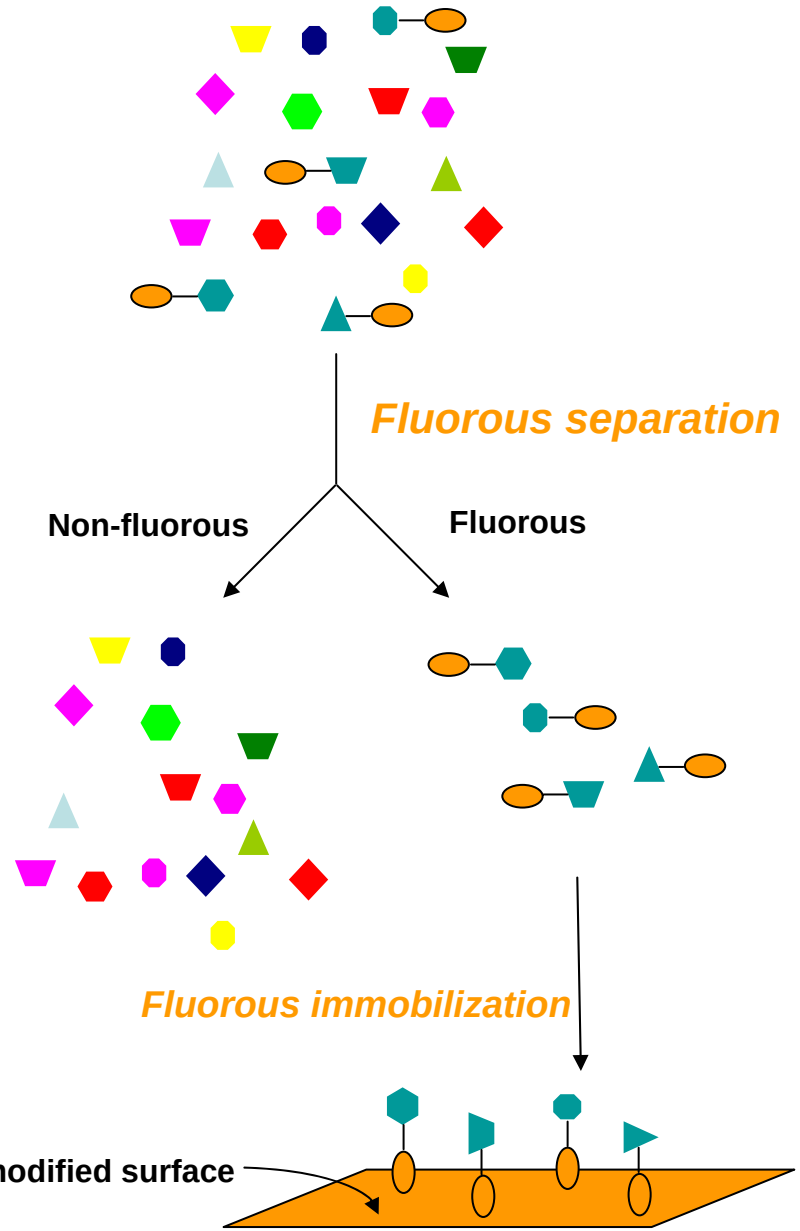
Fluorous Techniques in Small Molecule Synthesis

Presentation Outline

- Fluorous separation techniques
  - Solid-phase extraction (SPE)
  - Flash chromatography
  - Chromatography (HPLC)
- Combinatorial synthesis
  - Microwave reactions
  - Multicomponent reactions (MCR)
  - Parallel synthesis
  - Diversity-oriented synthesis (DOS)
  - Fluorous Mixture synthesis (FMS)

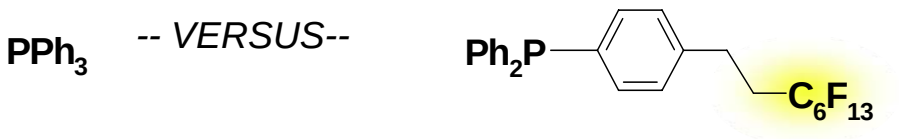
What is Fluorous Technology?

- Fluorous chemistry is a novel tagging technology that separates desired molecules from complex mixtures.
- Molecules can be rendered fluorous by the attachment of perfluorocarbon domains.
- Fluorous tagged molecules can be separated from non-fluorous molecules exploiting fluorophilicity.
- Fluorous techniques are marked by high selectivity, low reactivity, and exceptional breadth



Examples of Fluorous Molecules

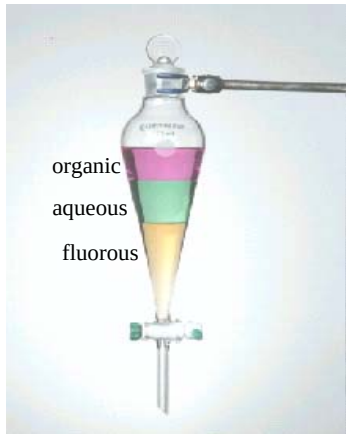
Compounds with permanent fluorinated domains (e.g. reagents):



Compounds with temporary fluorous tags (e.g. substrates):

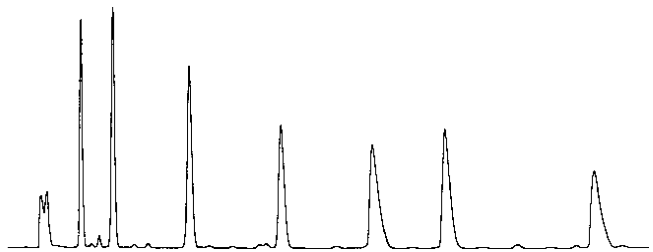
Fluorous Separation Methods

- **Liquid-Liquid Extraction**
  - "Heavy" fluorous technique
  - Generally requires large F content, ~60%



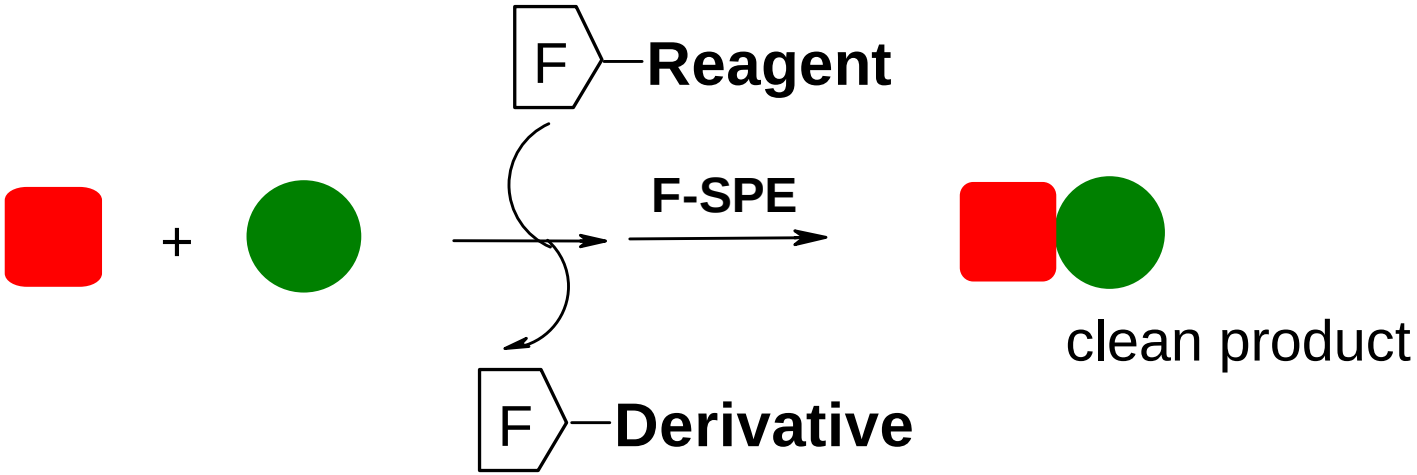
- **Fluorous Solid Phase Extraction (F-SPE)**
  - "Light" fluorous technique
  - Separates fluorous from non-fluorous
  - No fluorous solvents used

- **Fluorous Chromatography (F-HPLC)**
  - Separates fluorous from fluorous
  - More fluorous = Greater retention

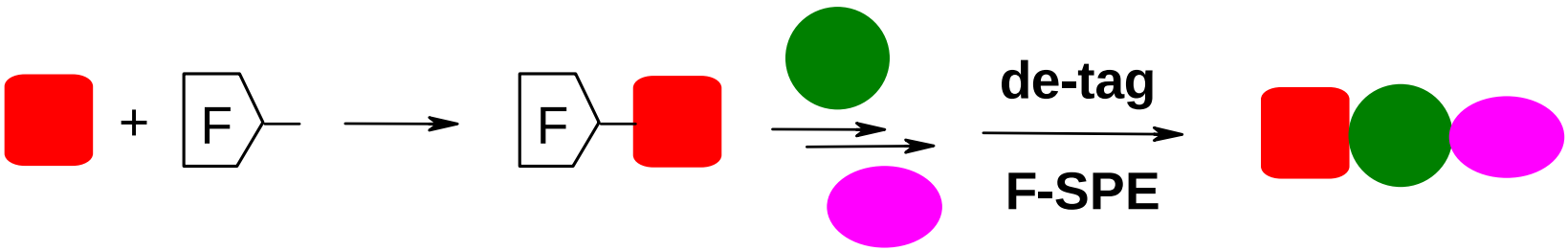


Fluorous Tagging Strategies

- *Tagging reagents/scavengers/catalysts*



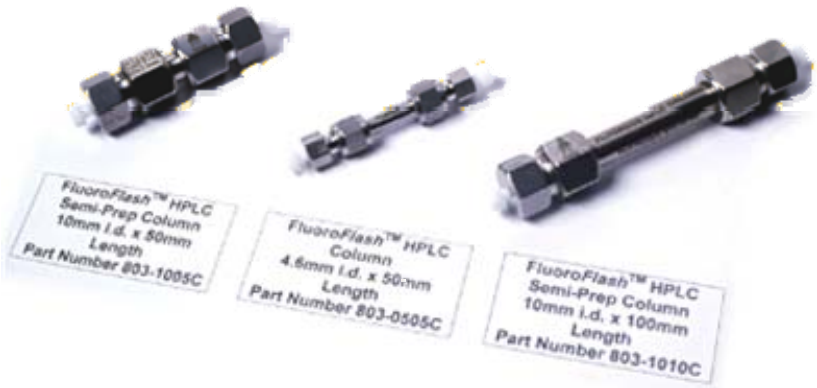
- *Tagging substrates for parallel and mixture syntheses*



Fluorous Sorbent for Separation

SPE Cartridges

Flash Columns and Samplets

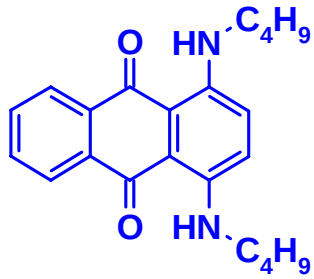


HPLC Columns

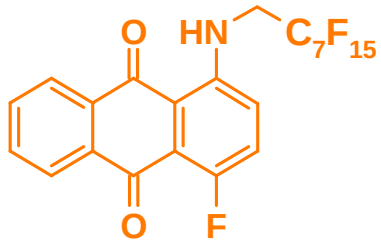
TLC Plates

Bulk Silica

Fluorous SPE



organic dye (blue)



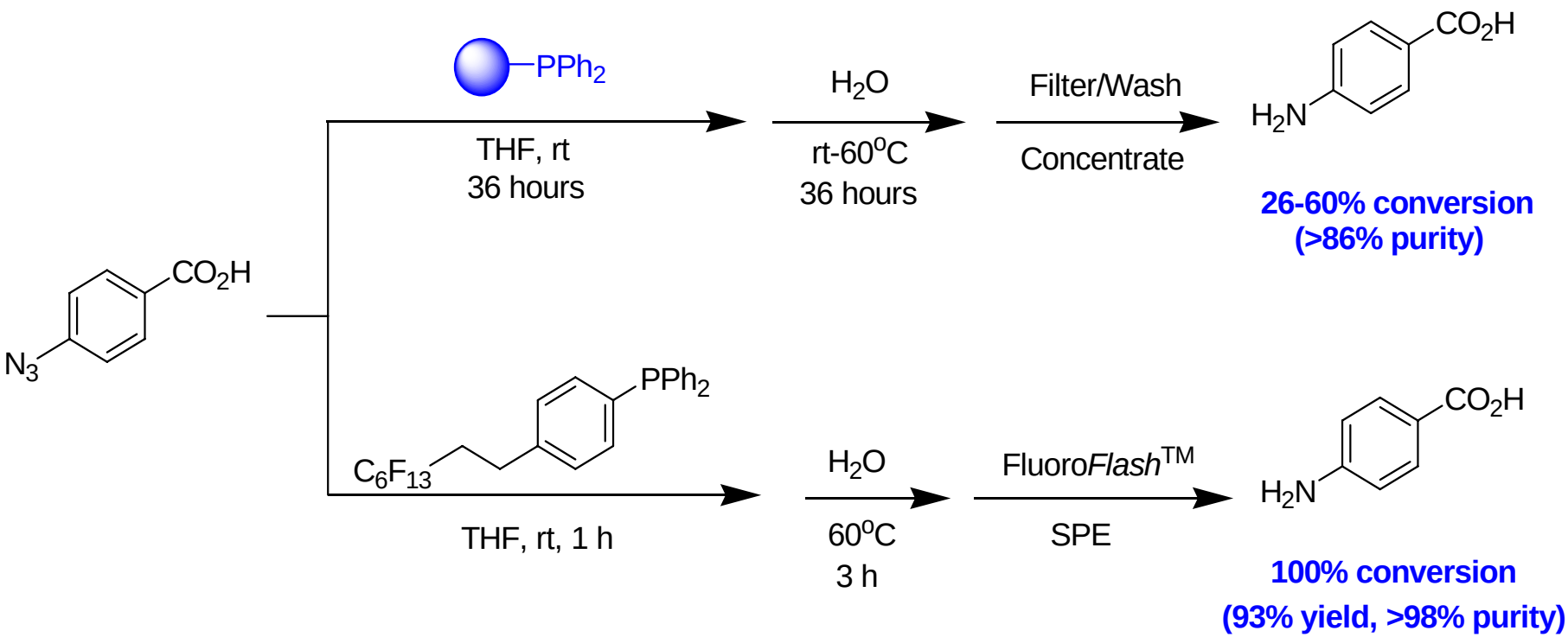
fluorous dye (orange)

Left tube: beginning of fluorophobic wash (80:20 MeOH:H2O)
Center tube: end of fluorophobic wash
Right tube: end of fluorophilic wash (100% MeOH)

Fluorophobic **Typical Solvents for F-SPE** ***Fluorophilic***

Water DMF DMSO MeOH ACN Acetone Toluene THF

Fluorous/Resin-PPh_3 Comparison



Lindsley, C. *et al*, *Tetrahedron Lett*. **2002,** *43*, 4467)

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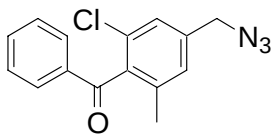
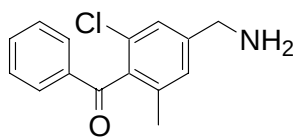
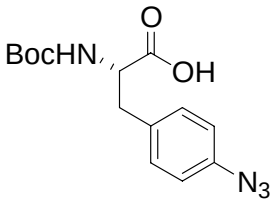
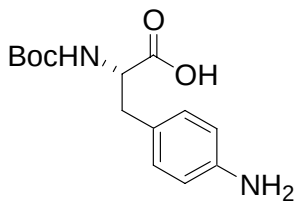
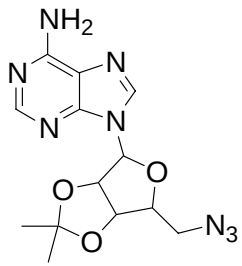
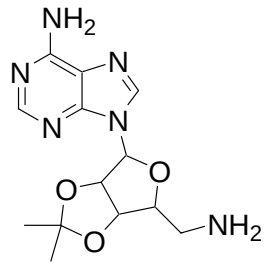
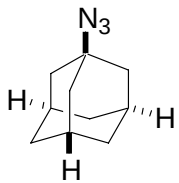
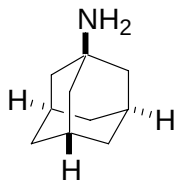
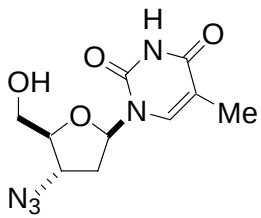
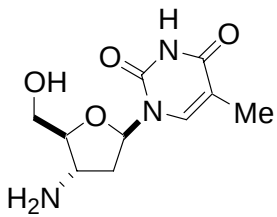
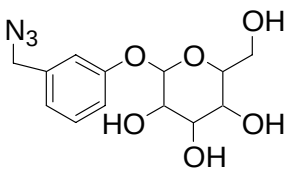
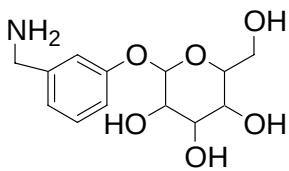
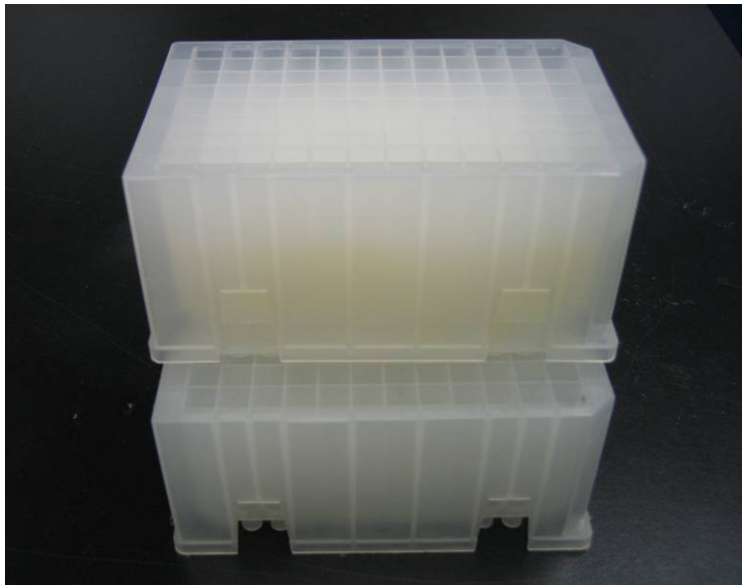
entry	RN_3	RNH_2	yield (%)	purity (%)
1			**86**	**98/95**
2			**91**	**98/95**
3			**88**	**98/95**
4			**92**	**98/95**
5			**82**	**95/92**
6			**80**	**97/93**

Plate-to-Plate F-SPE

24-Channel Plates

- 3-4 g F-silica gel
- 10 mL receiving well
- 10-100 mg product purification
- plate concentration by Genevac
- vacuum or gravity SPE

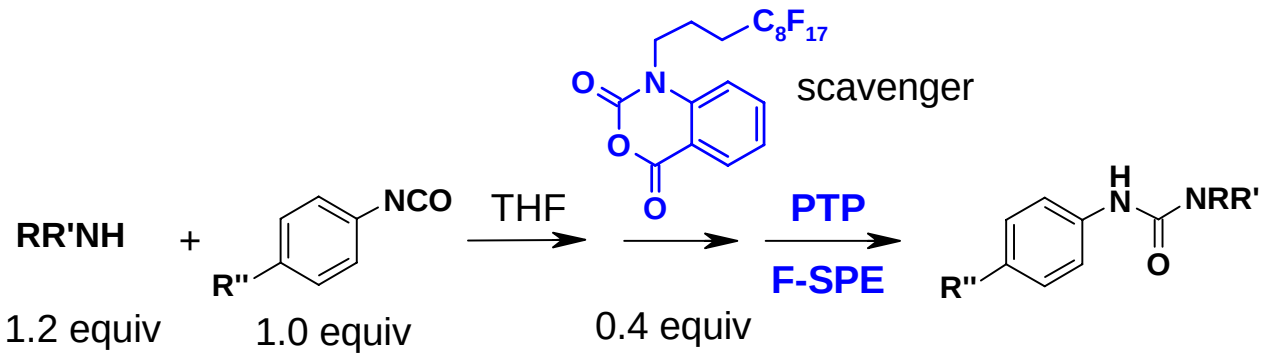
96-Well Ex-Block

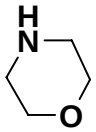
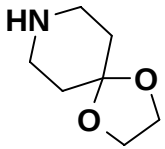
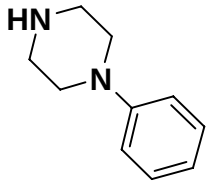
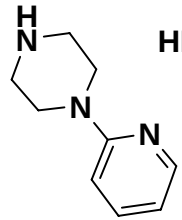
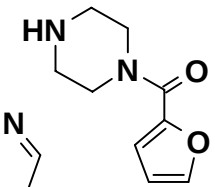
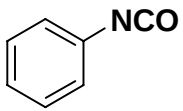
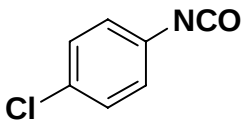
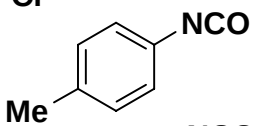
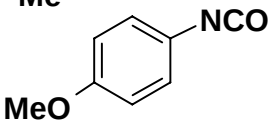


- up to 1.5 g of F-silica gel
- 3 mL receiving well
- use large size (100 μm) silica
- gravity SPE
- plate can be reused

Zhang, W.; Lu, Y.; Nagashima, T. *J. Comb. Chem.* 2005, *7*, 893–897.

PTP F-SPE for Scavenging Reactions



	H_2NBu					
	95(92)*	83(96)	95(93)	86(96)	92(91)	100(96)
	83(100)	81(99)	79(100)	81(100)	83(100)	90(100)
	100(80)	100(96)	100(97)	100(94)	100(96)	100(99)
	100(94)	100(99)	100(100)	100(100)	100(100)	100(100)

* yield% (purity%, UV254)

yield 79-100%, product purity >90% (one exception)

Zhang, W.; Lu, Y.; Nagashima, T. *J. Comb. Chem.* 2005, *7*, 893–897.

Automated F-SPE by RapidTrace™

Caliper Life Sciences (formerly Zymark Corp)

Single unit (10 Cartridges)

10 units parallel (10x10 cartridges)

- **Automatic sample loading (including samples containing suspended solids)**
- **Pump-controlled solvent delivery system with a choice of 8 solvents**
- **Automatically conditions, rinses and elutes cartridges**
- **10 Cartridges sequential, up to 10 modules parallel and controlled by a PC**

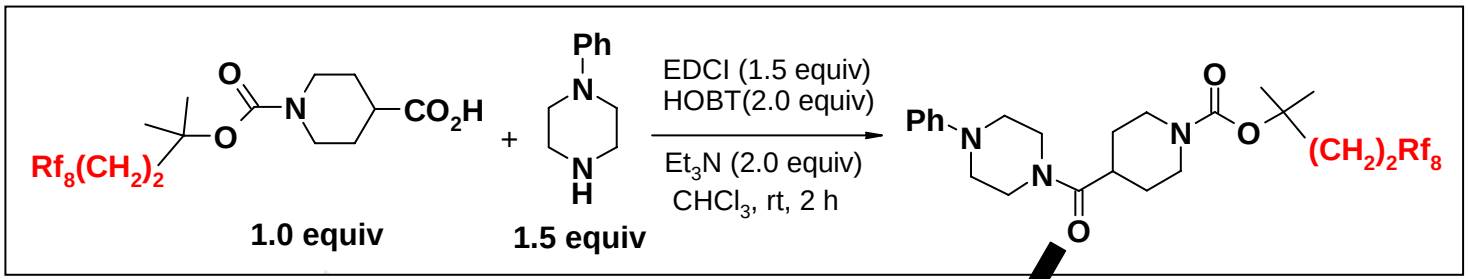
Large Scale Flash Chromatography

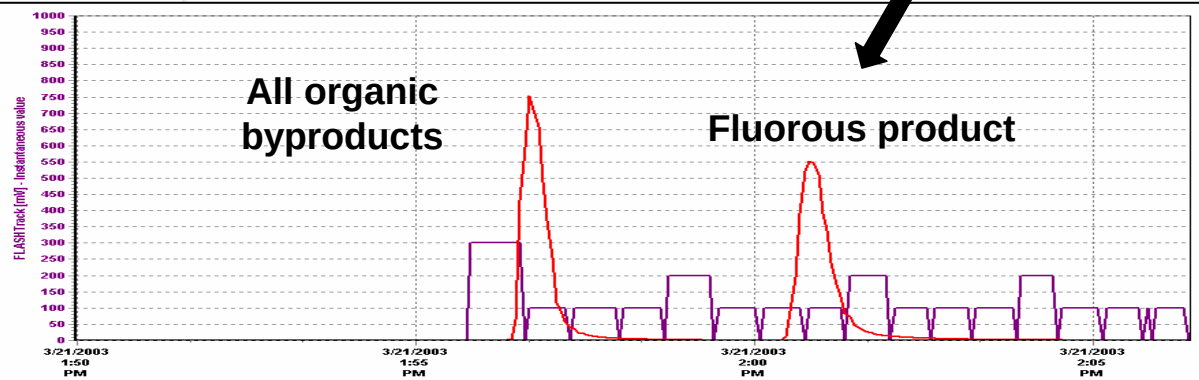
variable cartridge size, gradient solvent, UV-trigged fraction collection

ISCO

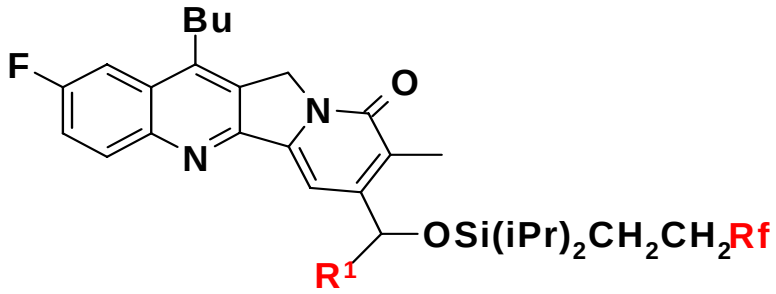
Biotage

FlashMaster II

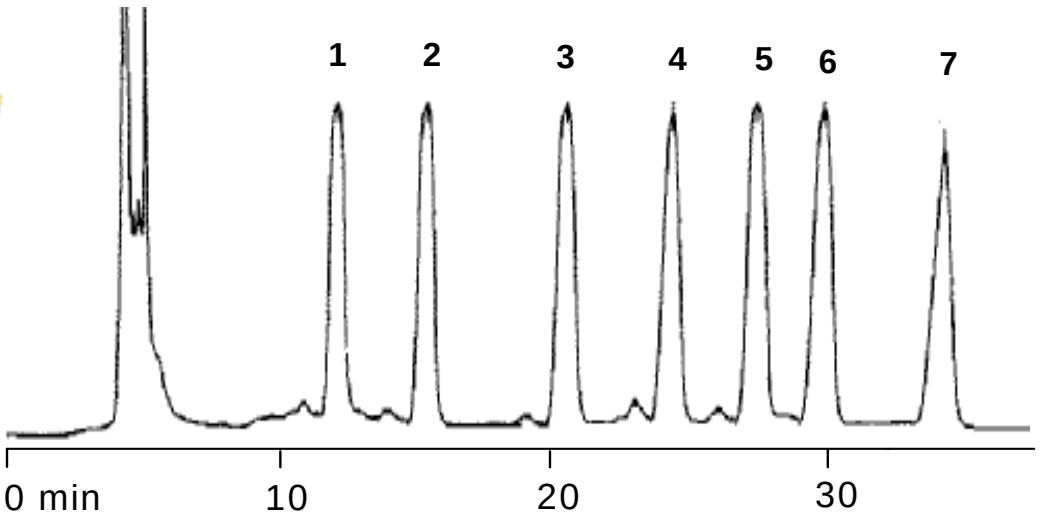




Fluorous HPLC for Demixing



	1	2	3	4	5	6	7
Rf	C_3F_7	C_4F_9	C_6F_{10}	C_7F_{15}	C_8F_{17}	C_9F_{19}	$C_{10}F_{21}$
R^1	Me	Pr	Et	*s*-Bu	*i*-Pr	*c*-C_6H_{11}	CH_2CH_2-*c*-C_6H_{11}



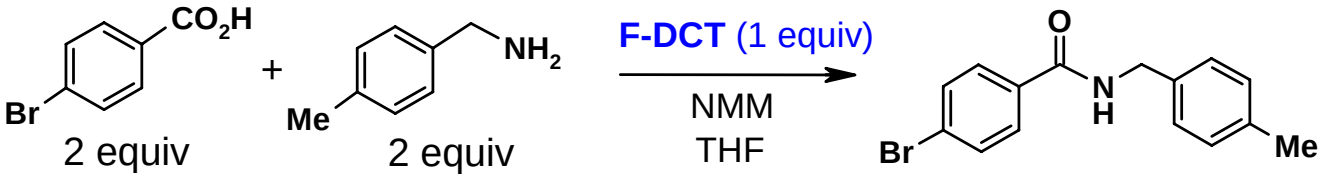
F-HPLC column (20 x 250 mm, 5 *m*m), gradient 88:12 MeOH-H_2O to 100% MeOH in 28 min, then to 100%THF in 7 min, 12 mL/min

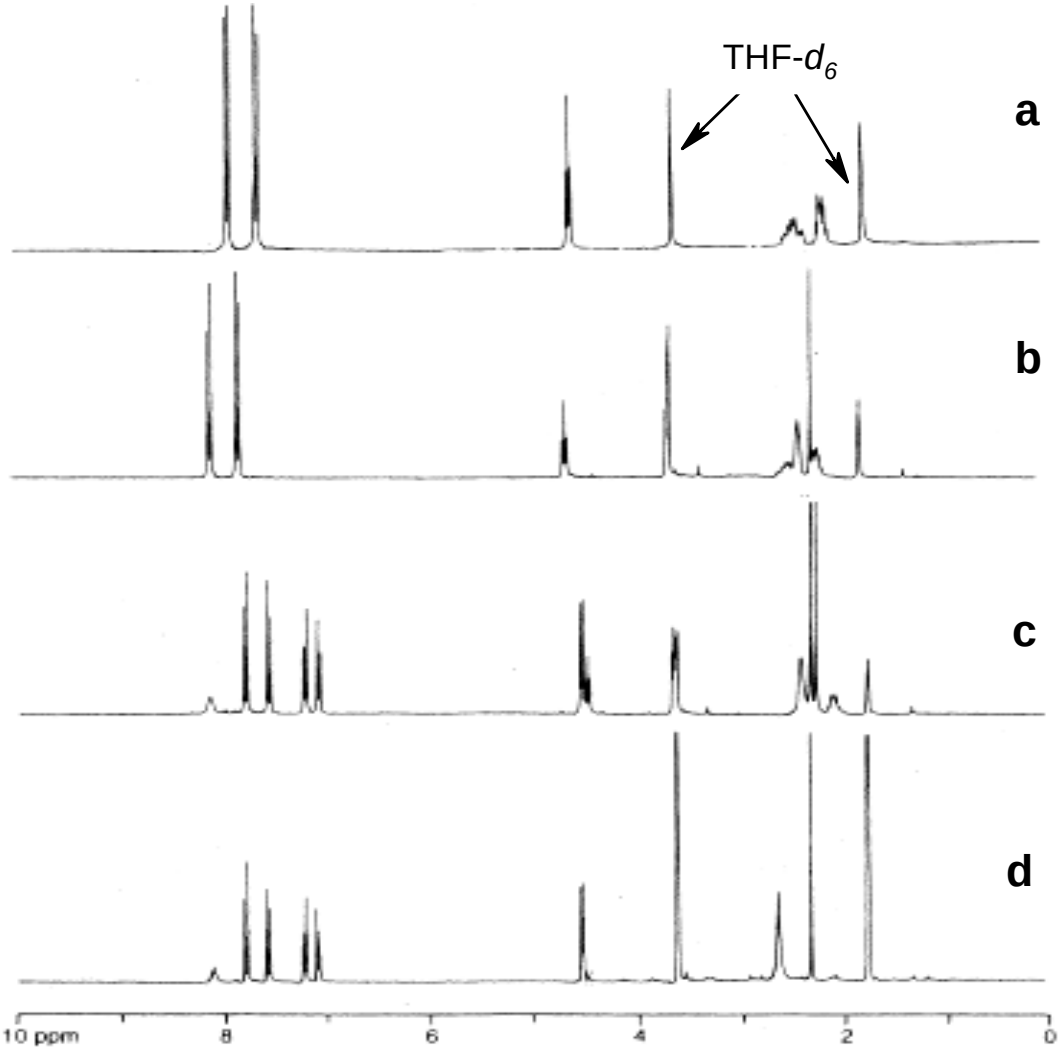
Separation fluorous mixture based on fluorine content

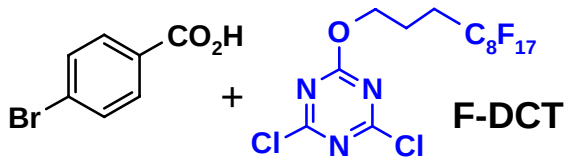
Features of Fluorous Synthesis

1) Solution-phase reaction kinetics
2) Easy adaptation of literature procedures, short method development time
3) Easy reaction monitoring by common analytical methods (TLC, HPLC, IR and NMR)
4) Separation by fluorous methods as well as conventional methods (distillation, crystallization and chromatography)
5) Light fluorous molecules soluble in many organic solvents, no fluorous solvents for reactions and separations
6) More than one fluorous reagent possible for a single reaction
7) Good "combinatorial" capability with existing technologies (microwave, microarray, MCR, DOS, SPS….)
8) Recover fluorous materials after separation

Reaction Monitoring







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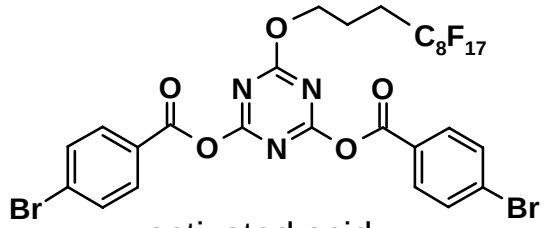
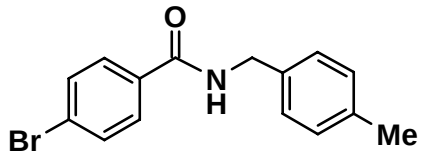
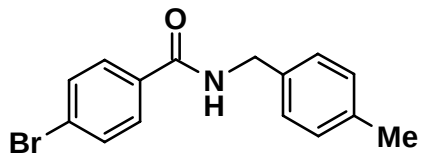


activated acid



amide product



F-SPE purified product

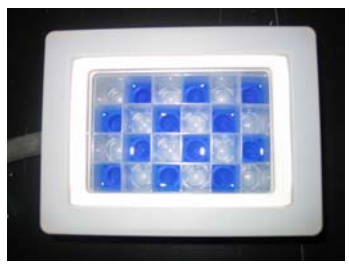
Fast Fluorous Synthesis System

+

+

MW Reactor
fluorous compounds are stable under μw irradiation

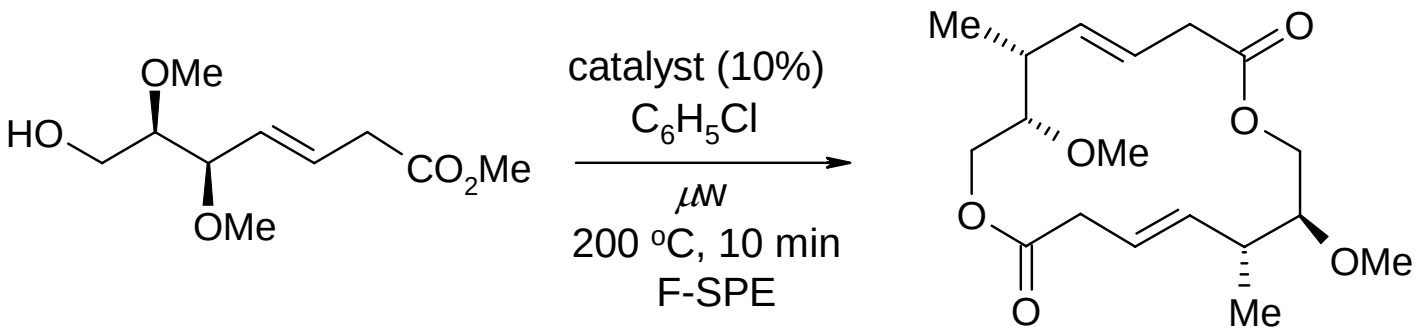
Plate to Plate F-SPE
for parallel separation

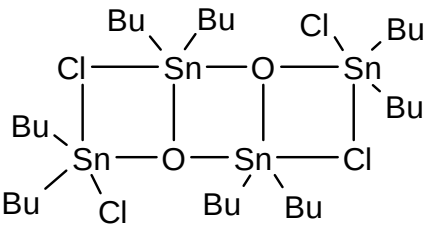


SpeedVac
for concentration of SPE receiving plates

Zhang, W. *Chimica Oggi/Chemistry Today* **2005**, *23*, 3, XI

F-Tin Oxide for Transesterifications

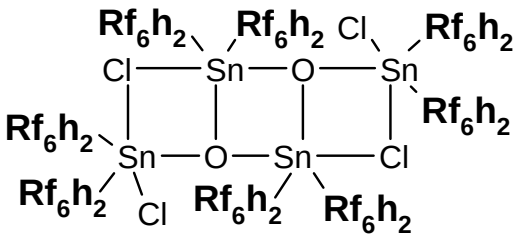




1

$[[Me(CH_2)_3]_2SnO]_n$

3



2

$[[CF_3(CF_2)_5CH_2CH_2]_2SnO]_n$

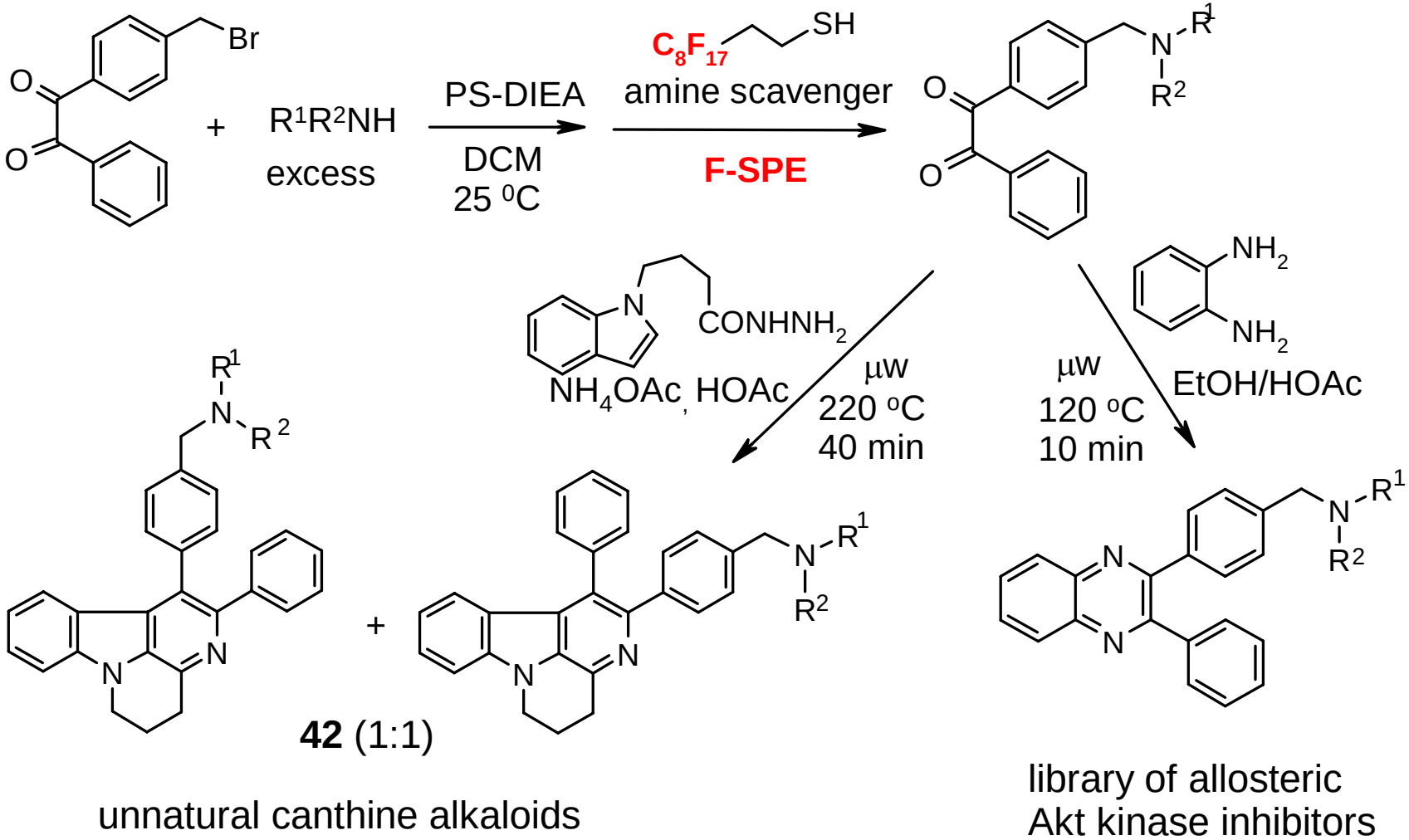
4

catalyst	yield
1	60%
2	78%
3	27%
4	80%

F-catalyst 4 has the best result

Beeler, A.B; Acquilano, D.E.; Su, Q.; Yan, F.; Roth, B.L.; Panek, J.S.; Porco, Jr J.A. *J Comb Chem.,* **2005**, *7*, 673

F-Thiol as Amine Scavenger



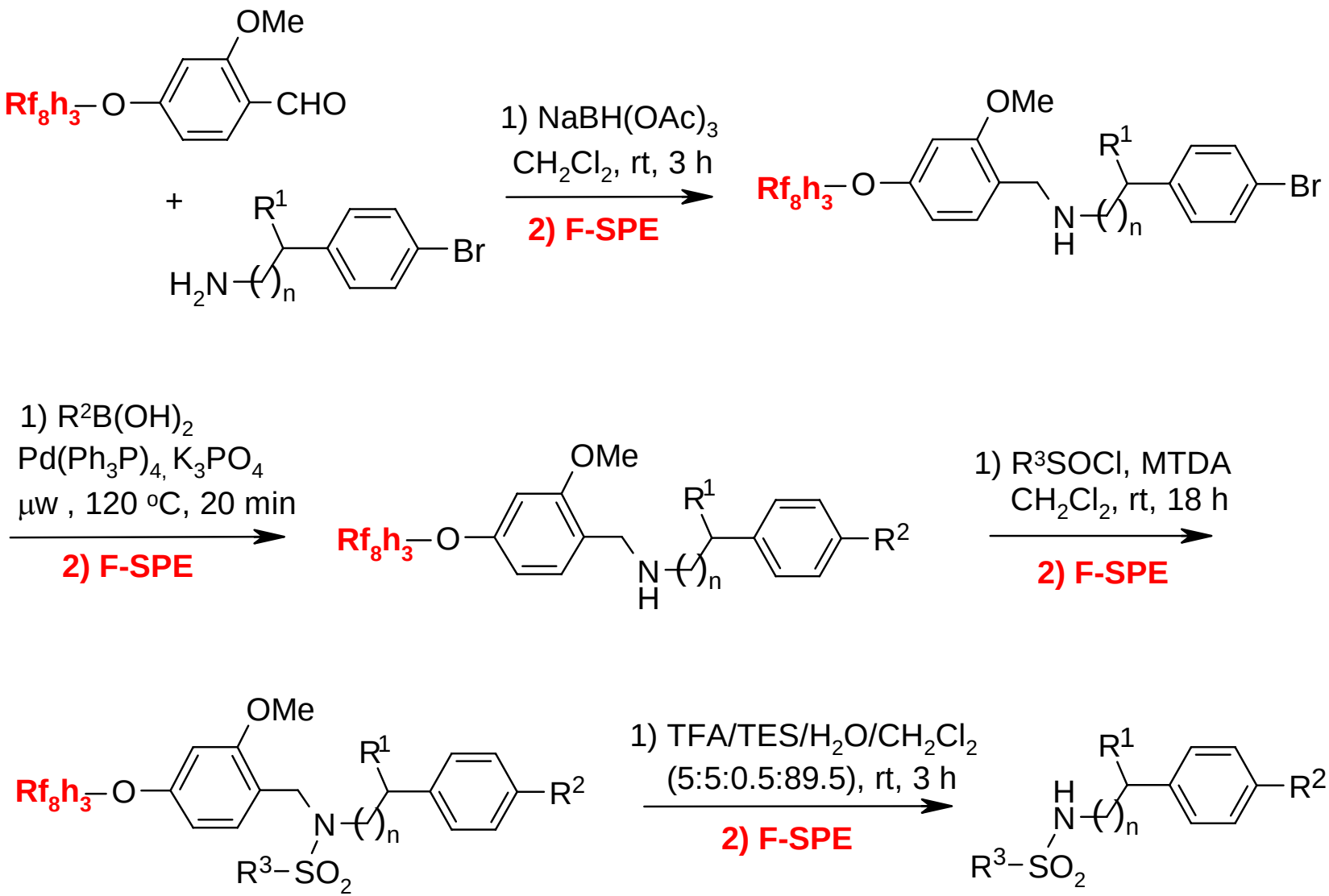
42 (1:1)

unnatural canthine alkaloids

library of allosteric
Akt kinase inhibitors

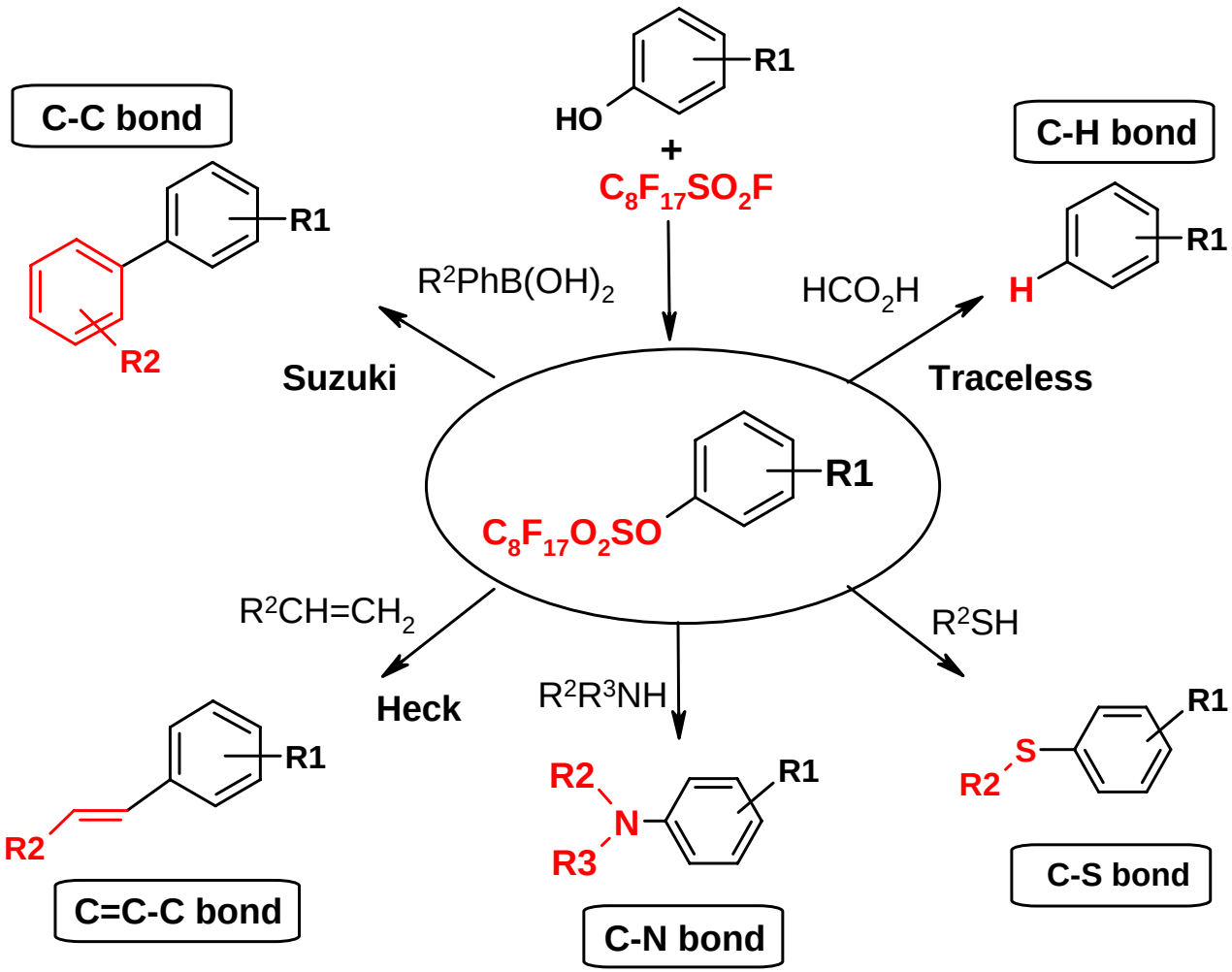
Lindsley, C. W. *et. al. Bioorg Med Chem Lett* **2005**, *15*, 761.*Tetrahedron Lett.* **2005**, *46*, 2779.

F-Benzaldehyde Protecting Group



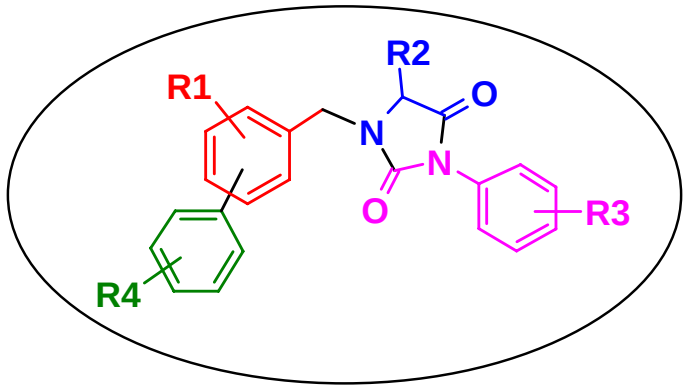
Villard, A-L.; Warrington, B. H.; Ladlow, M. *J Comb Chem* **2004**,*6*, 611

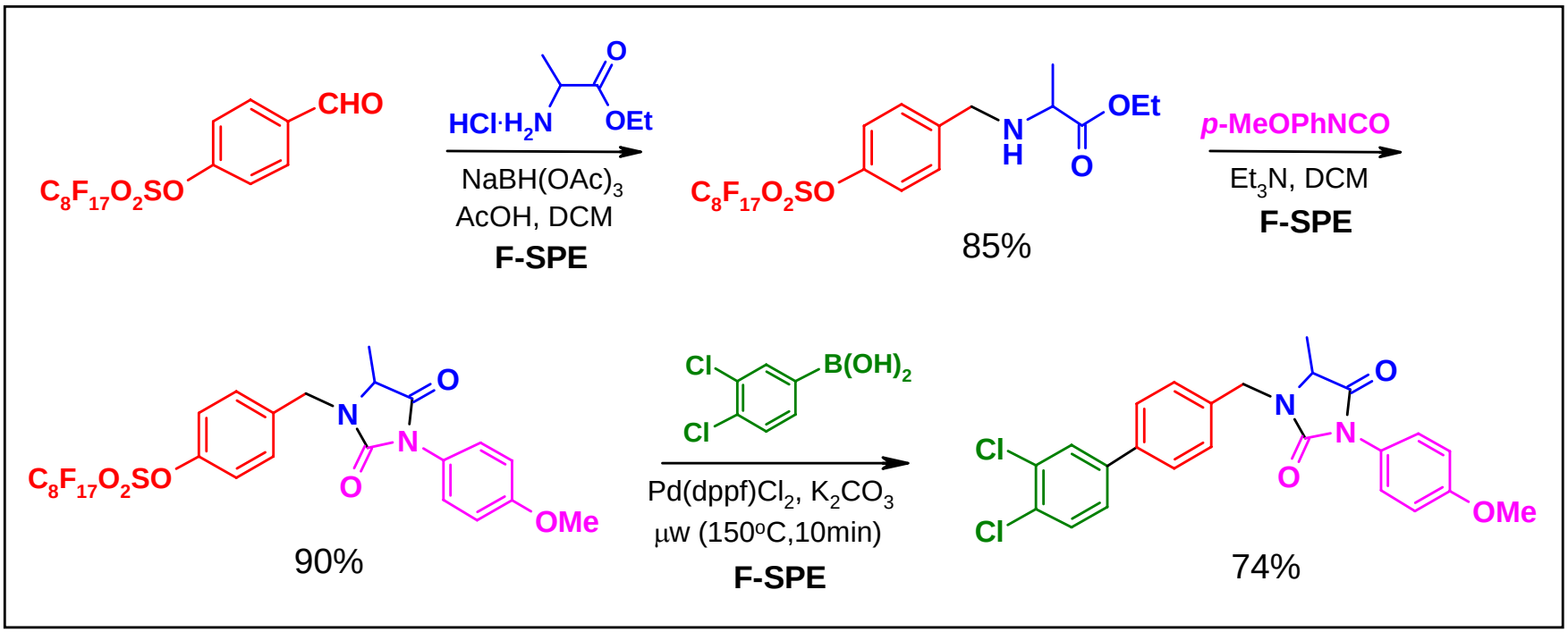
F-Sulfonates for Pd-catalyzed Couplings



Three functions of the fluorous tag: 1) OH protecting group; 2) F-tag for easy intermediate purification; 3) Activation of phenol for coupling

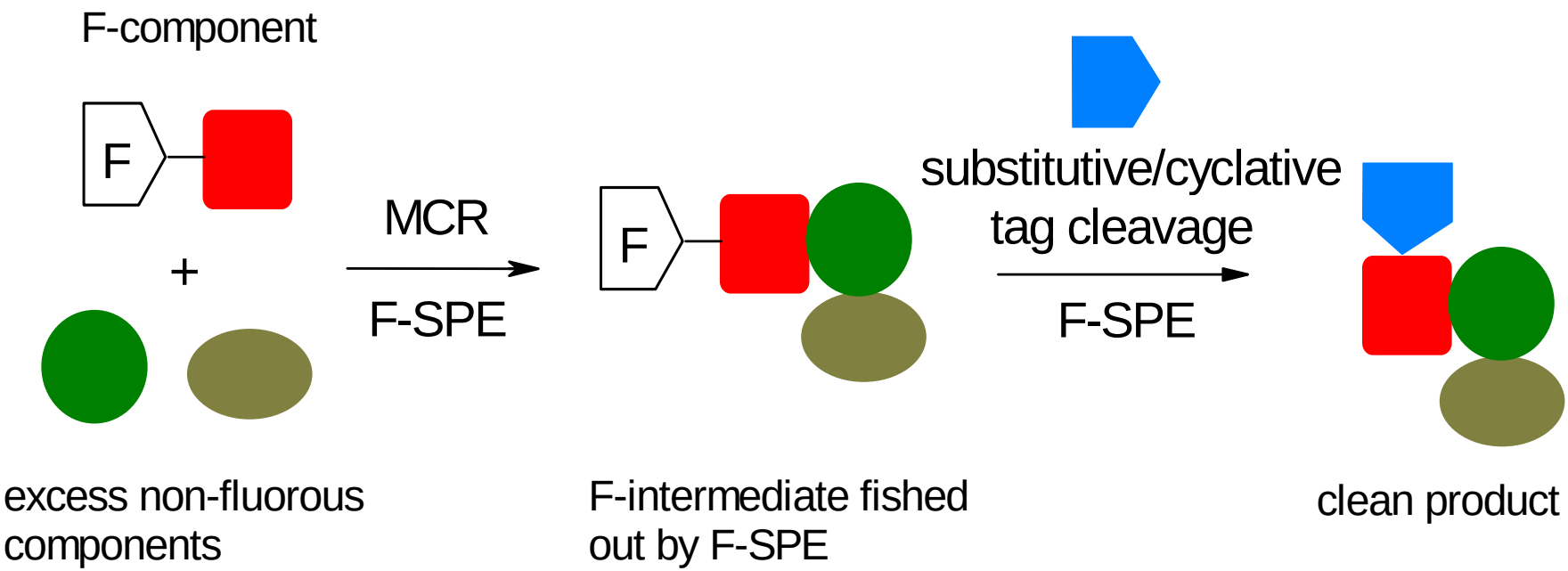
Biaryl-Substituted Hydantoins





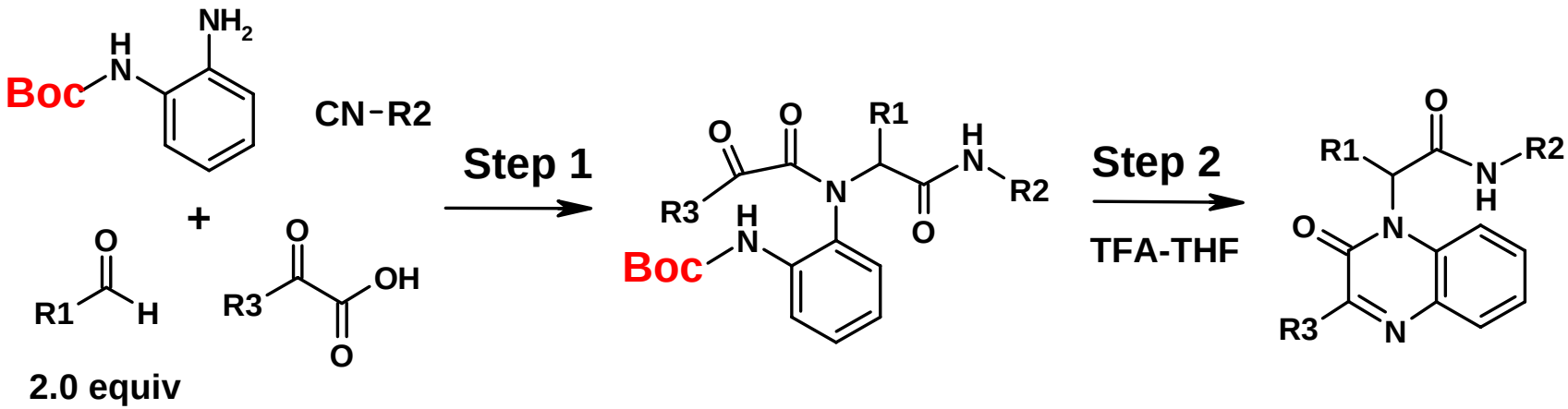
Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima T. *Org. Lett*. **2004**, *6*, 1473.

Fluorous-Enhanced MCRs



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

Ugi/de-Boc/Cyclization Synthesis

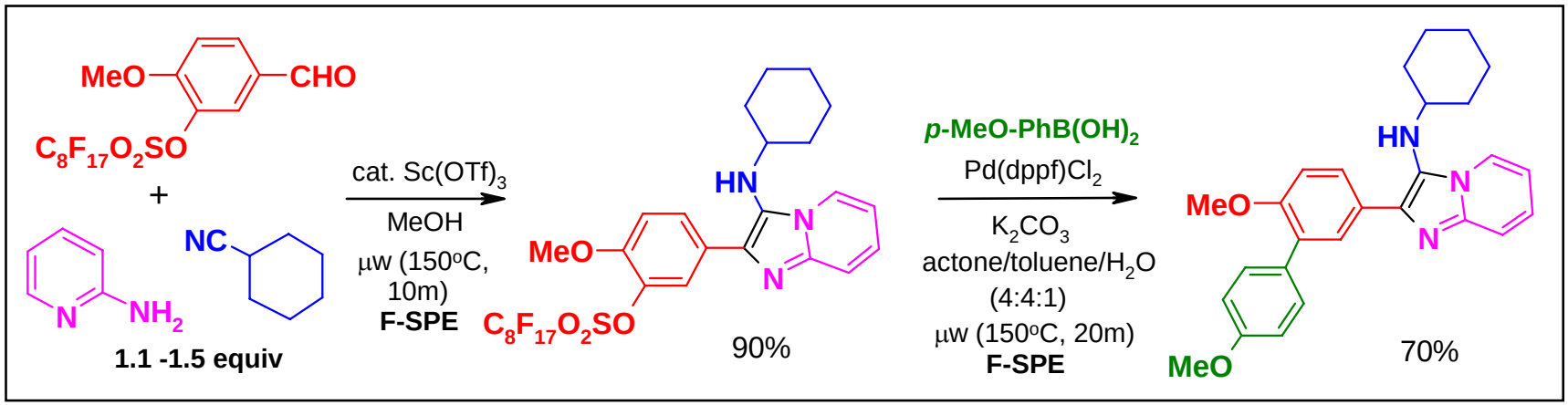


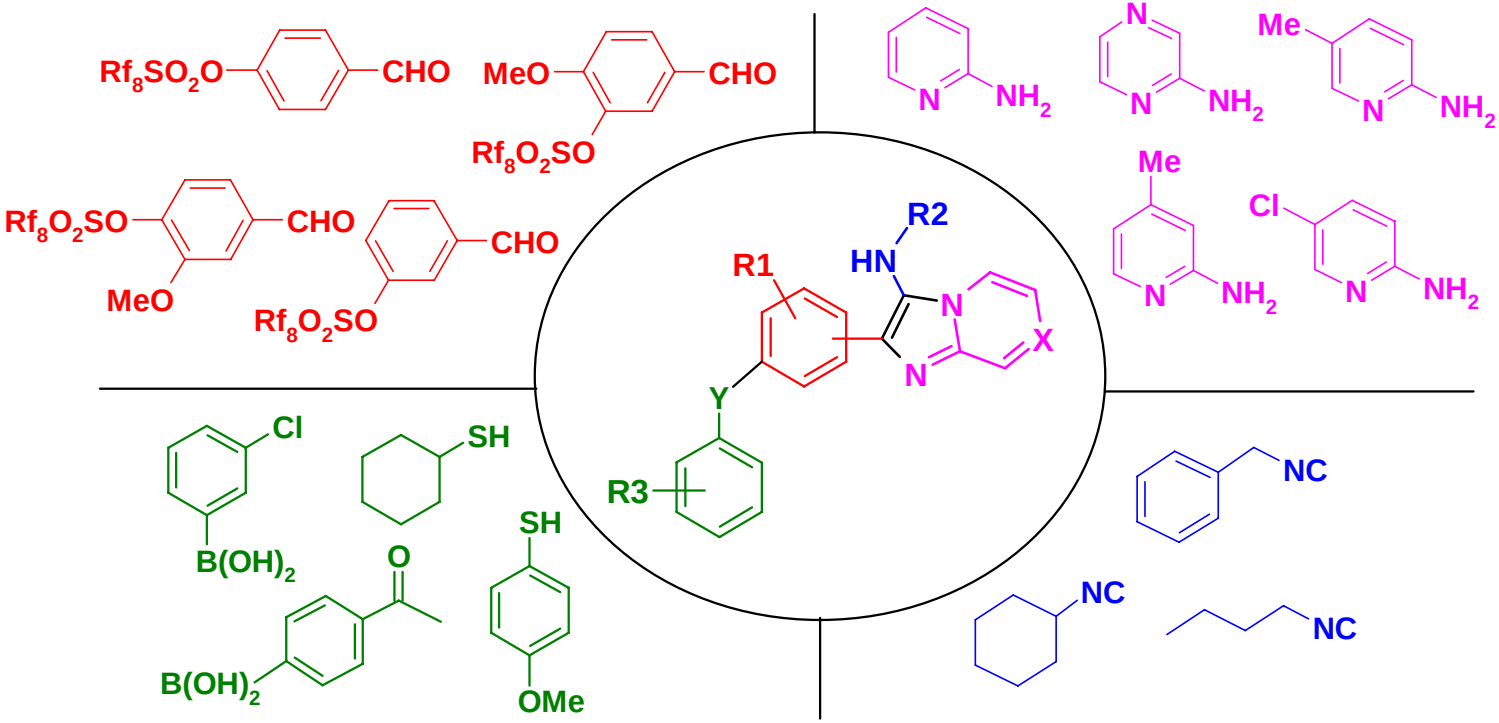
Step 1	*Step 2*
normal Boc:[1] 36-48h, double scavenging to remove aldehyde and acid	4-24 h, flash chromatgraphy
F-Boc + μW:[2] 120 ^{0}C, 20 min, F-SPE	120 ^{0}C, 20 min, F-SPE

The microwave + fluorous approach is faster and easier

[1] Nixey, T.; Tempest, P.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 1637.
[2] Zhang, W.; Tempest, P. *Tetrahedron Lett.* **2004**, *45*, 6757.

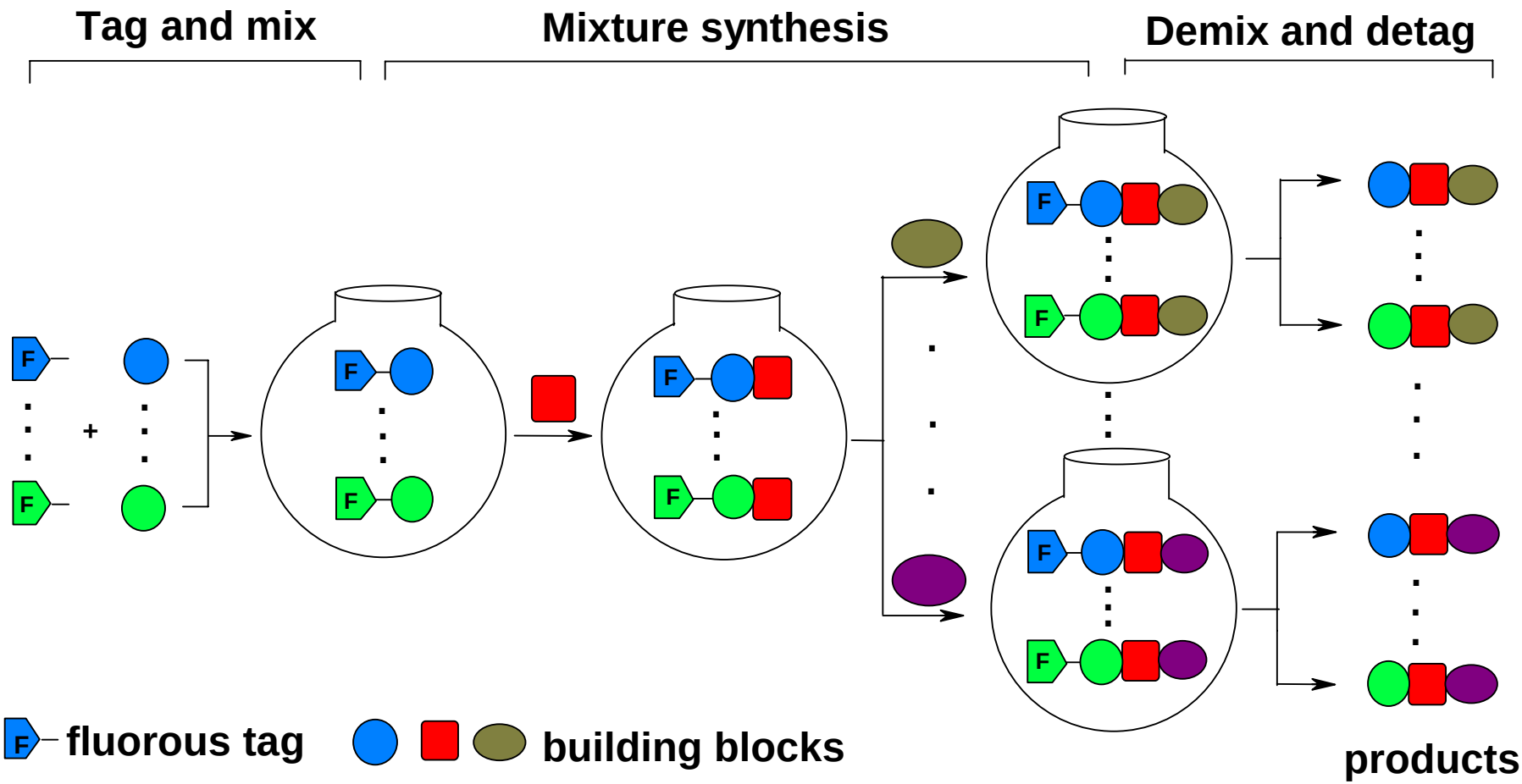
Biaryl Substituted Imidazo[1,2-a]pyridines



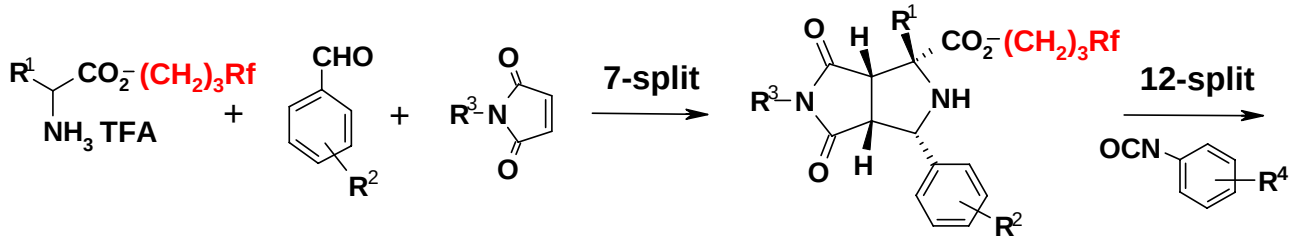


Lu, Y.; Zhang, W. *QSAR Comb. Sci*. **2004**, *23*, 827.

Fluorous Mixture Synthesis (FMS)



5-Component FMS



M-5{*1-5*} 6{*1-7*} 7{*1-4*} M-8{*1-5,1-7,1-4*} 9{*1-12*}

1 mixture of five *7 mixtures of five*

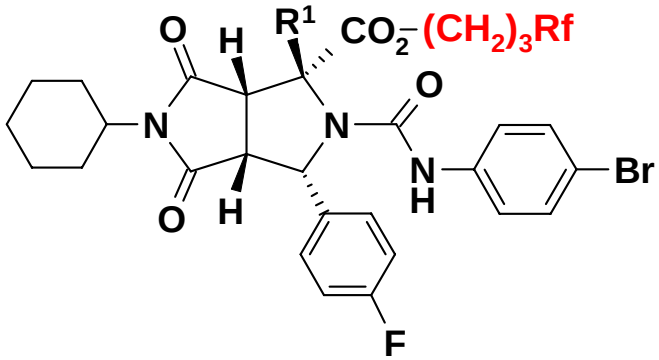
M-10{*1-5,1-7,1-4,1-12*} 10{*1-5,1-7,1-4,1-12*} 11{*1-5,1-7,1-4,1-12*}

84 mixtures of five *420 compounds* *420 compounds*

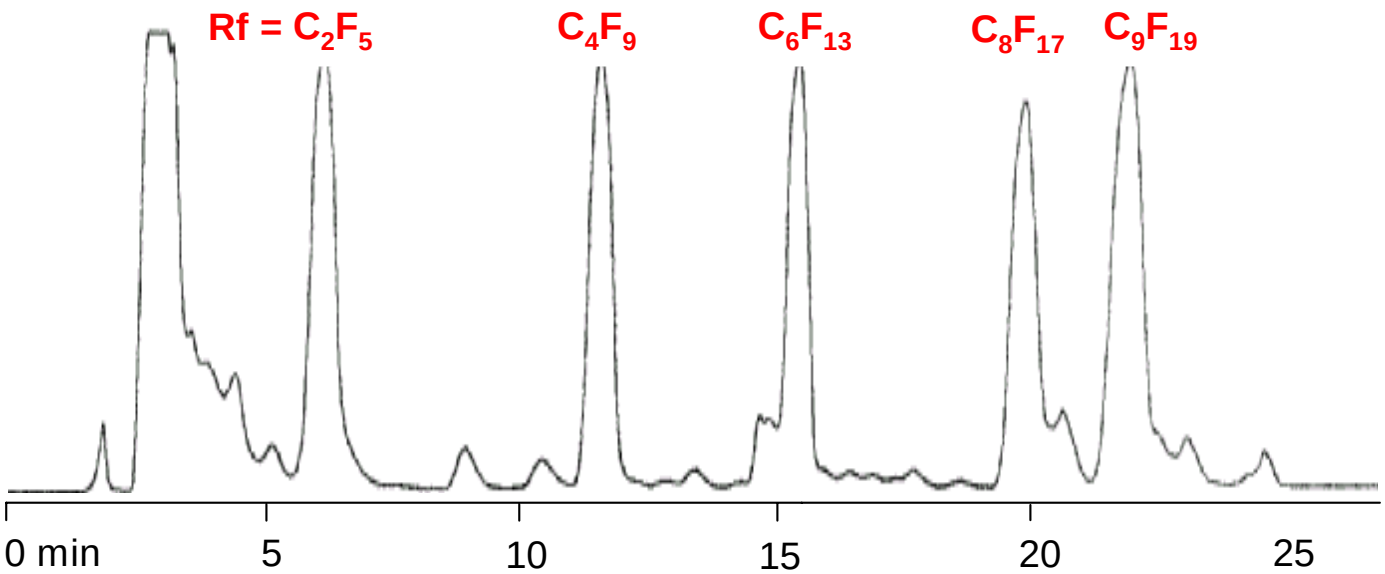
Rf/R^1*{1-5}*	R^2*{1-7}*	R^3 *{1-4}*	R^4 *{1-12}*
{*1*} C_2F_5/i-Bu	**{*1*}** H	**{*1*}** Et	**{*1*}** H
{*2*} C_4F_9/Bn	**{*2*}** *p*-Me	**{*2*}** *t*-Bu	**{*2*}** *p*-Me
{*3*} C_6F_{13}/*p*-ClBn	**{*3*}** *p*-Br	**{*3*}** *c*-C_6H_{11}	**{*3*}** *p*-Br
{*4*} C_8F_{17}/ Me	**{*4*}** *p*-OMe	**{*4*}** Bn	**{*4*}** *p*-OMe
{5} C_9F_{19}/Et	**{*5*}** *p*-F		**{*5*}** *p*-F
	{*6*} *p*-Cl		**{*6*}** *p*-Cl
	{*7*} *m*-Me		**{*7*}** *p*-CF3
			{*8*} 3,4-diCl
			{*9*} *m*-Me
			{*10*} *m*-Br
			{*11*} *m*-F
			{*12*} *m*-Cl

420 Ureas M-10 (84 x 5) by *91 FMS reactions* (7 cycloaddition + 84 isocyanatereactions)
Could need *455 parallel reactions* (35 cycloadditions + 420 isocyanate reactions)

A Typical HPLC Demixing

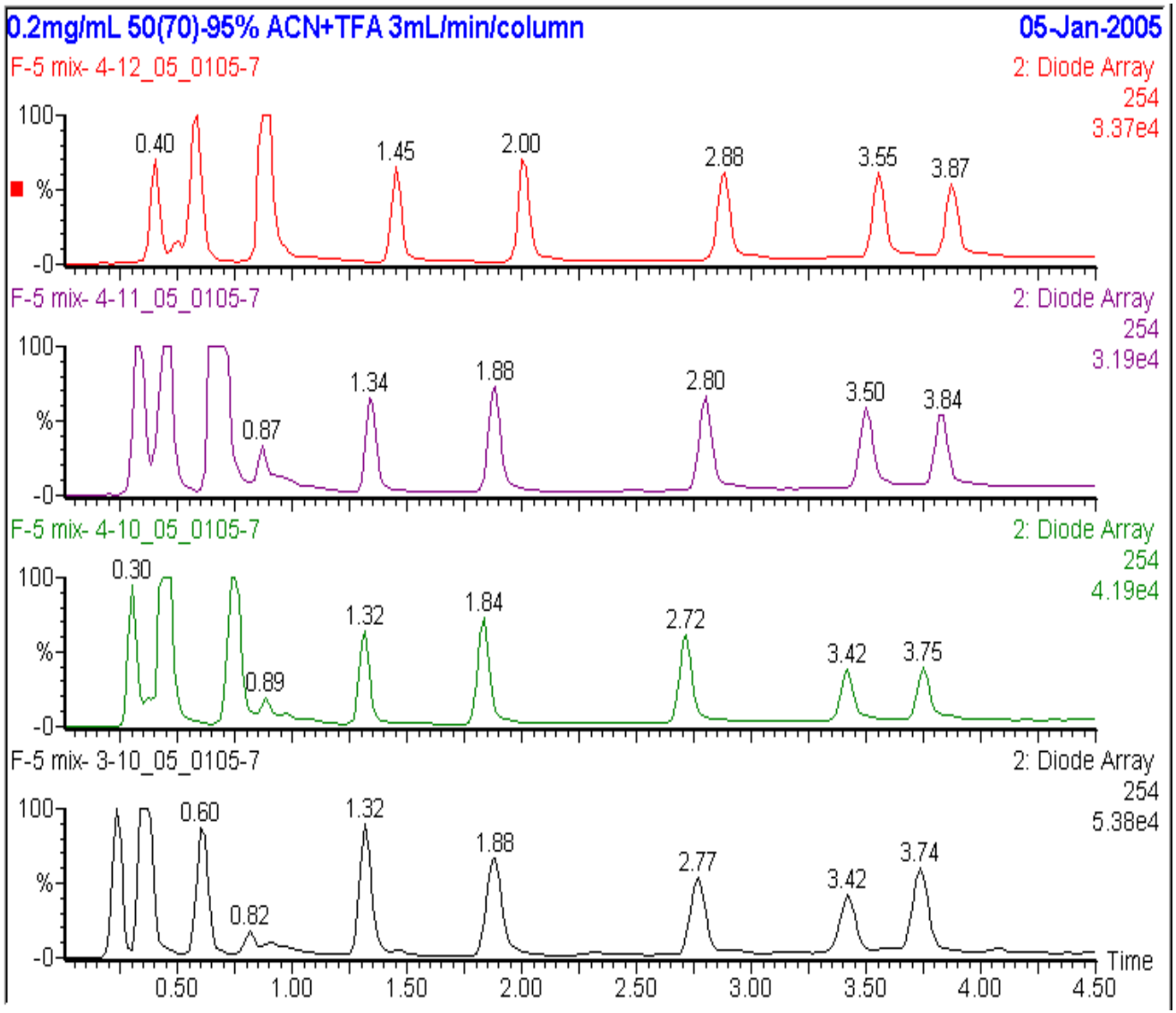


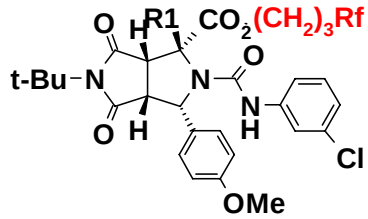
M-10{*1-5,5,3,3*}



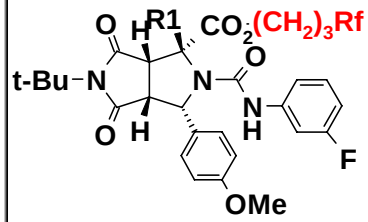
Fluoro*Flash*® column (20x250 mm, 5 μm), gradient 80:20 MeOH-H_2O to 100% MeOH in 23 min, then THF for 4 min, 20 mL/min.

4-Channel HPLC Demixing

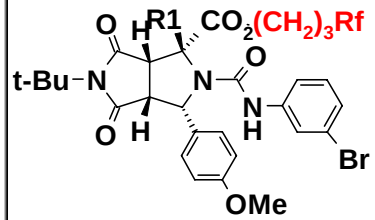




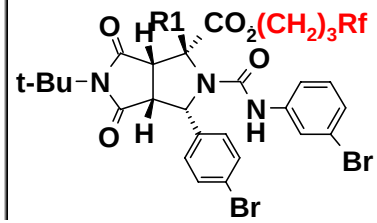
M-10{*1-5,4,2,12*}



M-10{*1-5,4,2,11*}



M-10{*1-5,4,2,10*}



M-10{*1-5,3,2,10*}

Demixing and purification of 20 (4x5) compounds in 5 min

Zhang, W.; Lu, Y.; Chen, C. H.-T. Zeng, L; Kassel, D. B. *J. Comb. Chem.* **2006**, *8*, 5, 687

Summary

Advantages of fluorous synthesis

- Homogeneous reaction
- Intermediate analysis/purification
- Selective orthogonal separation

Enhances existing technologies

- Microwave-assisted synthesis
- Multicomponent reactions
- Parallel and mixture synthesis
- Diversity-oriented synthesis
- SPE and chromatography
- Preparative parallel LC

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