



# Fluorous Chemistry in SAR Development

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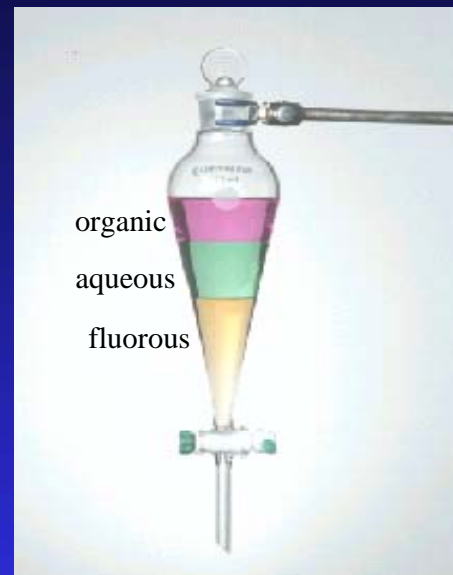
October 2004

# Presentation Outline

- **Introduction to Fluorous Chemistry**
  - ◆ Separation Techniques
  - ◆ Reaction Strategies
- **Transformation Based Fluorous Applications**
  - ◆ Acylation reactions
  - ◆ Scavenging reactions
  - ◆ Mitsunobu reactions
  - ◆ Other reactions
- **Array and Library Applications**
- **Recent Advancements**
  - ◆ Reverse fluorous SPE
  - ◆ Heavy fluorous liquid-liquid extraction
- **Conclusions**

# 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.
- Molecules can be rendered fluorous by the attachment of fluorous domains.

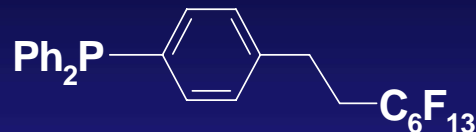


← organic

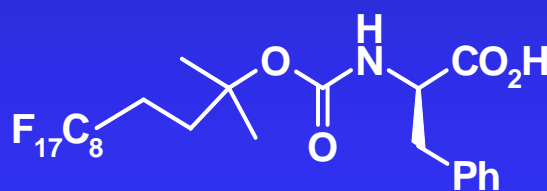
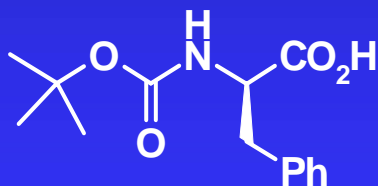
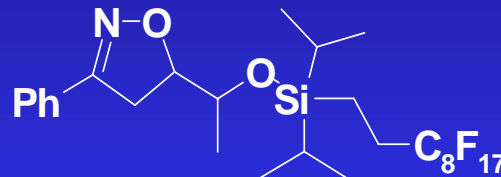
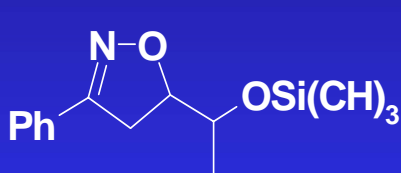
← fluorous

# Fluorous Versions of Organic Molecules

Fluorous compounds with permanent fluorinated domains:



Fluorous compounds with temporary fluorinated domains (tags):

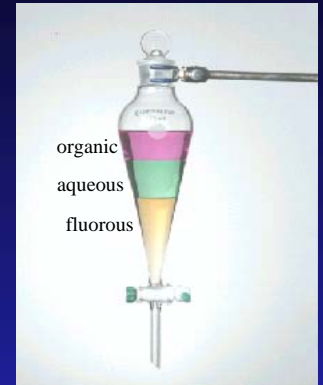


**Fluorous domains generally have little or no effect on reactivity, but provide a handle for facile separation**

# Fluorous Separation Methods

## ■ Liquid-Liquid Extraction

- “Heavy” fluorous technique
- Generally requires large F content, ~60%



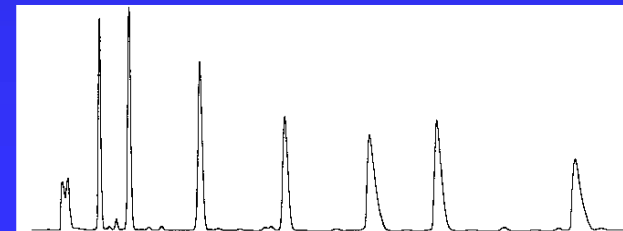
## ■ Fluorous Solid Phase Extraction (F-SPE)

- “Light” fluorous technique
- Separates fluorous from non-fluorous
- No fluorous solvents used



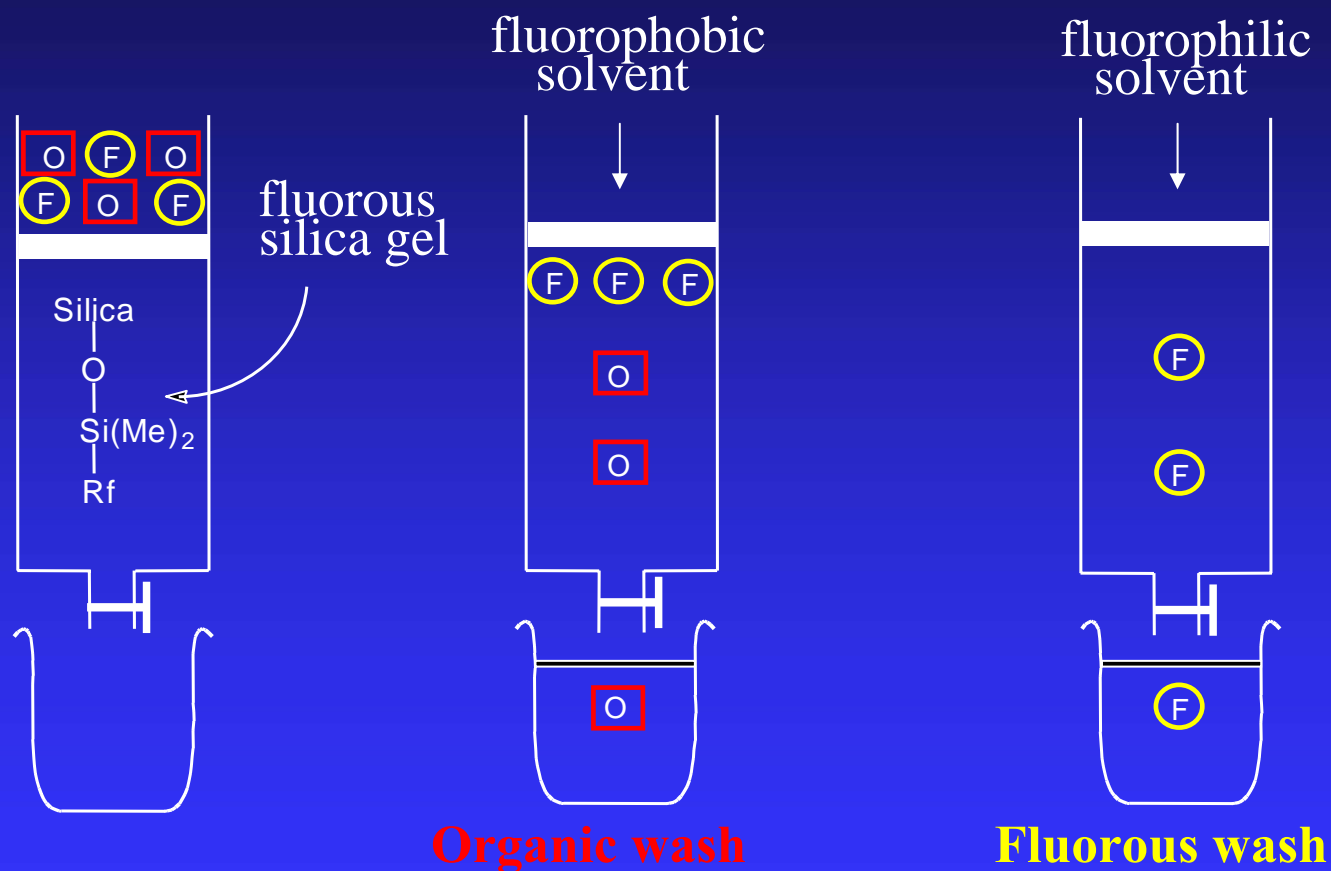
## ■ Fluorous Chromatography (F-HPLC)

- Separates fluorous from fluorous
- More fluorous = Greater retention

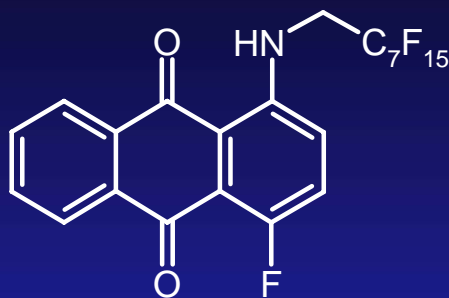


# Fluorous Solid Phase Extraction

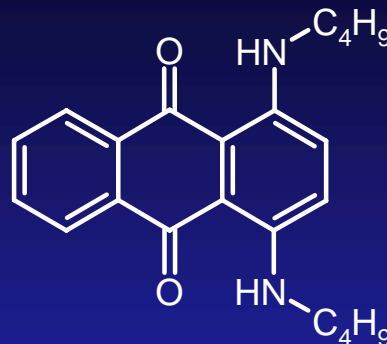
*A Light Fluorous Technique*



# Fluorous SPE: Dye Demonstration



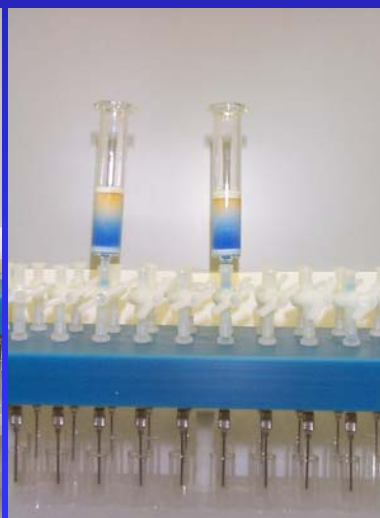
Fluorous Dye  
(orange)



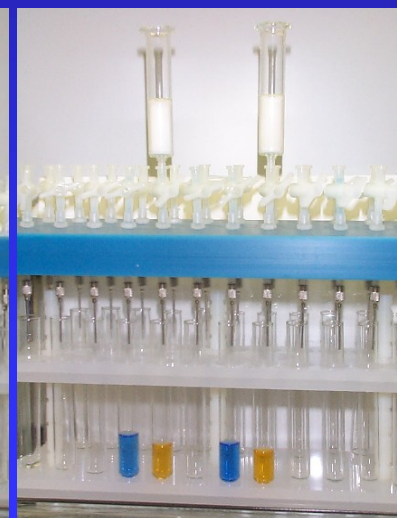
Non-fluorous Dye  
(blue)



1. Load sample



2. Wash non-fluorous dye  
with MeOH-H<sub>2</sub>O (85:15)



3. Wash fluorous dye  
with MeOH

# Solution Phase Fluorous Synthesis

*Two Fundamental Approaches*

## ■ Fluorous Reagents/Scavengers



## ■ Tagged Substrates

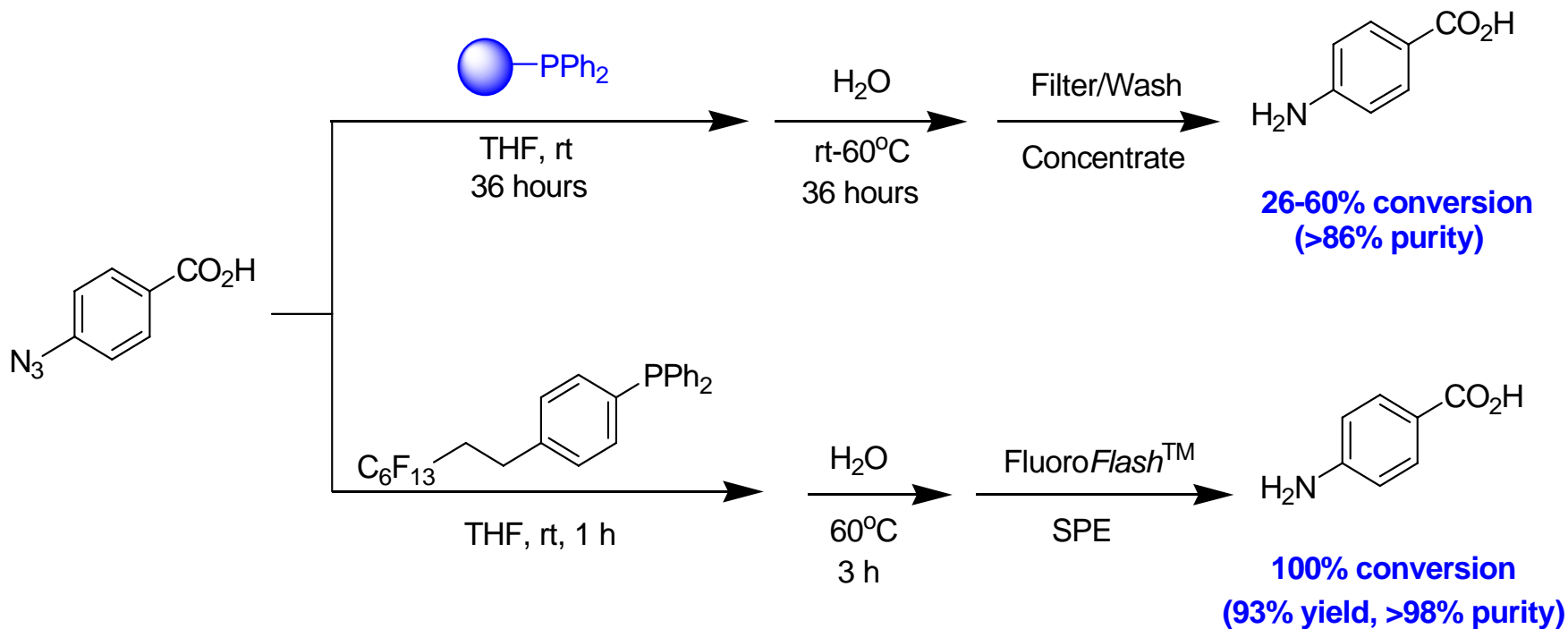


Fluorous tagged molecules can be analyzed by TLC, IR, MS, NMR and readily separated by F-SPE or F-HPLC

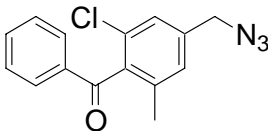
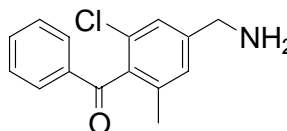
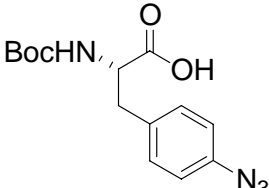
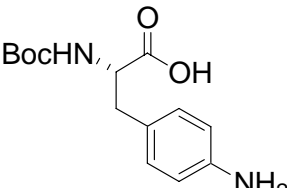
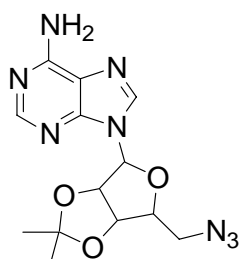
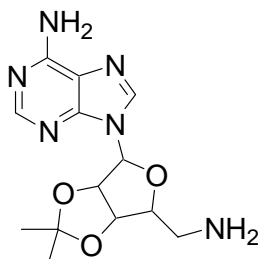
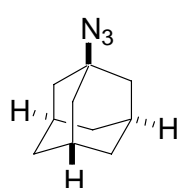
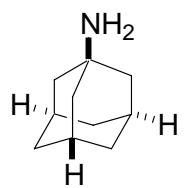
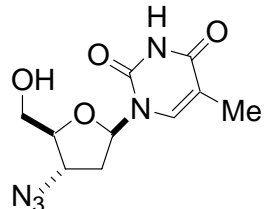
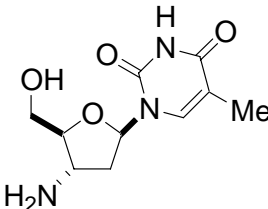
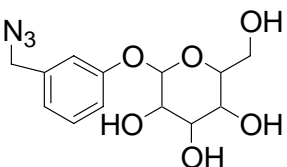
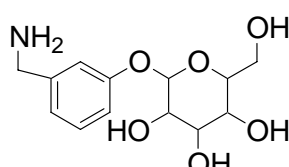
Curran, D. P. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 1175.



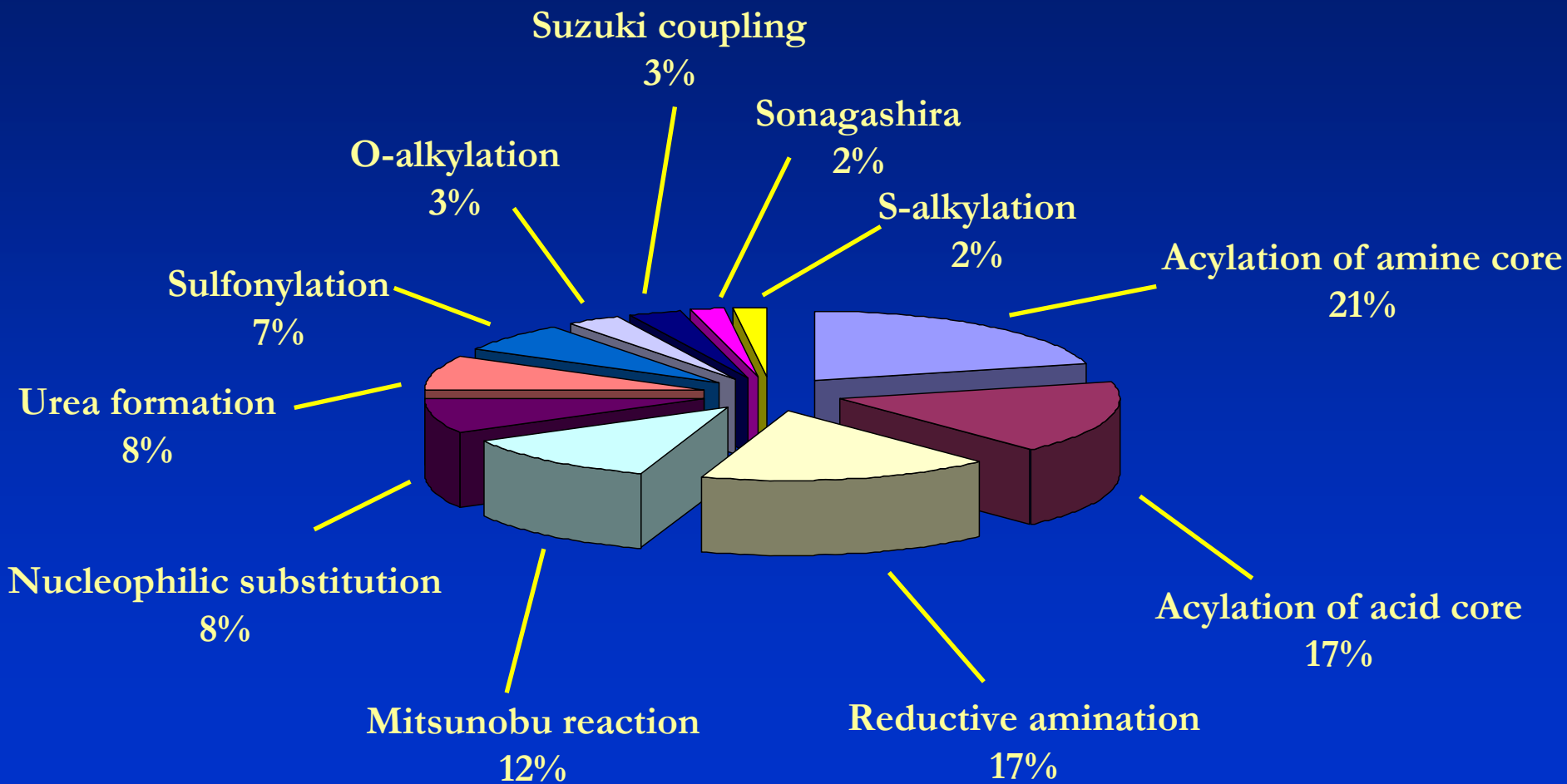
# Fluorous/Resin-PPh<sub>3</sub> Comparison



Craig Lindsley, Merck (*Tetrahedron Lett.* 2002, 43, 4467)

entry	RN <sub>3</sub>	RNH <sub>2</sub>	yield (%)	purity (%)
1			<b>86</b>	<b>98/95</b>
2			<b>91</b>	<b>98/95</b>
3			<b>88</b>	<b>98/95</b>
4			<b>92</b>	<b>98/95</b>
5			<b>82</b>	<b>95/92</b>
6			<b>80</b>	<b>97/93</b>

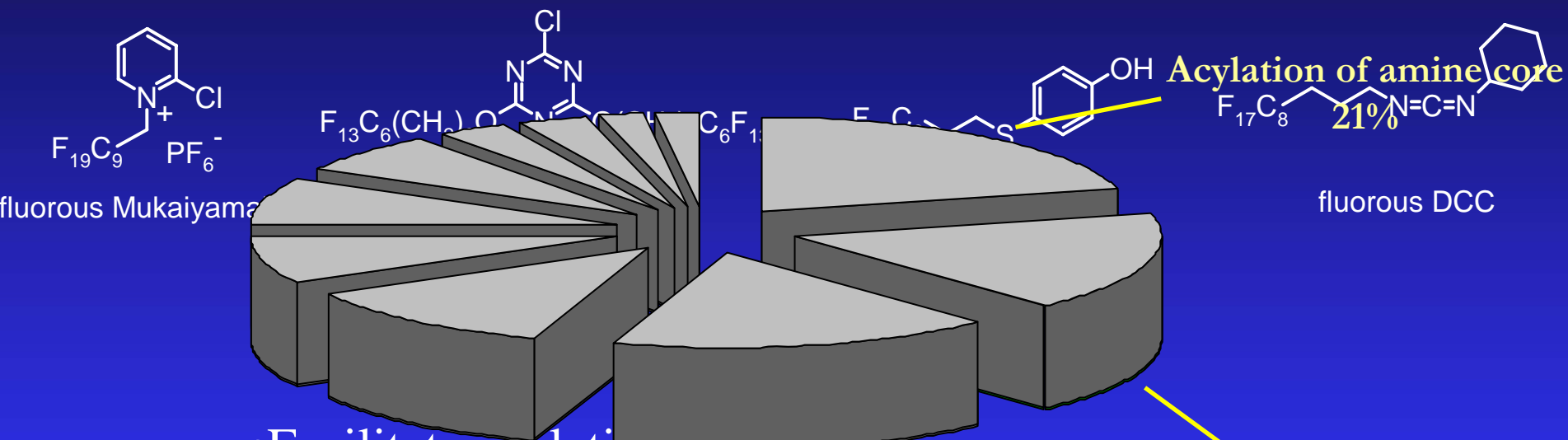
# Common Transformations in SAR Development



Data courtesy of Dr. Steve Djuric, Abbott Laboratories

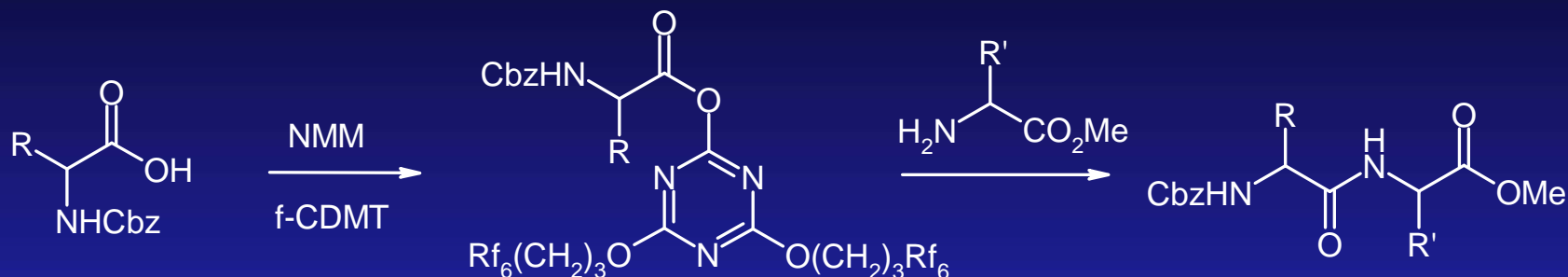
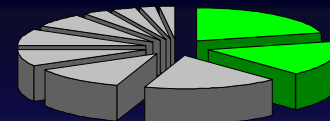
# Fluorous Acylation Reactions

## *Coupling Reagents*



- Facilitate acylation reactions
- Facile purification by F-SPE
- Design Flexibility
  - Solution Phase or Hybrid Solid/Solution Phase

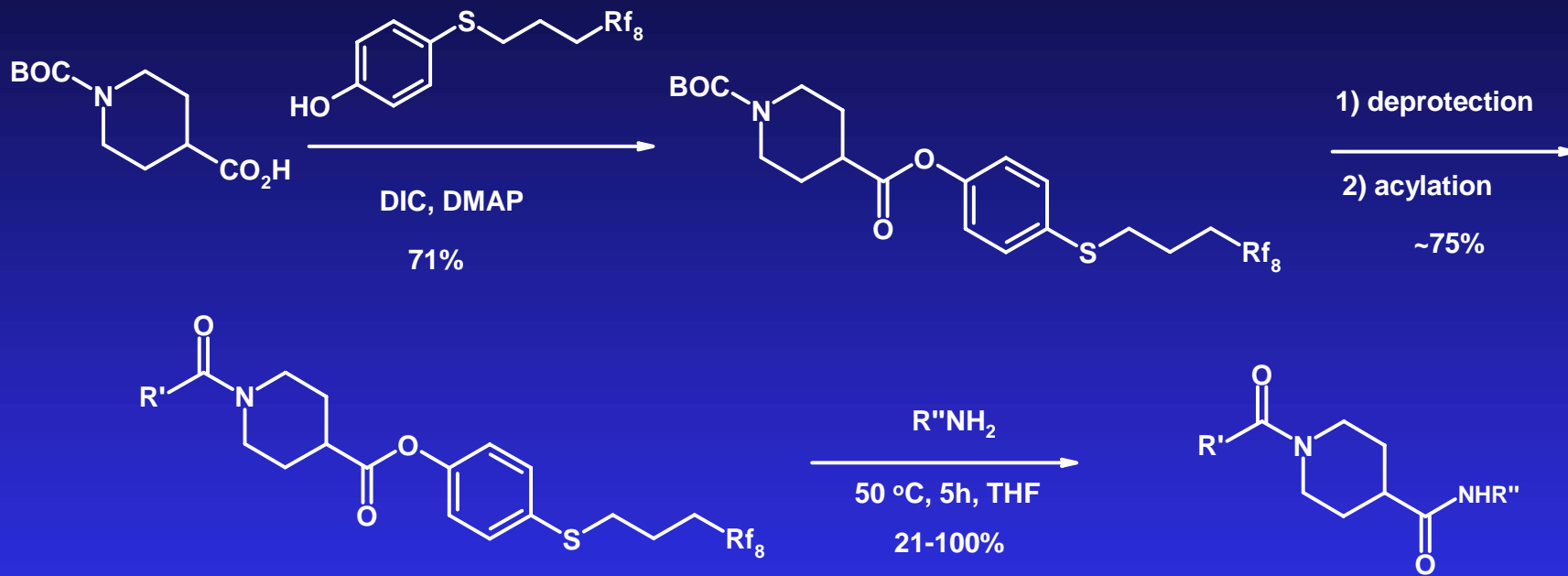
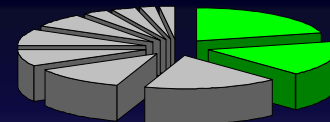
# Fluorous Acylation Reactions



Entry	Amide/Peptide	Yield(%)	Lit. yield(%)
1	Cbz-Ala-Ala-OMe	98	94
2	Cbz-Pro-Ser-OMe	96	89
3	Cbz-Phe-Met-OMe	91	73
4	Cbz-Ala-Ala-Ala-OMe	93	75

- No racemization observed
- f-CDMT suitable for use with  $\alpha,\alpha$ -disubstituted acids
- FSPE purification possible

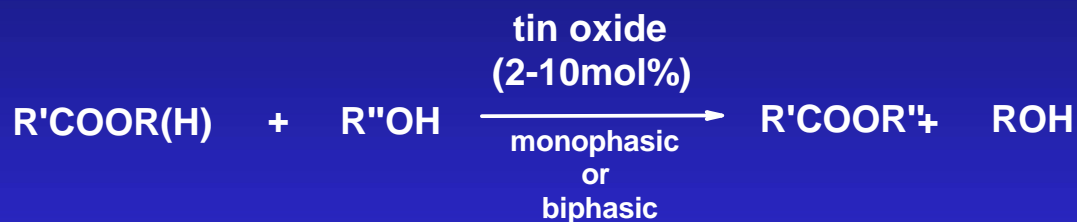
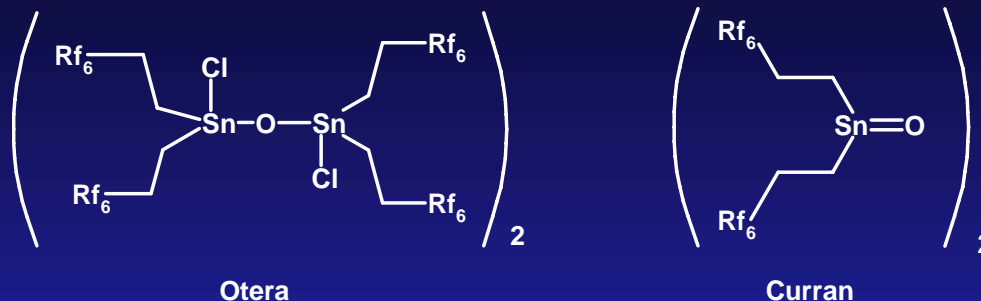
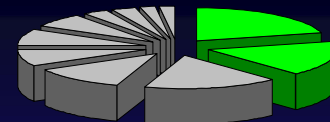
# Fluorous Acylation Reactions



- All intermediates and final products purified by FSPE
- FluoMar used as a tag as well as an activating group
- FluoMar can be recovered and reused

Chen, C.H.T. and Zhang, W. *Org. Lett.* **2003**, *5*, 1015.

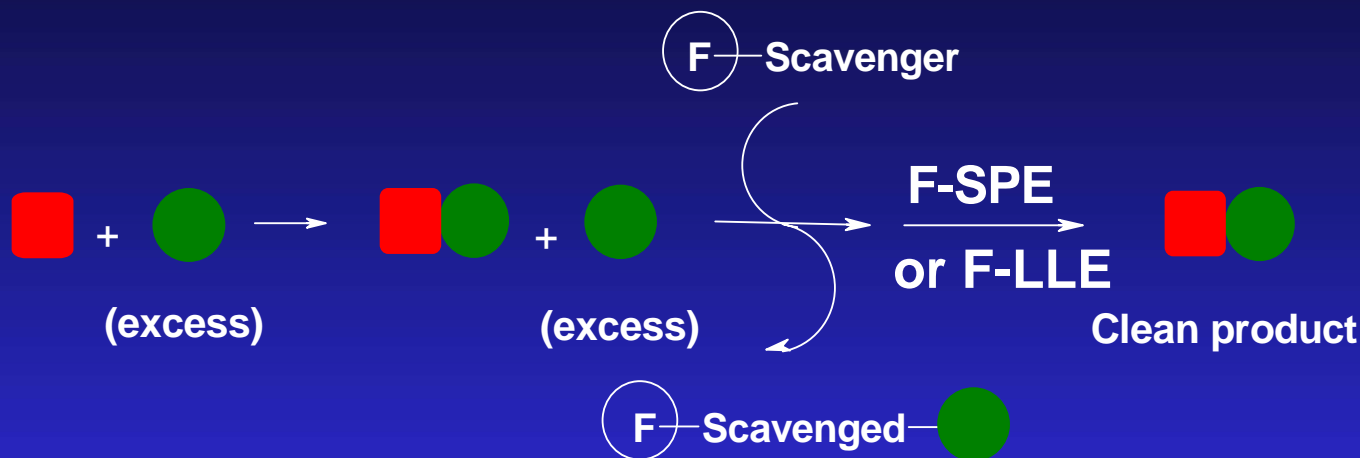
# Fluorous Acylation Reactions



Entry	Ester or Acid	Alcohol	Product	Yield(%)
1	Ph(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Et	PhCH=CH <sub>2</sub> OH		100
2	PhCH=CH <sub>2</sub> CO <sub>2</sub> Et	PhCH=CH <sub>2</sub> OH		99
3	Ph(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	BnOH	Ph(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Bn	99
4	Ph(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	borneol		63
5	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> H	BnOH	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> Bn	93

# Fluorous Scavenging

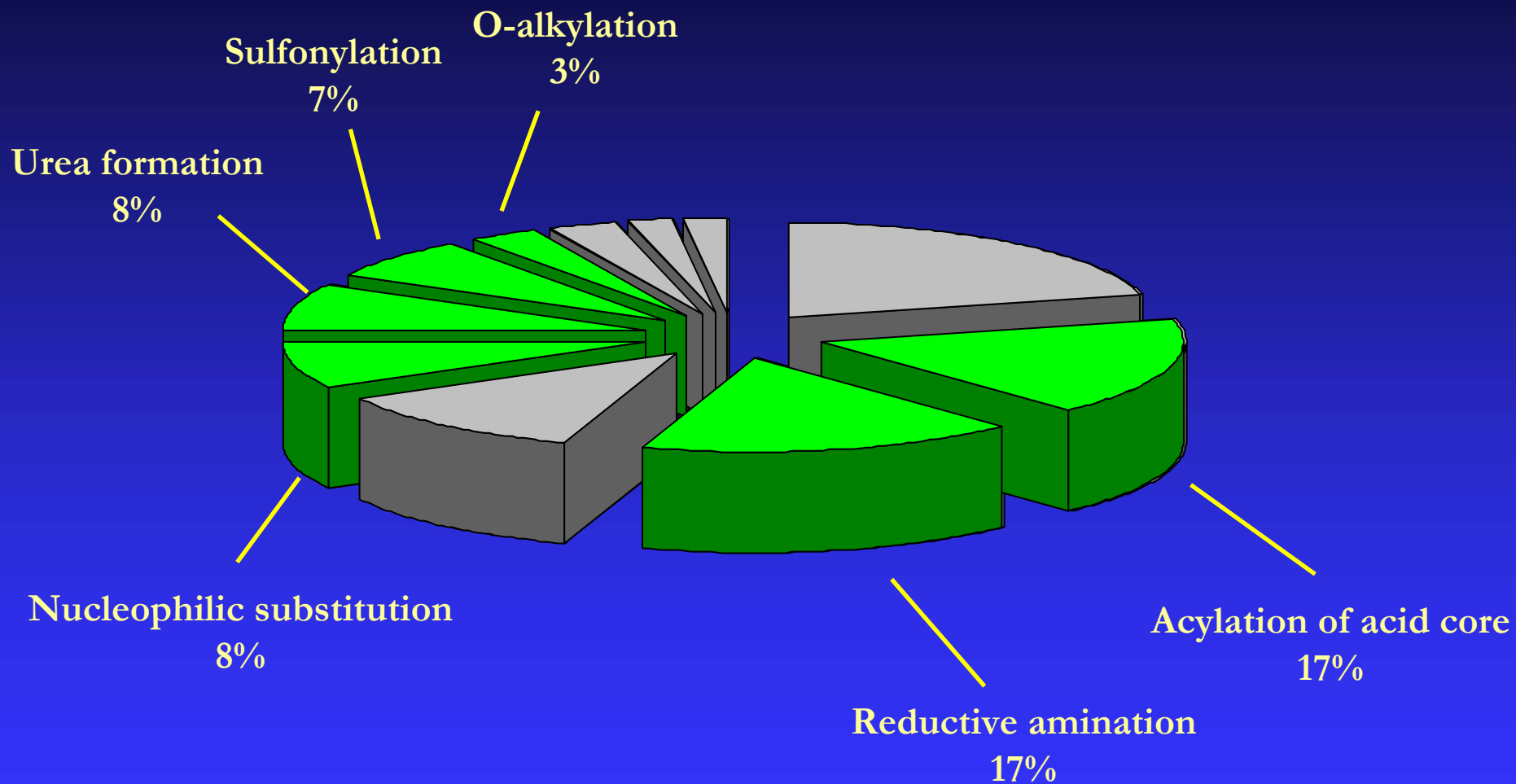
*A Strategic Alternative to Resin bound Scavengers*



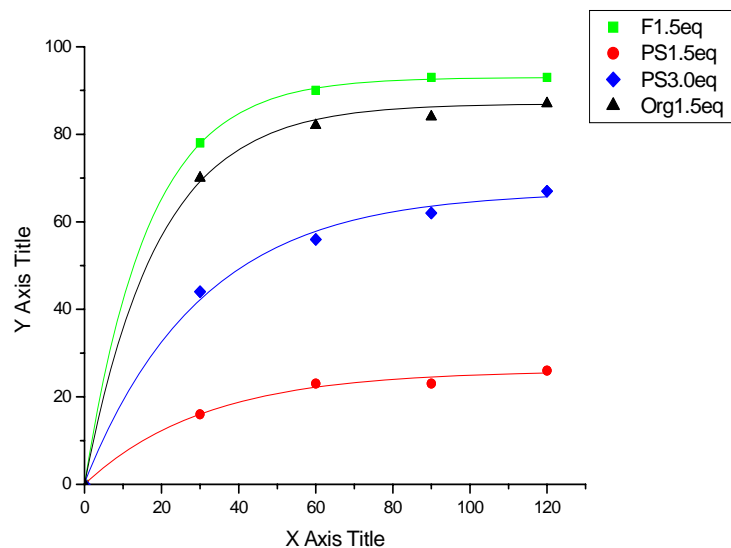
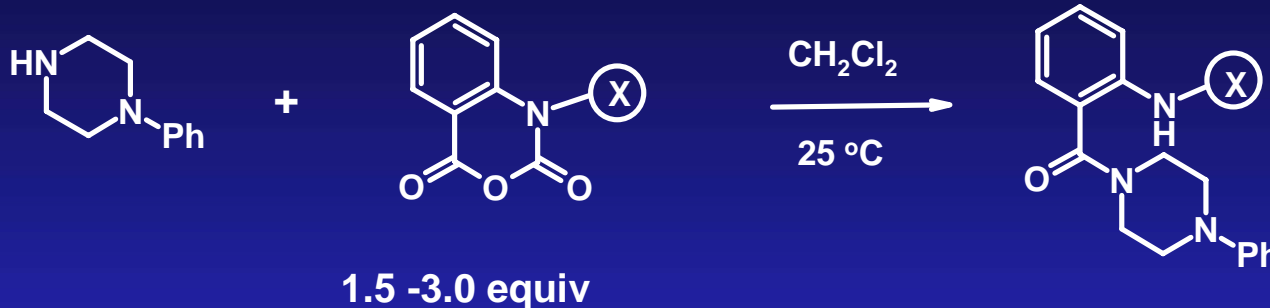
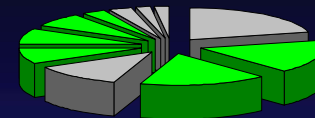
- Both reaction and scavenging carried out in homogenous solution phase
  - Favorable solution phase kinetics
  - Complete reaction monitoring, i.e. TLC, GC, LC, NMR
  - Adaptable to SPE, HPLC or liquid extraction workup
- Complete control of reagent stoichiometry



# Electrophilic Fluororous Scavengers

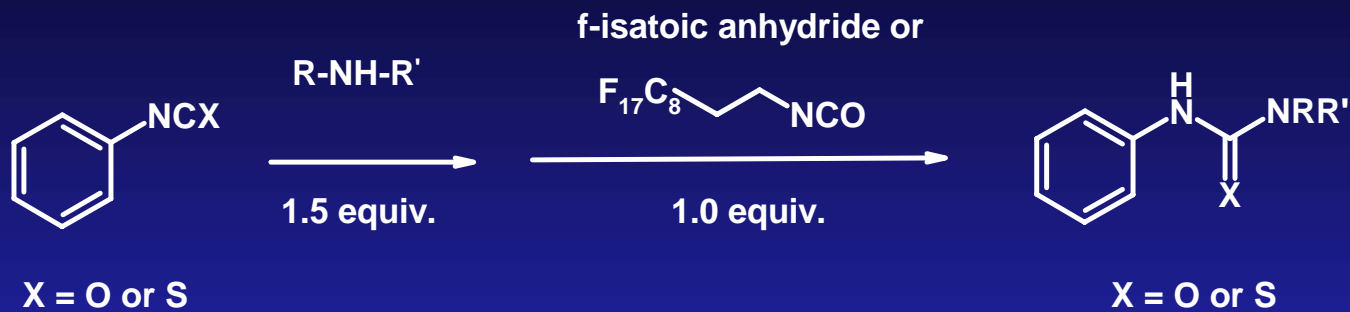
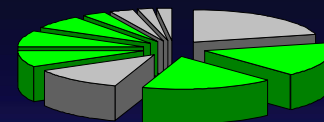


# Electrophilic Fluorous Scavengers



- Solution phase kinetics
- Less equivalents used
- Decreased loss of desired product
- Greater generality

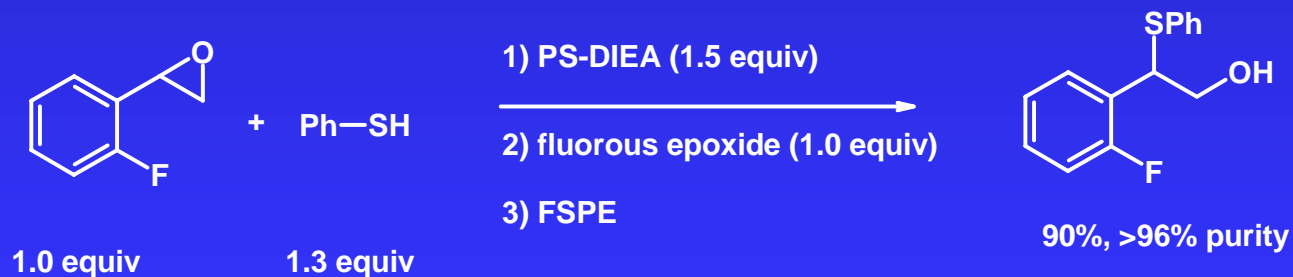
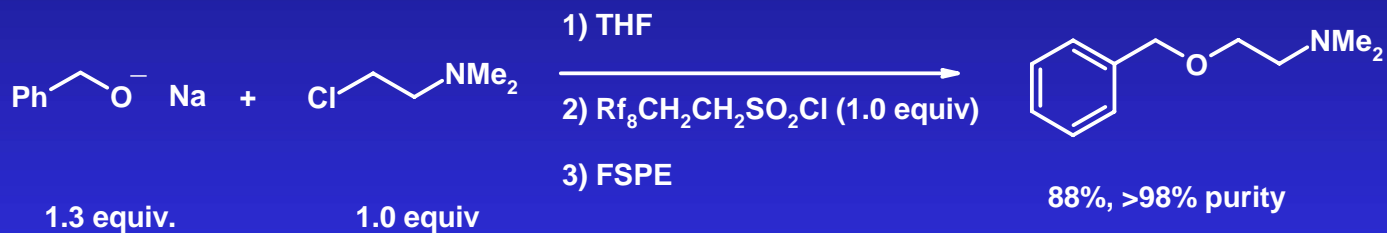
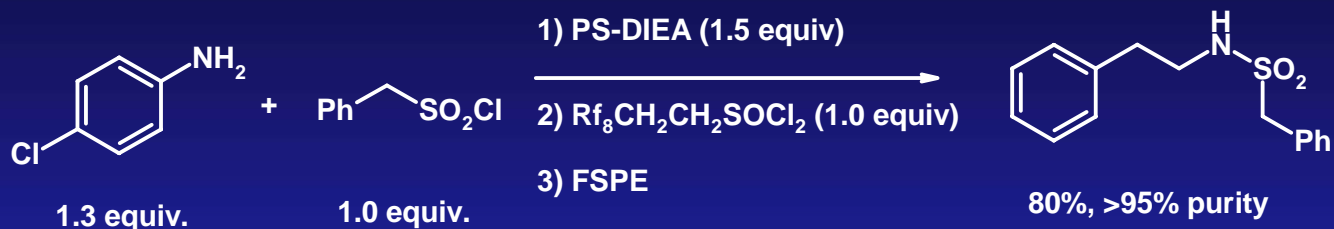
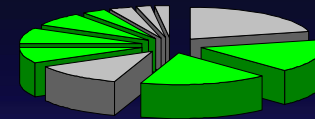
# Electrophilic Fluorous Scavengers



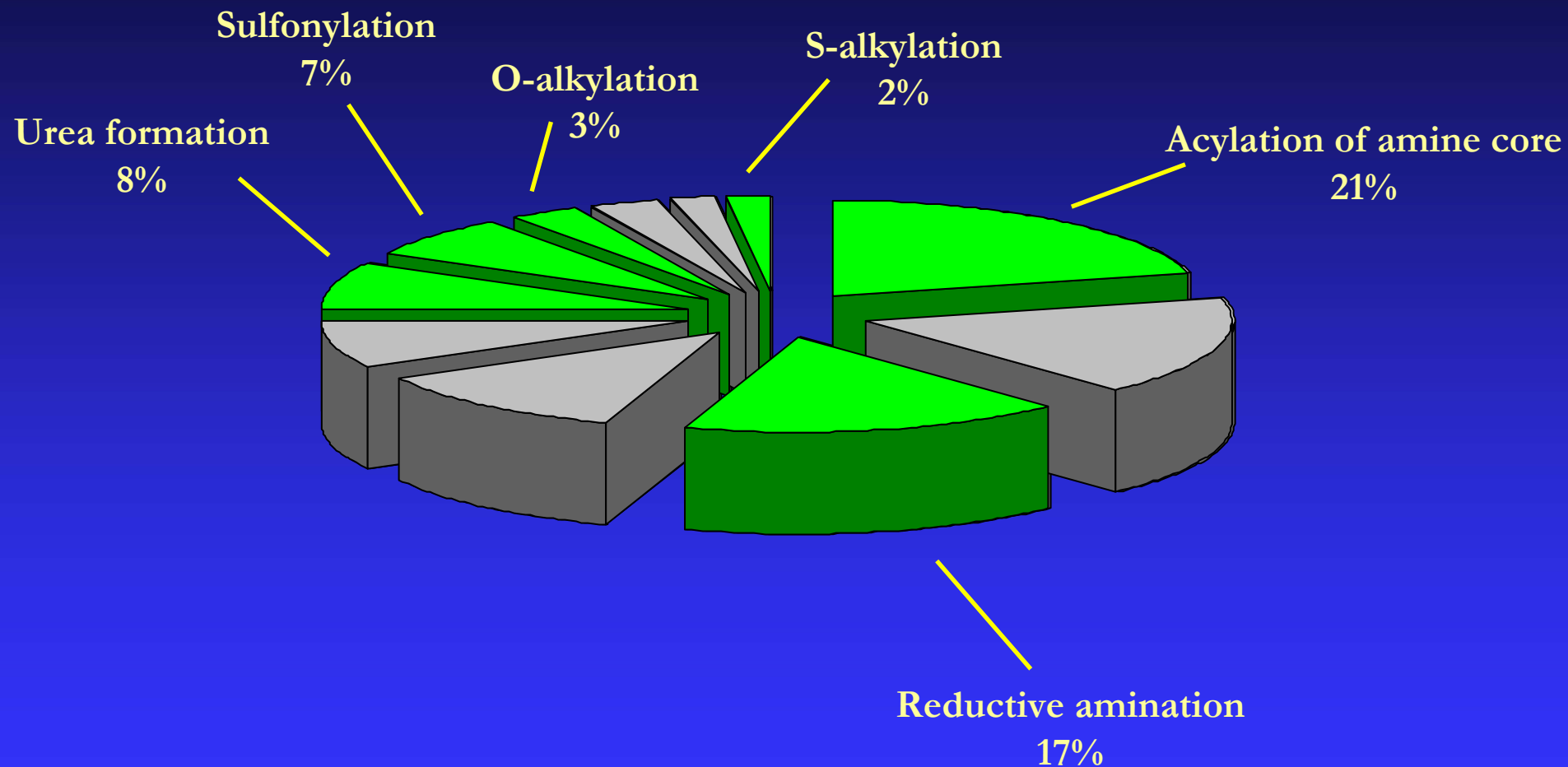
<u>Entry</u>	<u>X</u>	<u>Amine</u>	<u>Scavenger</u>	<u>Product</u>	<u>Yield (purity)</u>
1	O		f-IA		100% (>95%)
2	O		f-isocyanate		100% (95%)
3	S		f-IA		100% (95%)
4	S		f-isocyanate		34% (95%)

Zhang, W. *et al*, *Tetrahedron Lett.* **2003**, *44*, 2065.

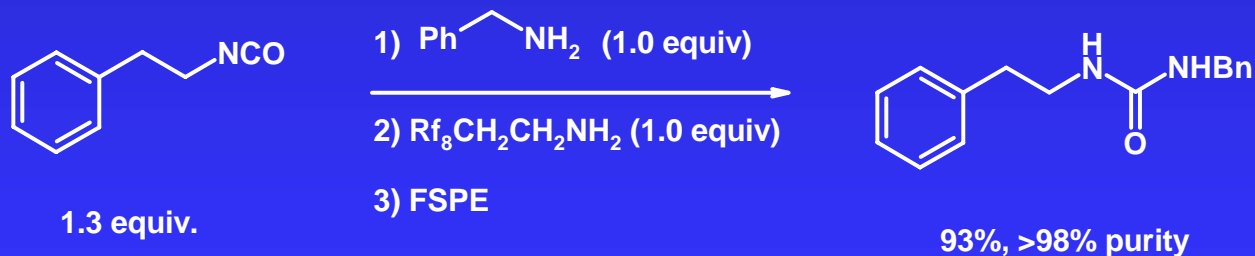
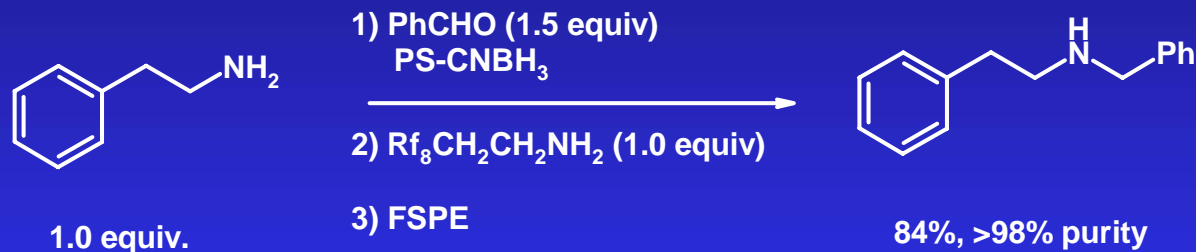
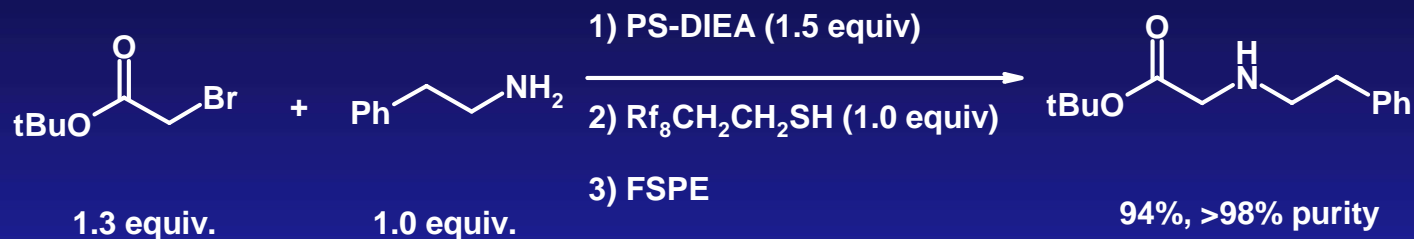
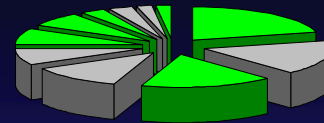
# Electrophilic Fluorous Scavengers



# Nucleophilic Fluorous Scavengers

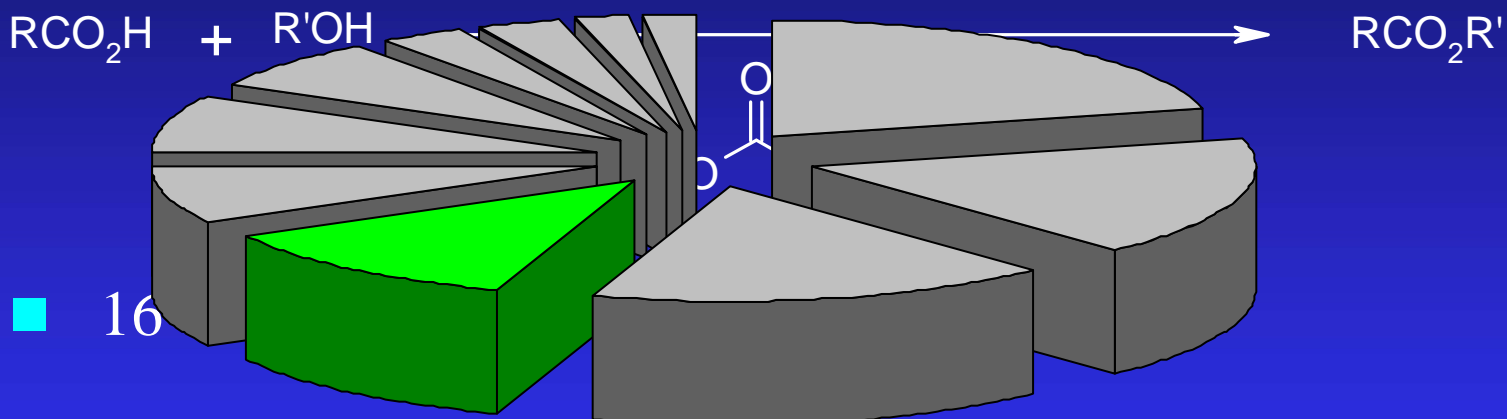
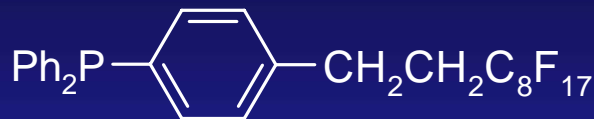


# Nucleophilic Fluorous Scavengers



# Fluorous Mitsunobu Reactions

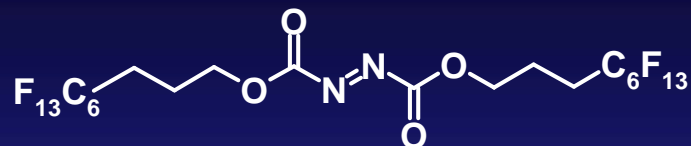
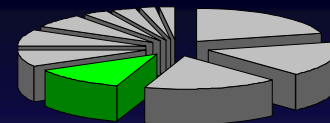
*Fluorous Phosphines & f-DEAD Reagent*



- F-SPE easily removes fluorinated byproducts  
Hydrazide + Phosphine Oxide in a single purification  
Mitsunobu reaction  
12%
- Liquid-liquid extraction possible

Dandapani, S.; Curran, D. P. *Tetrahedron*, **2002**, 58, 3855.

# Fluorous Mitsunobu Reactions



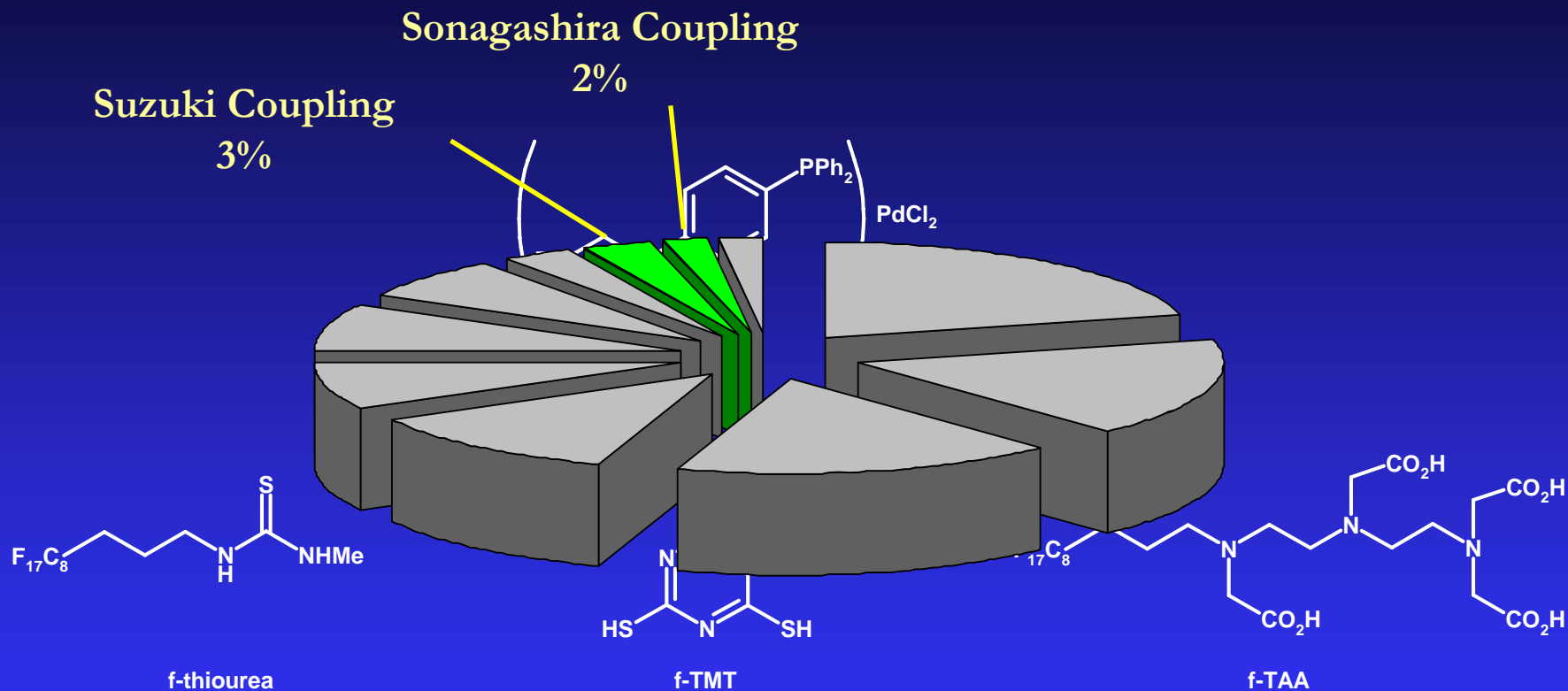
**f-DIAD**

Entry	Reactants	Conditions	% Yield (% purity)
1		TPP, DIAD	95
		<b>f-TPP, f-DIAD</b>	<b>92(99)</b>
2		TPP, DIAD	94
		<b>f-TPP, f-DIAD</b>	<b>94(96)</b>
3		TPP, DIAD	75
		<b>f-TPP, f-DIAD</b>	<b>60(97)</b>
4		TPP, DIAD	74
		<b>f-TPP, f-DIAD</b>	<b>55(97)</b>

Dandapani, S.; Curran, D. P. *Org. Lett.* **2004**, submitted.

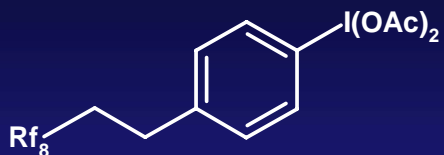


# Fluorous Catalysts and Scavengers



- Bis(f-TTP)PdCl<sub>2</sub> suitable for various Pd catalyzed reactions
- Other fluorous phosphines and ligands available
- Full evaluation of scavengers underway for removal of residual Pd
- Initial result with thiol resulted in 85% reduction of residual Pd

# Other Fluorous Reagents



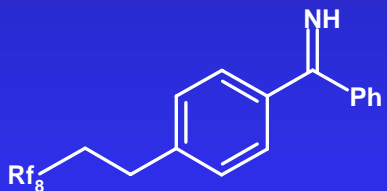
hypervalent iodine oxidations

Co(f-salen)

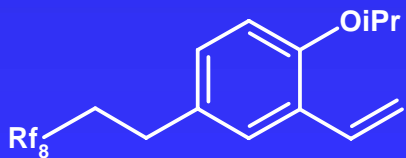
epoxidations



Radical mediated reductions  
and cyclizations



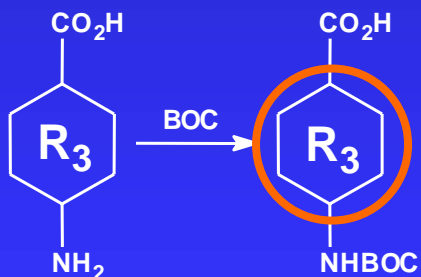
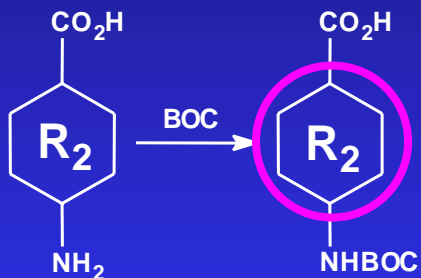
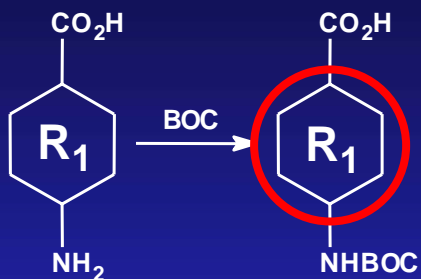
Buchwald-type aminations



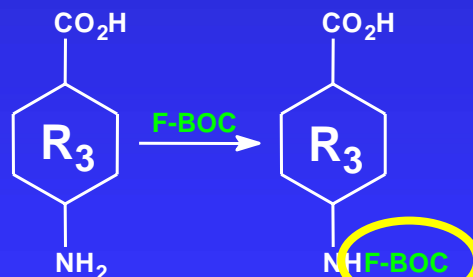
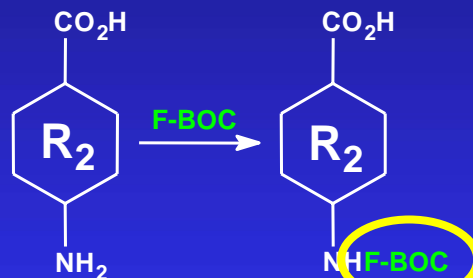
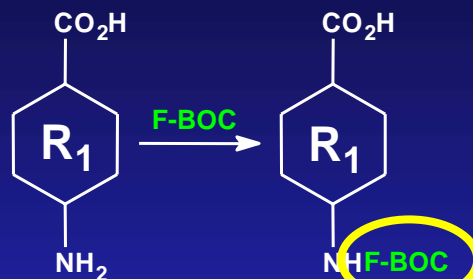
Olefin metathesis ligand

# Fluorous Parallel Synthesis

## Non-fluorous



## Fluorous



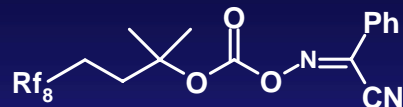
**Non-fluorous**: multiple chromatographic species, since separation controlled by variable domain.

**Fluorous**: single chromatographic species using single method on fluorous sorbent, since separation controlled by non-variable fluorous domain

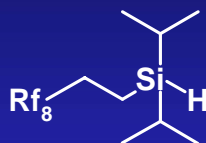
*Greater Productivity by Minimizing Method Development Time*

# Fluorous Tags

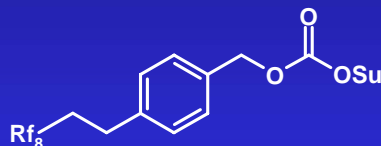
**f-BOC-ON**



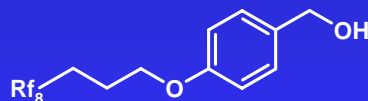
**f-silane**



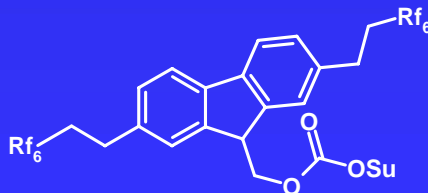
**f-Cbz-OSu**



**f-PMB**

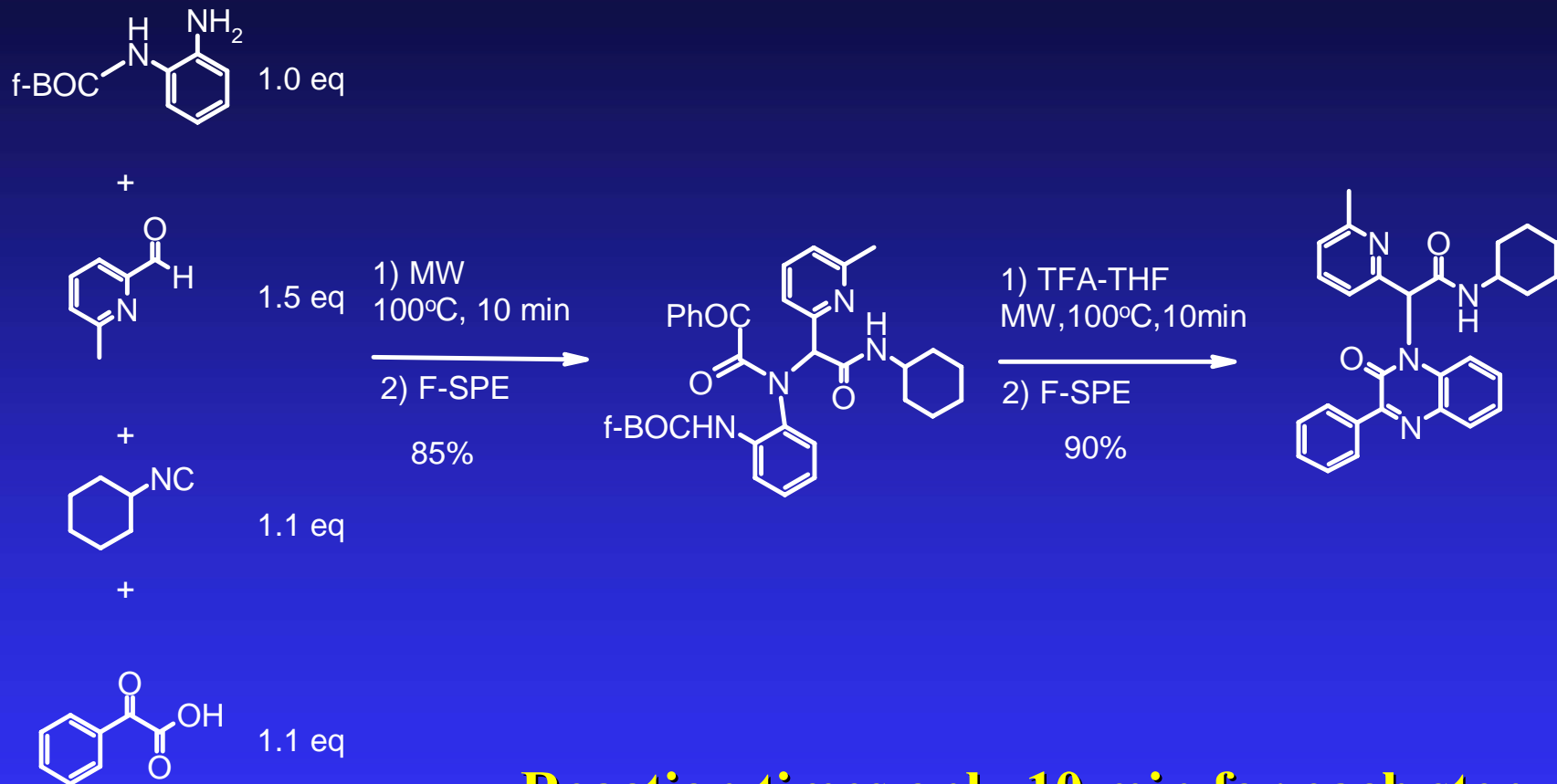


**f-Fmoc**



**Fluorous tags behave similar to traditional protecting groups, but provide a handle for facile purification.**

# Fluorous Tagged Approach



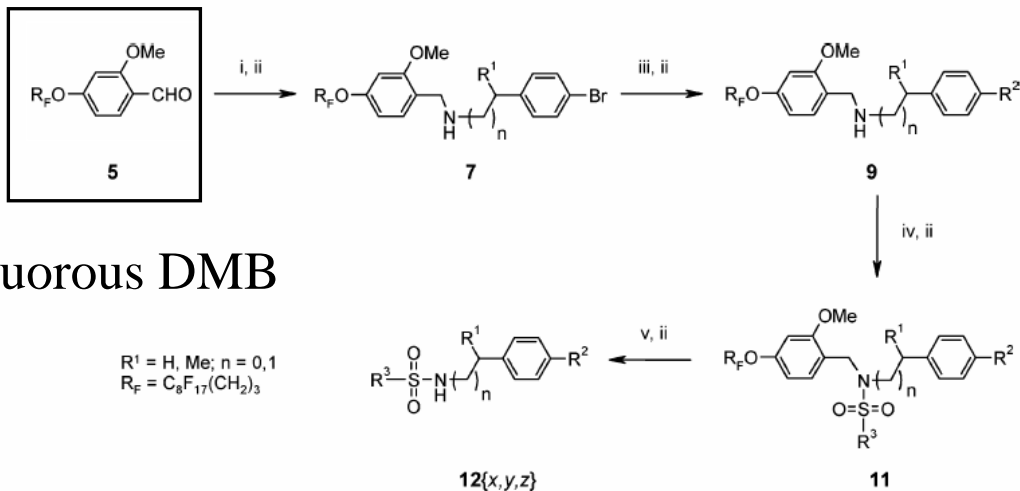
- **Reaction times only 10 min for each step**
- **F-SPE replaces double scavenging**

Zhang, W.; Tempest, P. *Tetrahedron Lett.* 45 (2004) 6757–6760.

# Fluorous Parallel Synthesis

Ladlow, M., Warrington, B. H., Villard, A.-L. *J. Comb. Chem.* 2004, 6(4), 611-622.

Scheme 2<sup>a</sup>



Fluorous DMB

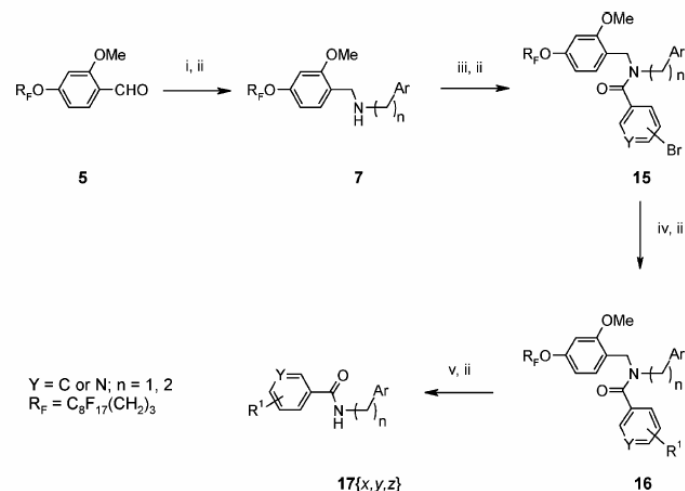
27-member  
Sulfonamide Array

<sup>a</sup> Reagents and conditions: (i) amine **6**[x], NaBH(OAc)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; (ii) R<sub>F</sub>-SPE; (iii) R<sup>2</sup>B(OH)<sub>2</sub> **8**[y], Pd(Ph<sub>3</sub>P)<sub>4</sub>, K<sub>3</sub>PO<sub>4</sub>, PhMe, H<sub>2</sub>O, MW, 120 °C, 20 min; (iv) R<sup>3</sup>SO<sub>2</sub>Cl **10**[z], MTDA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 18 h; (v) TFA, TES, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, [5:5:0.5:89.5], rt, 3 h.

All analogs >95% purity  
with no HPLC

18-member  
Carboxamide Array

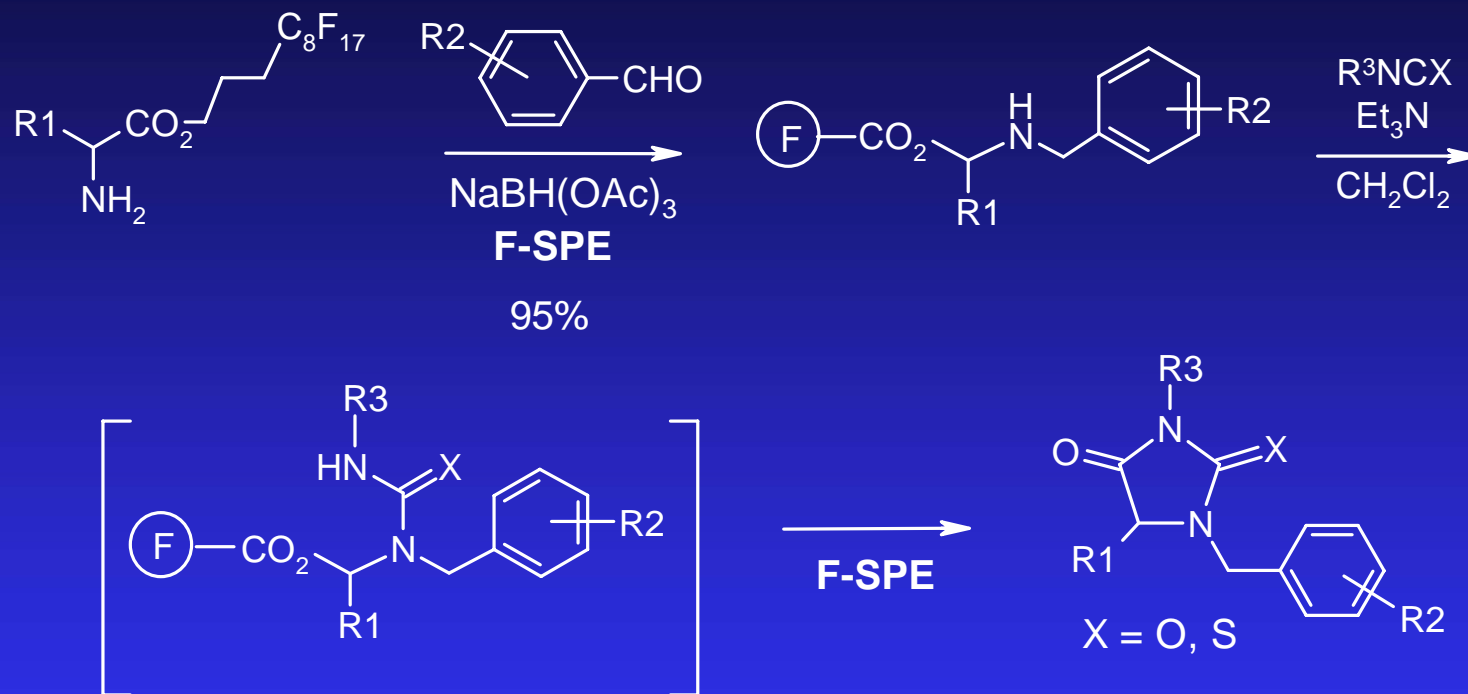
Scheme 4<sup>a</sup>



<sup>a</sup> Reagents and conditions: (i) amine **6**[x], NaBH(OAc)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; (ii) R<sub>F</sub>-SPE; (iii) acid chloride **14**[y], DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 20 h; (iv) R<sup>1</sup>B(OH)<sub>2</sub> **8**[z], Pd(Ph<sub>3</sub>P)<sub>4</sub>, K<sub>3</sub>PO<sub>4</sub>, PhMe, H<sub>2</sub>O, MW, 120 °C, 10 min; (v) TFA/TES/H<sub>2</sub>O, [90:5:5], rt, 18 h.

# Fluorous Parallel Synthesis

## Synthesis of Hydantoin Library



- 120 compound library produced. No HPLC purification
- Avg. yield = 30 mg (90% of compounds in >50% overall yield)
- 88% of compounds had >90% LC purity (MS detection)



## FSPE Practical Considerations

- Rf<sub>8</sub> derivatives are recommended for parallel synthesis.
- Most organic solvents can be used without issue. If solvation is a problem, the addition of BTF can help.
- Always try and design reactions to contain either one organic or one fluorous species.
- Generally run using a SPE vacuum manifold available from numerous vendors
- Fluorous TLC and HPLC can be valuable analytical tools for SPE evaluation.



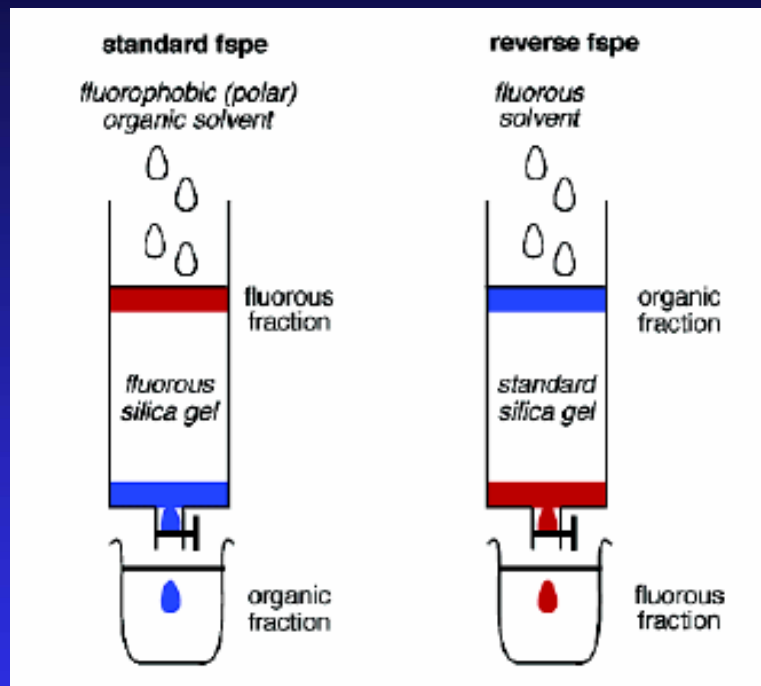


## FSPE Practical Considerations

- Maximum loading capacity of 20%, although 10-15% is recommended.
- Cartridge should be pre-treated with 80:20 MeOH:H<sub>2</sub>O and sample loaded using a minimum of solvent.
- First wash 80:20 MeOH:H<sub>2</sub>O and second wash 100% MeOH.
- Cartridge can be reused multiple times after washing with THF.

# Reverse Fluorous Solid Phase Extraction

*A Light Fluorous Technique*



## Standard FSPE

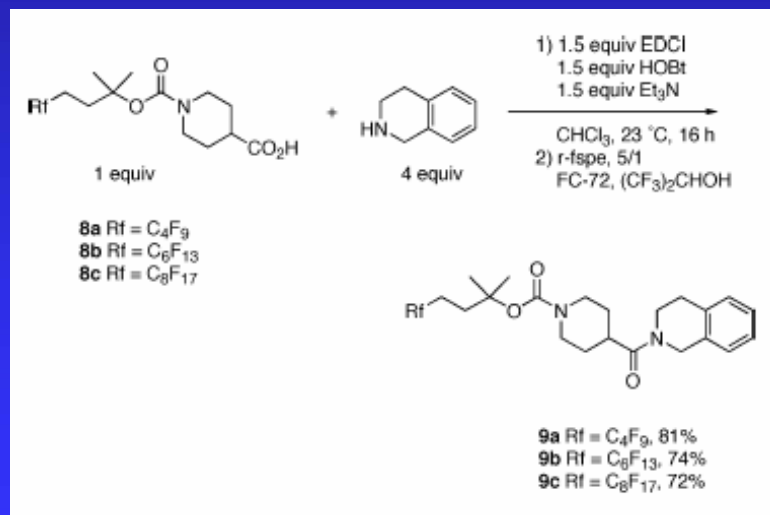
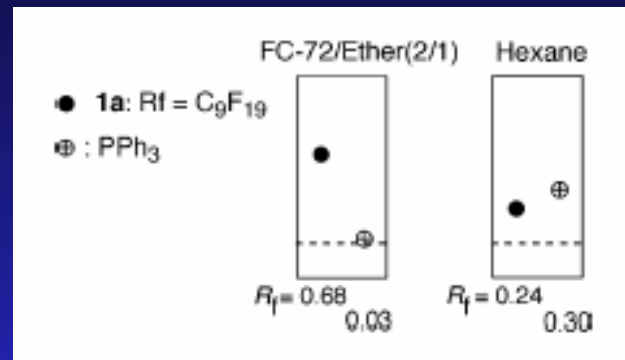
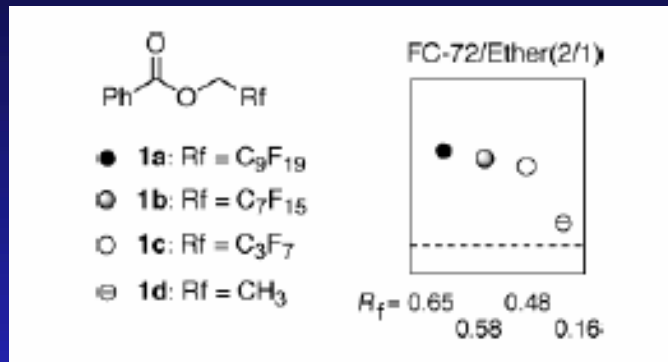
fluorous stationary phase  
fluorophobic mobile phase  
non-fluorous compounds washed

## Reverse FSPE

standard stationary phase  
fluorous mobile phase  
fluorous compounds washed

Matsugi, M. and Curran, D. P. *Org Lett.* 2004, 6, 2717.

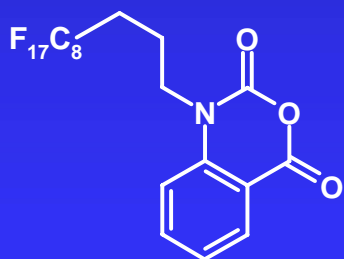
# Reverse Fluorous Solid Phase Extraction



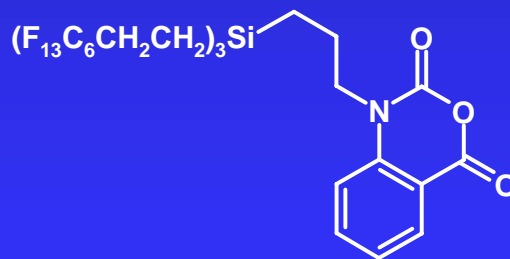
Matsugi, M. and Curran, D. P. *Org Lett.* **2004**, *6*, 2717.

# Fluorous L-L Extraction

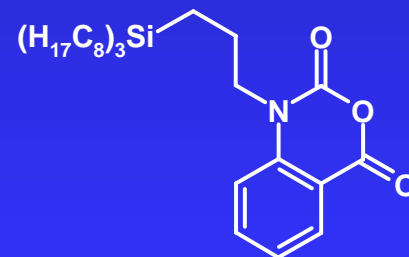
- Curran reported in 1999 that tris-silane based scavengers did not have sufficiently high partition coefficients to be useful.
- Numerous liquid-liquid supports and catalysts reported using 6 or more fluororous chains.
- Very little reported in solvent tuning as a method to influence partition coefficients.



light fluorous IA

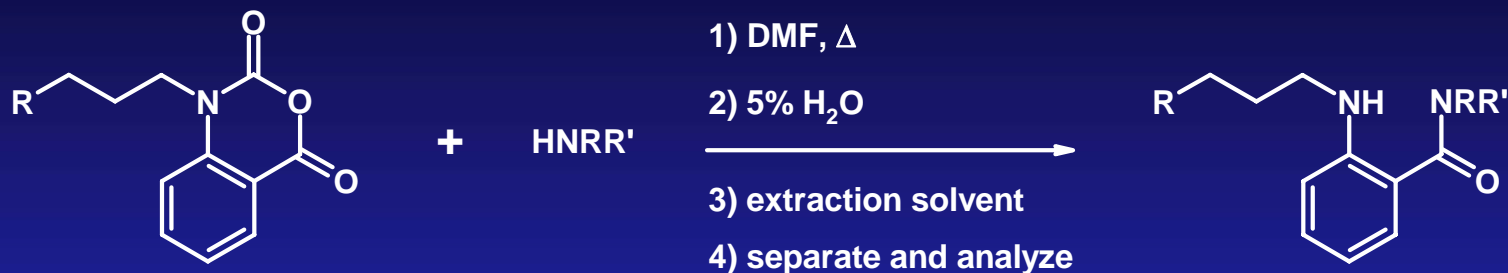


heavy fluorous IA



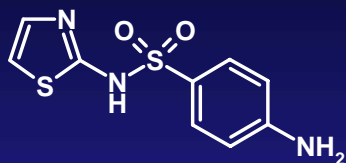
alkyl IA

# Heavy Fluorous Scavenging

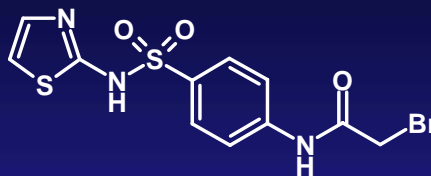


Entry	Amine	Scavenger	% in extraction solvent	% in 5% H <sub>2</sub> O in DMF
1		light	ND	>99.7
2		heavy	99	1
3		alkyl	88	12
4		heavy	98	2
5		alkyl	84	16
6		heavy	98	2
7		alkyl	38	62

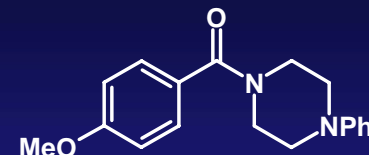
# L-L Extraction of Organic Controls



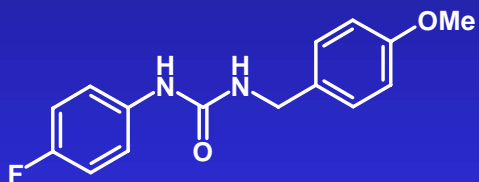
1.36



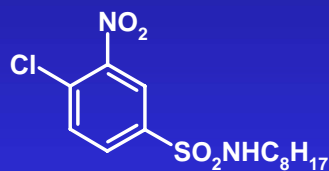
1.71



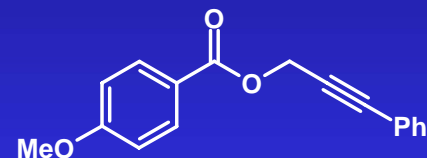
3.13



2.61



5.15



3.72

- 10 organic controls partitioned between 1:1 FC-72:HFE-7100 / 5% H<sub>2</sub>O in DMF.
- cLog P ranging from 1.36 – 5.65. All partitioned >99% in organic solvent
- No solubility problems at 50 mg in 1 mL.



# Other Emerging Fluorous Applications

- **Fluorous Biphasic Catalysis**
- **Fluorous Triphasic Separations**
- **Isotope Labeled Syntheses**
- **Oligomer Synthesis**
  - ◆ **Oligosaccharides**
  - ◆ **Oligonucleotides**
  - ◆ **Peptides**
- **Proteomics Applications**

# Chemical Reaction Compatibility

- **Ionic**

*Enolate, Grignard, lithiate, cationic*

- **Free Radical**

*Cyclization, dehalogenation, deoxygenation*

- **Lewis Acidic**

*Friedel-Crafts acylation,  $BBr_3$*

- **Transition metal catalyzed**

*Suzuki, Heck, Buchwald, Stille, Co, Rh*

- **Reduction/oxidation**

*LAH, hydrogenation,  $H_2O_2$ , Swern*





# Technology Synergies

- Fluorous Supplements Existing Technologies
  - Automated chromatography
  - Resin supported chemistry
  - Multi-component reaction platforms
- Compatible with Emerging Technologies
  - Microwave Assisted Synthesis
  - scCO<sub>2</sub> chromatography
- No Additional Capital Equipment Necessary

“Chemistry Solution to Chemistry Problems”



# How to Contact FTI

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