Fluorous Chemistry - A New Platform Technology

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advanced separation chemistry for life sciences
• What is fluorous chemistry?
• Fluorous separation techniques
  – Liquid-liquid extraction (LLE)
  – Solid-phase extraction (SPE)
  – Chromatography
• Combinatorial Applications
  – Microwave reactions
  – Multicomponent reactions (MCR)
  – Diversity-oriented synthesis (DOS)
  – Fluorous Mixture synthesis (FMS)
• New Development
  – Organocatalysis
  – Biomolecules
  – Microarray
  – Nanotechnology
What is Fluorous Chemistry?

- Fluorous chemistry is a novel tagging technology that separates desired molecules from complex mixtures.

- **Fluorous Synthesis** - Molecules are rendered fluorous by the attachment of perfluorocarbon domains.

- **Fluorous Separation** - Fluorous tagged molecules are separated from non-fluorous molecules exploiting fluorophilicity.

- **Fluorous Immobilization** - Fluorous tagged molecules are immobilized onto a fluorous-modified surface.
“Organofluorine” Chemistry

- Reaction-oriented chemistry
- Always associate with transformation of C-F bonds
- Fluorine atoms are usually present in the product

“Fluorous” Chemistry

- Purification/labeling-based chemistry
- Use highly fluorinated group to tag/label substrates
- No C-F bond formation is necessary
- Final products do not need to have fluorine atoms

ORGANIC CHEMISTRY. In the field of organic chemistry, 2001 saw significant new developments involving fluorous synthesis, ethane conformation, triplet carbenes, and the total synthesis of a major fish toxin.

Researchers reported that fluorous mixture synthesis--in which starting materials are tagged with fluorinated labels of different length--offers potential time savings over current methods for synthesizing combinatorial libraries of small organic molecules. The fluorous labels make it possible to run reactions on different starting materials in the same solution and yet easily...
Over 1200 papers on “fluorous” have been published since 1994
1st Component for Fluorous Synthesis - Fluorous Molecules

Organic Functional Group

Spacer

Fluorous Tag

F-Boc-ON (Amino protecting group)

F-Isatoic Anhydride (Nucleophile scavenger)

Organic group controls reactivity
Fluorous tag controls separation
More Fluorous Products

Reagents

Protecting Groups

Catalysts

Scavengers

F-Tag

C₆F₁₃(CH₂)ₙ

C₈F₁₇(CH₂)ₙ

FTI online catalog: www.fluorous.com
2nd Component for Fluorous Synthesis - Fluorous Separation Tools

LLE
use fluorous solvent

SPE
no fluorous solvent is needed!

HPLC

**New Solvent System for LLE**

![Fluorous Compound Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent system</th>
<th>Compound</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FC-72 / DMF</td>
<td>1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>2</td>
<td>FC-72 / DMF</td>
<td>2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>3</td>
<td>FC-72 / 5% H$_2$O in DMF</td>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td>4</td>
<td>FC-72 / 5% H$_2$O in DMF</td>
<td>2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>5</td>
<td>HFE-7100 / 5% H$_2$O in DMF</td>
<td>1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>6</td>
<td>HFE-7100 / 5% H$_2$O in DMF</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>FC-72:HFE-7100 / 5% H$_2$O in DMF</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>FC-72:HFE-7100 / 5% H$_2$O in DMF</td>
<td>2</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

$P^* = \frac{[\text{fluorous}]}{[\text{organic}]}$ as measured by GC

**FluoroFlash® Silica Gel**

with a perfluorinated \((C_8F_{17})\) stationary phase

- **F-SPE silica gel** (40 \(\mu\)m or 120 \(\mu\)m): 
  Selective retention of fluorous molecules

- **F-HPLC silica gel** (5 \(\mu\)m): Separation of a fluorous mixture based on fluorine content

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Fluorous Sorbent for Separation

SPE Cartridges

Flash Columns and Samplete

HPLC Columns

TLC Plates

Bulk Silica

FTI online catalog: www.fluorous.com
Fluorous SPE

Fluorophobic Solvent (MeOH-H₂O)

Fluorophilic Solvent (MeOH)

Cartridge can be reused after wash with acetone or THF

Basic Fluorous SPE

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

Fluorophilicity of common solvents

<table>
<thead>
<tr>
<th>Fluorophobic</th>
<th>Fluorophilicity of common solvents</th>
<th>Fluorophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>DMSO</td>
<td>MeOH</td>
</tr>
<tr>
<td>DMF</td>
<td></td>
<td>MeCN</td>
</tr>
<tr>
<td>MeOH</td>
<td></td>
<td>Acetone</td>
</tr>
<tr>
<td>MeCN</td>
<td></td>
<td>THF</td>
</tr>
</tbody>
</table>

organic dye (blue)
fluorous dye (orange)
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

96-Well Ex-Blok™

• up to 1.5 g of F-silica gel
• 3 mL receiving well
• use large size (120 μm) silica
• gravity SPE

plates can be reused

# PTP F-SPE for Scavenging Reactions

![Chemical structure](image)

**Reaction Scheme:**

\[
RR'NH + \text{excess 1.2 equiv} \quad \text{NCO} \quad \text{THF} \quad \text{F-SPE} \quad \text{NRR'NH}
\]

<table>
<thead>
<tr>
<th>Scavenger</th>
<th>Yield%</th>
<th>Product Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$NBu</td>
<td>95(92)*</td>
<td>86(96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81(99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81(99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100(96)</td>
</tr>
<tr>
<td></td>
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<td>100(96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100(96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92(100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92(100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90(100)</td>
</tr>
</tbody>
</table>

* yield% (purity%, UV254)

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

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**References:**

Automated F-SPE by RapidTrace

Caliper Life Sciences

Single unit (10 Cartridges) 10 units parallel (10x10 cartridges)

- Automatic sample loading (including slurry samples)
- Pump-controlled solvent delivery
- Automatically condition, rinse and elution
- 10 Cartridges each module, up to 10 modules

Large Scale Flash Chromatography

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

ISCO                         Biotage                         FlashMaster II

Rf₈(CH₂)₂

1.0 equiv

1.5 equiv

N

Ph

EDCI (1.5 equiv)
HOBOT (2.0 equiv)
Et₃N (2.0 equiv)
CHCl₃, rt, 2 h

Ph

N

N

O

CO₂H

(CH₂)₂Rf₈

All organic byproducts

Fluorous product
Fluorous HPLC for Demixing

Separate fluorous mixture based on fluorine content

Stationary Phase Comparison

Conventional C_{18}:

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Si} \\
\text{Me} \\
\hline
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

Fluoroscope PFP (C_{6}F_{5}):

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Si} \\
\text{Me} \\
\hline
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

FluoroFlash (C_{8}F_{17}):

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Si} \\
\text{Me} \\
\hline
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

7-component mixture:

\[
\begin{array}{l}
\{1\} \text{Me/C}_{3}F_{7} \\
\{2\} \text{Pr/C}_{4}F_{9} \\
\{3\} \text{Et/C}_{6}F_{13} \\
\{4\} \text{s-Bu/C}_{7}F_{15} \\
\{5\} \text{i-Pr/C}_{8}F_{17} \\
\{6\} \text{c-C}_{6}H_{11}/C_{9}F_{19} \\
\{7\} \text{c-C}_{2}H_{4}/c-C_{6}H_{11}/C_{10}F_{21} \\
\end{array}
\]

R_{f} = \text{CH}_{2}CH_{2}(\text{iPr})_{2}\text{SiO}
Solution-Phase vs Solid-Phase Synthesis

**Pro**

**Solution Phase**
- traditional reaction conditions
- easy intermediate analysis
- favorable reaction kinetics
- large scale possible

**Solid Phase**
- rapid purification by filtration
- split-pool mixture library synthesis
- excess reagent can be used
- automation possible

**Con**

- slow purifications
- heterogeneous reactions

**Fluorous Synthesis:** Combines the advantages of solution- and solid-phase synthesis, address both reaction and separation issues

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.
Fast Solution-Phase Reaction Kinetics

Fluorous vs PS-Scavengers

\[
\text{HN} \quad \text{N}_{\text{Ph}} + \quad \begin{array}{c}
\text{R} \\
\text{O} \\
\text{CH}_2C\text{O}
\end{array} \quad \xrightarrow{\text{CH}_2\text{Cl}_2/25 \degree C} \quad \begin{array}{c}
\text{N} \\
\text{R} \\
\text{O} \\
\text{N} \\
\text{Ph}
\end{array}
\]

1.0 equiv + 1.5 or 3.0 equiv scavenger

\[ R = (\text{CH}_2)_3\text{C}_8\text{F}_{17} \]

\[ R = \text{C}_8\text{H}_{17} \]

Follow the F-DCT Reaction by $^1$H NMR

$$\text{Br} \quad \text{CO}_2\text{H} \quad \text{Me} \quad \text{NH}_2$$

2 equiv 2 equiv

$\text{F-DCT} \quad (1 \text{ equiv})$

NMM

THF

$\rightarrow$

$$\text{Br} \quad \text{O} \quad \text{N} \quad \text{Me}$$

2 equiv

$\text{THF-}d_6$

a

$$\text{Br} \quad \text{CO}_2\text{H} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl}$$

F-DCT

(2:1) starting materials

b

add NMM

activated acid

c

add amine

amide product

d

F-SPE purified product

Fast Fluorous Synthesis System

**Fast reaction**

MW Reactor
fluorous compounds are stable under μw irradiation

**Easy purification**

Plate to Plate F-SPE
for parallel separation

**F-component recovery**

SpeedVac
for concentration of SPE receiving plates

Fluorous Tagging Strategies

- **Tagging reagents/scavengers/catalysts**

  ![Reaction Diagram]

- **Tagging substrates for parallel and mixture syntheses**

  ![Reaction Diagram]

Fluorous Reagents

Fluorous Phosphines and DIAD for Mitsunobu reactions

\[
\text{F-Phosphine} \quad \text{F-DIAD}
\]

F-Tin Oxide for Transesterifications

\[ \text{catalyst (10\%)} \]

\[ \text{C}_6\text{H}_5\text{Cl} \]

\[ 200 \, ^\circ\text{C}, 10 \, \text{min} \]

\[ \text{F-SPE} \]

\[
\begin{align*}
\text{catalyst} & \quad \text{yield} \\
1 & \quad 60\% \\
2 & \quad 78\% \\
3 & \quad 27\% \\
4 & \quad 80\%
\end{align*}
\]

F-catalyst 4 has the best result
Fluorous Scavengers

F-Scavenger + excess → F-SPE
F-Scavenger + unreacted
F-Scavenged

\[ \text{C}_8\text{F}_{17} \text{SH} \quad \text{F-Isocyanate} \quad \text{F-Isatoic anhydride} \]

F-Thiol as Halide Scavenger

Fluorous Catch and Release Tags

\[ \text{F} + \text{F} \xrightarrow{\text{de-tag}} \text{F-SPE} \]

\[ \text{F-Thiol} \quad \text{FluoMar} \quad \text{C}_8\text{F}_{17}\text{O}_2\text{SF} \]

Fluorous Protecting Groups

RfCH₂CH₂(iPr)₂SiH  
F-Silane

F-Cbz-OSu

Rf

F-Boc-ON

F-PMB

F-Benzaldehyde Protecting Group

Fluorous-Enhanced MCRs

F-component

+ excess non-fluorous components

MCR

F-SPE

F-intermediate fished out by F-SPE

substitutive/cyclative tag cleavage

F-SPE

clean product

Zhang, W. Comb. Chem. High Throughput Screening 2007, 10, 219
Ugi/de-Boc/Cyclization Synthesis

**Step 1**

- normal Boc: 36-48h, double scavenging to remove aldehyde and acid
- F-Boc + \( \mu \)w: 120 °C, 20 min, F-SPE

**Step 2**

- 4-24 h, flash chromatography
- 120 °C, 20 min, F-SPE

The microwave + fluorous approach is faster and easier

---

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

Preparation of F-Sulfonates

$$\text{C}_8\text{F}_{17}\text{SO}_2\text{F} + \text{HO} \cdot \text{C}_8\text{R} \xrightarrow{1) \text{K}_2\text{CO}_3, \text{DMF}} \text{C}_8\text{F}_{17}\text{O}_2\text{SO} \cdot \text{C}_8\text{R} \xrightarrow{2) \text{F-SPE or}} \text{soluble in many} \xrightarrow{\text{crystalization}} \text{organic solvents}$$

$0.6/g$

Biaryl-Substituted Hydantoins

\[
\text{CHO} \quad \begin{array}{c}
\text{C}_8\text{F}_{17}\text{O}_2\text{SO} \\
\text{N} \\
\text{OEt}
\end{array}
\]

\[
\text{C}_8\text{F}_{17}\text{O}_2\text{SO} \quad \begin{array}{c}
\text{NH}_2 \\
\text{OEt}
\end{array}
\]

\[
\text{Et}_3\text{N}, \text{DCM}
\]

\[
\text{F-SPE}
\]

\[
\text{R1} \quad \begin{array}{c}
\text{R2} \\
\text{R3} \\
\text{R4}
\end{array}
\]

Biaryl-Substituted Proline Analogs

1,3-dipolar cycloaddition
(120°C, 20 min)
F-SPE

MeO
C₈F₁₇O₂SO
CHO

MeO
Et
O
O

NH2

Et
O
O

R1
R2
R3
R4

C₈F₁₇O₂SO
CHO

C₈F₁₇O₂SO
CHO

Biaryl Substituted Imidazo[1,2-a]pyridines

\[
\begin{align*}
\text{R1} & \quad \text{R2} & \quad \text{R3} \\
\text{MeO} & \quad \text{CHO} & \quad \text{CN} \\
\text{C}_8\text{F}_{17}\text{O}_2\text{SO} & + & \text{cat. Sc(OTf)_3} \\
\text{MeOH} & & \mu\text{w (150°C, 10m)} \\
\text{MeO} & & \text{F-SPE} \\
\text{C}_8\text{F}_{17}\text{O}_2\text{SO} & & 90% \\
\text{NH} & & \text{MeO} \\
\text{K}_2\text{CO}_3 & \quad \text{Pd(dppf)Cl}_2 & \quad \mu\text{w (150°C, 20m)} \\
\text{actone/toluene/H}_2\text{O} & & \text{F-SPE} \\
\text{MeO} & & 70% \\
\end{align*}
\]

Diversified Scaffolds from F-Amino Esters

Hydantoin/Thiohydantoin Library

\[
\text{Rf}_{8h3} - O - NH_2 \xrightarrow{\text{R}_2\text{CHO}} \text{NaBH(OAc)_3} \xrightarrow{\text{CH}_2\text{Cl}_2 \ 80-90\%} \text{Rf}_{8h3} - O - NH - R_1 \xrightarrow{\text{R}_3\text{NCX} \ et_3\text{N}} \xrightarrow{\text{CH}_2\text{Cl}_2 \ 45-95\%} \text{R}_2 - R_1 - \text{R}_3 - \text{R}_1 \xrightarrow{\text{Rf}_{8h3}} \]

Parallel Synthesis of Dihydropteridinone Library

Synthesis of a New Ring System

One-pot reaction generates four new rings, six bonds, and seven diastereocenters

Fluorous-Enhanced DOS

3 novel heterocyclic scaffolds with skeletal and substitution diversities

Hydantoin-Fused System

structural similar to tricyclic thrombin inhibitors
Pyrrolopyrazinedione-Fused System

Related to diketopiperazine-based inhibitors of human hormone-sensitive lipase
Benzodiazepine-Fused System

[3+2] product

privileged benzodiazepine ring system
Concept of Fluorous Mixture Synthesis (FMS)

Tag and mix → Mixture synthesis → Demix and detag

Fluorous tag products
Building blocks

5-Component FMS

M-5\{1-5\} 6\{1-7\} 7\{1-4\} 84 mixtures of five

1 mixture of five

M-8\{1-5,1-7,1-4\} 7 mixtures of five

9\{1-12\}

M-10\{1-5,1-7,1-4,1-12\} 84 mixtures of five

420 compounds

10\{1-5,1-7,1-4,1-12\}

11\{1-5,1-7,1-4,1-12\}

420 compounds

<table>
<thead>
<tr>
<th>Rf/R1{1-5}</th>
<th>R2{1-7}</th>
<th>R3 {1-4}</th>
<th>R4 {1-12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>{1} C2F5/i-Bu</td>
<td>{1} H</td>
<td>{1} Et</td>
<td>{1} H</td>
</tr>
<tr>
<td>{2} C4F9/Bn</td>
<td>{5} p-F</td>
<td>{7} p-CF3</td>
<td>{2} p-Me</td>
</tr>
<tr>
<td>{3} C6F13/p-ClBn</td>
<td>{6} p-Cl</td>
<td>{8} 3,4-diCl</td>
<td>{3} p-Br</td>
</tr>
<tr>
<td>{4} C8F17/Me</td>
<td>{2} t-Bu</td>
<td>{9} m-Me</td>
<td>{4} p-OMe</td>
</tr>
<tr>
<td>{5} C9F19/Et</td>
<td>{3} c-C6H11</td>
<td>{10} m-Br</td>
<td>{5} p-F</td>
</tr>
</tbody>
</table>

420 Ureas M-10 (84 x 5) by 91 FMS reactions (7 cycloadditions + 84 isocyanate reactions)
Could need 455 parallel reactions (35 cycloadditions + 420 isocyanate reactions)
A Typical HPLC Demixing

FluoroFlash® column (20x250 mm, 5 μm), gradient 80:20 MeOH-H₂O to 100% MeOH in 23 min, then THF for 4 min, 20 mL/min.

Demixing and purification of 20 (4x5) compounds in 5 min
Nature Product Mappicine Library

7-component (tag), 4-step mixture synthesis

4 steps → 560 analogs

Mappicine Library by FMS

90 reactions (1+1+8+80) for FMS, 630 reactions (7+7+56+560) for parallel synthesis

Separate by Product as a Mixture

NaH, LiBr

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{R1} \\
& \quad \text{Si(iPr)CH}_2\text{CH}_2\text{Rf} \\
\text{R}^2 & \quad \text{Br} \\
\text{Me} & \quad \text{I} \\
& \quad \text{O} \\
& \quad \text{Si(iPr)CH}_2\text{CH}_2\text{Rf} \\
\text{Si(iPr)CH}_2\text{CH}_2\text{Rf} & \quad \text{a mix. of 7 (major)}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{R} \\
\text{O} & \quad \text{NH} \\
& \quad \text{O} \\
& \quad \text{I} \\
& \quad \text{R1} \\
& \quad \text{Si(iPr)CH}_2\text{CH}_2\text{Rf} \\
\text{Si(iPr)CH}_2\text{CH}_2\text{Rf} & \quad \text{a mix. of 7 (minor)}
\end{align*}
\]

after flash column

before flash column
Library Scaffolds

JACS02,10443
JCC04,942
TL05,1807
QCS04,827
TL04,6757
OL04,1473
OL03,1015
TL04,6757
TL07,563
unpublished
OL03,1011
JFC06,588
MD03,199
OL04,1473
unpublished
OL05,2269
JCC06,687
EJOC06,2055
JCC06,687
unpublished
New Applications

- Organocatalysis
- Ionic Liquid
- Biomolecules
- Microarray
- Nanotechnology
### F-Imidazolidinone (MacMillan) Catalyst

#### Diels-Alder, 1,3-dipolar cycloaddition, Michael, Friedel-Crafts Reactions

**Catalyst**

![Catalyst Diagram](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield</th>
<th>Endo:Exo</th>
<th>ee% (Endo)</th>
<th>Cat Recovery</th>
<th>Purity of Recovered Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic</td>
<td>82%</td>
<td>90.3 : 9.7</td>
<td>88.4</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>Fluorous</td>
<td>86%</td>
<td>93.4 : 6.6</td>
<td>93.4</td>
<td>84%</td>
<td>99%</td>
</tr>
</tbody>
</table>

*by acid-base extraction.  b by F-SPE

---

Comparison of Organic and Fluorous

Organic catalyst

C<sub>8</sub>F<sub>17</sub>

Fluorous catalyst

88.4% ee

93.4% ee

analyzed by chiral GC
Comparison of Organic and Fluorous

F-CBS Method for Asymmetric Reduction of Ketones
(Soose et al. Org. Lett. 2005, 7, 3243)

F-(S)-Pyrrolidine Sulfonamide for Michael Addition
(Wang et al. Org. Lett 2006, 8, 3077)
Fluorous Ionic Liquid

Dietz et al. *Talanta* 2006, 69, 527


Fluorous Enhanced PS-Synthesis of Biopolymers

**Cap** undesired sequences

1. Coupling
2. Capping
3. Cleavage
4. F-HPLC

**Tag** desired sequence

1. Coupling
2. Capping
3. 1) Tagging
4. 2) Cleavage
5. F-HPLC

**Symbols:**
- Polymer support
- Monomers
- Fluorous cap
- Cap
- Fluorous tag

**References:**
F-Reagents for Biomolecule Synthesis

F-Fmoc

F-Boc

F-Cbz

F-TMSE-OH

F-Msc

F-CDMT

Froc

Bio Applications - Oligosaccharides

The Cap Approach

PS synthesis without cap

after F-cap and F-SPE

Bio Applications - Oligonucleotides

The Tag Approach

oligodeoxyribonucleotides (ODNs)

<table>
<thead>
<tr>
<th>Length</th>
<th>Sequence</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-mer</td>
<td>TTTCTCTAGACAATTGTGCAATACGTCTTT</td>
<td>75-88%</td>
</tr>
<tr>
<td>50-mer</td>
<td>TTTCTGTTGACAATTTATCATCGGTCGTAT-AATGTGTGGAATTGGTCTTT</td>
<td>60-100+%</td>
</tr>
<tr>
<td>75-mer</td>
<td>TTTCTGGTTAAGGTGTGTAATATGCTCGGC-TACTAATTAGTGAATTATTCTCGCTACT-ATTAAACAGTGTCTTT</td>
<td>100+%</td>
</tr>
<tr>
<td>100-mer</td>
<td>TTTCTGGTTAAGGTGTGAATTATGCTCGCAGC-TACTAATTCTGACTATTTCAATGCTCAGCTACTAATTTAATGAAGAGGTTAAGGTGTCTTTACGAGTAATAGTACAGCTACTATTTAATGTTGTCTTT</td>
<td>76-100%</td>
</tr>
</tbody>
</table>

*estimated by HPLC integration

**fluoro-Pak™ Column**

1) Fluoro-Pak™ Column
2) on-column detritylation w/TFA

desired oligonucleotide

+ non-tagged impurities

**oligo**

using typical solid-phase synthesis chemistry; cleave/deprotect

**Base**

**PG**

**FDMT**

**RO**

**NR'2**

**OH 5’**

**O**

**3’OH**

**oligo**

**OH**

**O**

**5’**

**P**

**O**

**+ non-tagged impurities**
Bio Applications - Oligonucleotides

F-DMT phosphoramidites

Capture and on-column deprotection on Fluoro-Pak column

Chemical structures and chromatograms showing synthesis steps.
Bio Applications - Proteomics (Peptide Purification)

Fluorous affinity separation

Microarray and Screening

A fluorous droplet containing 24 fluorous chains, 12 palladium ions and 24 bridging ligands

Summary

Features of fluorous chemistry
- Selective affinity separation
- Homogeneous reaction
- Intermediate analysis/purification
- Recovery of fluorous components
- Enhances existing technologies
  - Microwave-assisted reactions
  - Multicomponent reactions
  - Parallel and mixture synthesis
  - Diversity-oriented synthesis

New developments
- Asymmetric organocatalysis
- Biomolecule separation
- Immobilization/Microarray
- Nanotechnology
First Fluorous Book (2004)
Two Special Issues 2002 & 2006

Tetrahedron Symposium-In-Print  
“Fluorous Chemistry”  
Guest Editors: J. A. Gladysz and D. P. Curran  
Tetrahedron 2002, 58, 3823-4131

“Fluorous Synthesis”  
Guest Editor: W. Zhang  
QSAR Comb. Science 2006, 25 (8-9), 679-768
Fluorous Conferences

1st International Symposium on Fluorous Technologies
Bordeaux, France, July 3-6 2005
Co-Chairmen: J.-M. Vincent and R. H. Fish

2nd International Symposium on Fluorous Technologies
Yokohoma, Japan, July 29-August 1, 2007
Chairman: Junzo Otera

ACS Symposium “Recent Advances in Fluorous Chemistry”
ACS National Meeting, Washington D.C
August 27-31, 2005
Chairman: D. P. Curran
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