Fluorous Techniques for High Throughput Synthesis

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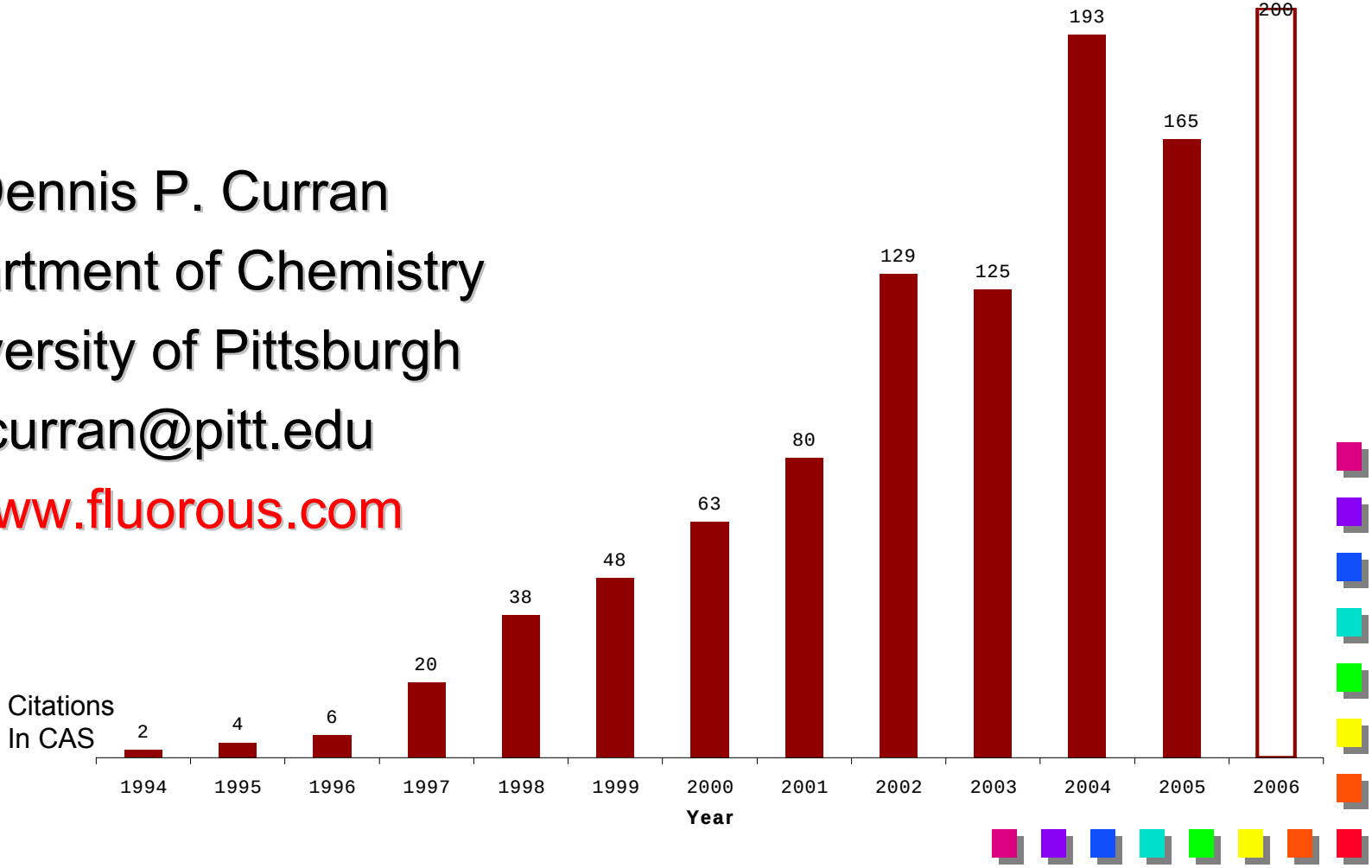
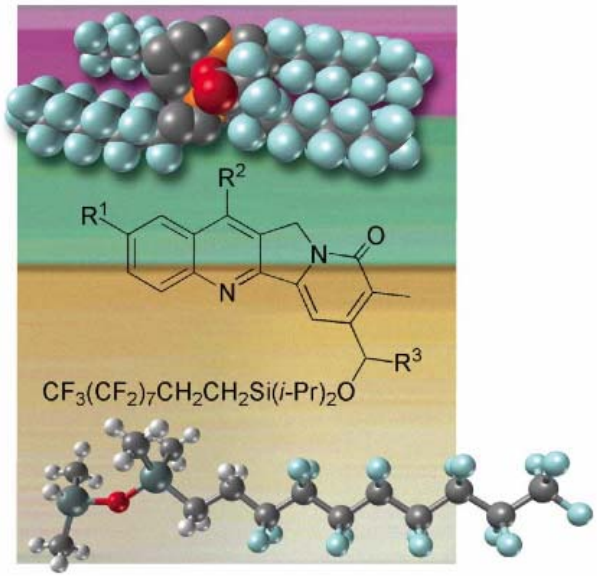


Edited by John A. Gladysz,
Dennis P. Curran, István T. Horváth

WILEY-VCH

Handbook of Fluorous Chemistry



Gladysz · Curran · Horváth (Eds.)

Handbook of Fluorous Chemistry

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VOL. 39, NO. 1 • 2006

Synthetic Applications of Buchwald's Phosphines in Palladium-Catalyzed Aromatic-Bond-Forming Reactions

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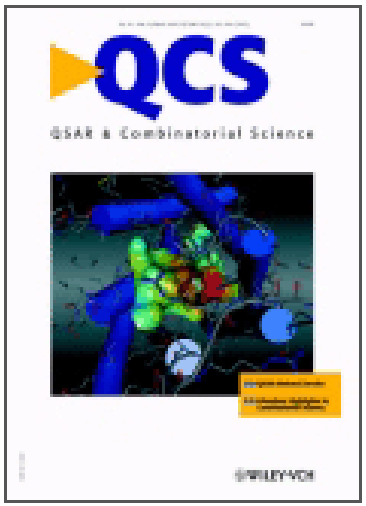
Tetrahedron Symposium-In-Print "Fluorous Chemistry"

Guest Editors: J. A. Gladysz and D. P. Curran
Tetrahedron 2002, 58, 3823-4131



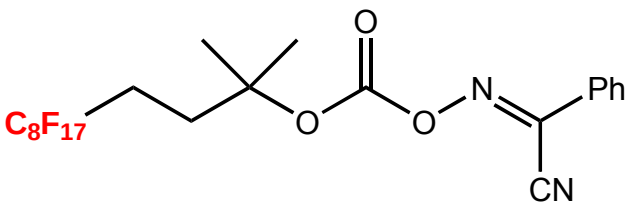
QSAR & Combinatorial Science (QCS)

"Fluorous Technologies for Parallel and High-Throughput Synthesis"

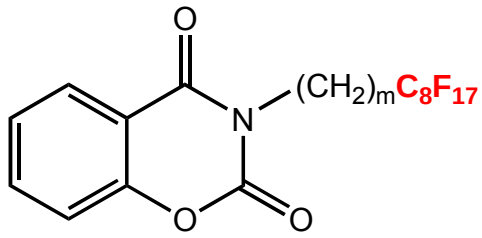
Guest Editor*: *Wei Zhang
Projected in Summer, 2006

Representative Light Fluorous Molecules

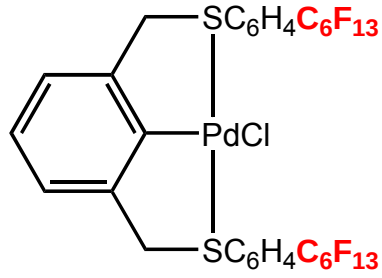
- The organic domain controls the reaction chemistry
  - Light fluorous molecules react like their organic “parents”
- The fluorous domain controls the separation chemistry
  - Fluorous separations are predictable and reliable
  - Traditional separation options remain



^{F}Boc-On

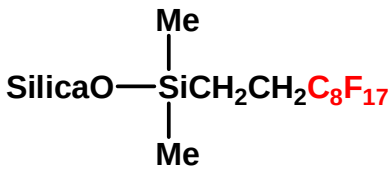


^{F}isatoic anhydride

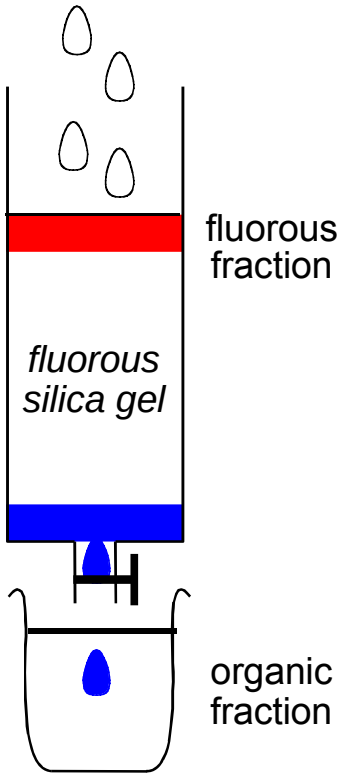


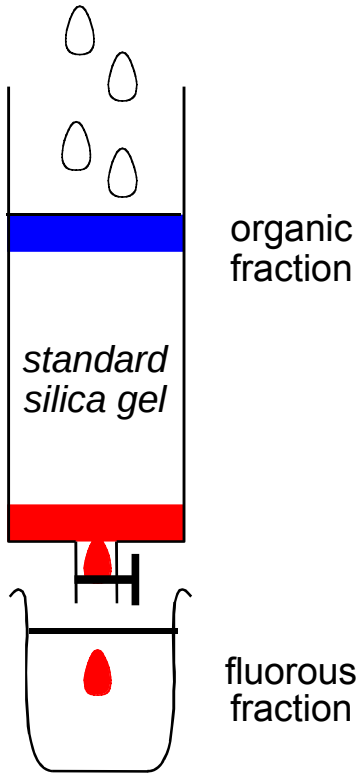
^{F}Pd-pincer complex

Standard/Reverse Fluorous spe



FluoroFlash® silica gel





1st solvent	fluorophobic (polar)	fluorous (FC-72/Et_2O)
2nd solvent	fluorophilic (Et_2O, THF)	any organic solvent

Synlett **2001**, 1488; HFC, Ch 7; *Org. Lett*. **2004**, *6*, 2717

Fluoro*Flash*® Silica Products

100 μm, gravity spe; 40 μm, vacuum/pressure spe; 5 μm, hplc

SPE Cartridges

Flash Columns and Samplets

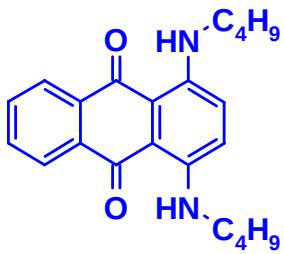
HPLC Columns

TLC Plates

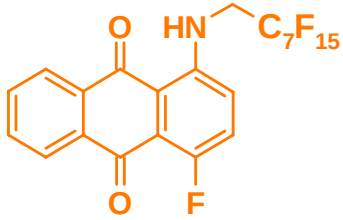
Bulk Silica

Fspe Techniques

Elution with MeOH-H_2O, then MeOH



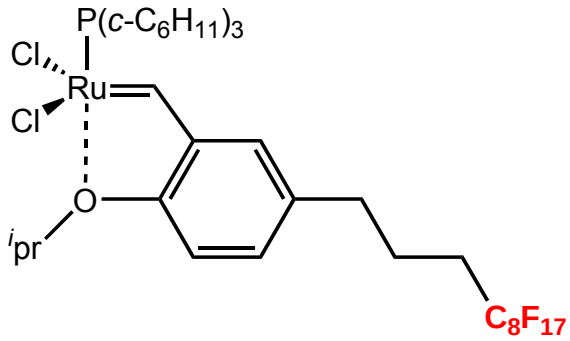
organic dye (blue)



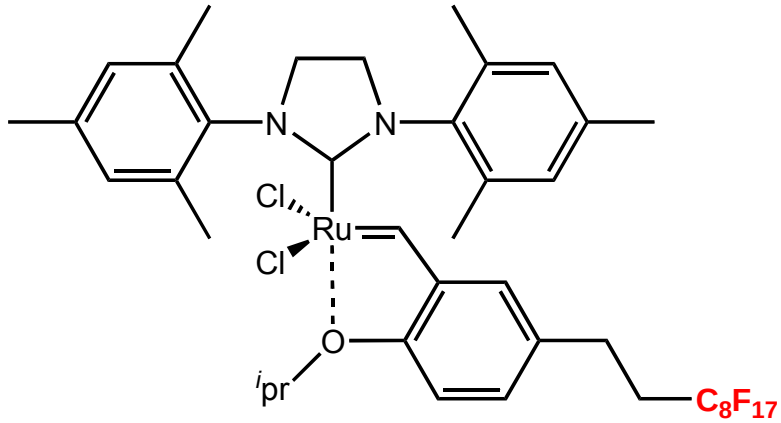
fluorous dye (orange)

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

Fluorous Grubbs-Hoveyda Catalysts



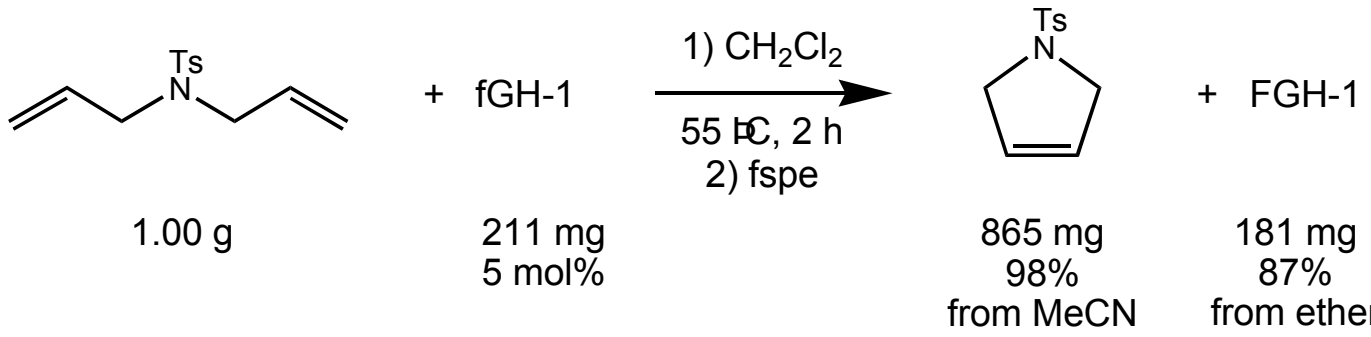
fGH-1

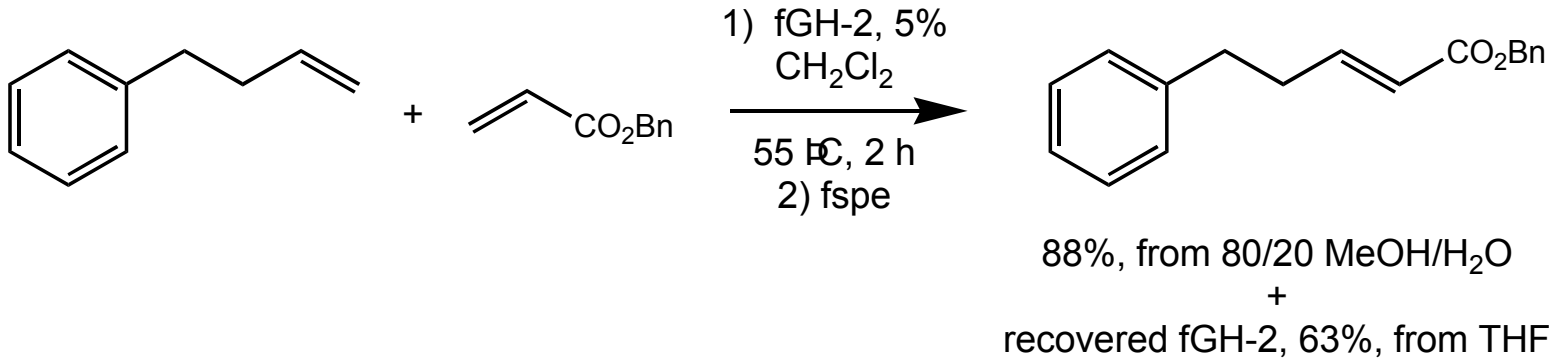


fGH-2

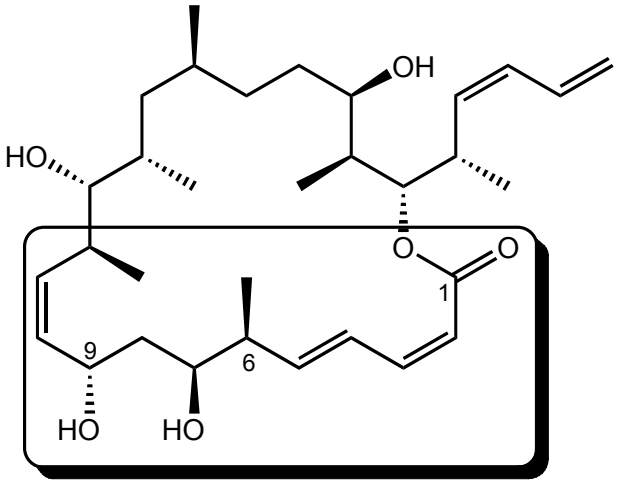
Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636-1642.

fGH Catalysts in Action

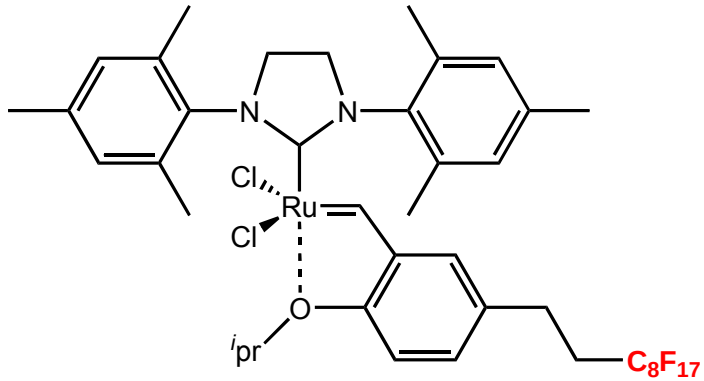




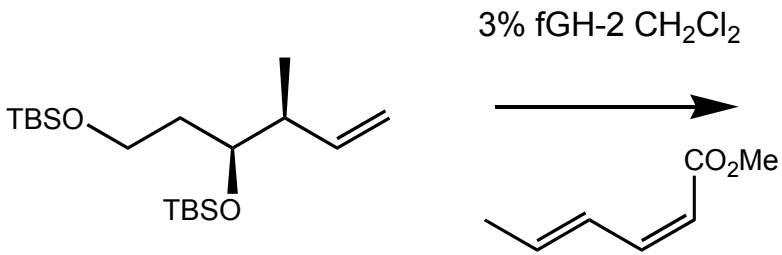
Dictyostatin Cross Metathesis

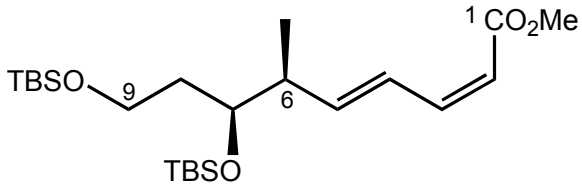


6-*epi*-dictyostatin



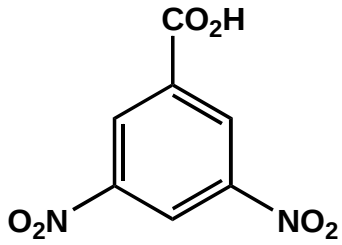
fGH-2





run	alkene	fGH	prod
1	15.0 g	1.3 g	10.9 g, 59%
2	11.0 g	1.0 g	8.1 g, 60%
3	7.5 g	0.7 g	5.2 g, 56%

Fluorous Mitsunobu



\+ **ROH**

$C_6F_{13}(CH_2)_2OCON{=}NCO_2(CH_2)_2C_6F_{13}$

$Ph_2P(p\text{-}C_6H_4CH_2CH_2C_8F_{17})$

THF

Ester

\+

hydrazide

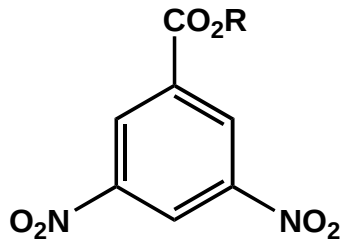
\+

phosphine oxide

SPE

organic

fluorous



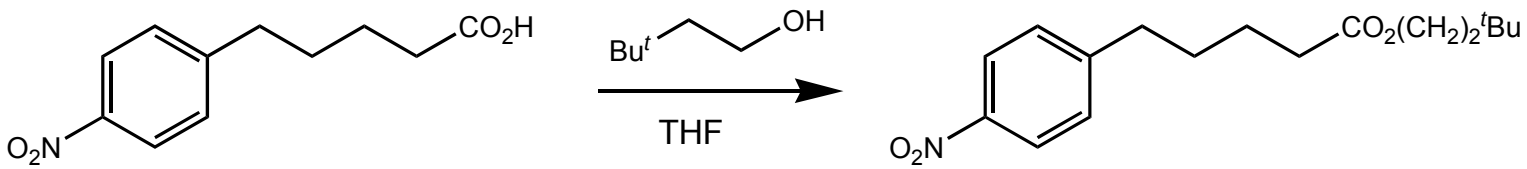
$Rf(CH_2)_2OCONHNHCO_2(CH_2)_2Rf$

\+

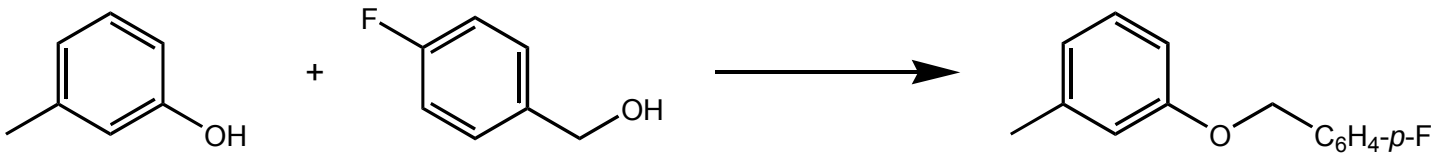
$Ph_2P(O)(p\text{-}C_6H_4CH_2CH_2Rf)$

- *Tetrahedron* **2002**, *58*, 3855
- Dobbs, *Tetrahedron Lett.* **2002**, *43*, 2807

2nd Generation F-DEADs



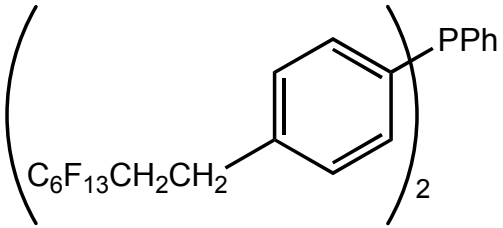
DIAD	$iprO_2CN{=}NCO_2ipr$	95%	column
^{F}DEAD-1	$C_6F_{13}(CH_2)_2O_2CN{=}NCO_2(CH_2)_2C_6F_{13}$	0%	—
^{F}DEAD-2	$C_8F_{17}(CH_2)_3O_2CN{=}NCO_2{}^tBu$	93%	Biotage
^{F}DEAD-3	$C_6F_{13}(CH_2)_3O_2CN{=}NCO_2(CH_2)_3C_6F_{13}$	91%	fspe



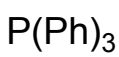
DIAD	75%	column
^{F}DEAD-1	18%	column
^{F}DEAD-2	60%	Biotage
^{F}DEAD-3	60%	spe

- *J. Org. Chem.* **2004**, *69*, 8751

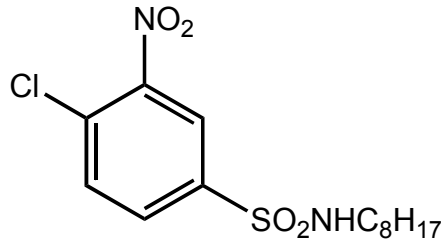
Extractions with HFE-7100 (C_4F_9OMe)



^{F}TPP



TPP

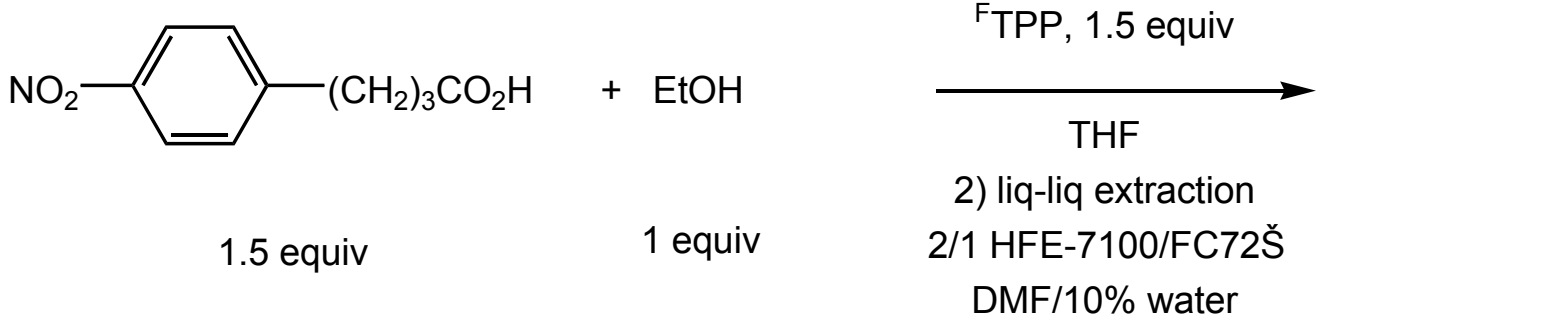


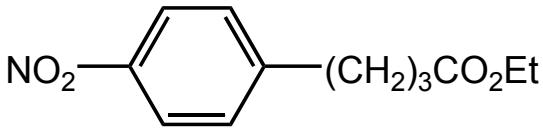
Sulfonamide

Fluorous solvent	Organic solvent	^{F}TTP K*p*	TPP K*p*	Sulfonamide K*p*
FC-72	DMF/5%H_2O	0.15	<0.02	<0.02
HFE-7100	DMF/5%H_2O	>100	0.12	0.05
HFE-7100/FC-72 1/1	DMF/5%H_2O	50	<0.02	<0.02

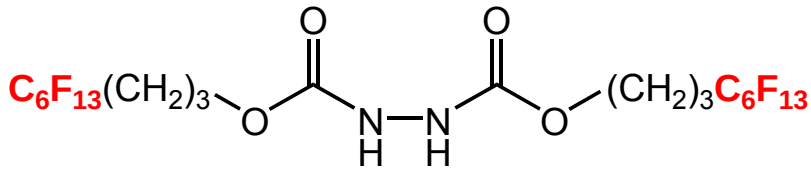
- HFE 7100 is cheaper and better performing
- M. Yu, D. P. Curran, T. Nagashima, *Org. Lett.* **2005**, *7*, 3293

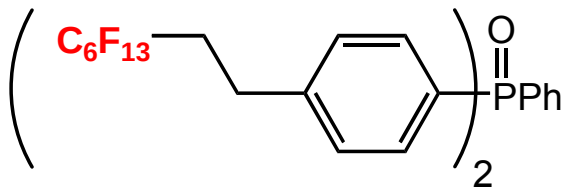
Mitsunobu with liq-liq Extraction





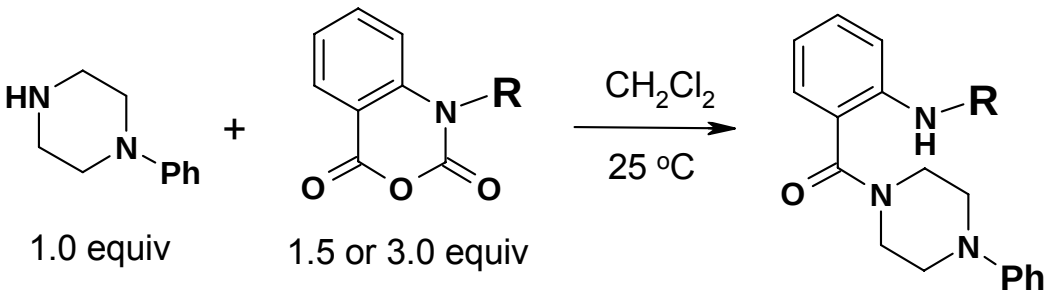
from organic liquid phase
83% yield, 92% GC purity





from fluorous liquid phase
75-80% after separation

Scavenging and Solution Phase Kinetics

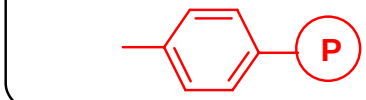


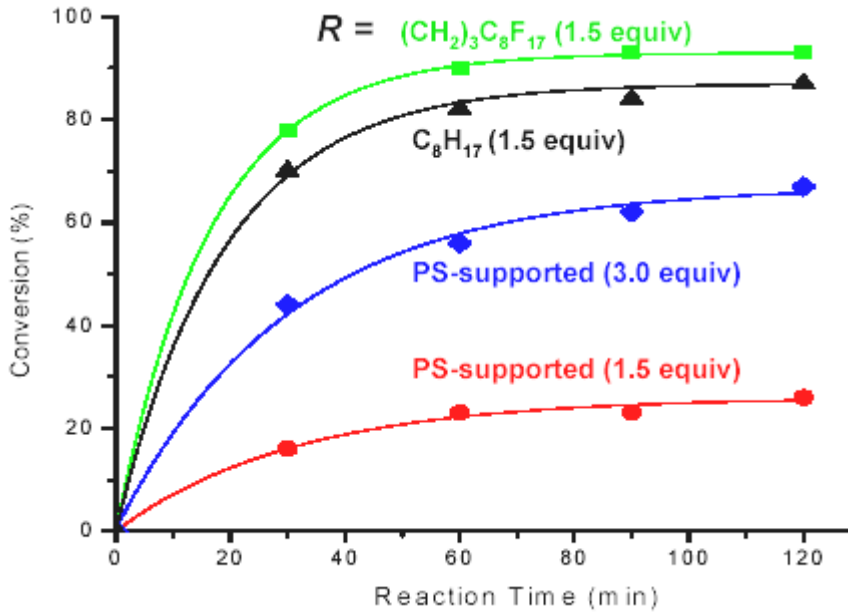
1.0 equiv

1.5 or 3.0 equiv

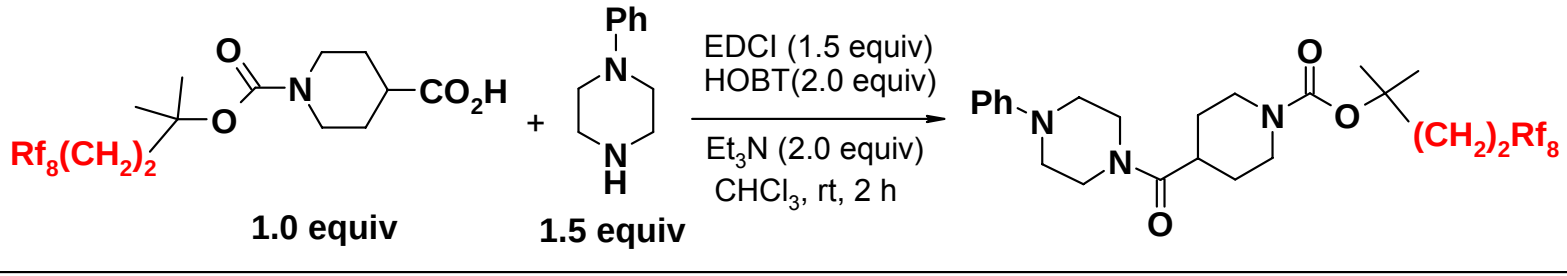
C_8H_{17}

R = $(CH_2)_3C_8F_{17}$

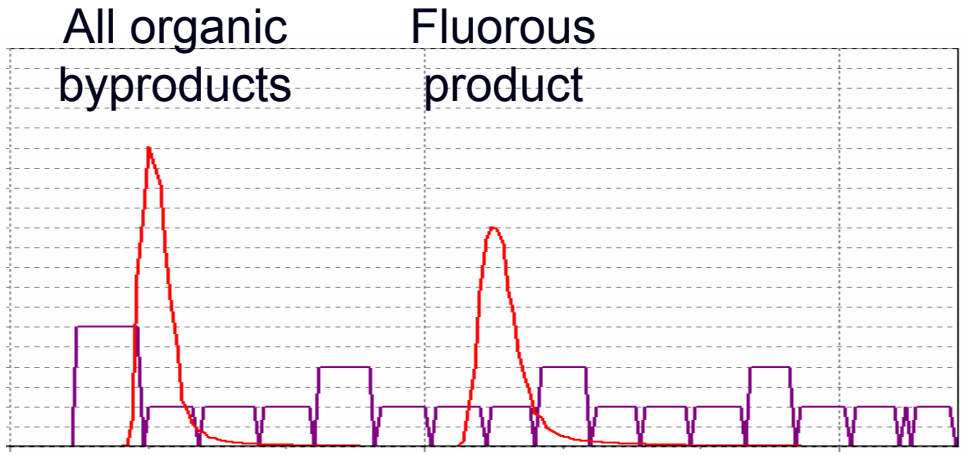




A Fluorous Boc (^{F}Boc) Group



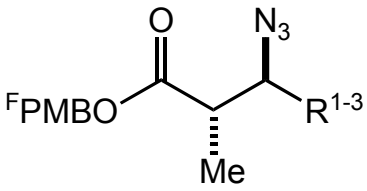
Biotage SP4



- Luo, Z. Y.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261.

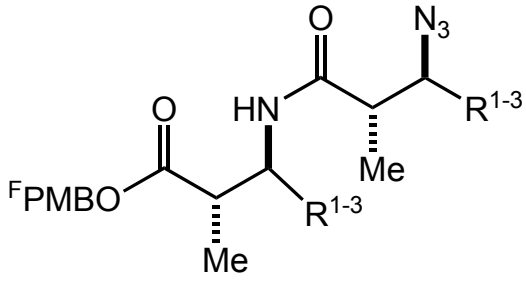
A Small β-Peptide Library

cycle 1



1) PPh_3, μwave
2) fspe

3) EDCI, acid azide
4) fspe



three precursors
from S. Nelson

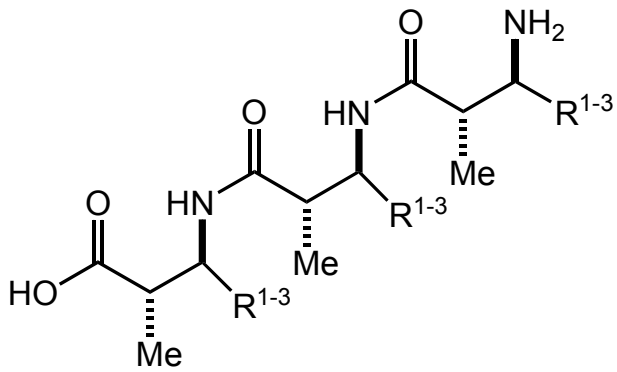
nine intermediates
fully characterized by
2D NMR

^{F}PMB is *p*-$C_8F_{17}(CH_2)_3OC_6H_4CH_2$–

cycle 2

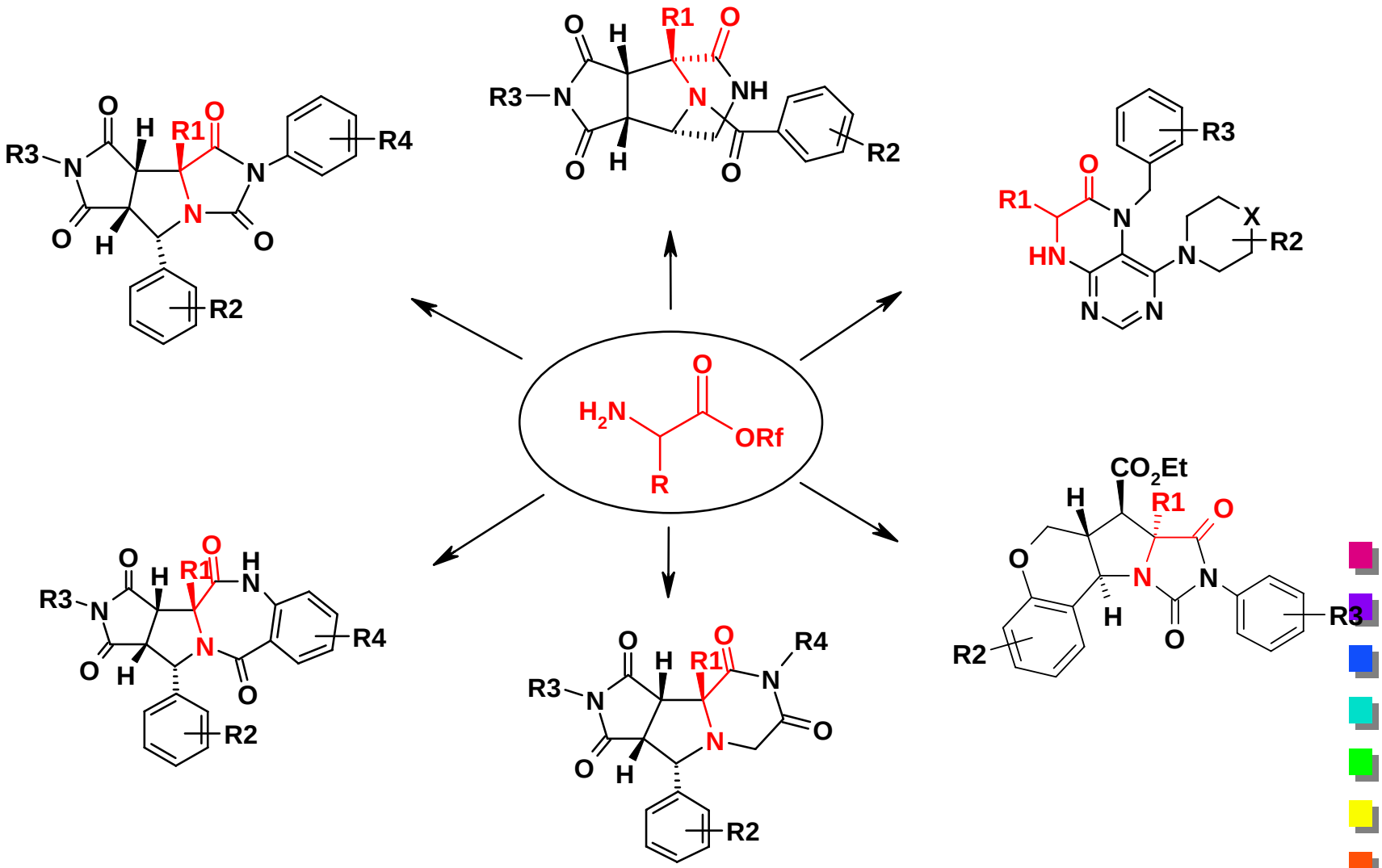
1) PPh_3, μwave
2) fspe

3) EDCI, acid azide
4) fspe
5) H_2/Pd
6) fspe



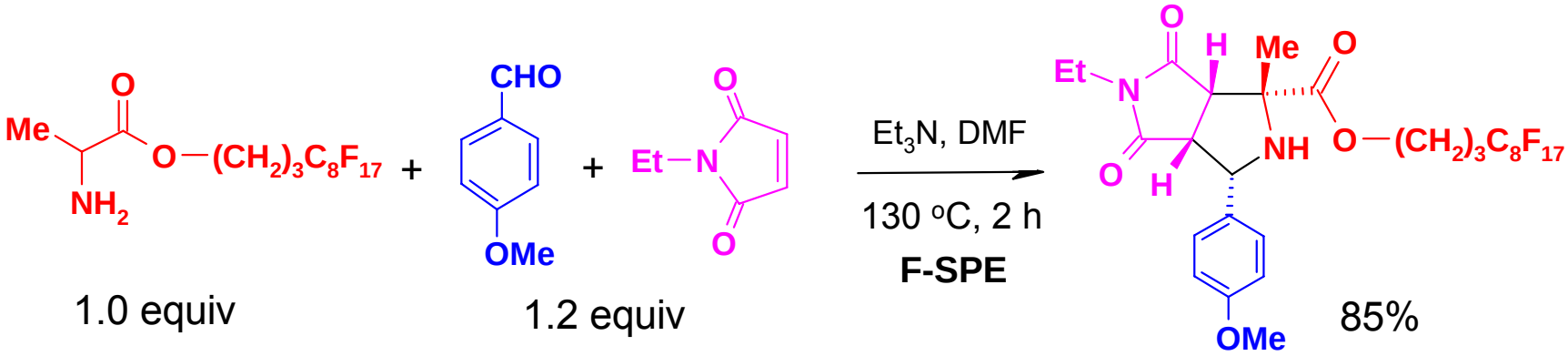
27 final products
24 > 90% pure by LCMS

Heterocyclic Libraries



Zhang, W., Fluorous synthesis of heterocyclic systems, *Chem. Rev.* **2004**, 104, 2531-2556.

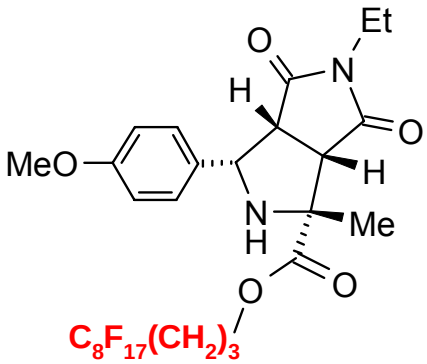
3 + 2 Dipolar Cycloaddition

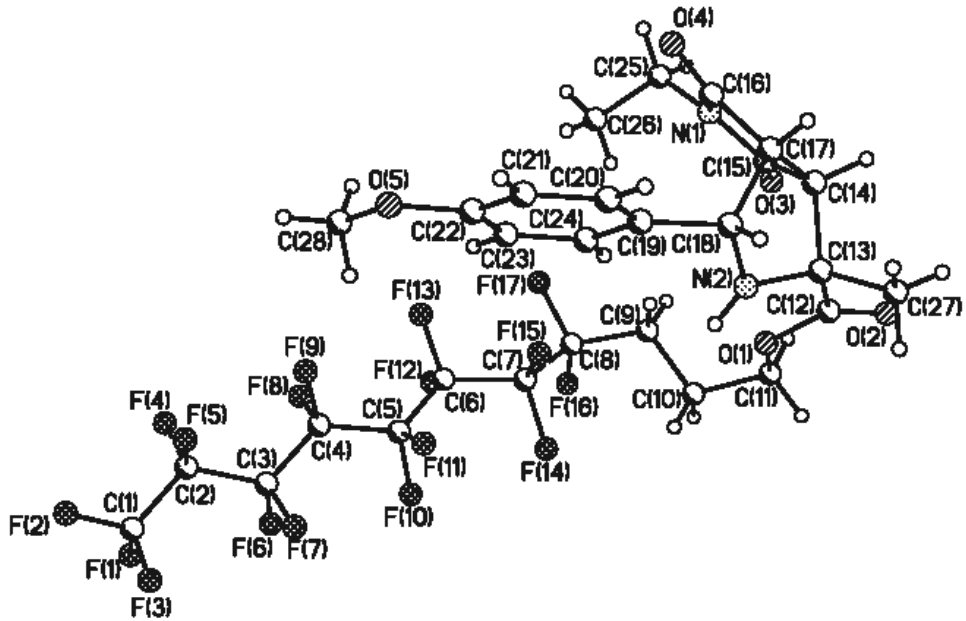


1.0 equiv

1.2 equiv

85%

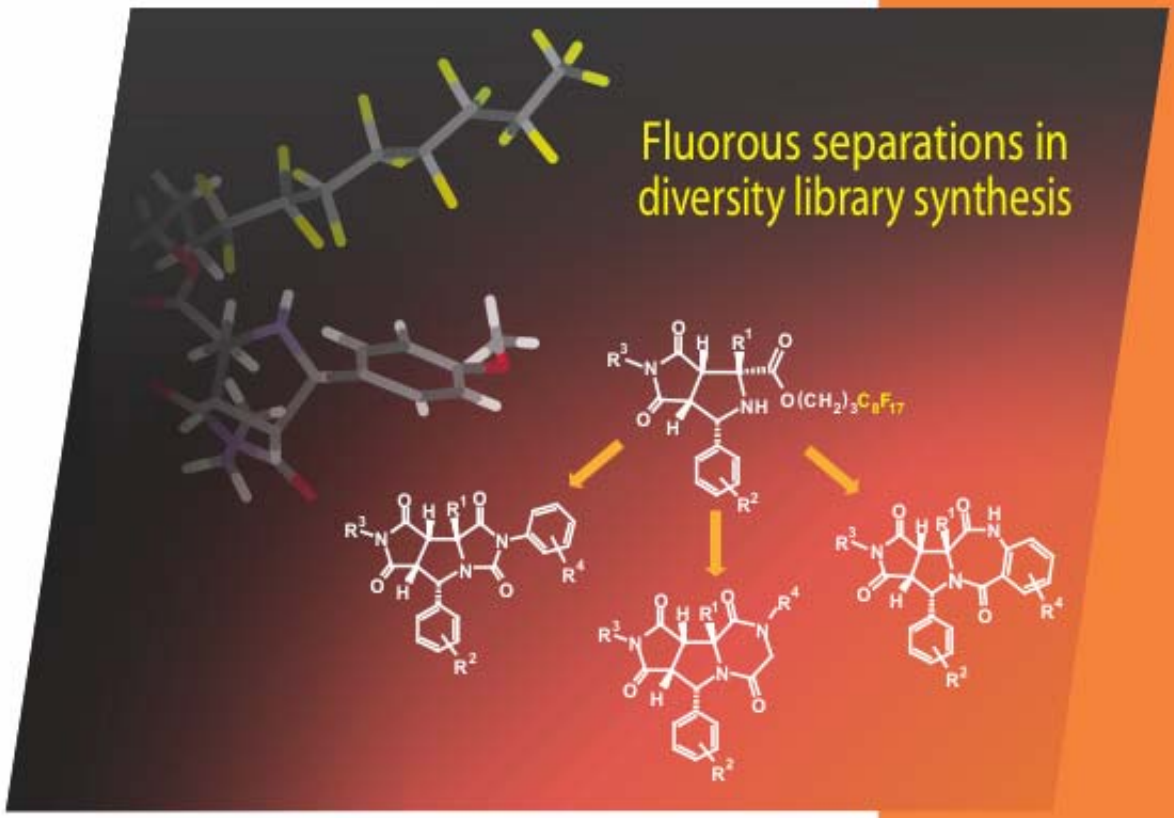




Zhang, W.; Lu, Y. Chen, C. H.-T; Curran, D. P.; Geib, S. *Eur. J. Org. Chem.* **2006**, 2055-2059

EurJOC

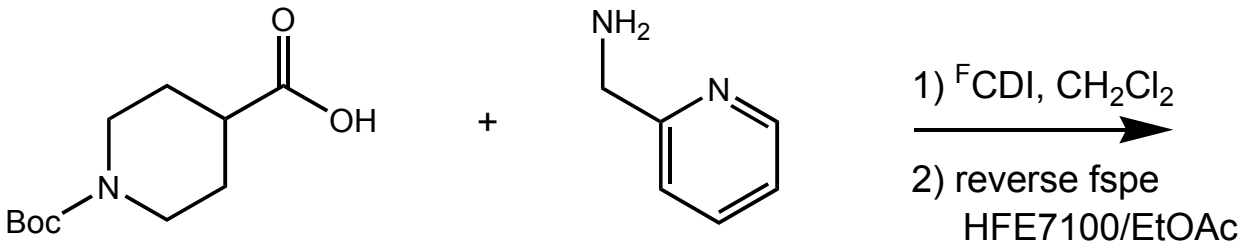
European Journal of Organic Chemistry



Fluorous CDI with Reverse fspe

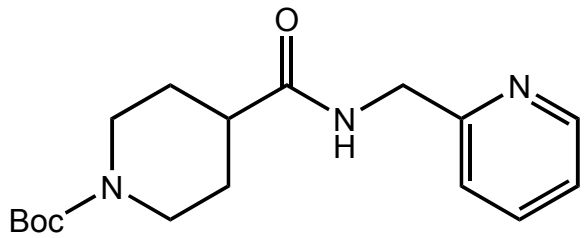
$((C_6F_{13}(CH_2)_2)_2CHO(CH_2)_2N{=}C{=}NiPr$

^{F}CDI, soluble in DCM

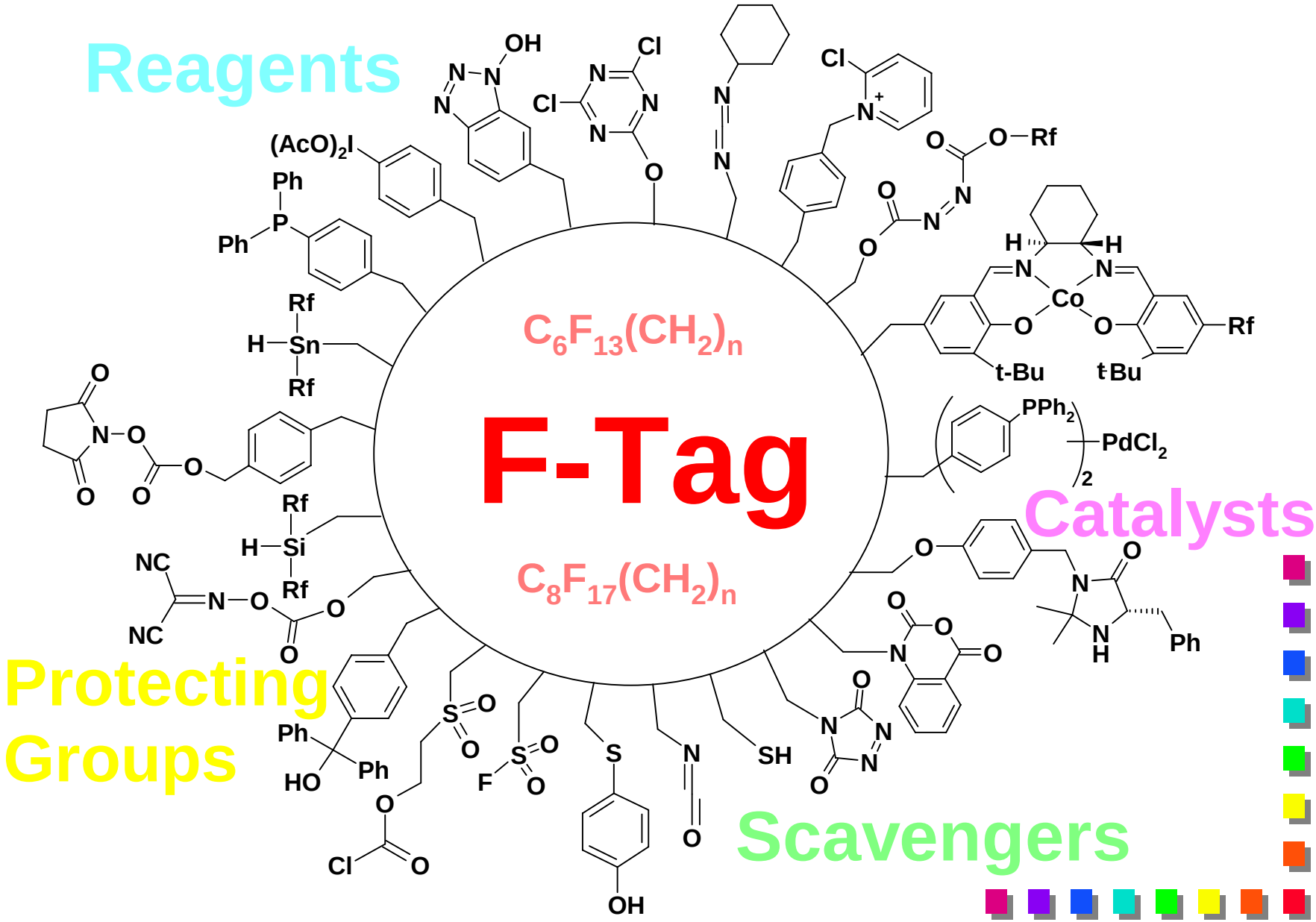


$((C_6F_{13}(CH_2)_2)_2CHO(CH_2)_2NHC(O)NHiPr$

fluorous fraction



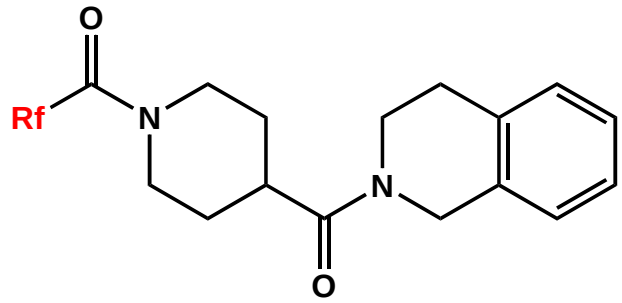
organic fraction
86% yld, 98% pure


Reagents
Protecting Groups
Catalysts
Scavengers
F-Tag
$C_6F_{13}(CH_2)_n$
$C_8F_{17}(CH_2)_n$

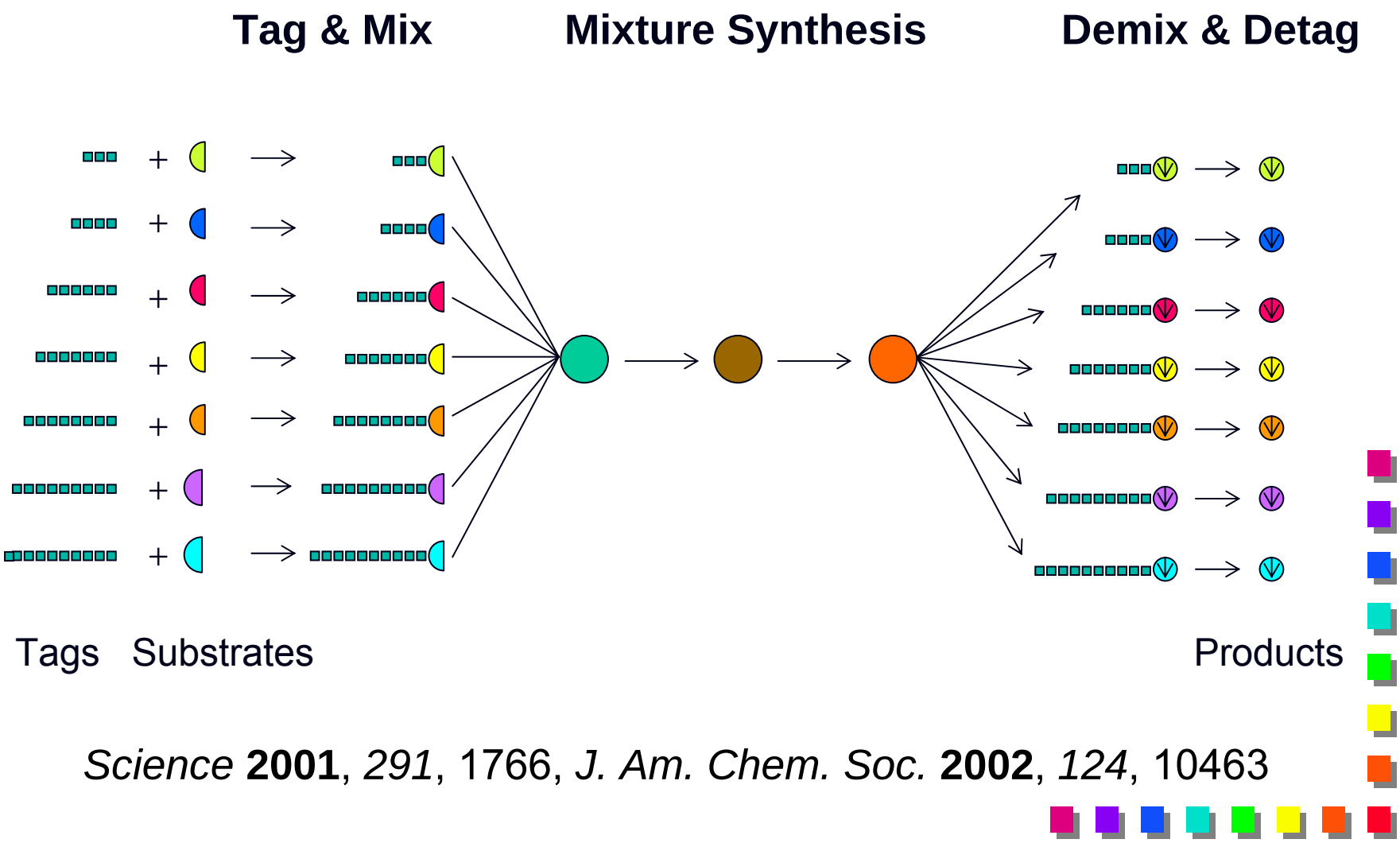
Separation by Fluorine Content

"**Fluoro*Flash*™**" Column

- Compounds are soluble in CH_2Cl_2, *not* FC-72
- Long retention times translate to separation by SPE

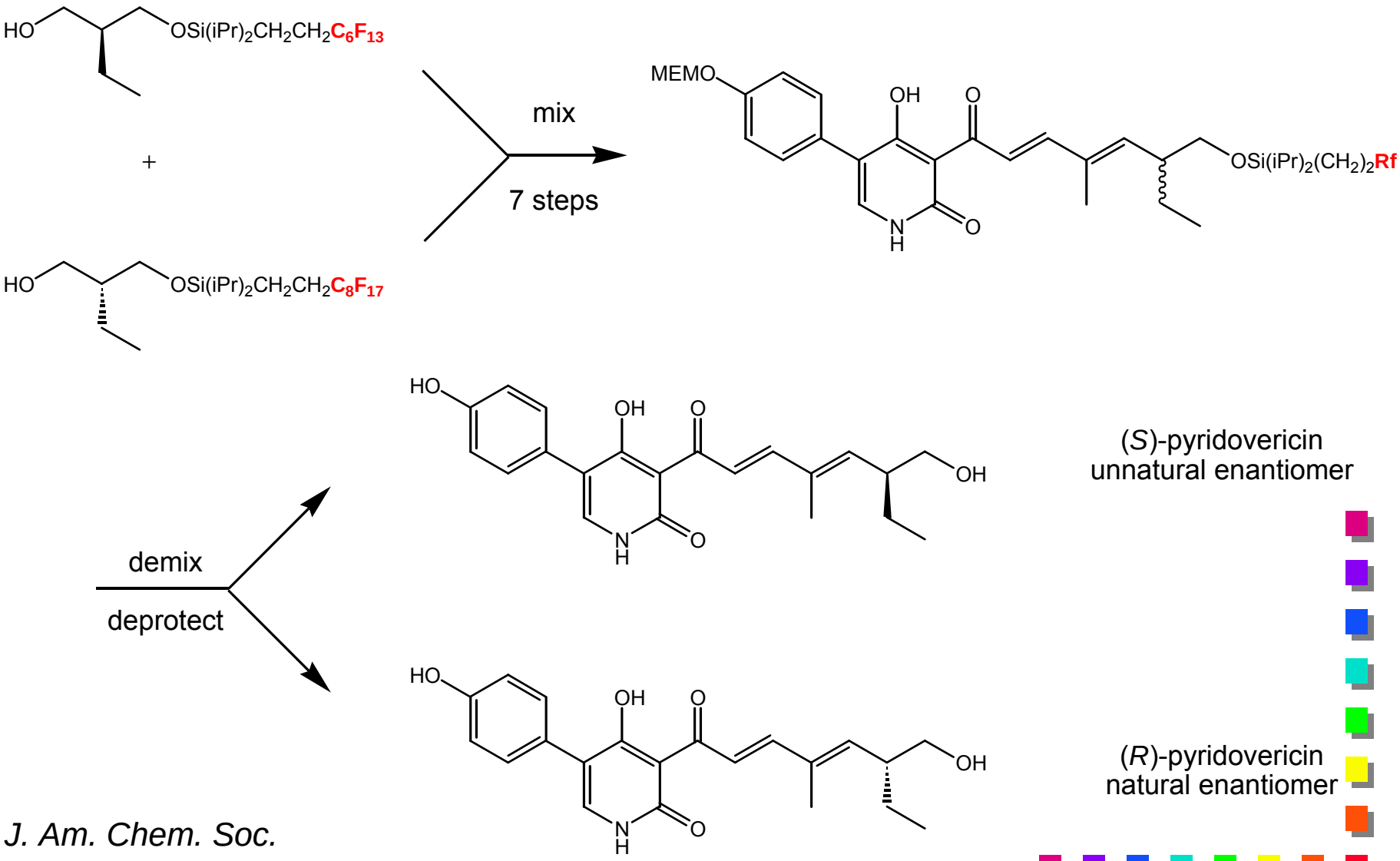


Fluorous Mixture Synthesis



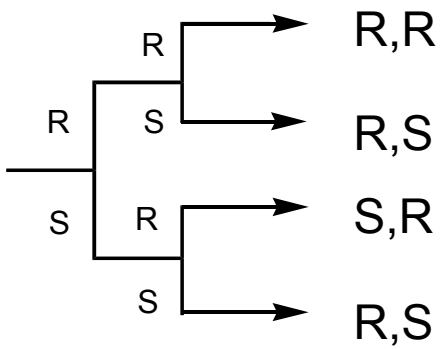
Science **2001**, *291*, 1766, *J. Am. Chem. Soc.* **2002**, *124*, 10463

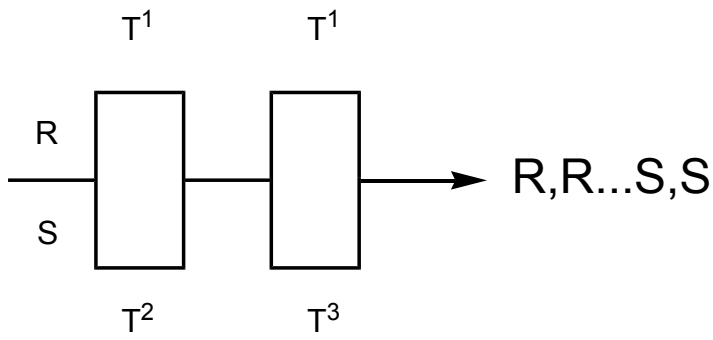
Quasiracemic Synthesis—Pyridovericin



J. Am. Chem. Soc.
2002, *124*, 5774

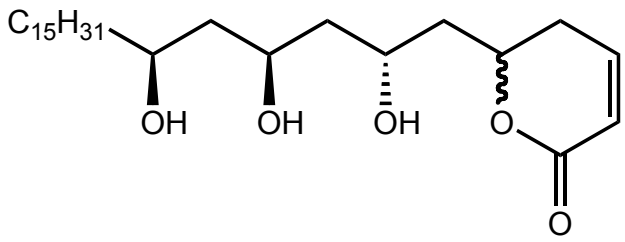
Introduction of Stereocenters en Route



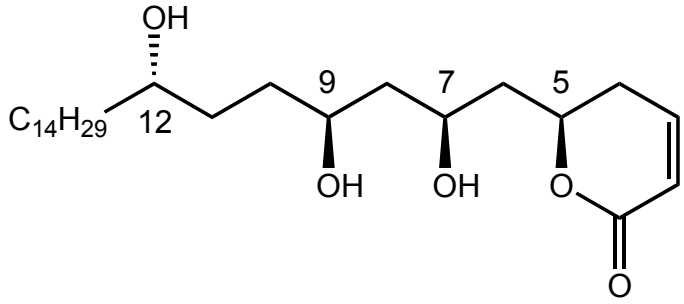


- Traditional iterative synthesis (no tags)
  - Number of reactions doubles as each stereocenter is introduced
- Iterative synthesis w/ tagging
  - Reactions reconverge after each stereocenter
  - # of tags is fewer than # stereocenters: n/2 + 1
  - T^1T^1, T^2,T^1, T^1T^3, T^2T^3

Passifloricin



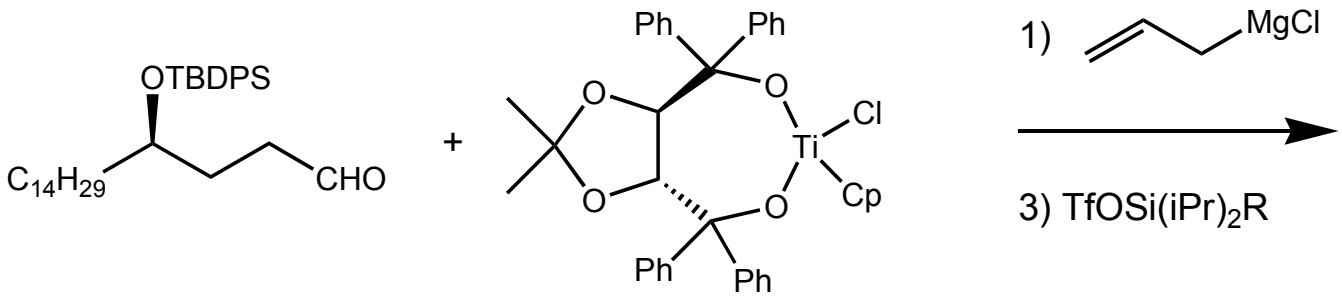
original proposal



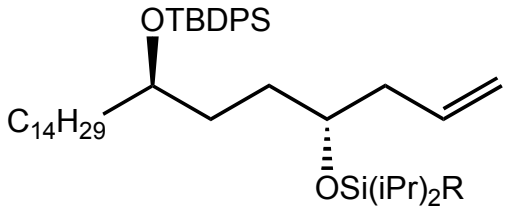
corrected

- Isolated by Echeverri, *et al*., 2001
  - Related lactones have anti-tumor, tumor-promoting activities
- Marco, Cossy show structure is incorrect, 2003
  - Synthesis by repetitive asymmetric allylation
- Marco corrects structure, *Tet. Lett.* **2003**, *44*, 7909
- FMS, *Angew. Chem. Int. Ed.* **2006**, *45*, 2423

Asymmetric Allylation with the DH Reagent

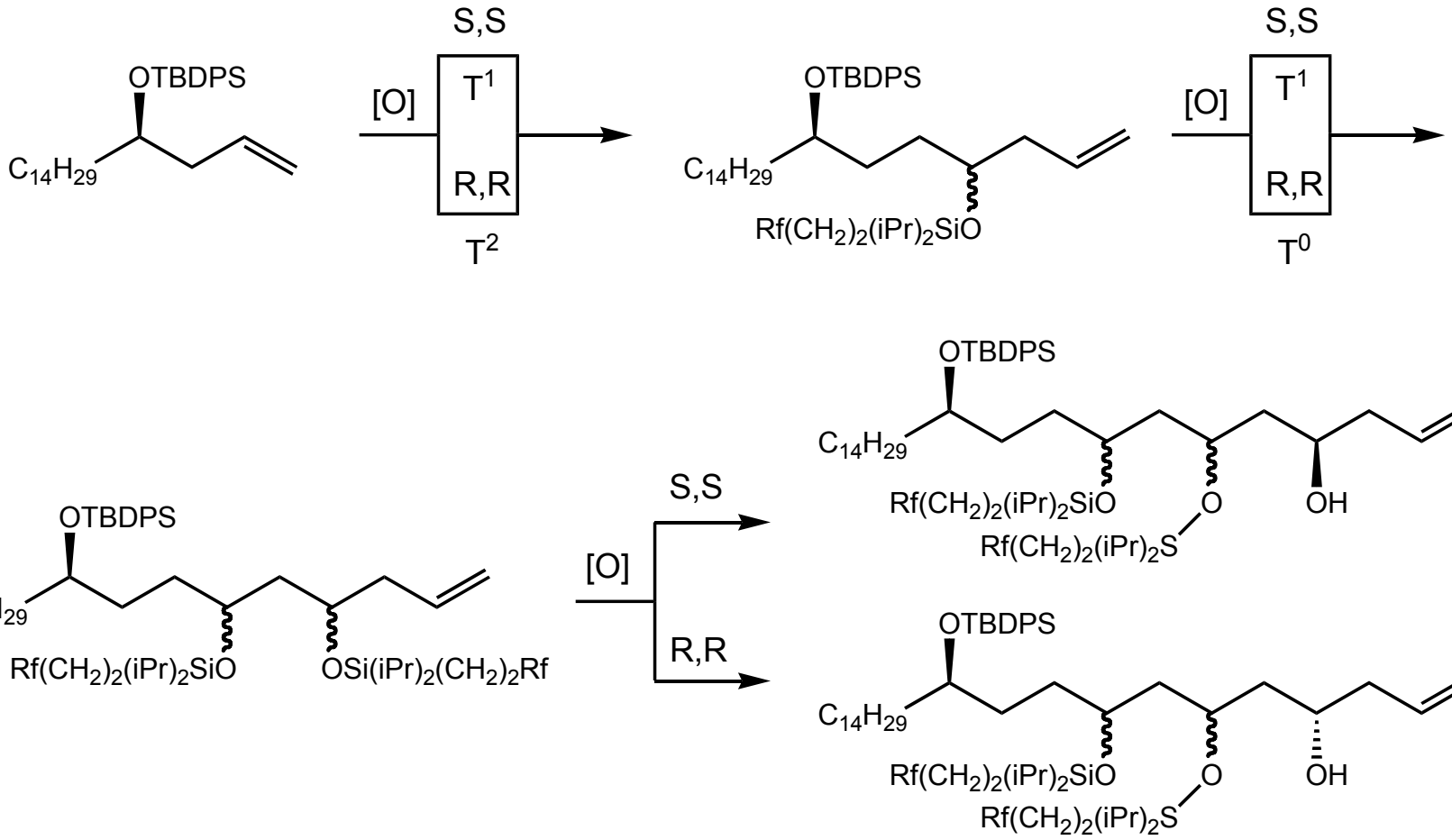


(*R*,*R*)-Duthaler-Hafner (DH) reagent

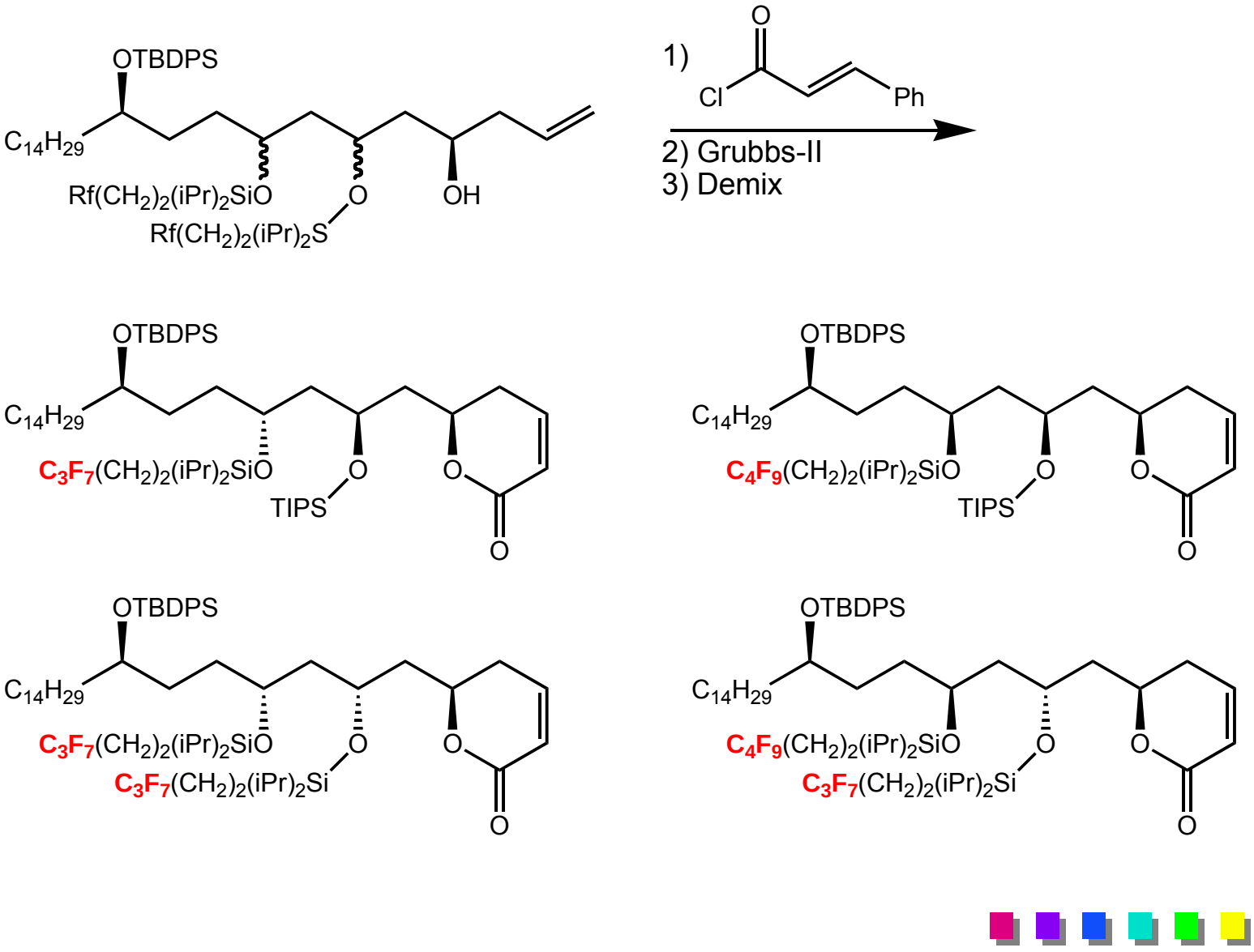


R = iPr, $(CH_2)_2C_3F_7$, $(CH_2)_2C_4F_9$

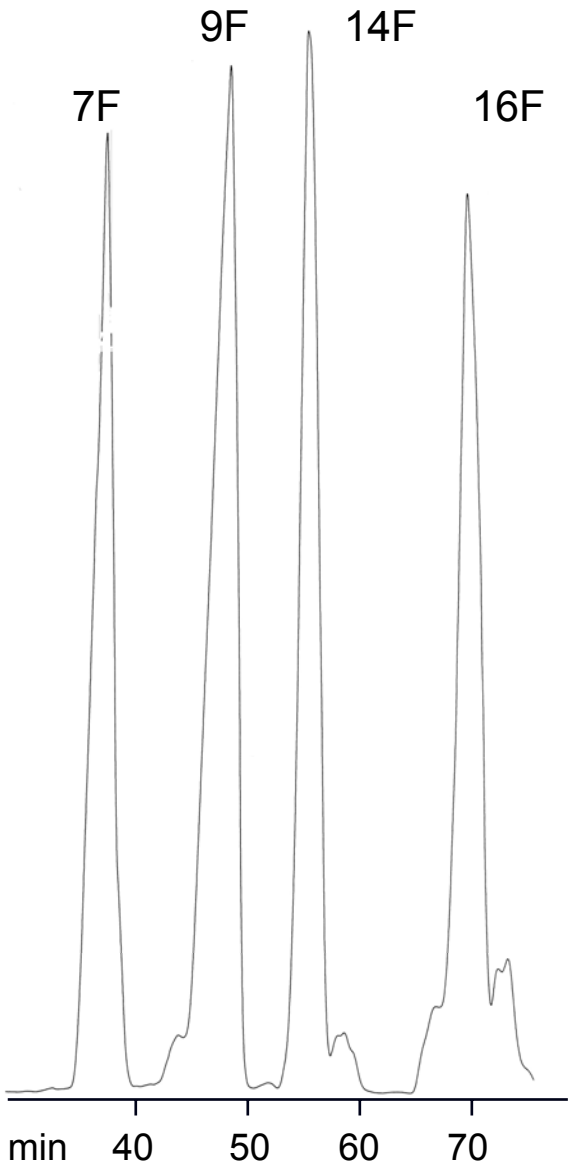
Passifloricin Mixture Synthesis



Lactone Formation, Postmix



Two-Tag Demixing



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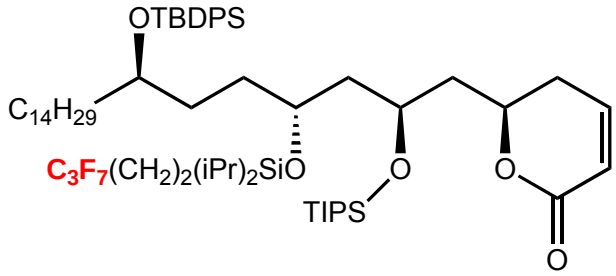

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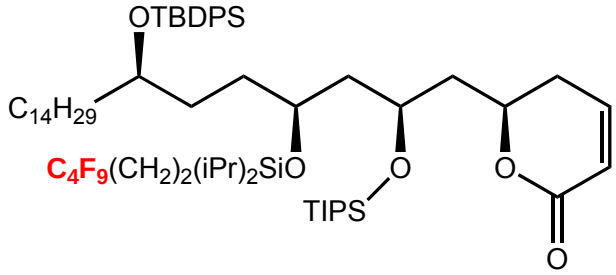

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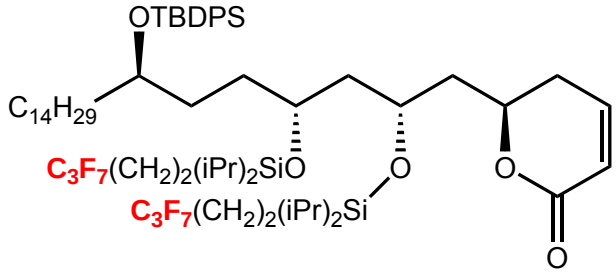

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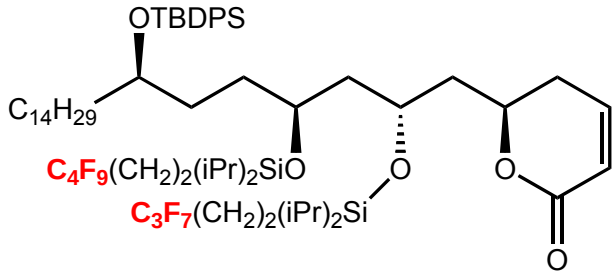
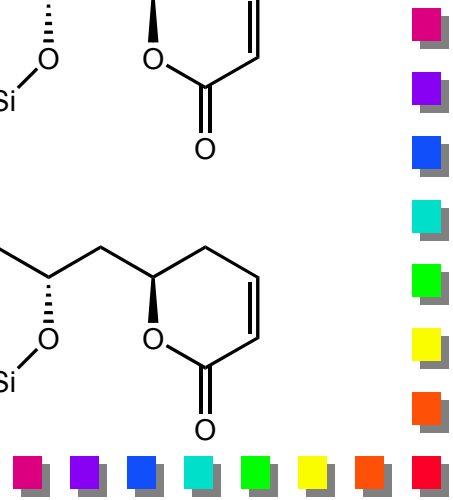
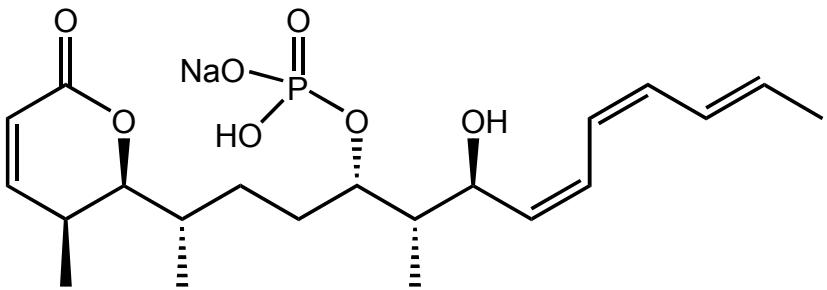
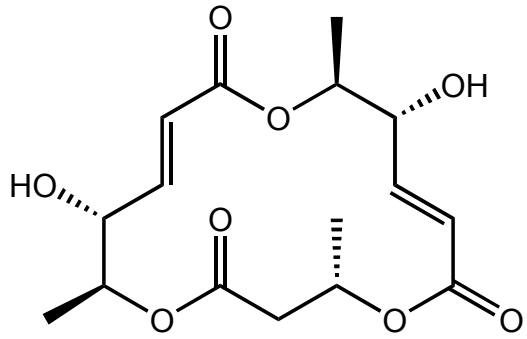




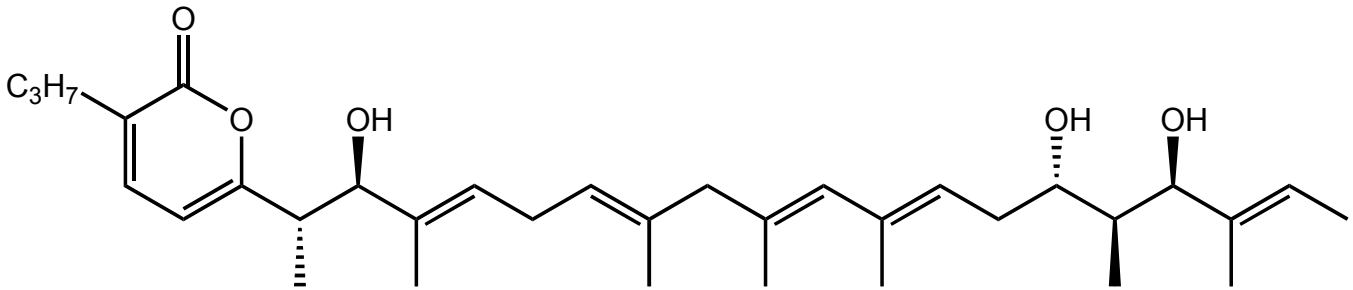
Ongoing FMS Projects



cytostatin

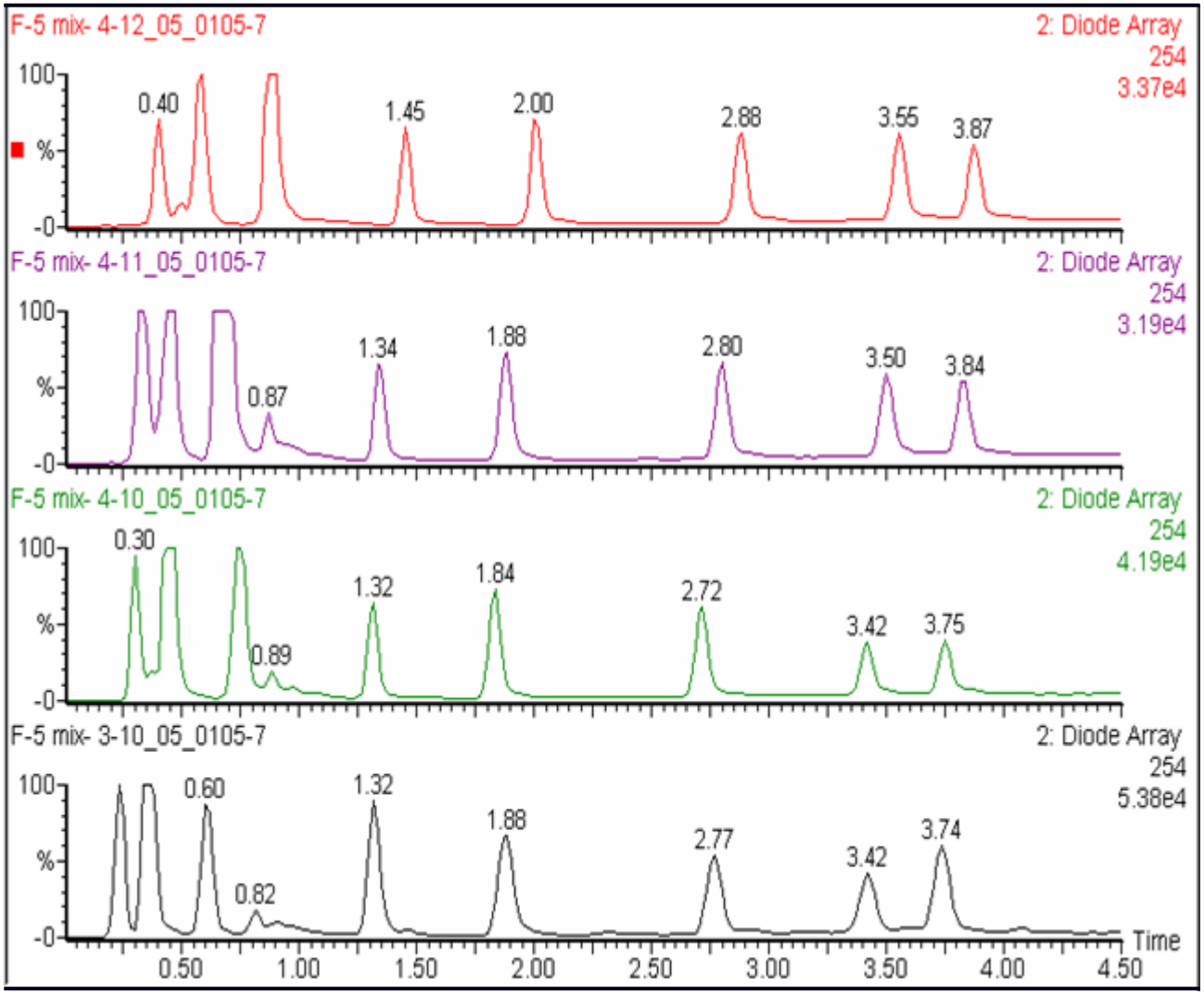


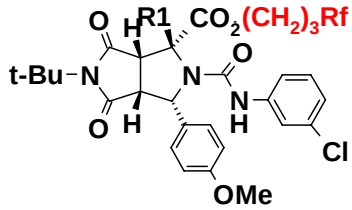
macrosphelide



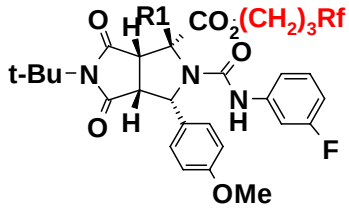
lagunapyrone

Fast, Parallel Demixing





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



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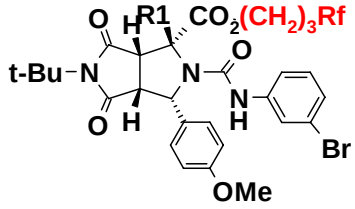

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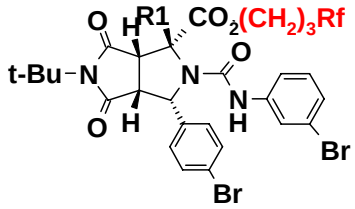


M-10{*1-5,3,2,10*}

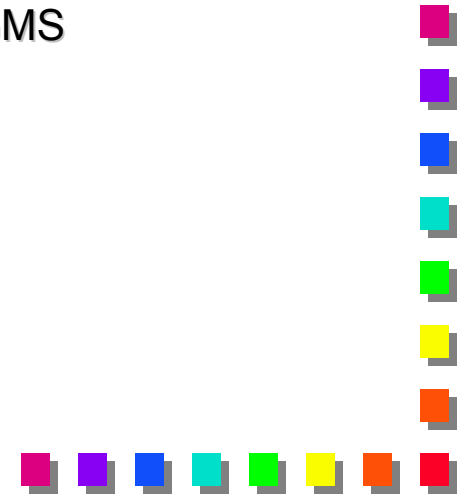
Demixing and purification of 20 (4 x 5) compounds in 5 min

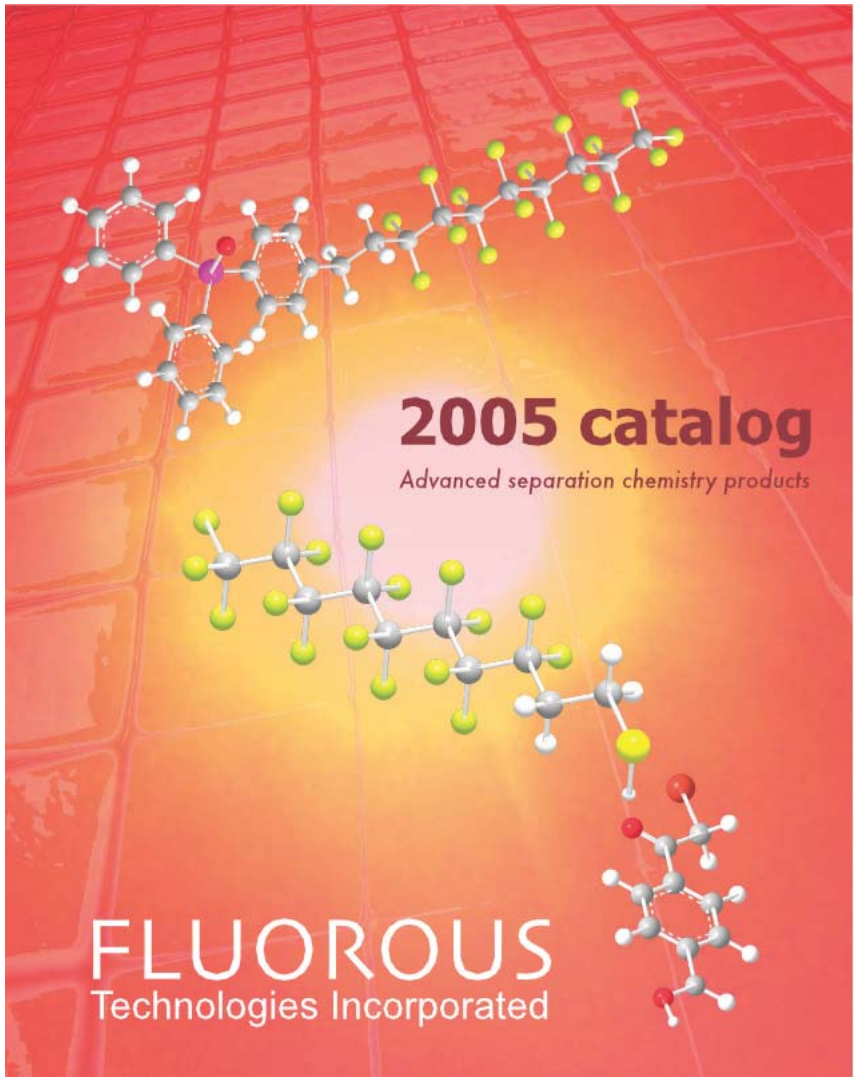
Features of Fluorous Chemistry

- Reaction
  - Solution phase reactions, kinetics; scalable
  - Compatible with standard lab equipment, other techniques
  - Tag stability ≈ stir bar stability
- Identification and analysis
  - Molecules, not materials
  - Follow reactions by tlc, hplc, gc, etc.
  - Small molecule spectroscopic techniques, NMR, IR, MS
- Separation
  - Purify by fluorous techniques or traditional techniques
  - Recoverable and recyclable

Acknowledgements

- Co-workers
  - Dr. Qisheng Zhang
  - Dr. Sivaraman Dandapani
  - Mr. Gustavo Moura-Letts
  - Dr. Masato Matsugi
  - Ms. Reena Bajpai
  - Mr. Elliot Wang
  - Dr. Carlos del Poza
  - Mr. Adam Keller
- DPC Holds an equity interest in FTI
- Collaborators
  - Dr. Wei Zhang (FTI)
  - Dr. Marvin Yu (FTI)
  - Daniel Kassel (Takeda)
  - Pro. Scott Nelson (Pitt)
- Support
  - NIH-NIGMS
  - Bayer
  - Merck





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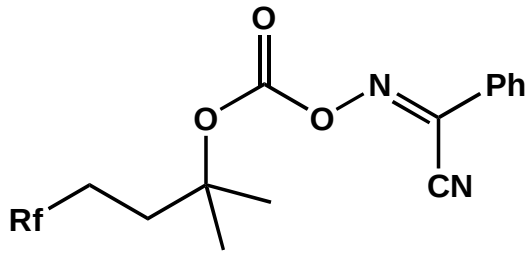

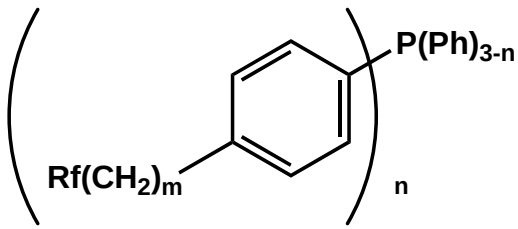

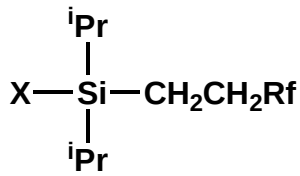

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