New Fluorous Separation Techniques for Parallel and High-Throughput Synthesis

Yimin Lu, Wei Zhang* (w.zhang@fluorous.com)

Fluorous Technologies, Inc. 970 William Pitt Way, Pittsburgh, PA 15238 USA

Introduction

Fluorous chemistry is a new solution-phase synthetic technology.[1,2] Perfluoroalkyl chains are used as "phase tags" to facilitate the separation process, which is achieved by strong and selective interactions between fluorous molecules and fluorous sorbents. This presentation describes recent advances of fluorous separation techniques:

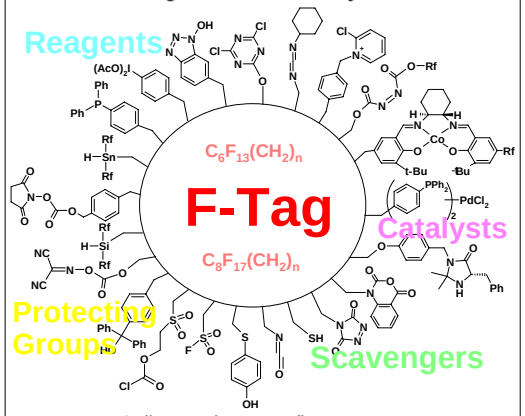
1) Plate-to-plate solid-phase extraction (SPE).[3-5] Pressure or gravity-driven 24-, 48- and 96-well plates SPE and water-free elution solvent systems have been developed;

2) Automated SPE.[6] F-SPE has been successfully implemented to RapidTrace SPE workstation;

3) Flash chromatography. Using the Biotage FlashMaster system, we have achieved variable scale separations of fluorous intermediates in library synthesis;

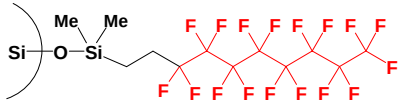
4) Fluorous HPLC[7] can be used for analytical and prep-scale separation of fluorous samples. It's application for fluorous mixture synthesis (FMS) and MS-directed high-throughput purification ahs also been developed.

Reagents for Fluorous Synthesis



Online catalog: www.fluorous.com

Fluoro*Flash*® Silica Gel



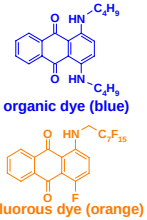
F-SPE silica gel (40-60 μm or 125-210 μm):
Selective retention of fluorous molecules

F-HPLC silica gel (5 μm): Separation of a fluorous mixture based on fluorine content

References:

1) Curran, D. P. *Aldrichimica Acta* **2006**, *39*, 3.
2) Zhang, W. *Tetrahedron* **2003**, *59*, 4475.
3) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837.
4) Zhang, W.; Lu, Y.; Nagashima, T. *J. Comb. Chem.* **2005,** *7*, 893.
5) Zhang, W.; Lu, Y. manuscript submitted.
6) Zhang, W.; Lu, Y. *J. Comb. Chem.* **2006**, *8*, 890.
7) Zhang, W.; Lu, Y.; Chen, C. H.-T.; Zeng, L.; Kassel, D. *J. Comb. Chem.* **2006**, *8*, 687.

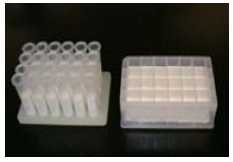
F-SPE Demo with a Dye Mixture



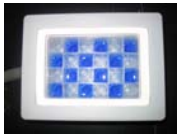
Left tube: beginning of fluorophobic wash (80:20 MeOH:H_2O)
Center tube: end of fluorophobic wash
Right tube: end of fluorophilic wash (100% MeOH)

I. Plate-To-Plate SPE

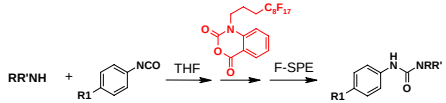
24-Well Plates 3 g Si-gel (40-60 μm), up to 0.3 g sample loading[4]



receiving plate



24-Parallel F-Scavenging Reactions



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

* yield% (purity% LC-MS, UV254)

96-Well Plate[5]

Gravity plate with large Si gel

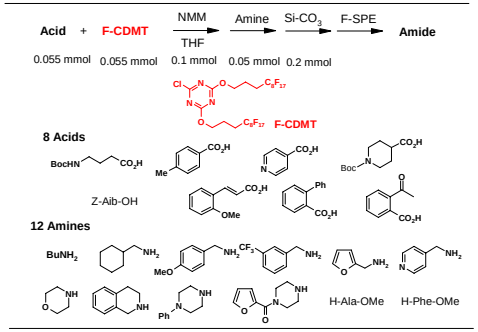
Positive pressure (Chem Tech)

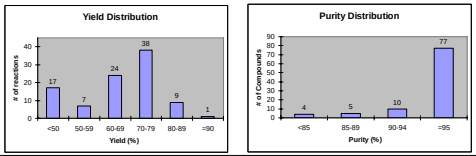
2-3 mL filtration plate; up to 75 mg sample loading; DMF and DMSO as water-free fluorophobic elution solvents

II. RapidTrace Automated F-SPE[6]

- Up to ten modular units, each unit conducts 10 SPEs
- A maximum of 100 SPEs can be finished in 1-2 h unattended
- Each SPE cartridge charged with 2 g of fluorous silica gel
- Automatic conditioning, sample loading, elution and rinsing
- Autosampler can load solution and suspension samples
- Back pressure up to 100 psi, maximum flow rate 30 mL/min
- Up to eight elution solvents and their gradient combinations

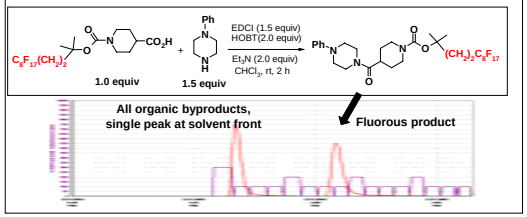
96 Parallel Amide Coupling Reactions with F-CDMT followed by RapidTrace F-SPE



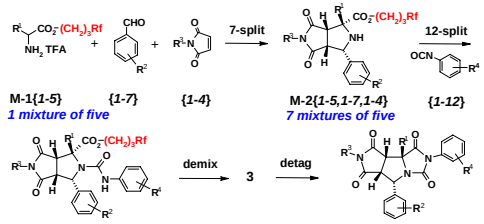


III. Large-Scale F-Flash Chromatography

variable cartridge size, UV-trigged fraction collection



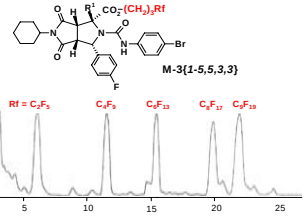
IV. F-HPLC Demixing in Mixture Synthesis[7]



Rf/R²{1-5}	R²{1-7}		R³ {1-4}	R⁴ {1-12}	
{1} C_2F_5/i-Bu	{1} H	{5} *p*-F	{1} Et	{1} H	{7} *p*-CF3
{2} C_4F_9/Bn	{2} *p*-Me	{6} *p*-Cl	{2} *t*-Bu	{2} *p*-Me	{8} 3,4-diCl
{3} C_6F_{13}/*p*-ClBn	{3} *p*-Br	{7} *m*-Me	{3} *c*-C_6H_{11}	{3} *p*-Br	{9} *m*-Me
{4} C_8F_{17}/ Me	{4} *p*-OMe		{4} Bn	{4} *p*-OMe	{10} *m*-Br
{5} C_9F_{19}/Et				{5} *p*-F	{11} *m*-F
				{6} *p*-Cl	{12} *m*-Cl

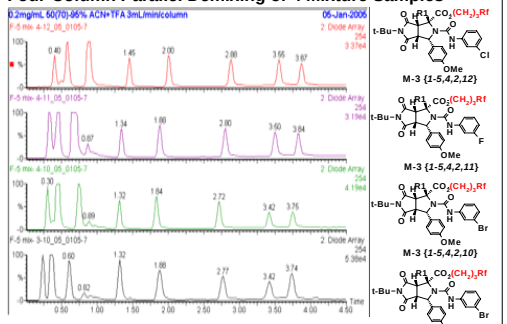
420 Ureas M-3 (84 x 5) by *91 FMS reactions* (7 cycloaddition + 84 isocyanatereactions)
Could need *455 parallel reactions* (35 cycloadditions + 420 isocyanate reactions)

Prep-Scale Demixing of a 5-Component Mixture



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

Four-Column Parallel Demixing of 4 Mixture Samples



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

Conclusions

A series of fluorous silica gel-based separation techniques including plate-to-plate SPE, RapidTrace automated SPE, large-scale flash chromatography, and F-HPLC have been developed for parallel and high-throughput purifications. The strong and selective interaction between F-molecules and F-silica gel provides very efficient and reliable separations.

Acknowledgement: This work was supported by NIH GMS SBIR Grant (2R44GM067326-02).