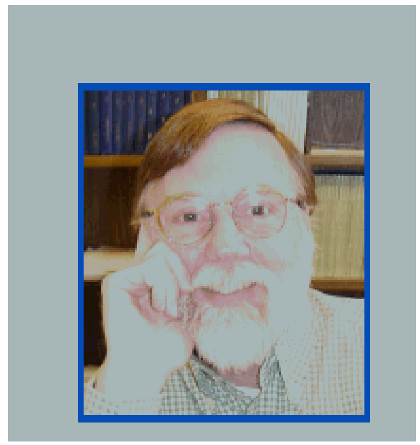
An Introduction to Fluorous Techniques for the Synthesis of Small Organic Molecules



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Introduction The Fluorous Approach

- Alternative to traditional solution-phase synthesis and solid phase synthesis.

- Light-Fluorous reagents
  - Reactants, catalysts, and scavengers for the synthesis of small organic molecules and bimolecules.
  - Typically coupled with a separation based on solid-phase extraction.

- The ease of separation and product recovery make Fluorous methods attractive for large scale chemistry while there speed & reliability are strong assets for small scale chemistry.

Fluorous Molecules

- Consist of an organic domain & and a fluorous (fluoroalkyl) domain
- The organic domain controls the reaction chemistry of the hybrid molecule
- The fluorous domain controls the separation chemistry

Why Important?

- Rapid synthesis in small organic molecules
- High purity
- Economical
- Innovative reaction & separation methods
- Environmentally friendly
- General applicability

The Fluorous Approach

- 1994 - Horvath & Rabai Launched fields with “fluorous biphasic catalysis”
  - Liquid-phase immobilization technique
- 1999 - Curran Group introduced “light fluorous chemistry”
  - Contains a single perfluorooctyl group

Fluorous Techniques

Strategic Synthesis and Separation

- Liquid-Liquid (or Solid-Liquid) Separation
- Solid Phase Extraction
- Chromatography over fluorous silica gel

Light-Fluorous Reactions and Reaction Components in Small-Molecule Synthesis

- Light-Fluorous Reagents
- Organometallic Catalysts with Fluorous Ligands
- Fluorous Scavengers
- Fluorous Protecting Groups
- Fluorous Tagging in Multicomponent Reactions and Heterocycle Synthesis

Fluorous Solid-Phase Extraction

- FSPE- resembles chromatography.
- Uses silica gel with a fluorocarbon bonded phase
- Fluorous silica gels selectively retains polyfluorinated molecules, and allows for a simple bifurcation of reaction mixtures containing fluorous and organic reaction components

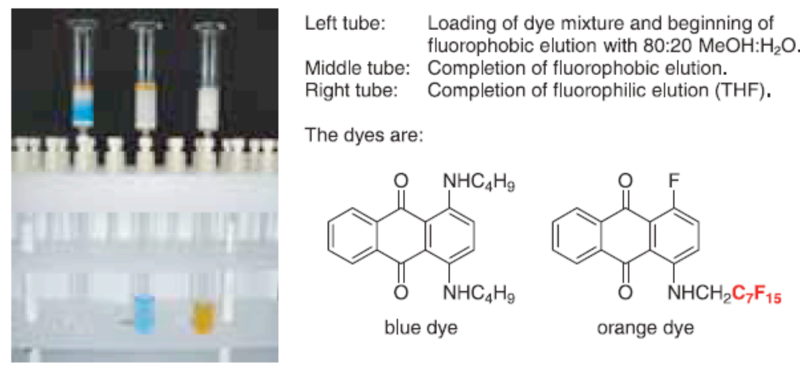

Figure 1. A Fluorous Solid-Phase Extraction of Organic (Blue) and Fluorous (Orange) Dyes over Fluoro*Flash*® Silica Gel.

Curran, Dennis. Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers. Aldrichimica ACTA. Vol. 39, No.1 2006

Light-Fluorous Reagents

- Reactions that use fluorous reagents to promote the transformation of a small molecule substrate into a product are the most common among all classes of light-fluorous reactions.

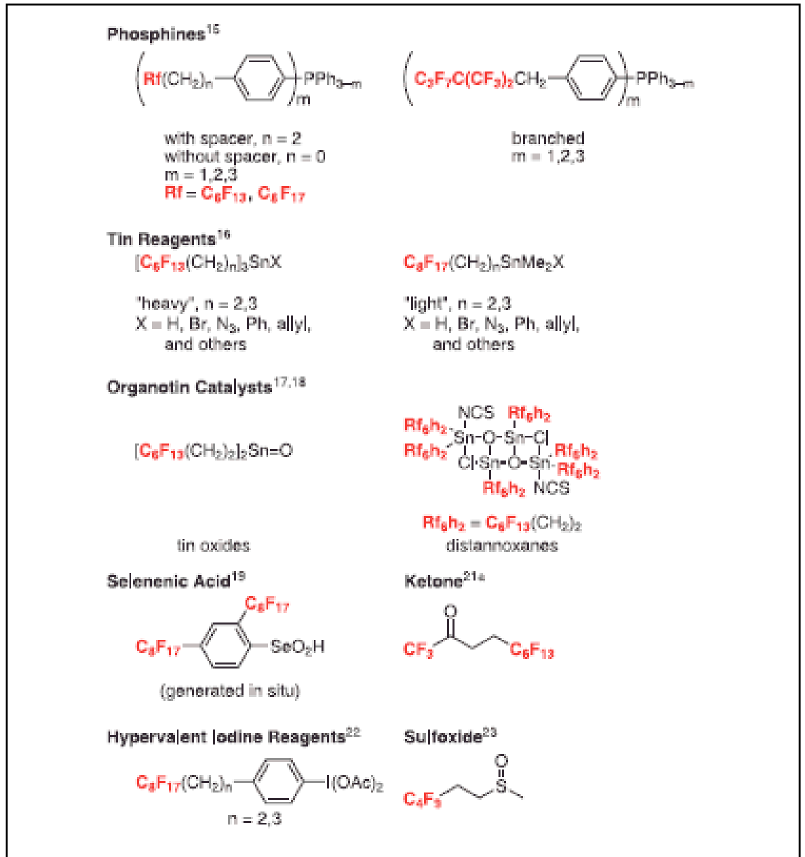

Figure 2. Some of the Known Fluorous Reagents and Catalysts.

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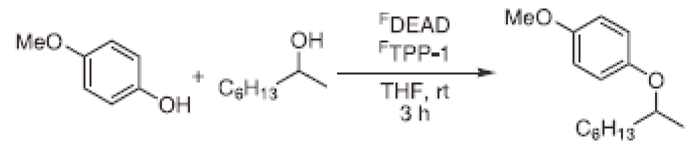
Light-Fluorous Mitsunobu & Staudinger Reactions

- Light Fluorous Mitsunobu Reaction (Top)

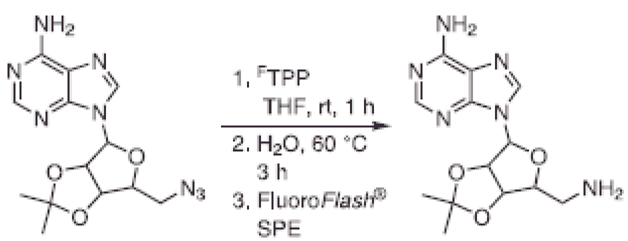


1 2 **3**, 55% yield
97% purity (GC)

^{F}DEAD = $C_6F_{13}(CH_2)_3O_2CN{=}NCO_2(CH_2)_3C_6F_{13}$
^{F}TPP-1 = 4-[$C_8F_{17}(CH_2)_2$]$C_6H_4P(C_6H_5)_2$

Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751.

- Staudinger Reaction (Bottom)



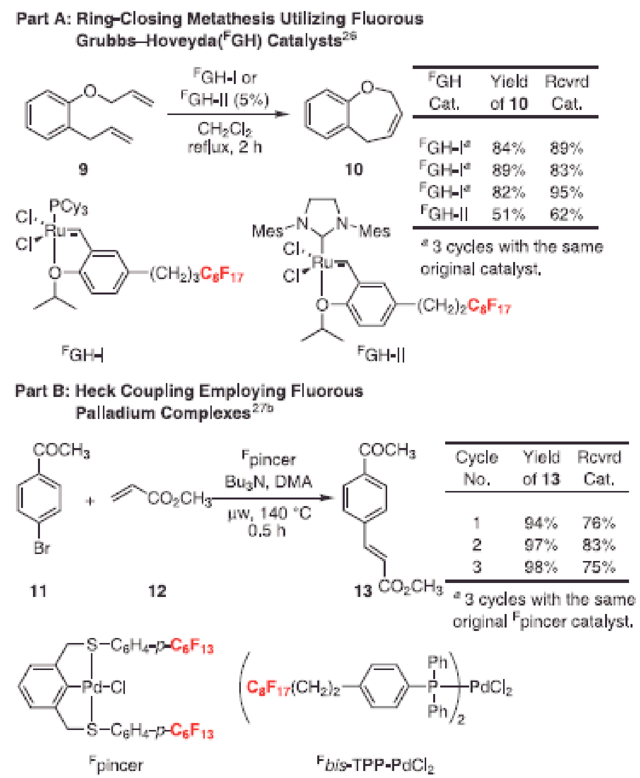
4 **5**, 88% yield
98% purity (LCMS)

^{F}TPP = 4-[$C_6F_{13}(CH_2)_2$]$C_6H_4P(C_6H_5)_2$

Lindsley, C. W.; Zhao, Z.; Newton, R. C.; Leister, W. H.; Strauss, K. A. *Tetrahedron Lett.* **2002**, *43*, 4467.

Organometallic Catalysts with Fluorous Ligands

- The use of catalysts instead of stoichiometric reagents to promote organic transformations is increasingly important, and many heavy fluorous catalysts are already known.
- Useful for large-scale synthesis
- Heavy-fluorous catalysts bearing multiple “ponytails” can be re-engineered into a light-fluorous one by reducing its fluorine content.



Scheme 2. Examples of the Use of Organometallic Catalysts Containing Fluorous Ligands.

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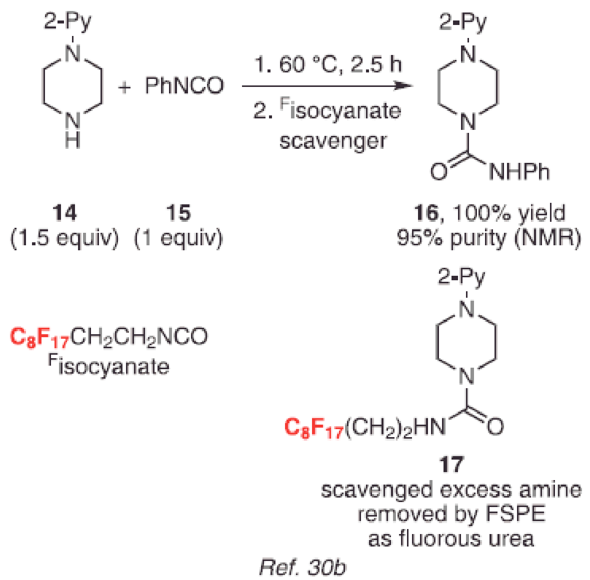
Fluorous Scavengers



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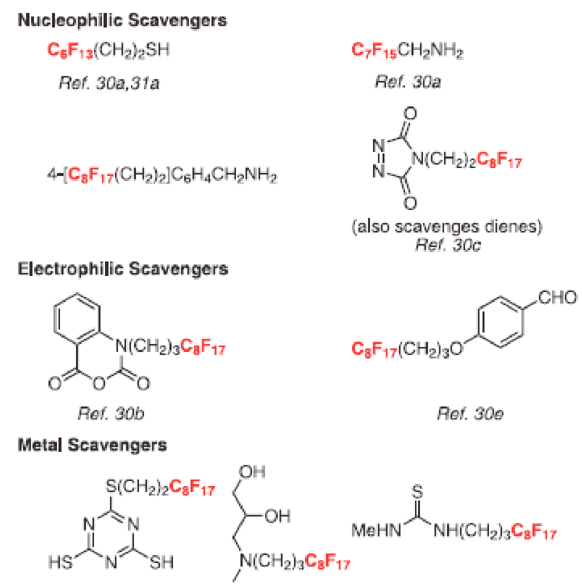


Figure 4. Representative Fluorous Scavengers.

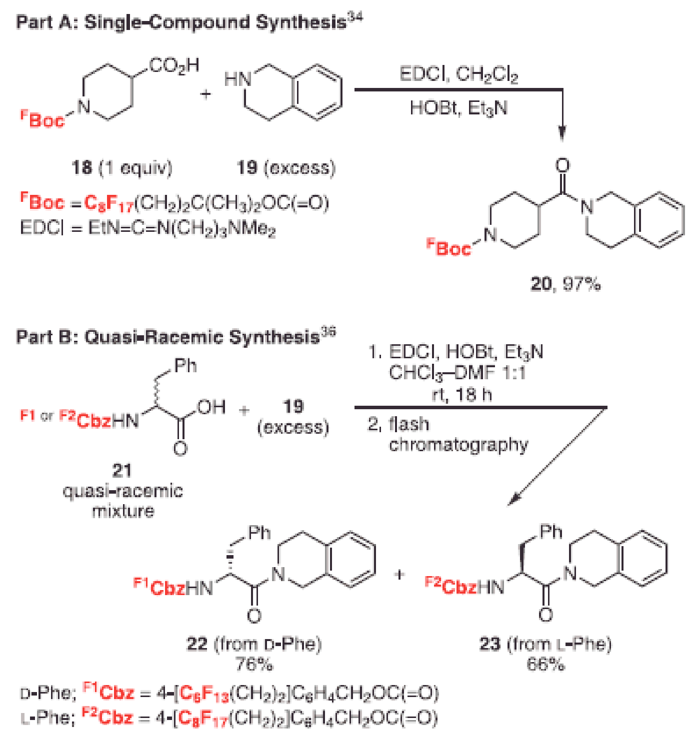
- Popular technique in medicinal chemistry and related areas
- Used for cleaning up crude reaction mixtures in which one of the key reaction components was used in excess to promote a rapid, high yielding reaction
- Clean, solution-phase kinetics
- Ease of separation by FSPE

Curran, Dennis. Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers. Aldrichimica ACTA. Vol. 39, No.1 2006

Fluorous Protecting Groups

- Substrates bearing fluorous protecting groups (tags or labels) are often used in multistep synthesis along with traditional nontagged reagents.

- A single fluorous protecting group makes a subsequent series of individual compounds fluorous, and each succeeding reaction product susceptible to the same fluorous solid-phase extraction which is amplified in parallel synthesis.



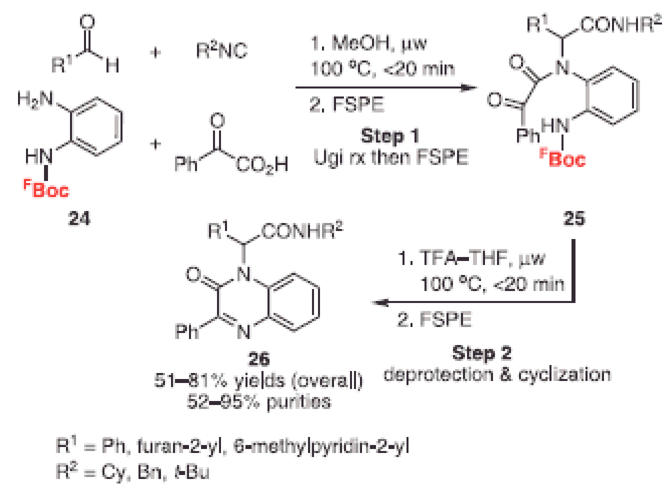
Scheme 3. Examples of Fluorous Protecting Groups in Single-Compound (Part A) and Quasi-Racemic (Part B) Syntheses.

Curran, Dennis. Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers. Aldrichimica ACTA. Vol. 39, No.1 2006

Fluorous Tagging in Multicomponent Reactions and Heterocycle Synthesis

- Use of a key fluorous-tagged component as limiting reagent in a multicomponent reaction allows for quick isolation of the tagged product away from what might be complex mixtures of unrelated reagents and products derived from the partial combination of several.

- After the multicomponent reaction is completed, the tag is replace by cyclization, is replaced by a proton or replaced by another diversity element in a phase switch that provides further purification for removing unwanted products.



Scheme 4. A Rapid, Two-Step Heterocycle Synthesis with Fluorous Tagging.

Curran, Dennis. Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers. Aldrichimica ACTA. Vol. 39, No.1 2006

Light-Fluorous Reactions and Reaction Components in Bimolecular Synthesis

- Bimolecules such as peptides & oligonucleotides are typically prepared by solid-phase synthesis.
- Fluorous techniques supplement solid-phase synthesis in important ways.

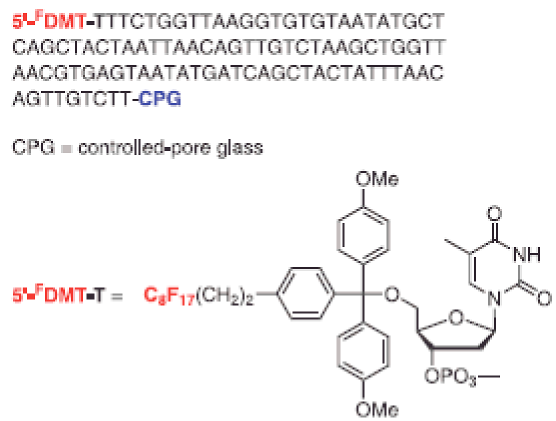


Figure 6. 100-mer Oligonucleotide Made by SPS with Fluorous Tagging and SPE Purification.

Pearsson, W.H; Berry,D.A.; Stoy,P; Jung, K-Y; Sercel, A.D. J. Org. Chem 2005, 70, 7114

Making Fluorous Reaction Components

- Preparation of fluorous material does not entail starting with incredibly reactive elemental fluorine.

- The fluorous building blocks can be made into a wide range of new fluorous molecules by using established methods and reactions.

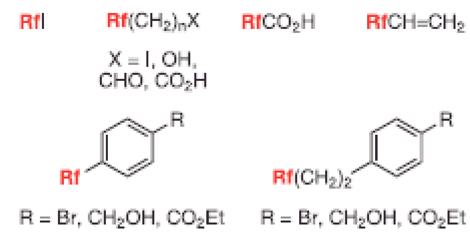


Figure 7. Representative Commercially Available Fluorous Building Blocks.

Rabai, J.. In Handbook of Flurorous Chemistry; Gladysz, J.A.; Curran, D.P.;Horvath, I.T., Eds.; Wiley-VCH; Weinheim, 2004, pp. 156-174

Fluorous Mixture Synthesis

- New solution phase technique which permits the synthesis of mixtures of compounds & provides for the isolation of individual, pure products through a sorting process called demixing.

- Fluorous Tags- attached to substrates in the guise of protecting groups bearing a homologous series of perfluoroalkyl groups.

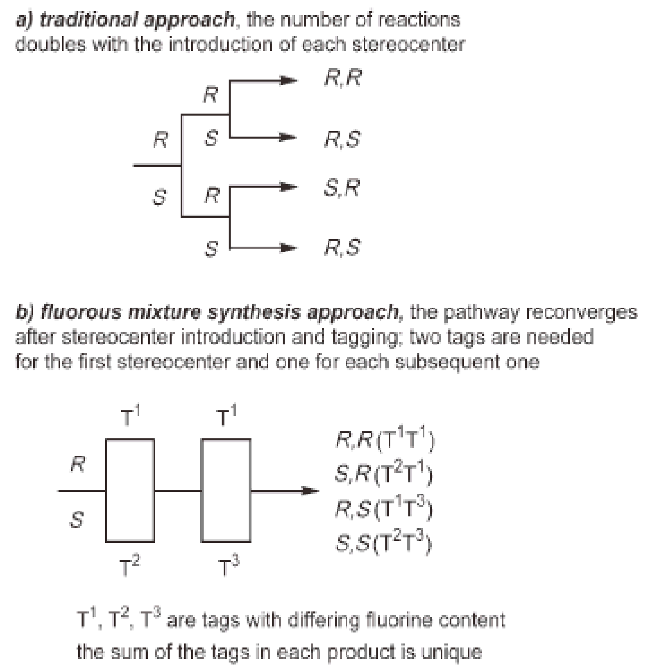
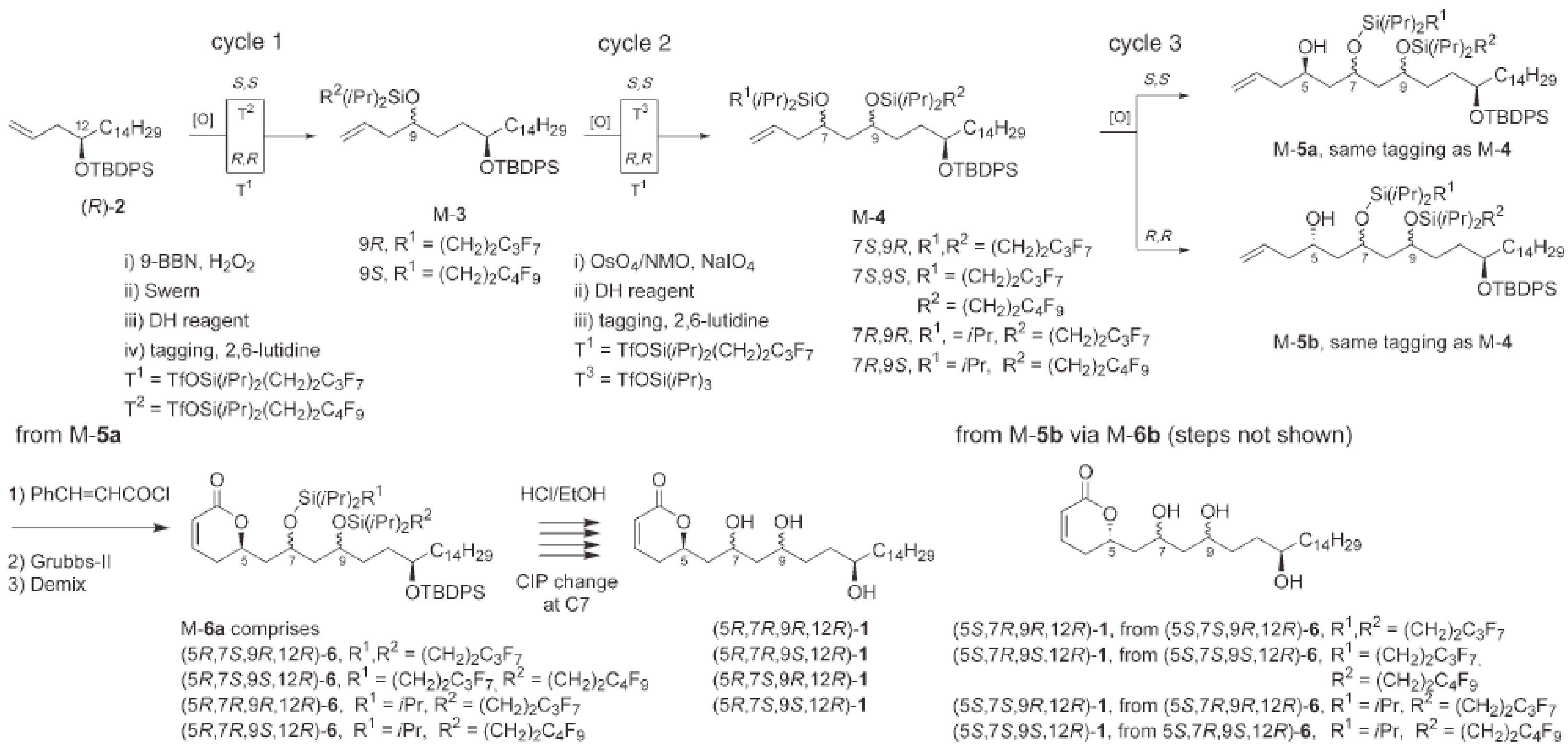


Figure 1. Strategies for the synthesis of stereoisomer libraries with the formation of stereocenters en route. Each branch represents the division of a product and introduction of a new stereocenter in both possible configurations.

Agnew. Chem. Int, Ed. 2006, 45, 2423-2426

Synthesis of Passifloricins

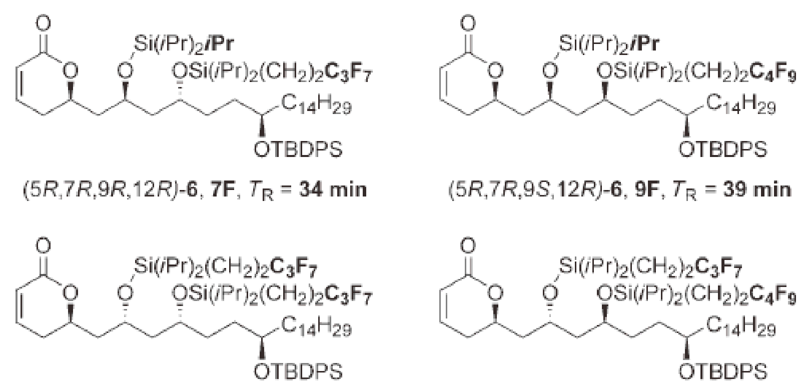


Scheme 1. Synthesis of passifloricins. 9-BBN = 9-borabicyclo[3.3.1]nonane, TBDPS = *tert*-butyldiphenylsilyl.

Agnew. Chem. Int, Ed. 2006, 45, 2423-2426

Demixing

- A mixture of compounds encoded with different fluorous tags can be kept together or pulled apart (demixed) during a separation depending on whether a fluorous or non-fluorous separating method is used



(5*R*,7*R*,9*R*,12*R*)-**6**, **7F**, T_R = **34 min**

(5*R*,7*R*,9*S*,12*R*)-**6**, **9F**, T_R = **39 min**

(5*R*,7*S*,9*R*,12*R*)-**6**, **14F**, T_R = **47 min**

(5*R*,7*S*,9*S*,12*R*)-**6**, **16F**, T_R = **51 min**

Scheme 2. Demixing of M-**6a** by fluorous HPLC: the quasi-diastereomers emerge in order of increasing total fluorine content.

Agnew. Chem. Int, Ed. 2006, 45, 2423-2426

Conclusions

- Fluorous Chemistry is poised to advance from a niche research area to a broad based suite of tools to solve real-world synthesis and separation problems.
- Availability of increasing varieties of fluorous compounds and separation media will make small scale applications of fluorous techniques more accessible to all.
- Additional R&D in academic and industrial settings is needed to realize the potential fluorous chemistry in large scale settings.
- High potential benefits of economy and environmental friendliness should provide strong incentive to move this work forward.

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