A bird's eye view of fluorous reaction and separation techniques

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Résumé **Un survol des techniques de réaction et de séparation fluorées**

Cet article présente une sélection diverse de techniques basées sur des composés fluorés récemment présentées, utilisables pour la synthèse et la séparation *in situ*. Les techniques de séparation incluent l'extraction liquide-liquide, l'extraction liquide-solide, de même que la chromatographie sur gel de silice fluorée. Les réactions monophasiques, biphasiques et triphasiques présentées ici utilisent des réactifs, des agents d'extraction et des groupes protecteurs fluorés dans un cadre de synthèse traditionnelle, de synthèse parallèle en solution ou encore de synthèse de mélanges. La facilité de la séparation et de la collecte des produits rendent les méthodes basées sur des molécules fluorées attrayantes pour la chimie à grande échelle, de même que leurs vitesses et leurs fiabilités représentent de grands avantages pour la chimie sur échelle réduite.

Mots-clés **Phase fluorée, stratégie de séparation, réactions biphasiques et triphasiques, réaction de Mitsunobu.**

Key-words **Fluorous phase, strategic separation, biphasic and triphasic reactions, Mitsunobu reaction.**

Reaction chemistry and separation chemistry comprise organic synthesis. Target products are formed by reacting precursors with reagents, reactants and catalysts under suitable reaction conditions, and then these products are separated from any residual reaction components and byproducts. The development of efficient, economical reactions is an important and enduring theme in organic synthesis. More recently, new separation methods and strategic methods to combine reaction and separation have come to the fore [1]. The need for innovative reaction and separation methods emanates both from large scale (process) chemistry, where inexpensive, atom economical and environmentally friendly methods are at a premium, and from small scale (discovery) chemistry, where general applicability and speed are the prime drivers. This short article provides a bird's eye view of the kinds of fluorous reaction and separation techniques that are actively being developed throughout the world [2]. This is a young field, with much promise for the future.

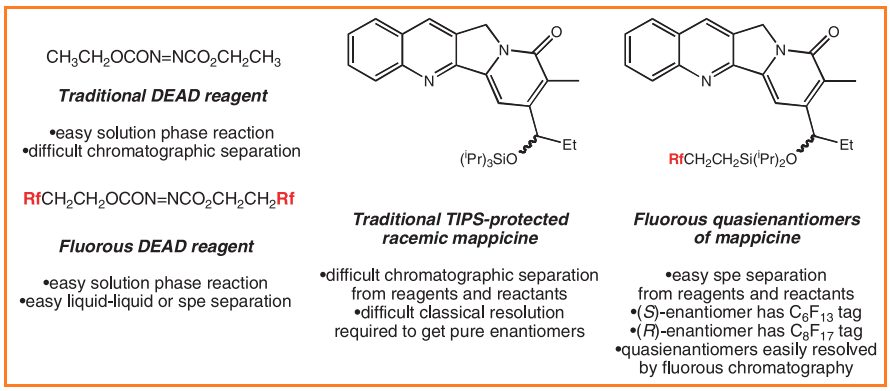

Figure 1 - Representative fluorous molecules.

In a simple view, fluorous molecules consist of an organic domain and a fluorous (fluoroalkyl) domain, as illustrated by the representative examples in *figure 1* [3]. Ideally, the organic domain controls the reaction chemistry of the hybrid molecule and the fluorous domain controls the separation chemistry. This « division of labor » allows synthetic chemists to design and fine tune these reaction and separation features independently, and that in turn allows for strategic separations [1]. A strategic separation is one in which the outcome can be predicted in advance, even if some components of the reaction mixture are new compounds whose physical and chromatographic properties are not yet known. The outcome of separation methods used in traditional solution phase synthesis – crystallization, distillation and chromatography – is difficult to predict; trial and error is the *modus operandi*. In contrast, the outcome of a typical separation in solid phase synthesis is easy to predict; all resin-bound products can readily be separated from soluble products by filtration. The predictability of fluorous separation techniques approaches that of solid phase synthesis without going to the extreme of using materials rather than small molecules as reaction components.

Fluorous molecules can be separated from organic molecules and from each other by three main types of separations: liquid/liquid (or solid/liquid) phase separation, solid phase extraction (spe, sometimes also called solid-liquid extraction) and chromatography [4]. Each of the three main separation methods is illustrated schematically in *figure 2*. All rely on the affinity that fluoroalkyl chains have for each other and on the phobia that they have for organic and inorganic molecules or molecular fragments. Liquid-liquid methods are targeted towards fluorous compounds with a high fluorine content (60% or more fluorine by molecular

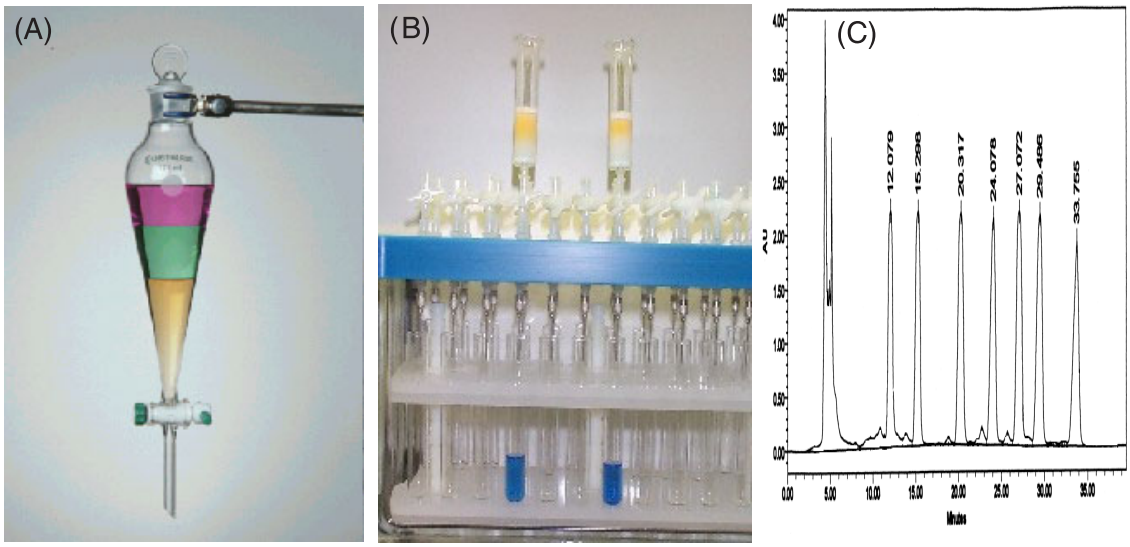

Figure 2 - Illustrations of fluorous liquid-liquid extraction, solid phase extraction and chromatography.
(A) a three-phase liquid-liquid extraction with organic (top, ether), aqueous (middle) and fluorous (bottom, perfluorohexanes) layers.
(B) the intermediate stage of a fluorous solid phase extraction over Fluoro*Flash*™ silica gel. An organic (blue) dye has been separated from a fluorous (gold) dye of similar polarity. With 85% aq. MeOH, the organic dye elutes immediately while the fluorous dye is immobilized. Changing the solvent to THF elutes the fluorous dye.
(C) a fluorous chromatographic separation of seven analogs of mappicine over Fluoro*Flash*™ silica gel. The analogs have different functional groups on the ring and different fluorous tags on a protecting group. The fluorous tags control the separation.

weight). These « heavy » fluorous molecules often have 18 or more difluoromethylene groups (each added CF_2 group adds 50 *mu*) and they are best used in catalytic applications for atom economy reasons. Solid-liquid and chromatographic methods use fluorous silica gel (silica gel with a fluorocarbon bonded phase) [5]. These methods are applicable to heavy fluorous molecules as well as to « light » fluorous molecules having 4-10 difluoromethylene groups, and they have significantly expanded the realm of fluorous chemistry.

The original technique of « fluorous biphasic catalysis » continues to increase in importance as more is learned about reaction and separation behavior of fluorous systems [6]. Briefly, this is a powerful liquid phase catalyst immobilization method where a heavy fluorous catalyst in a fluorous solvent like perfluorohexanes or perfluoromethylcyclohexane is contacted with a substrate in an organic solvent under conditions to promote formation of a new product. Fluorous solvents are immiscible with many organic solvents, so reactions are sometimes biphasic. But with proper solvent selection and temperature control, it is often possible to form a single phase during the reaction and to induce (usually by cooling) the formation of the biphase at the end of the reaction. Ideally, simple separation of the two liquid phases provides the product in the organic phase and the catalyst ready for reuse in the fluorous phase. In practice, a number of fluorous biphasic systems exhibit behavior sufficiently close to ideal to be of significant use, and the technique shows great promise for large scale applications in pharmaceutical manufacturing, fine and commodity chemical production, and other areas.
A recent and potentially broadly useful variant of fluorous biphasic catalysis is the limiting case where there is no fluorous solvent at all; the fluorous catalyst itself forms the fluorous phase. Called fluorous thermomorphic reactions, this technique capitalizes on the large temperature dependence of solubilities of some fluorous molecules in organic solvents. *Figure 3* shows a recent example of this class of reaction from the group of Gladysz [7]. Two organic reactants and a fluorous phosphine catalyst are heated in octane. The catalyst dissolves and promotes a conjugate addition. The reaction mixture is cooled and the precipitated fluorous catalyst is removed by filtration while evaporation of the octane provides the target product. The recovered catalyst can be reused. Fluorous solid supports such as Teflon™ can be added to facilitate the separation and to reduce the residual catalyst left in the organic liquid phase.

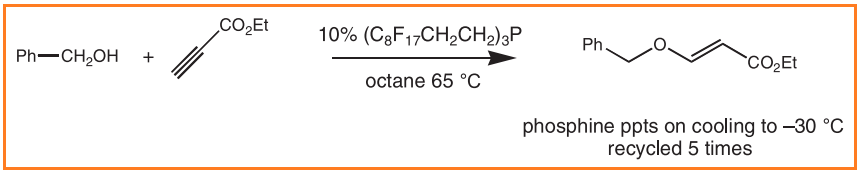

Figure 3 - Thermomorphic reactions: an example of fluorous biphasic catalysis without a fluorous solvent.

Fluorous triphasic reactions have just been introduced, and they offer unique opportunities to combine reaction and separation steps in a number of settings [8]. Among these, resolution has been an early focus [9], and the demonstration experiment in *figure 4* highlights some of the features of this technique. A racemic mixture of 2-naphthyl ethanol derivatized with a fluorous ester tag is

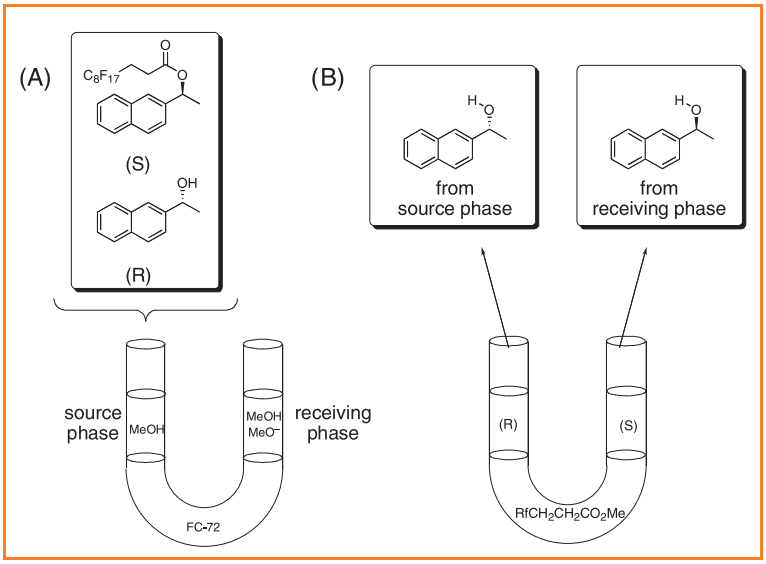

Figure 4 - A fluorous triphasic resolution.
(A) *Start*: a mixture of (*S*)-ester and (*R*)-alcohol generated by enantioselective cleavage of the racemic ester with *Candida antarctica B* lipase is added to the sources phase. Over time, the ester (but not the alcohol) transports through the fluorous phase to the receiving phase, where it is hydrolyzed and stranded.
(B) *Finish*: the (*R*)-alcohol is recovered from the source phase and the (*S*)-alcohol is isolated from the receiving phase.

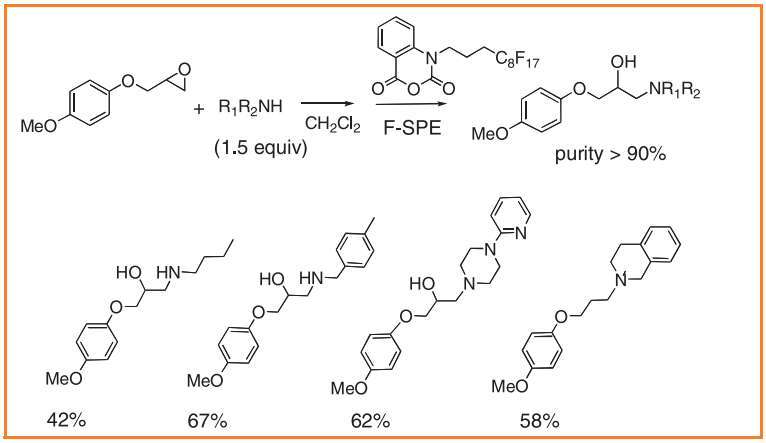

Figure 5 - Scavenging of unreacted amines with a fluorous isatoic anhydride.

small solvent volumes, resolutions and other triphasic reactions are very promising process methods of the future.

Reaping the benefits of fluorous biphasic reactions often requires an investment of time to develop suitable catalysts and reaction conditions. This is a worthwhile investment that should pay large dividends in the process chemistry arena. But it is a detraction in small scale discovery chemistry, where speed and reliability are at a premium. Here, the features of light fluorous reactants, reagents and catalysts shine [10]. Due to their reduced fluorine content, these compounds are much more soluble in typical organic reaction solvents, and standard literature conditions for related non-fluorous reactions can usually be used with little or no modification. Yet the light fluorous products can still be separated from non-fluorous ones by quick and easy solid phase extractions over silica gel with a fluorocarbon bonded phase.

Relying on the above features of light fluorous molecules and solid phase extractions, fluorous scavenging is an up-and-coming technique with broad potential applications in solution phase parallel synthesis [11]. The use of a fluorous isatoic anhydride scavenger, as illustrated in *figure 5*, is representative of this class of reaction [12]. An amine diversity element is used in modest excess to drive its reaction with an epoxide to completion. The fluorous isatoic anhydride is then added, and after a suitable reaction time, the scavenged amine and the unreacted scavenger are filtered away from the desired product by fluorous spe. Because the scavenging reactions occur in solution, they are rapid and clean and using large excesses of scavengers is neither necessary nor desirable.

For many applications in multi-step and parallel synthesis, the option to add a fluorous tag to the substrate and derived products becomes attractive. A single fluorous tag, often in the guise of a modified protecting group, can render a whole library of substrates fluorous. Multi-step reactions can then be conducted in solution with standard (non-fluorous) reactants, reagents and catalysts, and the fluorous target products can readily be separated from the other unreacted or spent reaction components by spe. *Figure 6* illustrates some of the fluorous protecting groups that are now commercially available for fluorous tagging exercises.
Fluorous mixture synthesis [13] takes fluorous tagging to the next level by allowing a unique leveraging of effort. Different

first enantioselectively detagged with the enzyme *Candida antarctica B lipase*. The resulting mixture is then added to the source side of a triphasic reactor. The receiving side contains a detagging reagent (NaOMe, in this case), and the two sides are separated by a fluorous solvent (perfluorohexanes). The detagged *R*-enantiomer cannot transport through the fluorous phase, while the tagged *S*-enantiomer passes through to the other side, where it is detagged and stranded. At the end of the experiment, the *R*-enantiomer is on the source side of the reactor, the *S*-enantiomer is on the receiving side, and the residual tag is in the middle. Because of the simplicity and

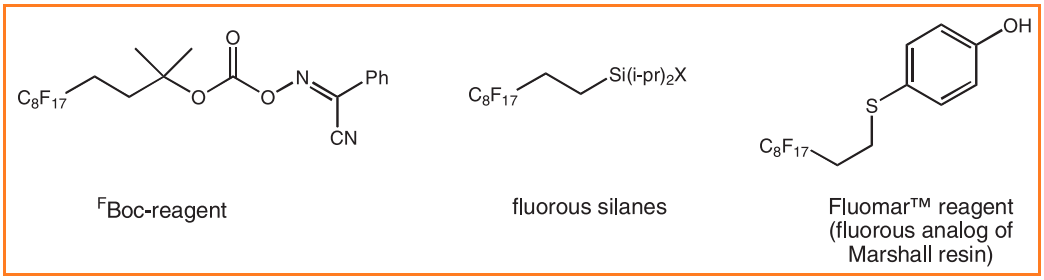

Figure 6 - Selected commercially available fluorous tagging reagents.

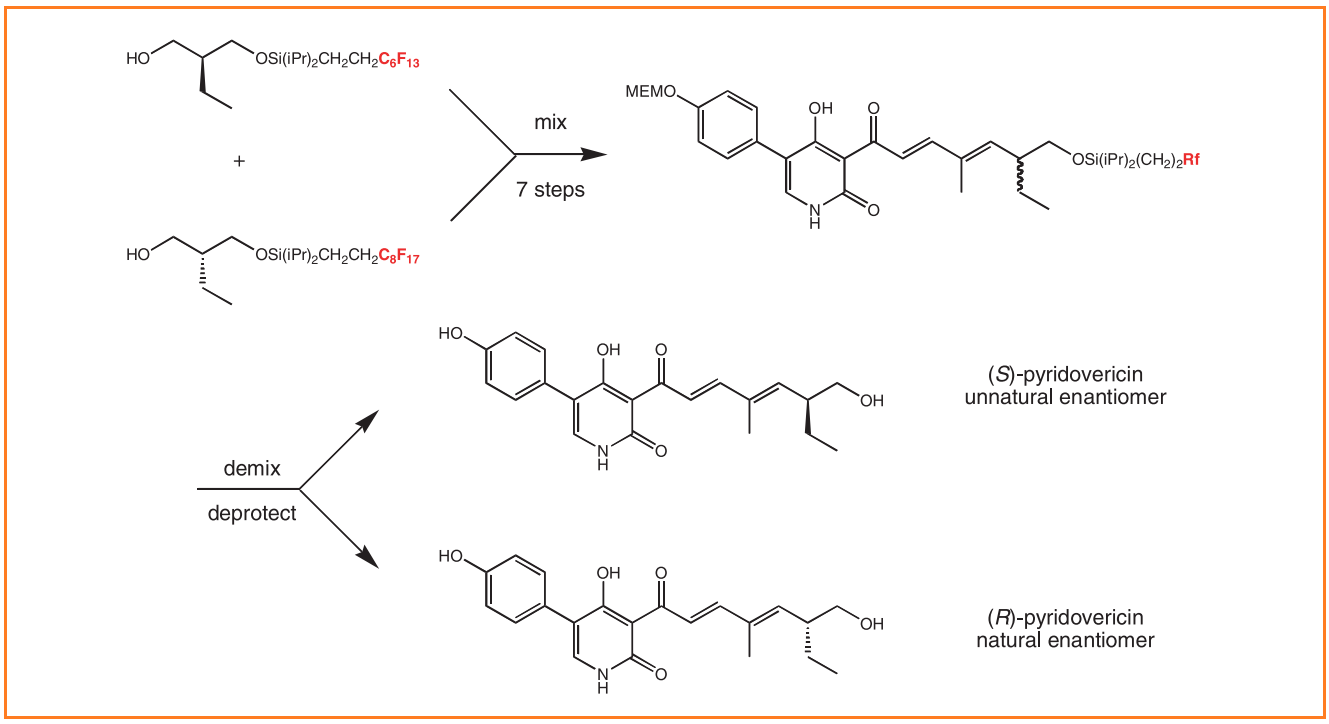

Figure 7 - Summary of the quasiracemic synthesis of pyridovericin.

substrates are tagged with homologous fluorous tags and then the tagged substrates are mixed in small groups (typically two to seven compounds). The resulting mixtures are then taken through a multi-step reaction sequence to provide mixtures of tagged products. In turn, just prior to removal of the fluorous tag, these mixtures are resolved into the individual components by fluorous chromatography. The process, called demixing, is (loosely speaking) the reverse of mixing and it relies on the ability of fluorous silica gel to separate compounds based on the fluorine content of their tags. The compounds emerge in order of increasing fluorine content, so the demixing is also an identification. Early applications range from preparing of both enantiomers of natural products in a single synthesis (quasiracemic synthesis [14]) through making multiple analogs by traditional synthesis [15], to a combination of mixture synthesis with splitting and diversification to provide libraries of hundreds of analogs of drug candidates [16]. The quasiracemic synthesis of pyridovericin is summarized in *figure 7*. Fluorous mixture synthesis is a powerful new tool in discovery chemistry because it produces more compounds in individual pure form without a proportional increase in effort.

An impediment to the academic and especially industrial use of fluorous chemistry has been the lack of commercially available reagents and separation media. Many chemical and sorbent suppliers, including Aldrich, Fluka, Keystone and a number of specialty fluorine companies provide a selection of highly fluorinated raw materials, but these must often be parlayed through several steps into more sophisticated fluorous reagents and tags. Recently, a startup company spun out of the University of Pittsburgh and called Fluorous Technologies, Inc. [17] has begun to offer an increasing supply of reagents, tags, scavengers, etc. along with complementary separation media and technological expertise.

Looking forward, the future of fluorous chemistry looks bright indeed. 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. New reagents, techniques and applications should continue to appear from academic groups. And the availability of increasing varieties of fluorous compounds and separation media will make small scale applications of fluorous techniques more accessible to all. Additional research and development in both academic and industrial settings will be needed to realize the potential of fluorous chemistry in large scale settings, and the high potential benefits of economy and environmental friendliness provide a strong impetus to propel this work forward [18].

References and notes

[1] Curran D.P., Strategy-level separations in organic synthesis: from planning to practice, *Angew. Chem. Int. Ed. Eng.*, **1998**, *37*, p. 1175.

[2] a) Gladysz J.A., Curran D.P., Introduction - fluorous chemistry: from biphasic catalysis to a parallel chemical universe and beyond, *Tetrahedron*, **2002**, *58*, p. 3823 ; b) See the Tetrahedorn-Symposium-in-Print that follows this introduction.

[3] Curran D.P., Fluorous techniques for the synthesis of organic molecules: a unified strategy for reaction and separation, *Stimulating concepts in chemistry*, Wiley-VCH, New York, **2000**, p. 25.

[4] a) Barthel-Rosa L.P., Gladysz J.A., Chemistry in fluorous media: a user's guide to practical considerations in the application of fluorous catalysts and reagents, *Coord. Chem. Rev.*, **1999**, *192*, p. 587; b) Curran D.P., Hadida S., Studer A., He M., Kim S.-Y. et al., Experimental techniques in fluorous synthesis: a user's guide, *Combinatorial chemistry: a practical approach*, Oxford Univ. Press, Oxford, **2001**, p. 327.

[5] Curran D.P., Fluorous reverse phase silica gel. A new tool for preparative separations in synthetic organic and organofluorine chemistry, *Synlett*, **2001**, p. 1488.

[6] a) Horvath I.T., Rabai J., Facile catalyst separation without water: fluorous biphase hydroformylation of olefins, *Science*, **1994**, *266*, p. 72; b) Horvath I.T., Fluorous biphase chemistry, *Acc. Chem. Res.*, **1998**, *31*, p. 641; c) de Wolf E., van Koten G., Deelman B.J., Fluorous phase separation techniques in catalysis, *Chem. Soc. Rev.*, **1999**, *28*, p. 37; d) Cavazzini M., Montanari F., Pozzi G., Quici S., Perfluorocarbon-soluble catalysts and reagents and the application of fbs (fluorous biphase system) to organic synthesis, *J. Fluorine Chem.*, **1999**, *94*, p. 183; e) Fish R.H., Fluorous biphasic catalysis: a new paradigm for the separation of homogeneous catalysts from their reaction substrates and products,

Chem. Eur. J., **1999**, *5*, p. 1677; f) Hope E.G., Stuart A.M., Fluorous biphase catalysis, *J. Fluorine Chem.,* **1999**, *100*, p. 75-83; g) Gladysz J.A., Recoverable catalysts. Ultimate goals, criteria of evaluation, and the green chemistry interface, *Pure Appl Chem.,* **2001**, *73*, p. 1319.

[7] Wende M., Meier R., Gladysz J.A., Fluorous catalysis without fluorous solvents: a friendlier catalyst recovery/recycling protocol based upon thermomorphic properties and liquid/solid phase separation, *J. Am. Chem. Soc.,* **2001**, *123*, p. 11490.

[8] Nakamura H., Linclau B., Curran D.P., Fluorous triphasic reactions: Transportative deprotection of fluorous silyl ethers with concomitant purification, *J. Am. Chem. Soc.*, **2001**, *123*, p. 10119.

[9] Luo Z.Y., Swaleh S.M., Theil F., Curran D.P., Resolution of 1-(2-naphthyl)ethanol by a combination of an enzyme-catalyzed kinetic resolution with a fluorous triphasic separative reaction, *Org. Lett.,* **2002**, *4*, p. 2585.

[10] a) Curran D.P., Luo Z.Y., Fluorous synthesis with fewer fluorines (light fluorous synthesis): separation of tagged from untagged products by solid-phase extraction with fluorous reverse-phase silica gel, *J. Am. Chem. Soc.*, **1999**, *121*, p. 9069; b) Zhang Q., Luo Z., Curran D.P., Separation of « light fluorous » reagents and catalysts by fluorous solid-phase extraction: synthesis and study of a family of triarylphosphines bearing linear and branched fluorous tags, *J. Org. Chem.*, **2000**, *65*, p. 8866.

[11] a) Lindsley C.W., Zhao Z., Leister W.H., Fluorous-tethered quenching reagents for solution phase parallel synthesis, *Tetrahedron Lett.*, **2002**, *43*, p. 4225; b) Zhang W., Curran D.P., Chen C.H.T., Use of fluorous silica gel to separate fluorous thiol quenching derivatives in solution-phase parallel synthesis, *Tetrahedron*, **2002**, *58*, p. 3871.

[12] Zhang W., Chen C.H.-T., Nagashima T., Fluorous electrophilic scavengers for solution phase parallel synthesis, *Tetrahedron Lett.*, **2003**, *44*, p. 2065.

[13] Luo Z.Y., Zhang Q.S., Oderaotoshi Y., Curran D.P., Fluorous mixture synthesis: a fluorous-tagging strategy for the synthesis and separation of mixtures of organic compounds, *Science*, **2001**, *291*, p. 1766; b) Curran D.P., Oderaotoshi Y., Thiol additions to acrylates by fluorous mixture synthesis: relative control of elution order in demixing by the fluorous tag and the thiol substituent, *Tetrahedron*, **2001**, *57*, p. 5243.

[14] Zhang Q.S., Rivkin A., Curran D.P., Quasiracemic synthesis: concepts and implementation with a fluorous tagging strategy to make both enantiomers of pyridovericin and mappicine, *J. Am. Chem. Soc.*, **2002**, *124*, p. 5774.

[15] Curran D.P., Furukawa T., Simultaneous preparation of four truncated analogues of discodermolide by fluorous mixture synthesis, *Org. Lett.*, **2002**, *4*, p. 2233.

[16] Zhang W., Chen C.H.-T., Luo Z., Curran D.P., Solution-phase preparation of a 560-compound library of individually pure mappicine analogs by fluorous mixture synthesis, *J. Am. Chem. Soc.*, **2002**, *124*, p. 10443.

[17] Fluorous Technologies, Inc., UPARC, 970 William Pitt Way, Harmarville, PA, 15238 USA (www.fluorous.com). DPC is the Founder and Chief Scientific Advisor and holds an equity interest in FTI.

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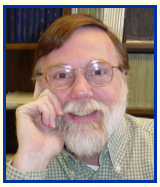

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