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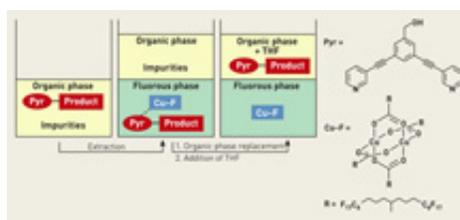
FLUOROUS BEGINS TO FLOURISH

Symposium spotlights diverse range of fluororous technologies spanning chemistry and biology

[MICHAEL FREEMANTLE, C&EN LONDON](#)

The tentacles of fluororous chemistry now reach beyond traditional organic chemistry into other realms such as supramolecular chemistry, biology, and medicine. Current and potential applications include biphasic catalysis, natural product synthesis, oligonucleotide purification, and pulmonary disease therapy.

Last month, almost 100 academic and industrial researchers convened in France at the [1st International Symposium on Fluororous Technologies](#) to report on the latest developments in the field. The symposium, held at the University of Bordeaux, Talence, was cochaired by Jean-Marc Vincent, a researcher at the university, and Richard H. Fish, a senior scientist at Lawrence Berkeley National Laboratory.



[Full-sized Image](#)

Fluororous chemistry is the chemistry of highly fluorinated organic compounds. One of its key features is the use of fluororous tags, also known as ponytails, tethered to nonfluorinated domains in molecules. The tags are typically perfluoroalkyl groups. They can be permanent or temporary attachments, depending on the application.

Fluororous compounds not only mimic the chemical reactivity of their nonfluororous counterparts but also, because of the tags, prefer to dissolve in fluororous solvents rather than in organic solvents or water. This combination of properties has proved useful for liquid-liquid and solid-phase extractions. For example, fluororous tags on catalysts enable them to dissolve in a fluororous phase, making them easier to separate from products that are more soluble in another phase.

The term "fluororous" was coined in the early 1990s by Exxon chemist [István T. Horváth](#), who is now a chemistry professor at [Eötvös Loránd University](#), Budapest. He introduced the term as an analog to the term aqueous to emphasize that chemical transformations in fluororous biphasic systems are primarily controlled by a reagent or catalyst designed to dissolve preferentially in the fluororous phase.

In a seminal paper on the topic, Horváth and József Rábai, a visiting scientist from Eötvös Loránd University, described the use of a trialkylphosphine-modified rhodium catalyst with a fluororous tag on each of the three alkyls for the preparation of aldehydes (*Science* **1994**, 266, 72). The reactions--hydroformylation of olefins such as 1-decene--were carried out in a biphasic system consisting of a fluororous phase and a conventional organic solvent as the other phase. After the reaction, the tagged catalyst remained in the fluororous phase, allowing it to be reused, and the aldehydes were extracted from the other phase.

THIS DISCOVERY was "a real catalyst for the development of fluororous technologies," Vincent said at the Bordeaux symposium. In recognition of the work, Horváth and Rábai received the first international award for fluororous technologies at the meeting.



Vincent

Fish

PHOTOS BY MICHAEL FREEMANTLE

"Soon after the paper by Hórvath and Rábai, other examples of the use of fluororous biphasic catalysis appeared," Fish told C&EN. "The technique has now been adapted for almost every classic organic reaction, including the homogeneous oxidation of alcohols and alkenols and the epoxidation of alkenes."

At the Bordeaux symposium, Fish described several fluororous biphasic catalysis oxidation-reduction scenarios that encompass the use of fluororous ponytailed ligands with sparingly soluble fluororous ponytailed metal carboxylates to form catalytic fluorocarbon complexes that are soluble in fluororous solvents.

Fish outlined, for example, a novel concept for the synthesis of methanol from synthesis gas (a mixture of carbon monoxide and hydrogen). The approach employs a nickel(II) carboxylate with C_8F_{17} ponytails, a cyclic triaza ligand with C_8F_{17} ponytails attached to each of the three nitrogen atoms, a methoxide ion, and perfluorodecalin as the fluororous solvent. The methanol forms a separate phase above the fluororous layer. The work was carried out in collaboration with researchers Maria Contel at the University of Zaragoza, Spain, and Devinder Mahajan at Brookhaven National Laboratory/State University of New York, Stony Brook.

Vincent and coworkers at the University of Bordeaux have also been working on fluororous metal carboxylates. The team has used the compounds to develop a technique, known as reversible phase-switching, for separation and purification applications. The technique involves a "catch-and-release" strategy that relies on the reversible coordination of ligands with a nonfluorous tag to a fluororous-tagged metal carboxylate complex. Substrates or products coordinated with the nonfluorous ligands are soluble in a hydrocarbon organic phase. When the molecules with the nonfluorous tags are coordinated with the fluororous metal carboxylate, they become soluble in the fluororous phase. When a chelating solvent such as tetrahydrofuran (THF) is added, the nonfluorous-tagged substrates or products separate from the fluororous metal carboxylate and can be extracted into a hydrocarbon solvent.

Last year, the group showed that the technique can be applied to the preparation of hydantoin in high yield and purity using a nonfluorous pyridyl tag and a fluororous copper(II) carboxylate complex ([Org. Lett. 2004, 6, 2765](#)).

"Due to the high lability of the coordination bonds, release of the nonfluorous-tagged molecules into the hydrocarbon phase is achieved by simply adding THF in excess to the biphasic system," Vincent said. "The THF acts as a competitive ligand."

Meanwhile, assistant professor of chemistry Andrea Biffis and coworkers at the University of Padua, in Italy, have synthesized a chiral dirhodium(II) carboxylate catalyst bearing perfluoroalkyl chains that can be used homogeneously with a conventional organic solvent, dichloromethane, or in fluororous biphasic conditions ([Org. Lett. 2005, 7, 1841](#)).

"The catalyst displays excellent chemo- and regioselectivity and good enantioselectivity in asymmetric cyclopropanation and C-H bond activation reactions," Biffis said. "It can be simply and thoroughly separated from the reaction mixture and is recyclable."

Joji Nishikido, chief chemist at [Asahi Kasei Corp.](#), Shizuoka, Japan, discussed the use of fluororous Lewis acid catalysts in the development of industrial processes such as Friedel-Crafts acylations and esterifications.

"Lewis acids like aluminum chloride and boron trifluoride are used widely in industry," he observed. "They need to be used stoichiometrically or in excess to achieve high yield and high selectivity. As they are rarely recovered or recycled, they cause large amounts of waste. Our key aim is to achieve a catalyst-recycling system using fluororous Lewis acid catalysts."

In a recent paper, Nishikido and coworkers at Noguchi Institute, Tokyo, described the use of a complex with a perfluorinated ligand--hafnium(IV) bis(perfluorooctanesulfonyl)amide, $\text{Hf}[\text{N}(\text{SO}_2\text{C}_8\text{F}_{17})_2]_4$ --as a catalyst for the Friedel-Crafts acylation of aromatic compounds such as anisole, toluene, and chlorobenzene (*Tetrahedron Lett.* **2005**, *46*, 2697).

"The corresponding aromatic ketones are obtained in satisfactory to high yields," the authors noted. "The catalyst is selectively soluble in the lower fluorine phase and can be easily recovered by phase separation."

At the [Institute of Catalysis & Surface Chemistry](#) in Kraków, Poland, assistant professor of chemistry Katarzyna Pamin and coworkers have been investigating use of pernitrometalloporphyrins with fluorine ponytails as catalysts for the epoxidation of alkenes with molecular oxygen.

"The physicochemical and catalytic properties of pernitrometalloporphyrins with ponytails are mainly governed by the strong electron-withdrawing effect of the nitro and fluoro substituents," she said.

The metalloporphyrins are typically cobalt porphyrins with four pentafluorophenyl substituents, four nitro groups, and four C_6F_{13} ponytails.

"These metallocomplexes are soluble in perfluorosolvents such as perfluorohexane," Pamin observed. "We applied them as catalysts in the epoxidation of alkenes in a perfluorohexane-acetonitrile biphasic system with molecular oxygen and sacrificial aldehyde as the reducing agent. The conversion of substrates and epoxide yields were high for cyclooctene and cyclohexene but less so for linear olefins."

CHEMISTS AT [Utrecht University](#) in the Netherlands have been studying fluorine versions of a triphenylphosphine rhodium catalyst: the Wilkinson catalyst, $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$. It is best known for carrying out selective hydrogenations for fine chemicals, said Berth-Jan Deelman, a part-time lecturer at the university and new product development and quality control manager at Arkema, Vlissingen. "Catalysts with fluorine triphenylphosphine ligands show reduced activity and/or selectivity compared with the Wilkinson catalyst because of the electron-withdrawing effects of the perfluoro tails. We have shown that by employing a SiCH_2CH_2 spacer between the phenyls and perfluoro tails, the properties of the catalyst center remain intact in fluorine biphasic processes."

The Utrecht team has also used fluorine versions of the Wilkinson catalyst for the hydrosilylation of 1-alkenes, such as 1-hexene, and shown that the precious rhodium catalyst can be recycled and reused without any observable changes in activity and selectivity.

Last year, Deelman and coworkers reported the combinatorial synthesis of a library of perfluoroalkylsilyl derivatives of triphenylphosphine and the measurement of their partition coefficients in the biphasic perfluoromethylcyclohexane-toluene solvent system (*J. Comb. Chem.* **2004**, *6*, 363). The aim was to optimize the partition coefficient--that is, the "fluorophilicity" of the catalyst--and thereby reduce the amount of leaching of the catalyst and free fluorine ligands into the organic phase.

"For fluorine separation techniques to compete effectively with aqueous biphasic separation, catalyst recycling efficiencies have to be greater than 99.9% and catalyst leaching, less than



Horváth

Rábai

PHOTOS BY MICHAEL FREEMANTLE

0.1%," Deelman said.

The Utrecht chemists varied four parameters in their combinatorial library: the number of substituted phenyl groups, the number of fluoros tails per silicon, the length of the tails, and the position of the silicon atom on the phenyl group. They found that meta-substituted fluoros phosphines with longer and more tails had a higher preference for the fluoros phase. Para- and 3,5-substituted phosphines, on the other hand, exhibited irregular behavior, as elongation of tails or an increase in the number of tails did not necessarily lead to higher partition coefficients.

"By using combinatorial techniques to optimize fluorophilicity, we are able to reduce rhodium leaching to less than 1 ppm," Deelman said.

Chemistry professor [John A. Gladysz](#) at the University of Erlangen-Nuremberg, in Germany, has been carrying out fluoros catalysis in the absence of fluoros solvents. "We have found that many fluoros compounds exhibit highly temperature-dependent solubilities in organic solvents," he said. "Such 'thermomorphic' behavior allows fluoros catalysts to be used under one-phase conditions at elevated temperatures in ordinary organic solvents and recovered by a simple liquid-solid phase separation at low temperature."

Recently, Gladysz and coworker Long V. Dinh reported a "catalyst-on-a-tape" method that employs a tape made of DuPont's Teflon to deliver and recover homogeneous fluoros catalysts from a reaction mixture ([Angew. Chem. Int. Ed. 2005, 44, 4059](#); [C&EN, June 27, page 38](#)). They showed that the technique can be applied to hydrosilylation and olefin metathesis reactions.

At the University of Pittsburgh, chemistry professor [Dennis P. Curran](#) has developed a technique known as fluoros mixture synthesis to prepare stereoisomer libraries of natural products. "This is a cutting-edge technique for making multiple compounds in a single reaction flask," Curran explained. "While we do synthesis on mixtures, the final demixing allows us to isolate individual pure compounds at the end."

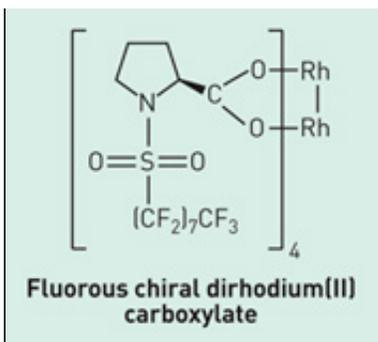
With this technique, members of a series of substrates are tagged with different fluoros tags, mixed, and taken through a series of reactions. The tagged products are then separated by fluoros high-pressure liquid chromatography using a fluoros silica gel column. The products elute in order of the size of the fluoros tag, from C₂F₅ up to C₈F₁₇. They are finally detagged to obtain the pure compounds.

Recently, Curran, chemistry professor Craig S. Wilcox, and colleagues devised a double separation tagging technique that combines fluoros tags and oligomeric ethylene glycol tags. The use of oligoethylene glycols as sorting tags for chromatography was first reported by Wilcox and coworker Serhan Turkyilmaz earlier this year ([Tetrahedron Lett. 2005, 46, 1827](#)).

The Curran and Wilcox team used the double-tagging approach to prepare, in a single-solution-phase synthesis, a stereoisomer library of 16 murisolsins--a class of natural products that exhibit powerful cell-killing effects. The team separated the 16-compound mixture into individual components by using a series of two demixings--one for each class of tag.

IN RELATED WORK, Curran's group has used double fluoros tagging to synthesize a stereoisomer library of eight passifloricins. The compounds, polyhydroxylated lactones, are found in the resin of *Passiflora foetida*, or fetid passionflower. Passifloricins exhibit high activity against the parasites that cause leishmaniasis.

Chemistry professor [Virgil Percec](#) and coworkers at the



University of Pennsylvania have shown that fluorination can be exploited to generate and amplify nonbonding intramolecular and intermolecular interactions in self-assembly processes.

Percec's recent work on this topic has focused on the self-assembly of semifluorinated dendritic supramolecular structures. The procedure involves replacing some of the hydrogen atoms of a dendron--a dendritic wedge--with fluorine atoms.

"Semifluorination changes the shape of a conical dendron into a crownlike dendron," Percec said. "As a result, the dendrimers self-organize into a pyramidal column rather than the usual spherical architecture."

Last month, Percec's group reported the self-assembly of semifluorinated Janus-dendritic benzamides into bilayered pyramidal columns (*Angew. Chem. Int. Ed.* **2005**, *44*, 4739). The Janus--or two-faced--dendrimers consist of two different dendrons connected at their apexes.

"When two identical dendrons of a twin-dendritic benzamide are either hydrogenated or fluorinated, they self-assemble into supramolecular columns," Percec explained. "When one of the dendrons is fluorinated and the other hydrogenated, we obtain a Janus-dendritic benzamide that self-assembles into the bilayered pyramidal architecture. The columns that are formed have twice the diameter of those of either the hydrogenated or fluorinated twin-dendritic benzamides.

"Apart from providing an unusual example of the fluorophobic effect in self-assembly, these new supramolecular pyramidal dendrimers open up numerous new strategies for the construction of complex molecular nanosystems," he added.

Fluorous technology also has immense potential in the biological realm, according to Philip E. Yeske, president and chief executive officer of Fluorous Technologies, Pittsburgh.

"Biologists have a much more restrictive set of separation tools than chemists," he told C&EN. "Fluorous technology, in this context, is selective, robust, and cost-effective, and the value comes out in biology-oriented applications like peptide synthesis, oligonucleotide purification, and peptide characterization."

An example is work being carried out by chemistry professor Willi Bannwarth's group at the University of Freiburg, in Germany. At the Bordeaux meeting, he described the use of a solid-phase extraction technique that employs fluorous reversed-phase silica gel as the sorbent for the purification of synthetic DNA fragments.

The technique uses a column packed with silica bound to a fluorocarbon phase, for example, silica- $\text{O}(\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{C}_8\text{F}_{17})$. When a solution of perfluoro-tagged and nontagged compounds is added to the column, the fluorous molecules selectively adsorb on the fluorous silica gel. The gel is first washed with a fluorophobic solvent to remove the nontagged organic compounds. After cleavage of the fluorous tags, the desired compound is obtained and the tags remain on the column.

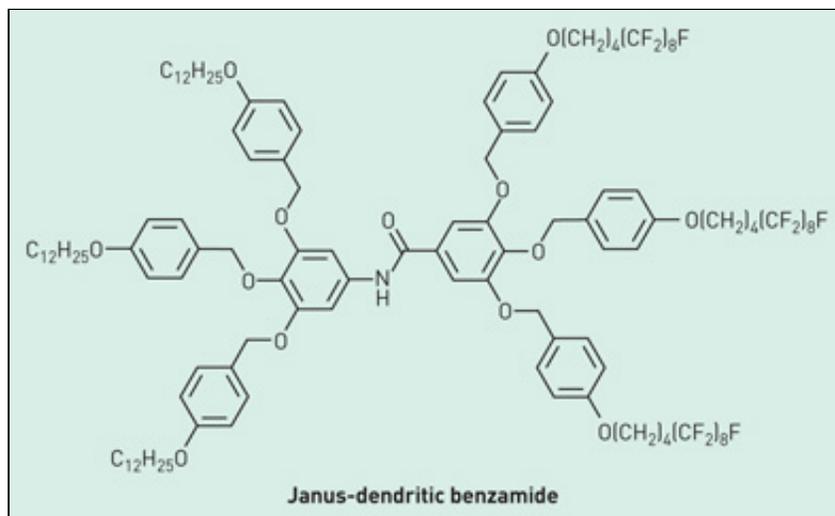
Bannwarth noted that perfluoro-tagged compounds are highly hydrophobic compared with those carrying linear alkyl chains. "In the aqueous phase, interactions between perfluoro tags on water-soluble biomolecules like DNA and RNA can become very intense. We have used these interactions to immobilize DNA fragments noncovalently on fluorous silica gel as a basis to develop a simple purification system for synthetic oligonucleotides."

In a recent paper, Bannwarth and coworker Christian Beller used this approach to separate a perfluoro-tagged 30-nucleotide sequence from shorter and longer nontagged

DNA sequences (*Helv. Chim. Acta* **2005**, *88*, 171). They found that the interaction between the perfluoro-tagged oligonucleotide and the fluorosilica gel was so intense that all the other sequences could be removed by a neutral aqueous-phase washing step.

"We are currently extending the approach to the immobilization of RNA and proteins and applications in molecular biology," Bannwarth said.

A team led by [Marie Pierre Krafft](#), a director of research at the Charles Sadron Institute, Strasbourg, France, noted that the use of perfluorocarbons is being explored in various biomedical applications, notably pulmonary disease therapy, because of their extreme biological inertness, their ability to dissolve oxygen, and their hydrophobicity. Her group has been investigating the use of perfluorocarbons for lung-surfactant replacement therapy--for example, in the treatment of neonatal respiratory distress syndrome.



THE NATIVE lung surfactant in mammalian species is a monolayer consisting of a mixture of lipids and proteins that helps breathing by lowering the surface tension between air and alveoli when the lungs are compressed. The main component of the surfactant is the phospholipid dipalmitoylphosphatidylcholine. However, when used alone, the phospholipid is a poor lung surfactant substitute because it tends to crystallize in the monolayer.

Krafft's group has shown that gaseous perfluorooctyl bromide, $C_8F_{17}Br$, is highly effective at fluidizing the phospholipid when it is semicrystalline and can prevent it from crystallizing (*Angew. Chem. Int. Ed.* **2005**, *44*, 2749).

"This combination of a perfluorocarbon and a phospholipid is a new concept in the design of lung surfactant replacements, especially for the treatment of neonates," she said. "A major advantage of the system is that it is entirely synthetic, whereas present commercial lung-surfactant replacement products are extracted from animals, bovine or porcine, depending on the product. Our new surfactant system is also more effective than the commercial products."

Jean G. Riess, a visiting scientist at the University of California, San Diego, pointed out that fluorocarbons such as perfluorooctyl bromide are not metabolized. "You can drink perfluorooctyl bromide by the liter and fill your lungs with it without risk of drowning," he said. "It is rapidly excreted."

Riess outlined the properties of the commercial product [Oxygent](#), a temporary intravenous oxygen carrier--or blood substitute--developed by Alliance Pharmaceutical. The main ingredients of the product, a submicrometer-size injectable emulsion, are $C_8F_{17}Br$, a small amount of $C_{10}F_{21}Br$, and a phospholipid surfactant emulsifier.

"The poor water solubility of perfluorocarbon gases has also allowed the development of stable injectable micrometer-size gas bubbles that serve as contrast agents for ultrasound imaging," Riess said. A typical product consists of phospholipid-coated microbubbles containing a perfluorocarbon, such as perfluorohexane, as the internal phase. "Microbubbles that resonate at a diagnostic frequency are ideal reflectors for ultrasound," he explained. "They enable us to image more accurately the cavities in the heart as well as blood flow in vessels and help us to assess conditions such as myocardial infarct, thrombus, tumor, and cholesterol plaque in arteries."

In a plenary lecture at the Bordeaux meeting, Horváth drew attention to some of the environmental issues associated with fluororous technologies. "Fluororous chemistry was invented to provide facile separation of products from reagents or catalysts," he noted. "While a fluororous system is designed to remain inside a laboratory or a production facility, low-level leaching of fluororous compounds into products or accidental releases could result in environmental issues. If such reagents or catalysts enter the environment, the oxidation of the hydrocarbon domains of the compounds could lead to the formation of fluororous carboxylic acids. Some of these acids have been shown to have negative health and environmental effects.

"Most fluororous compounds are nontoxic, and some of them are used in biomedical applications, for example, for collapsed lung ventilation," he continued. "But there is still the major problem of persistence in the environment and bioaccumulation."

He suggested that bioaccumulation could be limited by using shorter (C_1 to C_4) or longer ($>C_{10}$) fluororous ponytails. Another possibility is to develop fluororous bioremediation techniques that employ "fluororous bugs" to consume perfluorocarbons as a carbon source and produce manageable fluororous waste.

The bioaccumulation and bioremediation of fluororous compounds will, no doubt, be among the many topics to be discussed at the next international symposium on fluororous technologies, planned for Japan in 2007.

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