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Review

Fluorous chemistry in Pittsburgh: 1996–2008[☆]

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Dedicated to István Horváth, József Rábai and John Gladysz.

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ABSTRACT

The article summarizes a lecture presented at the American Chemical Society Symposium for the 2008 Award for Creative Work in Fluorine Chemistry on 7 April 2008. A high level, historical overview of work in the fluorous field at the University of Pittsburgh is presented.

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In 1994, the journal *Science* published a seminal paper by István Horváth and József Rábai on fluorous biphasic catalysis [1]. That article and the associated commentary by Gladysz [2] inaugurated the field of fluorous chemistry. Coincidentally, we were already thinking about using fluorinated solvents for some tin hydride extractions, and these publications encouraged us to move our nascent ideas from pen and paper into the lab.

Dr. Sabine Hadida undertook the challenge to prepare and study the reactions and separations of a fluorous tin hydride, and her preliminary work appeared in our first paper dealing with fluorous chemistry in 1996 [3]. The field of combinatorial chemistry was dawning during this period, and Dr. Hadida used her fluorous tin hydride to conduct in parallel a series of nine Giese reactions, as summarized in Fig. 1. The tin hydride was used as a catalyst (10 mol%), and sodium cyanoborohydride was the terminal reductant. The reactions were run with benzotrifluoride (BTF) as a cosolvent to promote the solubility of all components. Following evaporation of the solvents (also removed the excess alkene), the crude products were partitioned in a three-phase extraction between water (contains salts), dichloromethane (contains the target products) and FC-72 (perfluorohexanes;

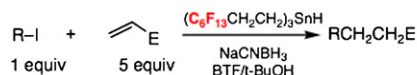
provides the recovered tin hydride catalyst). The product yields and purities were highly satisfactory, especially considering the ease of the experiments.

This paper provided the first examples of fluorous tin reagents, introduced the use of “hybrid” solvents like benzotrifluoride [4] (now usually called “amphiphilic” solvents), and provided the first examples of triphasic (fluorous/organic/aqueous) extractions. Reactions with amphiphilic solvents and triphasic reactions have since been extensively developed, and are now standard methods in fluorous chemistry. However, in these early days, members of the community (including reviewers of papers) were skeptical of the results. How could Sabine Hadida’s tin hydride, itself an organic compound, be easily and completely extracted out of an organic solvent? The reviewers of our 1996 *JACS* paper asked for proof of the extraction results by ¹⁹F NMR, so Sabine Hadida recorded the ¹⁹F NMR spectra of her nine library products. Since the fluorous tin products had all been removed by extraction, she obtained nine ¹⁹F NMR spectra of nothing, except baseline and the reference standard. One of these resonance-free spectra is enshrined in the Supporting Information of the paper [3].

At this early stage, the field of fluorous chemistry was wide open—almost nothing had been done, but we and a few others had visions. We focused our efforts on more innovative developments rather than low-hanging fruit. In a 1997 *Science* paper, we introduced the concept of “fluorous synthesis” (Fig. 2) [5]. Here we drew the analogy between attaching organic molecules to polymers (solid phase synthesis) and attaching them to fluorous

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R ¹ : E	CN	CO ₂ Me	COMe
C ₁₅ H ₃₁	72%	92%	67%
<i>o</i> -C ₆ H ₁₁	75%	65%	75%
Ad	89%	94%	78%

- Excess alkene evaporates
- Product in organic liquid phase
- Salts in water phase
- Tin hydride in fluorous phase

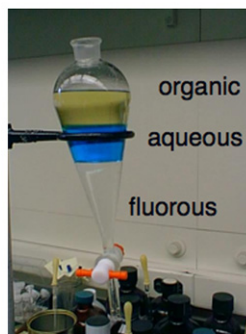


Fig. 1. Giese reactions with a fluorous tin hydride.

groups (fluorous synthesis). At the same time, we stressed the differences between solid phase synthesis (materials chemistry) and fluorous synthesis (molecular chemistry). Meanwhile, the term “fluorous synthesis” has since evolved to encompass essentially all fluorous methods of synthesis, and the technique of making substrates fluorous is now more commonly called “fluorous tagging” or “fluorous protection”. Though fluorous tags were the first tags for solution phase organic synthesis, we pointed out that the concept of separation tagging for solution phase synthesis was a general one [6], and many other classes of separation tags have since been introduced [7].

During this work, we also encountered difficulties in extracting large organic molecules into fluorous solvents. This led us to test fluorous silica gel for separation, and in 1997 we introduced the technique of fluorous solid phase extraction (FSPE) in a short Note in *J. Org. Chem.* [8]. This technique is now widely used, and its availability soon led to the sprouting of a light fluorous chemistry branch [9] alongside the existing (and still rapidly growing) heavy fluorous branch. The FSPE separation (Fig. 2) allow the uses of much smaller (and therefore lighter) fluorous tags, and the method is especially useful for small scale discovery chemistry and library applications in drug discovery and other areas. A recent review of FSPE features almost 100 papers that

have used the technique. [10] We and others have introduced scores of light fluorous reagents and protecting groups, and representative assortment of light fluorous protecting groups is shown in Fig. 3.

The fast pace of developments continued in the late 1990s as we introduced, among other things, the combination of microwave chemistry (fast reactions) with fluorous tagging (fast separations) [11], fluorous reactions in supercritical carbon dioxide [12], fluorous carbohydrates [13], fluorous chromatography [14], and fluorous solid–liquid biphasic reactions [15].

In 2000, we started Fluorous Technologies, Inc. [16] with the goal of providing reagents and technological expertise in fluorous chemistry to the community at large. Fig. 4 encapsulates the development of the company, which parallels the development of the field. I know that the employees of FTI, past and present, are especially proud to have played a key support role in many fluorous developments throughout the world. Beyond that, the company has contributed with cutting edge research in reagents and separations, library synthesis, peptide chemistry, bi- and triphasic reactions, microarrays, and much more.

The turn of the millennium witnessed continued rapid developments with the use of fluorous BINOLs [17], the union of fluorous tagging and solid phase synthesis (by the group of Wipf et al.

Compounds for fluorous synthesis have removable (temporary) fluorous tags

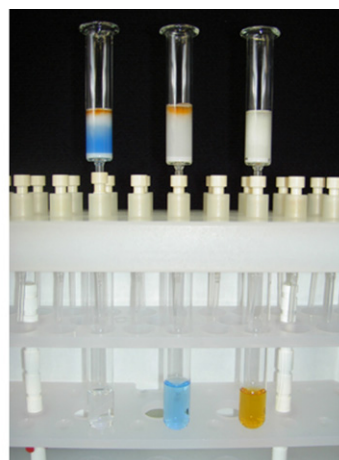
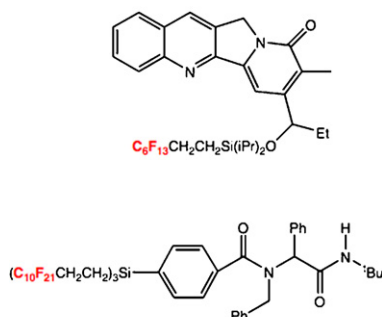


Fig. 2. Fluorous synthesis (left) and fluorous solid phase extraction (right).

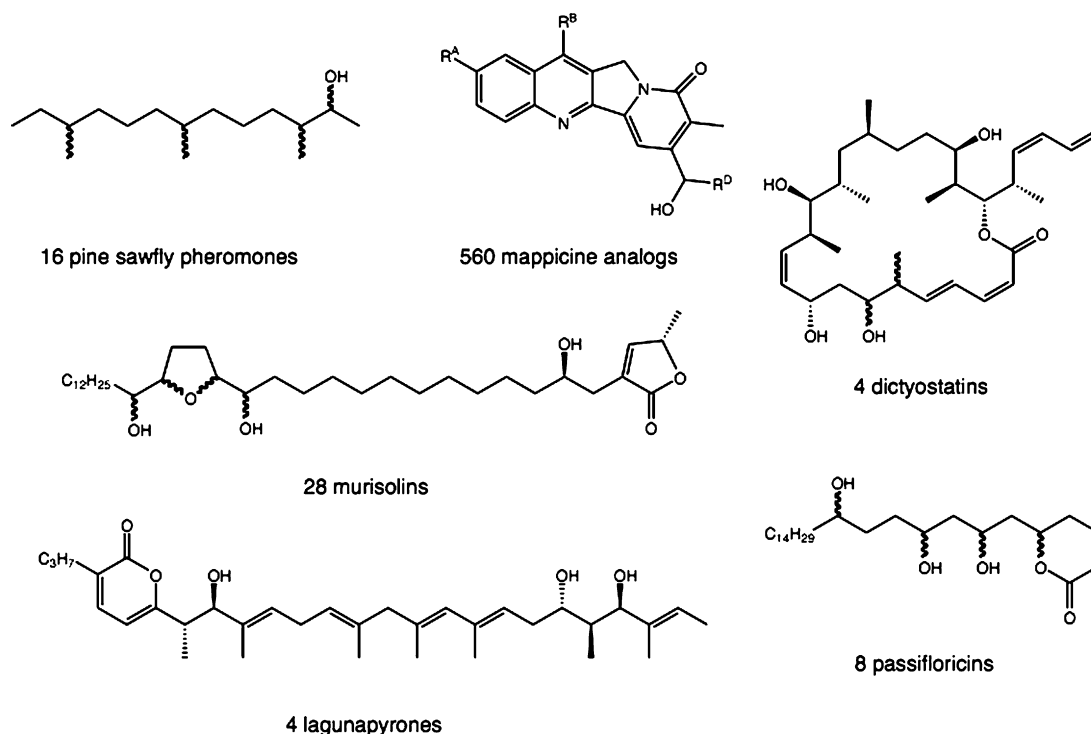


Fig. 6. Natural products made by FMS.

In 2002, we detailed the principles of fluororous quasiracemic synthesis [23] and soon after we introduced the concept of complete stereoisomer libraries [24] (made by fluororous mixture synthesis), a concept that has been featured in much of our natural products work since then. We later united fluororous and OEG tags in the technique of double mixture synthesis [25]. These techniques have gone well beyond “proof-of-principle”; the derived products (see Fig. 6) have been used to solve structure problems and provide important biological information [26]. Then in 2004/2005 we introduced the concepts of solvent tuning with hydrofluoroethers

(HFE) solvents [27], and the technique of fluororous reverse solid phase extraction [28].

During the 2002–2004 timeframe, it was also becoming clear that the fluororous field had grown to a critical mass of research groups, as illustrated by the publication in 2002 of the first journal volume dedicated to fluororous papers (a *Tetrahedron Symposium-in-Print*, which provided the modern definition of “fluororous” [29]), and by the convening in 2003 of the first scientific meeting devoted entirely to fluororous chemistry (a symposium sponsored by the Noguchi Institute in Tokyo). In 2004, the first book-length



The author with John Gladysz (left) and István Horváth (center), 2004

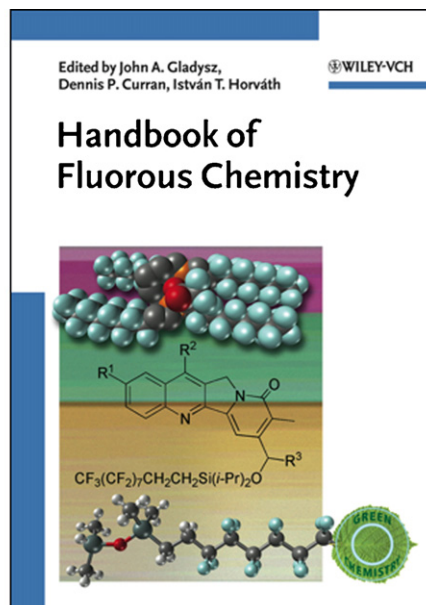


Fig. 7. The Handbook of Fluororous Chemistry, 2004.

treatment of the field, "The Handbook of Fluorous Chemistry", was published by Wiley–VCH (Fig. 7) [30]. With three coeditors and dozens of chapter coauthors, the book well reflected both the breadth and depth of the field at the time.

The first meeting of the fledgling International Society of Fluorous Technologies (ISOFT-1) convened with about 90 enthusiastic participants in Bordeaux in 2005 [31], the second meeting took place in Yokohama in 2007 [32], and the third is slated to be held in 2009.

One of the most enjoyable aspects of our research in fluorous chemistry has been the people. Sabine Hadida was the first of over 50 coworkers to have worked in our lab in Pittsburgh on fluorous chemistry. Much of research work has also been driven by enjoyable collaborations with people like Eric Beckman (Pittsburgh, reactions in CO₂), Paul Knochel (Munich, fluorous chromatography), Anders Hallberg and Mats Larhed (Uppsala, microwave chemistry), Roger Read (Sydney, amino acids), Ilhyong Ryu and Hiroshi Matsubara (Osaka, tin reagents, triphasic and phase vanishing [33] reactions), Seiji Takeuchi (Niigata, chiral catalysts), Hiroyuki Nakamura (Tokyo, triphasic reactions), Koichi Mikami (Tokyo, fluorous racemic mixture synthesis [34]), Peter Wipf (Pittsburgh, fluorous tagging), Craig Wilcox (Pittsburgh, double mixture synthesis), Tadamichi Nagashima, (FTI, reagents) and Marvin Yu (FTI, solvent tuning). The independent group of Wei Zhang at Fluorous Technologies has been especially productive in fluorous library methods and allied techniques [35], and I have been pleased to be associated with some of their projects.

I warmly thank this excellent cadre of collaborators and coworkers for the intellectual and experimental contributions as well as for their support and friendship. I thank the Institute of General Medical Sciences of the National Institutes of Health for sustained funding of our work in fluorous chemistry over more than a decade. I am also most grateful to the American Chemical Society Division of Fluorine Chemistry for their recognition of our work with the ACS Fluorine Chemistry Award.

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