Tails and steeds versus heads and beads

The case for fluorous phase methodology in combinatorial and parallel syntheses

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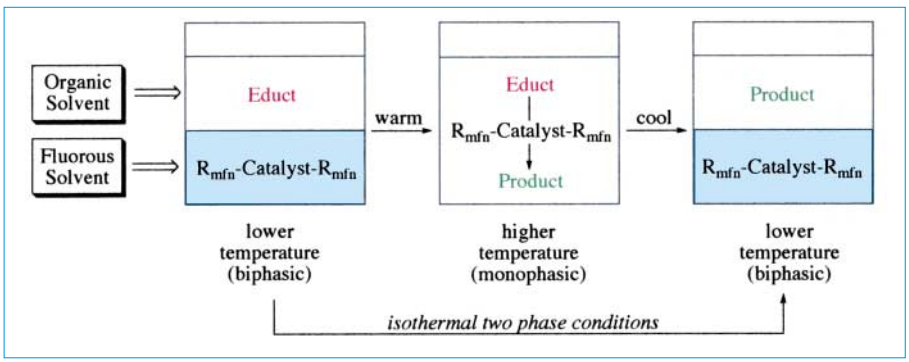
Summary : *The development of fluorous phase synthetic chemistry is reviewed from its recent origins in strategies for recoverable catalysts through emerging applications in high-throughput library synthesis. The roles of « pony tails », $(CH_2)_m(CF_2)_{n-1}CF_3$, as solubility control or « phase labelling » elements, are described. The synthesis and properties of fluorous aliphatic amines are detailed, and lead references to fluorous protecting groups and chromatographic methods are given.*

Mots clés : ***Fluoré, pony tail, coefficients de partition, amines, basicité.***
Key-words : *Fluorous, pony tail, partition coefficients, amines, basicity.*

Le récent développement de la chimie en phase fluorée est revu depuis ses premières utilisations en catalyse jusqu'à ses applications émergentes en chimie combinatoire. Le rôle des « pony tails », $(CH_2)_m(CF_2)_{n-1}CF_3$, comme éléments de contrôle de la solubilité, est décrit. La synthèse et les propriétés d'amines aliphatiques fluorées sont détaillées, ainsi que les premières références concernant les groupes protecteurs et méthodes chromatographiques fluorés.

The term « fluorous » was introduced by Horváth in 1994 as an analog to « aqueous » for highly fluorinated alkane, ether, and tertiary amine solvents [1]. Such solvents are very nonpolar, and many are commercially available [2]. They commonly give bilayers with organic solvents at room temperature, as illustrated by the first container in *scheme 1*. At the same time, many such solvent combinations become miscible at elevated temperatures, as illustrated by the second container in *scheme 1*. Many synthetic chemists had been unaware of these characteristics.

Organic compounds - even hydrocarbons such as dodecane - normally have low affinities for fluorous solvents relative to organic solvents. However, compounds that consist mainly of perfluoro-alkyl segments show high affinities. This reflects a « like dissolves like » effect, and similar strategies are used to design dyes that can adhere to Teflon. Accordingly, Horváth noted that high fluorous affinities could be imparted to common catalysts and reagents by appending « pony tails » $(CH_2)_m$-$(CF_2)_{n-1}CF_3$ (abbreviated $(CH_2)_mR_{fn}$) in sufficient numbers or lengths. Compilations of fluorous/organic phase partition coefficients are available [2], and continually updated on the authors' web page (http://www.organik.uni-erlangen.de/gladysz/research/partition.html).



Scheme 1 *- Some possibilities for catalysis with fluorous solvents ($R_{mfn} = (CH_2)_m(CF_2)_{n-1}CF_3$).*

The $(CH_2)_m$ segments of the pony tails can be used to fine-tune electronic properties. When sufficiently long, they insulate the active site from the electron withdrawing fluorines. When short, catalysts and reagents have enhanced Lewis acidities.

However, the most important function of the pony tail is as a solubility control device, which furthermore provides the basis for an innovative new approach to recoverable catalysts and reagents, combining all advantages of one-phase chemistry with biphase pro-

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duct separation. Reactions can be effected under homogeneous conditions in the high temperature monophasic limit, and the organic products disassociated from the fluorous catalyst or transformed reagent in the low temperature biphasic limit (*scheme 1*, middle and right containers). Many applications of this protocol have been developed over the last few years [3-4].

A variant involving (trifluoromethyl)toluene, $CF_3C_6H_5$, deserves note. This solvent is able to dissolve both fluorous and non-fluorous substances. It can be removed at the end of a reaction, and a non-fluorous or fluorous solvent added to extract the desired material.

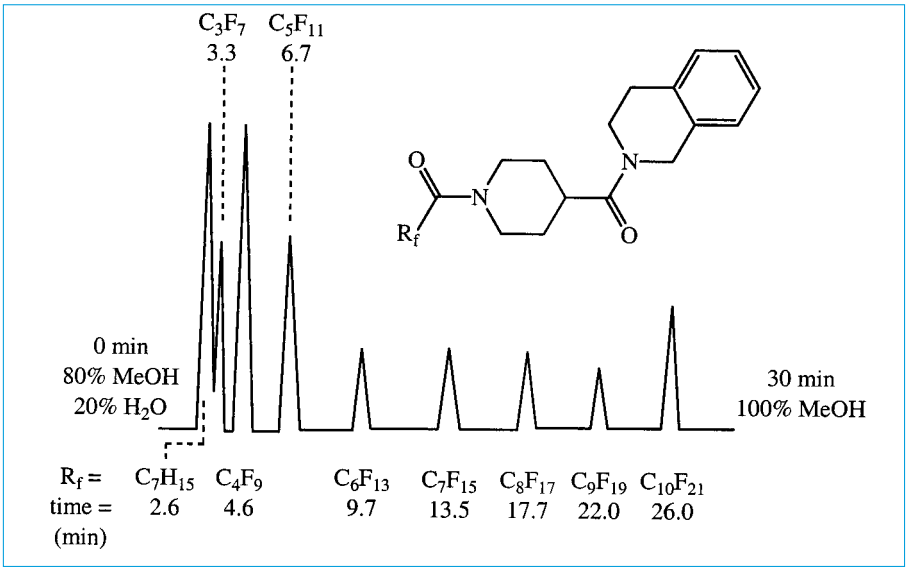
In more general terms, fluorous chemistry represents a new use of « orthogonal phases » in separation strategy. As nicely articulated by Curran [5], organic workups commonly involve manipulations of target molecules and by-products through various states and media : (1) solid phases, (2) gas phases, (3) aqueous liquid phases, (4) organic liquid phases, and (5) fluorous liquid phases. These can be idealized as mutually exclusive, but various approximations are obvious. For example, some water is soluble in most organic liquids, and gases dissolve to some extent in all liquids (particularly fluorous liquids, which readily accommodate small molecules irrespective of polarity) [2].

High-throughput combinatorial and parallel syntheses entail an even more demanding series of manipulations involving different orthogonal phases. Hence, it is not surprising that fluorous chemistry was rapidly extended in this direction [6]. The applicability to solution-phase methodologies is particularly obvious. Advantages and disadvantages of solution methodologies versus the presently dominant solid-phase technologies have been extensively discussed and debated [7]. However, as analyzed below, fluorous chemistry has impressive potential for all types of high-throughput synthesis.

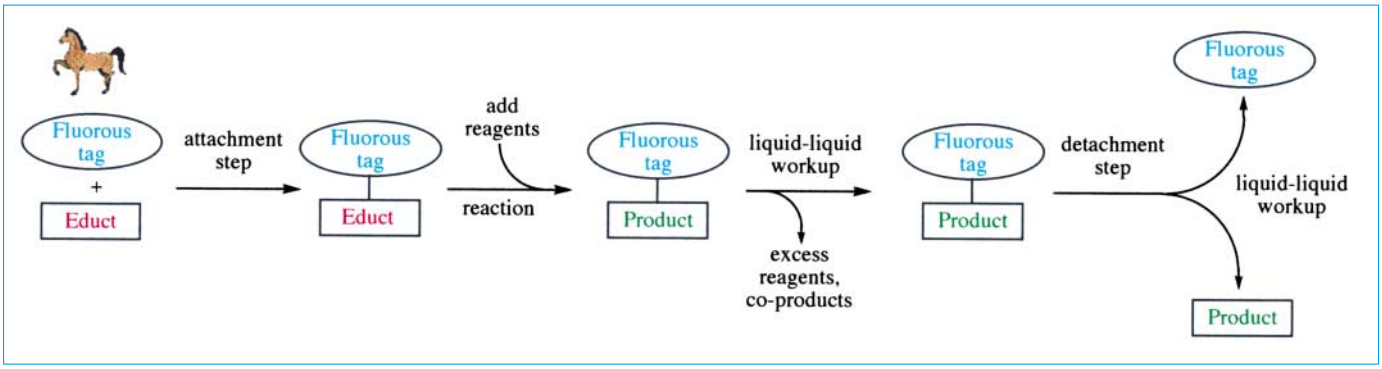
A current goal of polymer bead-based synthesis is to be able to reproduce - as much as possible within certain intrinsic limitations - the entire repertoire of organic reactions. Fluorous chemistry has a similar goal : to develop a complete « parallel universe » of fluorous functional organic molecules, reagents, and catalysts. Although much work remains to be done, this « fluorous library » will be achieved in the forseeable future. Fluorous analogs of, for example, Swern oxidations or Mitsunobo reactions would give fluorous sulfur, phosphorus, and nitrogen-containing by-products that could be removed under the conditions of *scheme 1*. These would have immediate application in solution phase parallel synthesis.

Curran and Wipf have developed a « tagging » or « phase labeling » protocol (*scheme 2*) for fluorous variants of the Ugi and Biginelli multicomponent condensations [8]. The basic idea is to derivatize the educt with some type of removable assembly of pony tails. A series of liquid phase reactions are then conducted, and the labeled product recovered by means of its enhanced fluorous phase affinity. The partition coefficients do not need to be as high as those required in *scheme 1*. At the end of the sequence, the tag or phase label is removed.

Fluorous silica gel is easy to prepare, and analytical columns are commercially available [9]. As illustrated in *scheme 3*, efficient reverse-phase separations are possible, with homologous compounds eluting in inverse order of fluorous content. This provides an alternative to extraction, especially for compounds with low fluorous phase affinities. Curran prepared a 4 x 4 amide library where each member was puri-



Scheme 3 *- Chromatogram of homologous fluorous amides on a fluofix 120E column.*



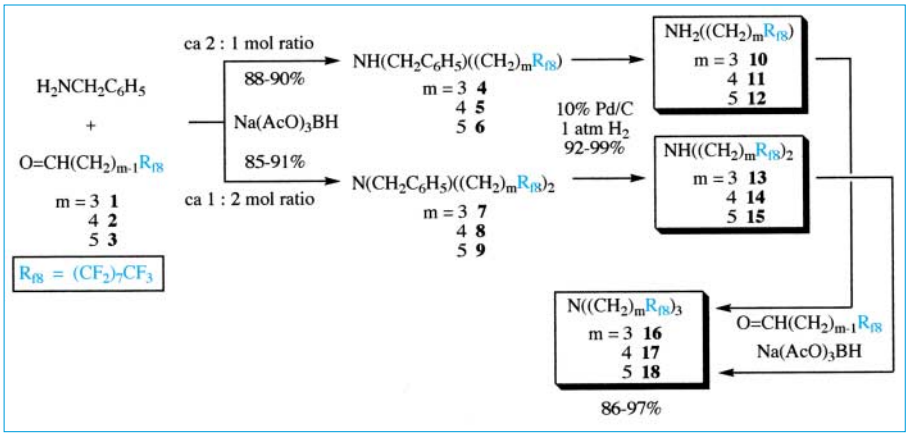
Scheme 2 *- Reversible « phase labelling » of educts and products.*

fied by a simple fluorous silica gel filtration [9].

Protecting groups that have been phase labeled are also of obvious utility in high-throughput synthesis. To date, fluorous analogs of benzyl, THP, and alkoxy ethyl ether protecting groups for alcohols have been developed (*scheme 4A*) [10-11]. Fluorous strategies for the rapid purification of non-fluorous [12] and fluorous [4d] organometallic compounds have been described (*scheme 4B*). Inhibitors are sometimes employed in high-throughput syntheses. Noteworthy in this regard is a fluorous diaryl diselenide that, in conjunction with stannanes, retards certain radical rearrangements (*scheme 4C*) [13].

Scavengers play important roles in both solid and solution phase parallel synthesis. For example, the quest for optimal covalent scavengers for primary and secondary amines has been detailed in a recent review [14]. The use of fluorous amines for scavenging excess isocyanates has been reported [15]. These and other factors prompted us to develop systematic syntheses of fluorous aliphatic amines with fine-tuned fluorous phase affinities and basicities. These data are summarized in the final portion of this article [4i].

The fluorous aldehydes **1-3** shown in *scheme 5* are easily prepared, and reductive aminations can be conducted

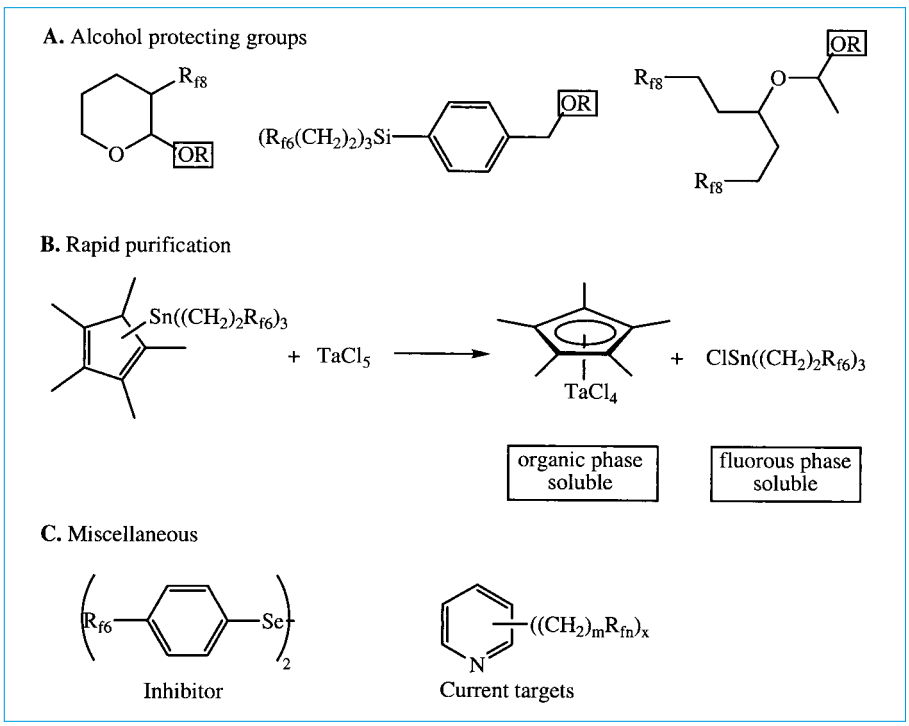


Scheme 5 *- Versatile syntheses of fluorous primary, secondary and tertiary amines.*

with $Na(AcO)_3BH$ in THF at different aldehyde/amine stoichiometries. When two-fold excesses of benzyl amine are used, workups give the secondary amines **4-6** in 88-90 % yields. When two-fold excesses of aldehydes are used, the **4-6** generated can condense further. Workups give the tertiary amines **7-9** in 85-91 % yields. The benzyl protecting groups in **4-9** can be removed under mild hydrogenolysis conditions, giving the primary amines **10-12** and the secondary amines **13-15** in > 99-92 % yields.

As shown in *scheme 5*, the secondary amines **13-15** are then condensed with 1.0-1.2 equivalents of aldehydes **1-3** under identical reductive amination conditions. Workups give the corresponding tertiary amines **16-18** in 97-86 % yields. The fluorous amines **10-18** dissolve in quite a broad range of solvents. All are highly soluble in $CHCl_3$, $CF_3C_6H_5$, and fluorous solvents such as $CF_3C_6F_{11}$. The primary and secondary amines **10-15** are also very soluble in methanol. The highly fluorous tertiary amines **16-18** remain sparingly soluble in methanol. None of the amines are soluble in water or DMSO.

Quantitative data on relative fluorous phase affinities are given by the $CF_3C_6F_{11}$/toluene partition coefficients in *table I*. As would be expected from a simple « like dissolves like » model, affinities decrease as the methylene chain is lengthened (**10** vs **11** vs **12** ; **13** vs **14** vs **15** ; **16** vs **17** vs **18**). They also decrease when pony tails are replaced by hydrogen atoms (**16** vs **13** vs **10** ; **17** vs **14** vs **11** ; **18** vs **15** vs **12**). The two amines with the highest partition coefficients (**16**, **17**) show no detectable residual quantity in the organic phase (< 0.3 %). This represents, with respect



Scheme 4 *- Additional fluorous compounds and applications.*

Table I - Partition coefficients (24 °C)

	analyte	$CF_3C_6F_{11}$/toluene
10	$NH_2(CH_2CH_2CH_2R_{f8})$	70.0:30.0
11	$NH_2(CH_2CH_2CH_2CH_2R_{f8})$	63.2:36.8
12	$NH_2(CH_2CH_2CH_2CH_2CH_2R_{f8})$	56.9:43.1
13	$NH_2(CH_2CH_2CH_2R_{f8})_2$	96.5:3.5
14	$NH_2(CH_2CH_2CH_2CH_2R_{f8})_2$	95.1:4.9
15	$NH_2(CH_2CH_2CH_2CH_2CH_2R_{f8})_2$	93.0:7.0
16	$N(CH_2CH_2CH_2R_{f8})_3$	>99.7:<0.3
17	$N(CH_2CH_2CH_2CH_2R_{f8})_3$	>99.7:<0.3
18	$N(CH_2CH_2CH_2CH_2CH_2R_{f8})_3$	99.5:0.5

to the protocol in *scheme 1*, a very high degree of immobilization.

Brønsted basicity measurements show that the inductive effect of the perfluoroalkyl groups is strongly felt in tertiary amine **16**, which has three methylene groups in each pony tail. Amine **18**, which features longer five-methylene segments, remains a weaker base than tri(dodecyl)amine (ca. 25-30:75-70 protonation ratio in $CDCl_3$). The corresponding fluorous trialkylphosphines exhibit similar behavior [4c, h]. Hence, more than five methylene groups are required to fully insulate heteroatom lone pairs from electronegative perfluoroalkyl groups.

In conclusion, a two-part summary/outlook is offered. First, the work detailed from our laboratory has provided three series of nearly isosteric fluorous amines - primary, secondary, and tertiary - with finely modulated fluorous phase affinities and basicities. Similar families of pyridines, sketched in *scheme 4C*, will be reported in the near future. These constitute valuable « toolkits » for the systematic development of new catalytic and stoichiometric reactions, including high-throughput synthesis, based upon fluorous nitrogen bases and nucleophiles.

Second, the many developments outlined above clearly indicate a growing role for fluorous techniques in all of combinatorial and parallel synthesis. Additional innovative applications can be expected at a rapid pace. Some cognoscente caution, however, that commercial uses are already covered by an extremely broad patent [16], such that licensing inquiries would be prudent.

Acknowledgment

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