



# Fluorous tags and phases for synthesis and catalysis

Jean-Marc Vincent

## ► To cite this version:

Jean-Marc Vincent. Fluorous tags and phases for synthesis and catalysis. Jean-Philippe Goddard; Max Malacria; Cyril Ollivier. Biphase chemistry and the solvent case, 1, Wiley, pp.57-98, 2020, 9781786305091. 10.1002/9781119695080.ch2 . hal-03046752

**HAL Id: hal-03046752**

**<https://hal.science/hal-03046752v1>**

Submitted on 25 Jan 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Chapter 2

# Fluorous tags and phases for synthesis and catalysis

### 2.1 Introduction

The development of more efficient, rapid and environmentally friendly synthesis processes, whether for the production of high-tonnage compounds, pharmaceutical compounds or on a laboratory scale, is an important objective of current research. Most research efforts focus on optimizing the activity of existing reagents or catalysts or discovering new reactions. However, in a synthesis process, the purification step should not be neglected, as the isolated product yield and the overall energy cost of synthesis depend strongly on the nature and efficiency of the latter (Curran 1998). Methodologies for easily separating or recycling a catalyst, reagent or by-product from a reaction medium are to be encouraged in the context of sustainable chemistry. Ideally, these methods should make it possible to avoid as much as possible chromatographic purifications that consume large amounts of organic solvents, and if possible, distillations, which are costly in terms of energy and can lead to catalyst degradation. The use of liquid (perfluorocarbons) or solid (perfluorinated silicas or Teflon) perfluorinated phases is fully in line with this approach. Perfluorocarbons (PFCs), such as *n*-perfluorohexane ( $C_6F_{14}$ ), are liquids with extreme physicochemical properties. They are chemically inert, non-toxic and are the most non-polar liquids available. They are both hydrophobic and lipophobic, so they form liquid/liquid two-phase systems at room temperature with most organic solvents. The principle of *fluorous chemistry* consists of increasing the affinity of catalysts, reagents or substrates for liquid or solid perfluorinated phases, i.e. increasing their fluorophilicity. This is achieved by modifying catalysts, reagents or substrates with perfluoroalkyl fragments called fluorous tags (*F*-tags). As we will see later, fluorous compounds present in a reaction medium can then

be easily separated from non-fluorous products by liquid/liquid or solid/liquid separation techniques that are simple to use, fast and effective.

## 2.2. Structures and properties of fluorous tags and phases

### 2.2.1. History of fluorous chemistry

Although the physicochemical properties (chemical and thermal stability, hydrophobicity, low coefficient of friction, etc.) of perfluorinated polymers such as Teflon have been recognized and exploited since the 1950s for various industrial and domestic applications, surprisingly the use of perfluorinated phases for catalysis and synthesis has only recently developed. In 1994, István Horváth and Josef Rábai first described in the journal *Science* the use of a perfluorocarbon (PFC)/hydrocarbon (HC) biphasic system to facilitate the separation and recycling of a catalyst (Horváth and Rábai 1994). These two researchers, who were then working for Exxon, demonstrated the relevance of their approach by applying it to a very important industrial reaction, alkene hydroformylation. To do this, they have developed a rhodium catalyst that is extremely fluorophilic and therefore soluble only in PFCs. In this founding article, they introduced the term *fluorous* which will make it possible to define a new field of chemistry. The term *fluorous* was proposed by analogy with the term *aqueous*. Their article clearly shows that, in addition to aqueous and organic media, perfluorinated media should be considered for separation and recycling applications. Fluorous chemistry was born. Since this pioneering work, the extensive research carried out in this field has considerably increased the fields of application of fluorochemistry applied to synthesis (Gładysz *et al.* 2004b). In this chapter, we will focus on the field of fluorous chemistry with a broad synthetic focus, i.e. the methodologies developed to facilitate the recycling of catalysts and the purification of reaction products.

### 2.2.2. Fluorous tags

In fluorous chemistry, the physicochemical properties of molecules (catalysts, substrates, reagents) whose affinity for fluorous phases will be increased by the presence of mixed alkylperfluoroalkyl chains  $-(\text{CH}_2)_n(\text{CF}_2)_m\text{CF}_3$ , known as fluorous tags (*F*-tags) (Gładysz 2004), are used. The most commonly used perfluoroalkyl moiety is the perfluorooctyl group  $-(\text{CF}_2)_7\text{CF}_3$  (symbolized by  $-\text{Rf}_8$ ). The fluorine atom is the most electronegative element of the periodic table (3.98 on the Pauling scale compared to 2.20 for the hydrogen atom and 2.50 for the carbon atom). The role of the alkyl fragment, known as a spacer, is to isolate the coordinating atom of a ligand or the active center of a reagent from the strong electron-attractor effect of the perfluoroalkyl fragment (Jiao *et al.* 2002). Spacers with two or three  $-\text{CH}_2-$  are the

most commonly used. Ligands, catalysts and fluorous reagents will therefore have the same properties in terms of affinity for a metal or reactivity as their non-fluorous analogs.

Fluorous compounds are classified into two categories, light fluorous compounds which generally have only one *F*-tag, and heavy fluorous compounds modified with at least three *F*-tags. The light fluorous compounds are lipophilic and weakly fluorophilic. They will be used under the usual conditions of organic synthesis, and will be separated/recycled by elution on fluorous silica gel. Heavy fluorous compounds are generally extremely fluorophilic and lipophobic, and therefore very poorly soluble in conventional organic solvents. In a two-phase liquid/liquid PFC/HC system, these compounds will partition exclusively into PFC, which will allow them to be efficiently recovered by simple decantation. In all cases, fluorous catalysts, reagents and substrates are soluble molecular compounds, therefore easily characterized and whose reactivity is similar to that of their non-fluorinated analog.

### 2.2.3. Fluorous solvents

Fluorous solvents are used in fluorochemistry to form biphasic or triphasic systems with organic phases. These multiphase systems are used to separate/recycle highly fluorophilic catalysts and reaction products by simple decantation. They can also be used as a *vanishing phase* in some reactions. Due to the high stability of the C-F bond (CF<sub>3</sub>-F binding energy of 130.5 kcal/mol compared to 105 kcal/mol for a CH<sub>3</sub>-H bond) and its low polarizability, these solvents are chemically inert, very thermally stable and non-toxic, making them particularly interesting compounds for applications in industrial environments.

The most commonly used solvents are perfluoroalkanes, perfluorinated trialkylamines and perfluorinated ethers/polyethers (Table 2.1) (Gladysz and Emnet 2004, p. 11).

Fluorous solvents are very dense and therefore always form the lower phase of two-phase systems with other solvents (density CHCl<sub>3</sub> 1.492 g/ml). It should also be noted that boiling points (boiling temperature *n*-octane 126°C) and surface tensions are significantly lower than those of their hydrogenated analogs, reflecting their low cohesion energy.

| Solvent                          | Formula  | Boiling point (°C) | Melting point (°C) | Density (g/ml) | Psa         |
|----------------------------------|--|--------------------|--------------------|----------------|-------------|
| Perfluoro hexane                 | C <sub>6</sub> F <sub>14</sub>                 | 57.1               | – 90               | 1.669          | 0.00 (2.56) |
| Perfluoro octane                 | C <sub>8</sub> F <sub>18</sub>                 | 103-104            | – 25               | 1.766          | 0.55 (2.86) |
| Perfluoro methylcyclo hexane     | CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> | 76.1               | – 37               | 1.787          | 0.58 (3.34) |
| Perfluoro decalin                | C <sub>10</sub> F <sub>18</sub>                | 142                | – 10               | 1.908          | 0.99 (4.07) |
| Perfluoro tributylamine          | C <sub>12</sub> F <sub>17</sub> N              | 178                | -                  | 1.883          | 0.68 (3.93) |
| Perfluoro tripentylamine         | C <sub>15</sub> F <sub>33</sub> N              | 212-218            | -                  | 1.93           | -           |
| Perfluoro-2-butyltetrahydrofuran | C <sub>8</sub> F <sub>16</sub> O               | 99-107             | -                  | 1.77           | -           |

<sup>a</sup> Spectral polarity index; the number in brackets corresponds to the Ps of the hydrogenated analog

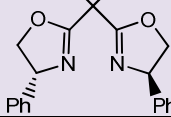
**Table 2.1.** Examples of "common" fluorous solvents and some physicochemical characteristics

The main property of perfluorinated solvents used in fluorous chemistry is their very low polarity, which is linked to the very low polarizability of the C-F bond limiting Van der Waals intermolecular interactions. These are the only solvents that are both hydrophobic and lipophobic. The measurement of polarity is expressed by the spectral polarity index Ps determined by studying the solvatochromic properties of fluorophilic dyes. At the end of the hydrophobic and lipophobic scale is perfluorohexane. In comparison, the Ps of isopropanol is 7.85. The other perfluoroalkanes are slightly more polar but remain significantly less polar than their hydrogenated analogs. As a result, PFCs form two-phase systems at room temperature with their hydrocarbon analogs. On the other hand, by increasing the temperature, a single-phase medium is obtained, while the two-phase system is reformed at room temperature. This thermomorphic property will be used for the separation and recycling of catalysts.

Due to the very low cohesion energy of PFCs, the formation of cavities in these solvents allowing gas dissolution is much more favorable than for other solvents, particularly water, whose extreme cohesion energy is linked to the three-dimensional network of hydrogen bonds. As a result, PFCs can solubilize larger quantities of gases than organic solvents, and particularly water. For comparison, the solubilities of O<sub>2</sub> in perfluoromethylcyclohexane (PFMC), tetrahydrofuran and water are 23.2, 10.0 and ~ 1 mM respectively at 37°C. This exceptional oxygen solubility has been used for the

clinical development of blood substitutes in the form of PFC emulsions. For catalysis or synthesis applications, however, the difference in solubility compared to organic solvents is not large enough to expect an increase in reaction rates when one of the reagents is a gas ( $O_2$ ,  $H_2$ ,  $CO$  etc.).

The relative solubility of fluorous compounds in PFCs is an important parameter when considering a liquid/liquid separation of PFC/HC. This relative solubility is expressed by the partition coefficient of the fluorous compound between two liquids, the most commonly used being perfluoromethylcyclohexane (PFMC) and toluene (Table 2.2) (Gładysz *et al.* 2004a, p. 56). Comparison of the data from inputs 2 and 6 shows that, besides the percentage of fluorine by mass, it is the number of *F*-tags per molecule that will make a partition very favorable to PFC. Partitions  $> 99.5$ :  $< 0.5$  in favor of PFC are preferred in separation/recycling processes by liquid/liquid separation.

| Solute  | Fluorine by mass % | PFMC partition:<br>toluene |
|---|--------------------|----------------------------|
| $C_6F_{13}(CH_2)_3OH$   | 65.32              | 44 : 56                    |
| $C_{10}F_{21}(CH_2)_3OH$  | 69.01              | 80.5 : 19.5                |
| $C_{10}F_{21}I$   | 61.76              | 94.5 : 5.5                 |
| $C_{10}F_{21}(CH_2)_2$  $(CH_2)_2C_{10}F_{21}$ | 55.93              | 40 : 60                    |
| $[C_8F_{17}(CH_2)_2]_3P$  | 70.61              | $> 99.7$ : $< 0.3$         |
| $[(C_8F_{17}(CH_2)_2)_3P]_3RhCl$  | 68.31              | 99.88 : 0.12               |

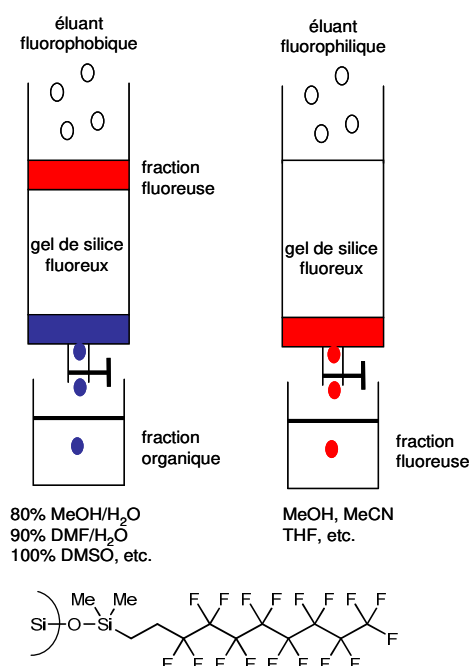
**Table 2.2.** Comparison of fluorous compound partitions between two liquid phases

#### 2.2.4. Solid fluorous phases

Two types of solid fluorous phases, fluorous silica and Teflon, are mainly used instead of PFCs to immobilize catalysts, reagents or fluorinated substrates. The use of fluorous silicas has been considered since 1997 by Dennis Curran *et al.* (Curran *et al.* 1997; Zhang and Curran 2006). These silicas, which are functionalized by perfluorooctyl groups  $-C_8F_{17}$ , have a very high affinity for fluorous compounds (Figure 2.1). Non-fluorous compounds will be eluted first using typically a  $MeOH/H_2O$  mixture as eluent, while switching to a less polar and therefore more fluorophilic eluent, such as pure  $MeOH$  or  $THF$ , will allow fluorous compounds to be eluted with high selectivity. This purification strategy does not require the use of PFCs and works perfectly with light fluorous compounds. Heavy fluorous compounds, and in particular catalysts, can be very effectively physisorbed onto the surface of fluorous silicas. The supported

catalysts thus obtained without any grafting step by chemical reaction on the silica, can then be used as heterogeneous catalysts that can be recycled by simple filtration. Again, this approach does not require the use of PFCs.

Teflon, the trade name for the polytetrafluoroethylene polymer ( $[\text{CF}_2\text{-CF}_2]_n$ ), is also a fluorous phase on which fluorous catalysts can be adsorbed (Dinh and Gladysz 2005). The catalysts can be desorbed by increasing the temperature of the reaction medium and then reabsorbed at the end of the reaction by lowering the temperature.



**Figure 2.1.** Separation of non- fluorous and fluorous compounds by elution on fluorous silica (adapted from (Zhang and Curran 2006))

## 2.3 Separation/recycling methodologies using fluorous tags and phases

### 2.3.1. Application for catalysis

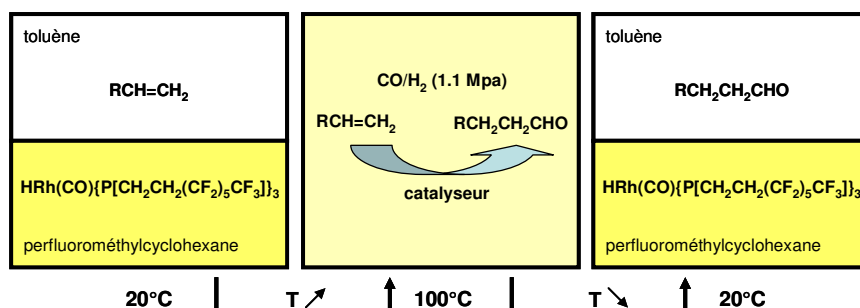
#### 2.3.1.1. Separation of liquid/liquid phase: fluorous biphasic catalysis

In 1994, Horváth and Rábai described in the journal *Science* the first example of fluorous two-phase catalysis that they applied to a very important reaction for the

chemical industry: rhodium-catalyzed hydroformylation of alkenes (I) (Horváth and Rábai 1994). The principle of the biphasic system developed is presented in Figure 2.2. The thermomorphic properties of PFCs and HCs were exploited to perform hydroformylation reactions under optimal conditions of homogeneous catalysis at high temperature (100°C); the highly fluorophilic catalyst is recovered in the PFC at the end of the reaction at room temperature after settling and liquid/liquid separation. This pioneering study clearly demonstrated that this approach could be extremely effective in terms of catalyst recovery efficiency. After nine cycles (cycle = reaction-separation-recycling), the total loss of rhodium does not exceed 4.2% for a total number of catalytic cycles (mole of aldehyde/mole of alkene) of 35,000 (Horváth *et al.* 1998). This very high recycling efficiency is related to two important parameters: the very high fluorophilicity of the phosphine ligand (*I*) (Figure 2.3) and therefore of the rhodium complex  $[\text{HRh}(\text{CO})(\text{I})_3]$ , and the high reactivity and stability of the catalyst, comparable to the non-fluorous analog  $[(\text{Ph}_3\text{P})_3\text{RhH}(\text{CO})]$ . This is due to the two or three  $-\text{CH}_2-$  spacers that isolate the coordinating phosphorus atom from the very strong electron-attractor effect of the *F*-tag ( $-\text{C}_7\text{F}_{15}$ ). One of the major advantages of this PFC/HC system is that it has made it possible, for the first time, to perform hydroformylations very efficiently on both short-chain (ethylene) and long-chain (1-decene) alkenes. Indeed, there is alkene solubility issues encountered with the two-phase water/HC system used at the industrial level, a system that is not very efficient for long chain alkenes due to their very low solubility in water, even at high temperatures. The results of this work show that this fluorous biphasic catalysis methodology has great potential in high-tonnage processes for which catalyst recycling is being considered.

Since this publication, many examples of fluorous biphasic catalysis have been described that confirm the relevance of the approach. Figure 2.3 shows some examples of heavy fluorous ligands representative of the variety of applications studied. This methodology has been successfully applied to many rhodium-catalyzed reactions such as hydroboration (Juliette *et al.* 1999), hydrogenation (Richter *et al.* 2000) or hydrosilylation (de Wolf *et al.* 2001) of alkenes. A large number of fluorous phosphines are commercially available, while almost all types of monodentate, bidentate or chiral fluorous phosphines can be prepared by published protocols (Hope and Stuart 2004). Due to the high chemical stability of PFCs, this concept has been developed for oxidation reactions of alkanes, alkenes, alcohol or sulfides (Crich and Zhou 2004; Pozzi and Quici 2004; Vincent *et al.* 2004) mainly using nitrogen and/or oxygenated polydentate ligands such as diketone (2) (Klmet *et al.* 1997), nitrogen macrocycles (3) (Pozzi *et al.* 1997) and (4) (Vincent *et al.* 1997), bipyridine (5) (Betzemeier *et al.* 1998), or carboxylic acid (6) (Contel *et al.* 2005).

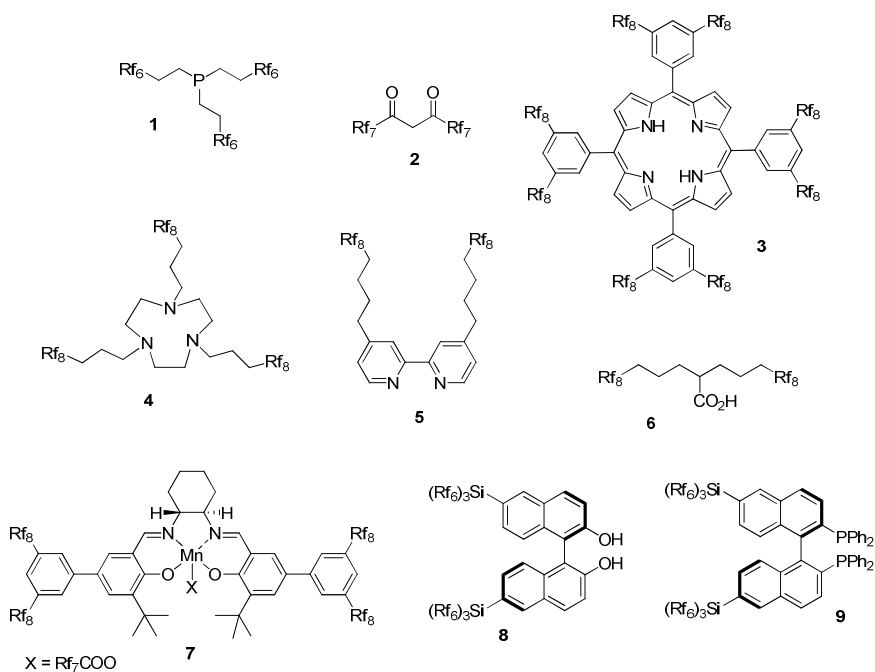




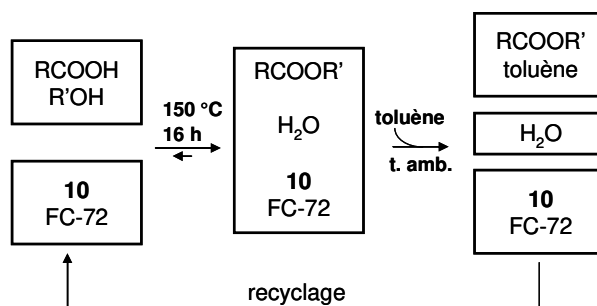
**Figure 2.2.** Biphasic fluororous catalyst applied to the hydroformylation of alkenes

This biphasic methodology has proven to be very effective for the recycling of very expensive chiral catalysts. Pozzi *et al.* used the manganese (III)-salen (7) complex as a recyclable catalyst in enantioselective epoxidation reactions (Cavazzini *et al.* 2001). Other enantioselective reactions catalyzed in the presence of PFCs include the reduction of ketones by chiral fluororous Ir-diamine/diimine catalysts (Maillard *et al.* 2002) and the asymmetric formation of carbon-carbon bonds by chiral complexes of titanium or palladium with BINOL (8) (Nakamura *et al.* 2002a) or BINAP (9) (Nakamura *et al.* 2002b) ligands.

Otera *et al.* have exploited the extreme hydrophobicity of PFCs to develop a high-performance esterification methodology using fluorophilic distannoxane [ $\{\text{Cl}(\text{Rf}_6\text{C}_2\text{H}_4)_2\text{SnOSn}(\text{C}_2\text{H}_4\text{Rf}_6)_2\text{Cl}\}$ ] (10) as a catalyst (Xiang *et al.* 2002). The conditions used are presented in Figure 2.4. An equimolar amount of alcohol and acid is heated to 150 °C in the presence of (10) (3-5 mol %) in FC-72 (perfluorohexanes). After 16 hours, the reaction medium is cooled to room temperature and toluene is added to facilitate the recovery of the ester. When reactions are carried out on larger quantities (> 10 mmol), the ester is recovered pure after settling, without adding toluene. The effectiveness of this methodology has been demonstrated by performing 10 reaction cycles (reaction/separation/recycling) on a 10 mmol scale. For each cycle, the isolated ester yield is > 99.5%, and 95% of the initial catalyst is recovered after the 10th cycle. The extreme efficiency of the methodology is related to the very low solubility of water in the PFC, which allows the equilibrium to be shifted towards ester formation without using dehydration methods, an excess of alcohol or an acid activation step. This biphasic system is therefore close to an ideal esterification method.



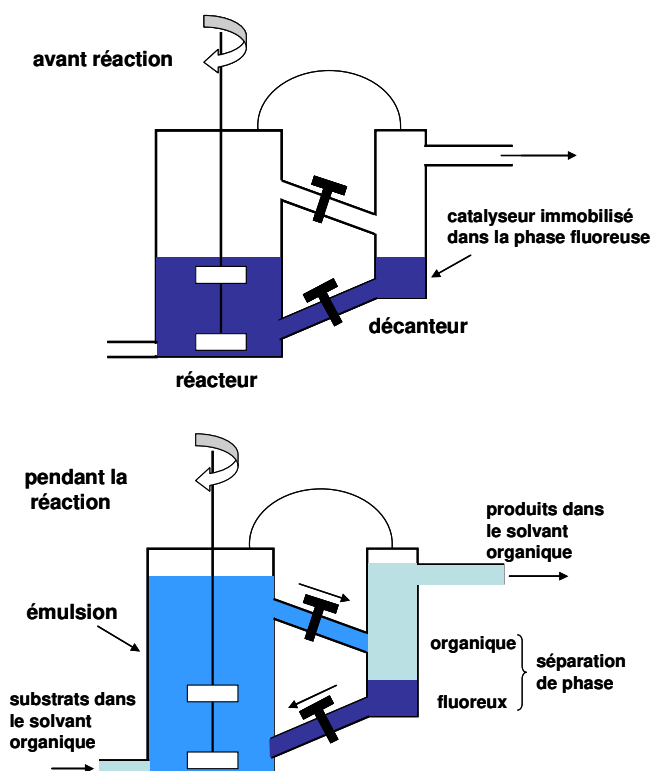
**Figure 2.3** Examples of heavy fluorinated ligands



**Figure 2.4.** Esterification in fluorinated biphasic medium (adapted from (Xiang *et al.* 2002))

The potential of fluorinated biphasic catalysis for industry has been clearly established by Nishikido *et al.* who developed and used a semi-industrial continuous flow process to easily recycle the very expensive solvent and fluorinated catalyst (Yoshida *et al.* 2003). The principle of the continuous flow process is shown in Figure

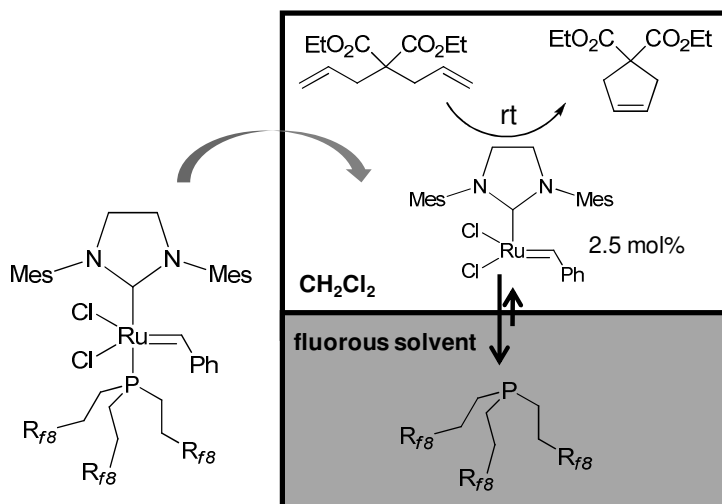
2.5. The assembly consists of a reactor (mechanical agitator) connected to a decanter that continuously separates the products and recycles the catalyst. Using a semi-industrial pilot assembly (500 ml reactor, introduction of reagents into a 6 l of toluene solution at a rate of  $0.967 \text{ ml min}^{-1}$ ), an acetylation reaction of cyclohexanol (200.32 g, 2 mol) with acetic anhydride (245.02 g, 2.4 mol) catalyzed by a ytterbium (III) complex  $\text{Yb}[\text{N}(\text{SO}_2\text{-}n\text{-Rf}_8)_2]_3$  (2.584 g, 0.83 mmol in solution in 250 ml of a PFC) was carried out at  $40^\circ\text{C}$  continuously for 500 hours. Yields were maintained  $> 90\%$  throughout the process, representing  $\sim 10,000$  catalytic cycles. Very low contamination of cyclohexyl acetate by ytterbium ( $\leq 2 \text{ ppm}$ ) was measured, demonstrating the high efficiency of the recycling step.



**Figure 2.5.** Principle of a semi-industrial continuous flow process for recycling fluororous catalysts (adapted from (Yoshida et al. 2003))

Gladysz and Corrêa da Costa published very interesting results in 2006 showing that fluororous phases can be used in an innovative way, i.e. not to facilitate the separation of

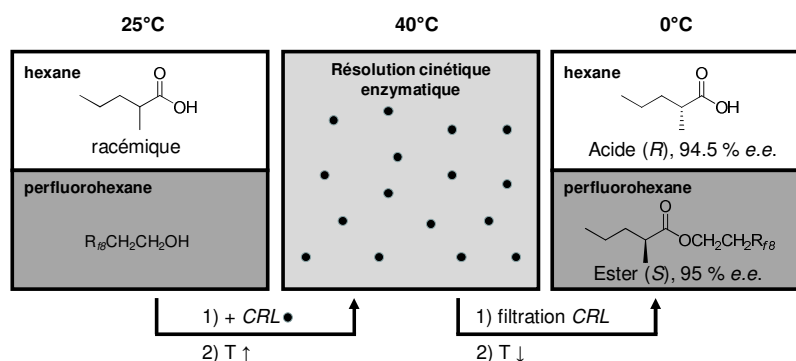
the catalyst, but to activate it (Corrêa da Costa and Gladysz 2006). This new concept of catalyst activation by fluorous phase transfer activation has been applied to the metathesis of alkenes. The activation principle is shown in Figure 2.6. Second generation fluorous Grubbs catalysts have been prepared. Since fluorous phosphines have a high affinity for PFCs, it has been hypothesized that they can be effectively sequestered in the fluorous phase, thus activating a non-fluorophilic catalyst essentially present in the organic phase containing the reactants. It has been shown that reaction rates are indeed much faster when performed in the presence of a fluorous solvent. For example, in the presence of perfluoro-2-butyltetrahydrofuran, cyclopentene (Figure 2.6) was formed with a yield of 74% in 2 hours, compared to 6% using only DCM.



**Figure 2.6.** Principle of catalyst activation by fluorous phase transfer activation applied to the alkene metathesis (adapted from (Corrêa da Costa and Gladysz 2006))

Fluorous ligands are also very useful for carrying out reactions in supercritical fluids, in particular supercritical carbon dioxide ( $\text{CO}_2\text{sc}$ ). Indeed, fluorous compounds are generally very soluble in these non-polar environments. For example, using a fluorous phosphine, Leitner *et al.* were able to perform rhodium catalyzed hydroformylation reactions in  $\text{sCO}_2$  very effectively (Koch and Leitner 1998), while bipyridine (5) was used by Matyjaszewsky *et al.* to perform copper catalyzed atom transfer radical polymerization (ATRP) reactions in  $\text{sCO}_2$  (Xia *et al.* 1999).

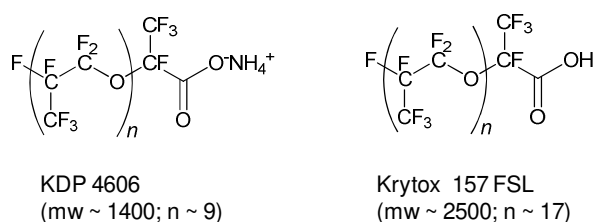
PFCs have also been used as solvents for enzymatic reactions to develop simple purification procedures for biocatalytic processes (Hobbs and Thomas 2007). The liquid/liquid PFC/hexane system is particularly interesting because: 1) the enzymes retain their activity in hexane at a rather high temperature (40-60°C); 2) this solvent combination is biphasic below 20-25°C but becomes monophasic at slightly higher temperatures. In 2002, O'Hagan and colleagues reported for the first time that fluorous biphasic catalysis could be applied to biocatalysis (Beier and O'Hagan 2002). Transesterification between esters and fluorous alcohols catalyzed by *Candida Rugosa* lipase (CRL) was performed at 40°C in a hexane/perfluorohexane monophasic system while the enzyme was used as a heterogeneous catalyst (Figure 2.7). After a conversion of about 50%, the reactions were stopped, the enzyme was removed by filtration and the reaction mixture was cooled to 0°C, allowing the enantioenriched (*R*) acid to be recovered in the organic phase, while the fluorous ester (*S*) was essentially found in perfluorohexane. Interestingly, increased stereoselectivity has been observed compared to previous studies conducted in hexane alone. In addition, it has been shown that this biphasic process can be applied on a preparatory scale. From 6 g racemic acid, 1.97 g (66%) of the acid (*S*) (ee 96%) was isolated after hydrolysis of the corresponding ester, while 1.81 g (57%) of unreacted acid (*R*) (ee 79%) was obtained.



**Figure 2.7.** Kinetic resolution of a racemic acid catalyzed by *Candida Rugosa* lipase (CRL) using a fluorous biphasic system (adapted from (Beier and O'Hagan 2002))

In 2007, Thomas and his collaborators demonstrated that enzymatic reactions could be effectively carried out in a fluorous and completely homogeneous environment using a soluble enzyme (Hobbs *et al.* 2007). Proteins such as cytochrome c or  $\alpha$ -chymotrypsin (CMT) have been effectively transferred from an aqueous phase to perfluoromethylcyclohexane (PFMC) by creating hydrophobic ion pairs using a carboxylate (KDP 4606) and a carboxylic acid (Krytox 157 FSL), both highly fluorophilic

(Figure 2.8). Concentrated and clear solutions of proteins in PFC were obtained (up to 20 mg cytochrome c per ml). The transesterifications are then carried out at 40 °C in a completely homogeneous hexane/PFMC solution. At the end of the reaction, lowering the temperature separates the two phases and allows the enzyme to be recycled. It has been shown that under these conditions the enzyme retains its activity during four reaction cycles.



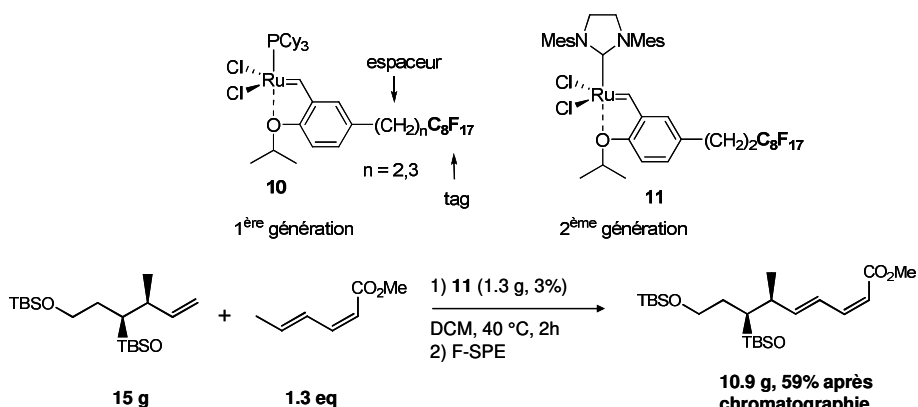
**Figure 2.8.** Structures of carboxylate KDP 4606 and carboxylic acid Krytox 157 FSL

#### 2.3.1.2. Solid/liquid phase separation

As perfluorocarbons are expensive solvents and present a risk of persistence in the environment due to their extreme chemical stability, many efforts have been made to develop separation methodologies that limit their use.

As Curran *et al.* have shown, molecules modified by a single *F*-tag known as "light fluororous compounds" are very effectively separated from non-fluorous compounds by fluororous solid-phase extraction, FSPE. Non-fluorous compounds are eluted first by typically using a mixture of MeOH/H<sub>2</sub>O (10/1) as eluent, while fluororous compounds are eluted with more fluorophilic mobile phases such as pure MeOH. This approach has the advantage of using catalysts containing less fluorine and therefore having a similar solubility in conventional solvents and a reactivity comparable to reference catalysts. In addition, this approach does not require the use of PFCs. Using this methodology, Stuart *et al.* were able to recycle three times the catalyst [Ni{Rf<sub>6</sub>C(O)CHC(O)Rf<sub>6</sub>}<sub>2</sub>] used as a Lewis acid in reactions between β-diketones and ethyl cyanoformate (Croxtall *et al.* 2003). Curran *et al.* prepared the fluororous analogs (10) and (11) of Grubbs-Hoveyda first and second generation metathesis catalysts (Matsugi and Curran 2005). These catalysts have the same reactivity as the original complexes and are used under standard conditions, as shown in the reaction shown in Figure 2.9, which provides an intermediate in the synthesis of an anti-cancer agent, dictyostatin (Moura-Letts and Curran 2007). The product is easily separated from the catalyst by fluororous silica chromatography by eluting with MeOH/H<sub>2</sub>O (9/1) and

then pure THF to elute the catalyst. After evaporation of the fraction containing the catalyst and subsequent recrystallization, 1.0 g (77%) of (11) could be recovered.



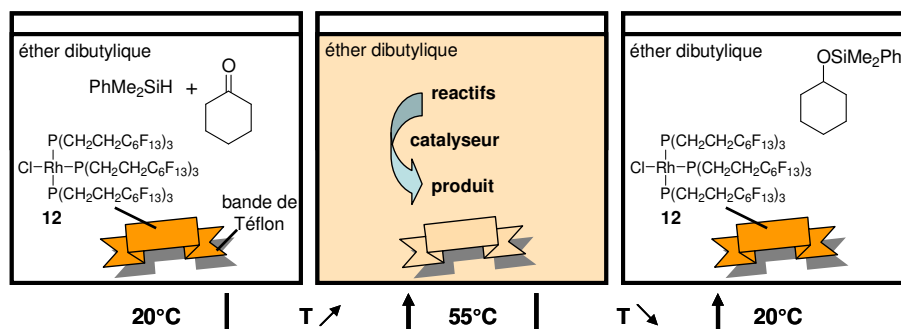
**Figure 2.9.** Light fluoruous Grubbs-Hoveyda metathesis catalysts of first (10) and second (11) generations

Other examples of recycling of light fluoruous catalysts by FSPE have been described, in particular for recycling chiral catalysts (Takeuchi and Nakamura 2004).

Adsorption (physisorption) of fluoruous catalysts on solid fluoruous substrates such as fluoruous silica or Teflon is another very interesting strategy for efficient and easy recycling of catalysts under conditions that do not require PFCs. Bannwarth *et al* (Tzschucke *et al.* 2002) and Biffis *et al* (Biffis *et al.* 2003) were independently the first to show that fluoruous catalysts were effectively adsorbed to the fluoruous silica surface. These catalysts can then be used as conventional supported catalysts under heterogeneous conditions with the advantage of being separable by simple filtration or decantation. This methodology has been applied to Suzuki and Sonogashira couplings catalyzed by fluoruous Pd-phosphine complexes (Tzschucke *et al.* 2002), and to alcohol silylation catalyzed by Rh-carboxylate complexes (Biffis *et al.* 2003). The supported catalysts retain a high reactivity associated with a low contamination of the final product by the metal (~ 2%). Curran *et al.* showed that these supported catalysts could be desorbed from silica and then re-adsorbed by modifying the polarity of the solvent (Matsugi and Curran 2005). For example, the catalyst (11) adsorbed onto the silica, due to its hydrophobic nature, does not desorb when suspended in a MeOH/H<sub>2</sub>O mixture (8/2). On the other hand, the catalyst is completely desorbed when a more lipophilic solvent such as DCM is used. Metathesis reactions can therefore be performed under homogeneous DCM reflux catalysis conditions in the presence of the "supported" catalyst (5 mol%). After reaction, the DCM is evaporated and the residue returns to

MeOH/H<sub>2</sub>O and is filtered to separate the product from the supported catalyst. The complex thus recovered was reused five times without any sign of loss of activity.

With the aim of making this type of recycling even more practical, Gladysz *et al.* discovered that Teflon, in particular Teflon tapes used in plumbing (Teflon tape) or Gore-Tex-type Teflon fibers, could be used as a fluorous carrier to allow, when necessary, adsorption/desorption of catalysts, while facilitating their handling at low load. When a homogeneous solution of the fluorous rhodium complex (**12**) (7 mg, 4 mol, 0.15 mol%) in dibutyl ether at 55°C containing a piece of Teflon tape (50 x 12 mm) is cooled, the complex adsorbs to the surface rather than precipitating (Dinh and Gladysz 2005). The hydrosilylation of ketones was thus performed using the reaction sequence shown in Figure 2.10. The catalyst adsorbed on Teflon was used for three reaction cycles without observing a significant decrease in catalytic activity (yields >96% and similar reaction rates). More recently, Gladysz *et al.* have shown that Teflon fibers (trade name "Gore-Rastex") are a powerful carrier for this methodology (Siedel and Gladysz 2008).

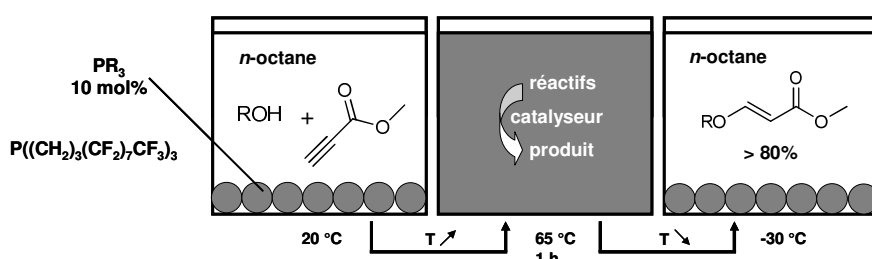


**Figure 2.10.** Recycling of fluorine catalysts by physisorption on Teflon tape

Heavy fluorous catalysts, due to their low solubility in conventional organic solvents at room temperature, can be separated from the reaction medium by precipitation and therefore recovered by simple filtration. In addition, the variation in solubility as a function of temperature is very important, which makes it possible to carry out reactions under homogeneous catalysis conditions by heating the reaction medium and to precipitate the catalyst by lowering the temperature. These thermomorphic properties were exploited by Sheldon *et al.* to recycle perfluoroheptadecan-9-one (C<sub>8</sub>F<sub>17</sub>C(O)C<sub>8</sub>F<sub>17</sub>) used as an organic epoxidation catalyst in the presence of H<sub>2</sub>O<sub>2</sub> (Van Vliet *et al.* 1999). The reactions are carried out at reflux in an EtOAc/1,2-dichloroethane mixture, cooling the reaction medium in an ice bath leading to the crystallization of the catalyst which is isolated by filtration with a 92% yield. These thermomorphic properties of fluorous compounds, in particular the large variation in solubility with temperature, were established by Gladysz *et al.* (Wende *et al.* 2001; Rocaboy and

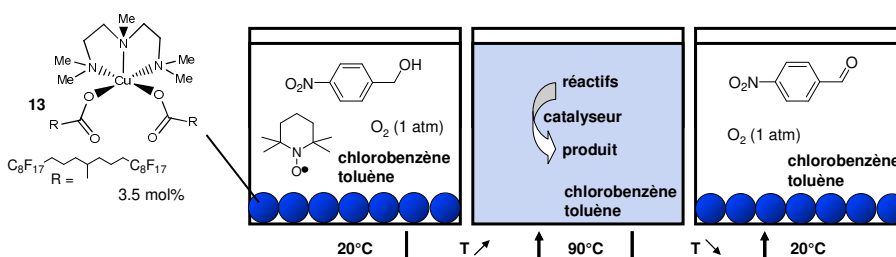


Gladysz 2002; Wende and Gladysz 2003). For example, a solubility change by a factor  $\sim 600$  was measured in *n*-octane between  $-20$  and  $80^\circ\text{C}$  for phosphine  $\text{P}[(\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3]_3$  (Wende and Gladysz 2003). This type of phosphine was used as an alcohol addition catalyst on methyl propiolate under homogeneous conditions at  $65^\circ\text{C}$  and recovered by filtration with yields of 90-95% after precipitation at  $-30^\circ\text{C}$  (Figure 2.11). Yamamoto *et al.* have also demonstrated the utility of this concept for fluorous acid catalyzed acetylation and aldolization reactions (Ishihara *et al.* 2001; Ishihara *et al.* 2002).



**Figure 2.11.** Thermomorphism of heavy fluorous compounds applied to catalyst recycling (phosphine)

This approach has also been used for the recycling of metal complexes. Contel, Fish, Vincent *et al.* carried out oxidation reactions of benzyl alcohols catalyzed by Cu(II)-carboxylate complexes such as (**13**) in the presence of TEMPO/ $\text{O}_2$  (Contel *et al.* 2005). Using the conditions shown in Figure 2.12, aldehyde conversions  $> 90\%$  were obtained while 85-90% of the catalyst is recovered by filtration.



**Figure 2.12.** Thermomorphism of heavy fluorous compounds applied to catalyst recycling (copper complex)

### 2.3.2. Application for synthesis

The development of automated parallel syntheses has grown considerably over the past twenty years and they are now part of the current techniques used in research and

development laboratories. The advantage of this type of synthesis is to be able to quickly obtain a wide variety of molecules in sufficient quantities and purity to be tested on biological targets, generally by high throughput screening methods. The rise of these automated techniques is linked to the development of operating modes using "simple", fast and efficient reaction conditions and purifications that can be performed by robots on small quantities. Reagents, substrates, trapping agents immobilized on solid supports, most often cross-linked polystyrene beads, are by far the most widely used because they allow in most cases to reduce the purification stage to a simple filtration. Nevertheless, chemistry on a solid support, due to heterogeneous conditions, has major disadvantages such as longer reaction times and the difficulty of characterizing the grafted products or monitoring the progress of reactions by typical techniques (thin film or gas chromatography, NMR etc.).

The fluorous chemistry applied to synthesis, known as fluorous synthesis, offers a very interesting alternative to chemistry on a solid support since it allows the combination of an optimal reactivity in homogeneous condition with the simplicity of the separation step. The potential of fluorous synthesis to facilitate the preparation of synthetic compounds or natural products has been demonstrated by the pioneering work of Dennis Curran (Curran and Hadida 1996; Curran 2008). As Wei Zhang pointed out in a review on fluorous synthesis for heterocyclic preparation (Zhang 2004), the main characteristics of fluorous synthesis compared to those of traditional solution synthesis or solid phase synthesis are as follows:

- 1) the reactions are done in homogeneous condition with optimal kinetics;
- 2) fluorous molecules can be purified/separated by fluorous or traditional separation techniques (chromatography, distillation, recrystallization...);
- 3) fluorous reactions can be monitored by traditional analytical methods (CCM, HPLC, IR, NMR);
- 4) fluorous tags are chemically stable and have little effect on the reactivity of the molecules on which they are grafted;
- 5) the solubility of fluorous compounds in organic solvents can be adjusted according to the amount of fluorine and temperature;
- 6) the use of a large excess of reagent is not necessary to achieve complete reactions;
- 7) unlike solid-phase supported reagents, several fluorous reagents can be used in the same reaction;
- 8) the adaptation of the reaction conditions of the literature is less problematic than for the supported reagents;

9. fluororous synthesis can be combined with other methods such as microwave reactions, in supercritical CO<sub>2</sub> and solid phase synthesis;

10. fluororous compounds can be recovered and reused after separation using a solid or liquid fluorine phase.

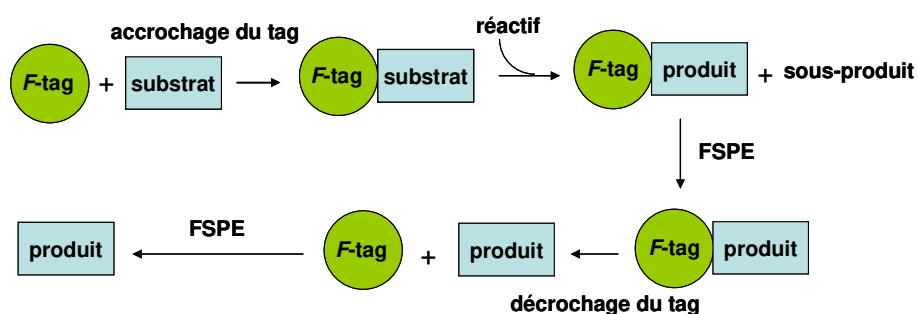
### 2.3.2.1. Light fluororous synthesis

#### 2.3.2.1.1. Substrates and fluororous protecting groups

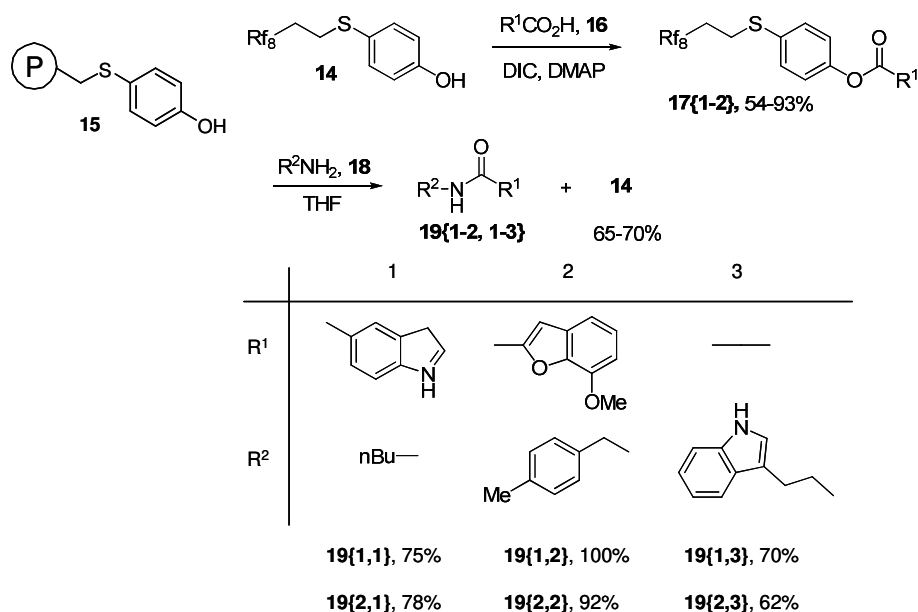
The general principle of light fluororous synthesis is to use in a synthesis a substrate or reagent modified by a single *F-tag*. After reaction, the fluororous product or by-product is separated by solid-liquid extraction on fluororous silica (FSPE).

The principle of the methodology using fluororous substrates is presented in Figure 2.13.

Zhang *et al.* have developed a fluororous molecular analog (14) (FluorMar™) of the Marshall resin (15) widely used in solid phase synthesis, particularly for the preparation of amides (Zhang and Hiu-Tung Chen 2003). An example of the application of a group of amides to the synthesis is shown in Figure 2.14.



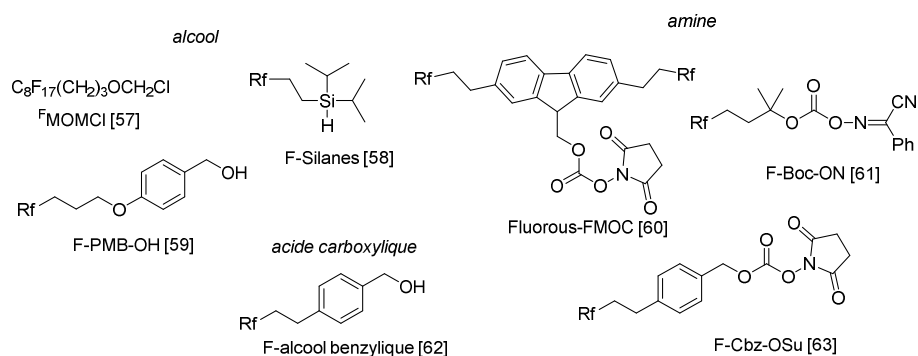
**Figure 2.13.** Light fluororous synthesis



**Figure 2.14.** Example of application to the synthesis of a group of amides

Compounds **17**{1-2} are prepared under standard conditions in DMF using 2 equivalents of diisopropylcarbodiimide (DIC) and 1 equivalent of (dimethylamino) pyridine (DMAP). They are purified by flash chromatography on non-fluorous silica. The addition of amines (**18**) leads to the 6 amides (**19**) and the release of (**14**). Separation is carried out by F-SPE, the amides being recovered pure in the MeOH/H<sub>2</sub>O fraction, while the FluorMar tag (**14**) is recovered pure in the MeOH fraction with a yield of 65-70%. This approach has been successfully used to prepare libraries of heterocyclic compounds such as hydantoins and thiohydantoins (Zhang and Lu 2003), disubstituted pyrimidines (Zhang 2003), or polysubstituted indoles (McCormick *et al.* 2006).

Fluorous protective groups for amine, alcohol or ketone functional groups have also been developed. In addition to the traditional role of protective groups, fluorous derivatives will facilitate the purification of protected molecules. Some representative examples of protective groups are presented in Figure 2.15 (Curran 2001; Luo *et al.* 2001a; Luo *et al.* 2001b; Curran and Furukawa 2002; Curran *et al.* 2003; Curran and Ogoe 2006; Matsugi *et al.* 2006). These protective groups have the same reactivity as their non-fluorous analogs and allow the protected compounds to be purified very effectively by FSPE. Examples of important applications include the purification of oligonucleotides (up to 100-mers) (de Visser *et al.* 2003) or synthetic peptides (Pearson *et al.* 2005).

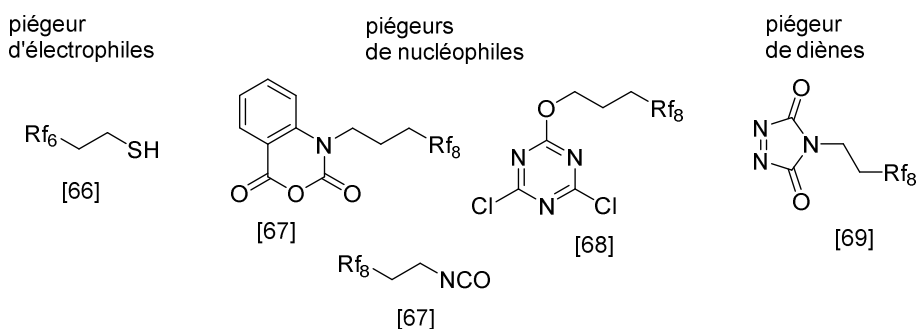


**Figure 2.15.** Examples of protective groups

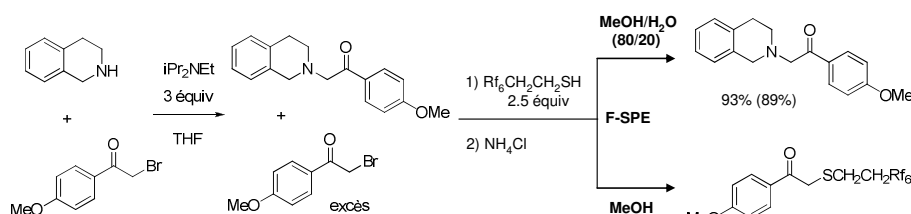
#### 2.3.2.1.2. Fluorous trapping agents

In parallel syntheses on a solid support, the use of scavengers immobilized on resin is extremely useful to facilitate the elimination of a soluble reagent used in excess. Some examples of fluorous trapping agents are shown in Figure 2.16 (Zhang *et al.* 2002a; Werner and Curran 2002; Zhang *et al.* 2003; Lu and Zhang 2006).

For example, thiol  $\text{Rf}_6(\text{CH}_2)_2\text{SH}$  has been used to trap excess  $\alpha$ -bromoketones used in secondary amine alkylation reactions (Figure 2.17). Many amines have thus been obtained after purification by F-SPE with yields between 75 and 95% and purities between 80 and 95% (determined by CPLH).



**Figure 2.16.** Examples of fluorous trapping agents

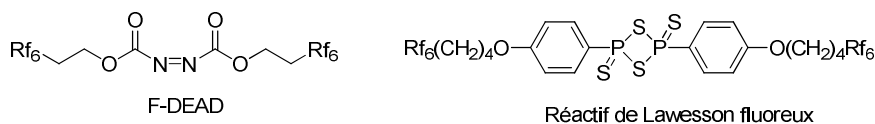


**Figure 2.17.** Trapping of excess  $\alpha$ -bromoketones during secondary amine alkylation reactions

### 2.3.2.1.3. Fluorous reagents

Two examples of light fluorous reagents are shown in Figure 2.18. These fluorous reagents are the diethylazodicarboxylate (DEAD) and Lawesson reagent analogs used for Mitsunobu (Dandapani and Curran 2002) and carbonyl thionylation reactions, respectively (Zoltán *et al.* 2006). By using these compounds, excess reagent and fluorous by-products are easily removed by F-SPE chromatography.

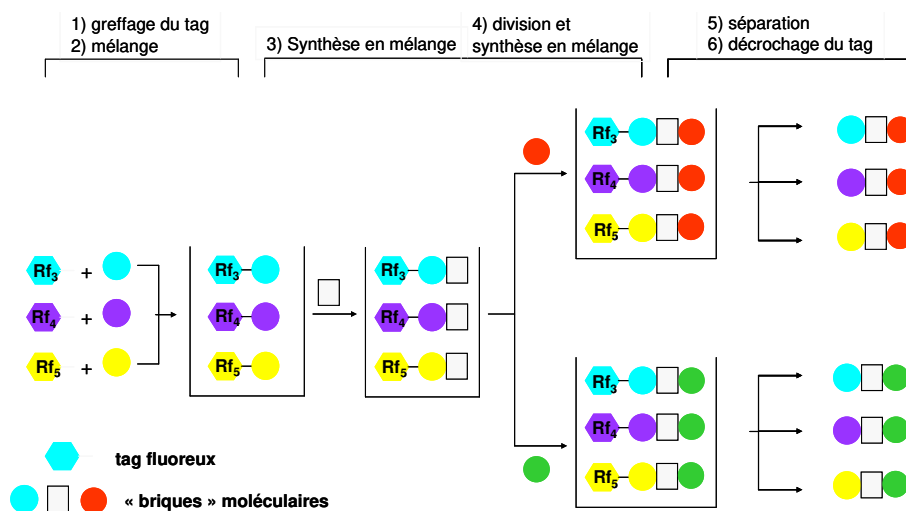
In the case of the Mitsunobu reaction, Curran *et al.* used a fluorinated triphenylphosphine as co-reagent, which eliminates the two by-products, triphenylphosphine oxide and hydrazine, during the separation step on fluorinated silica.



**Figure 2.18.** Examples of light fluorous reagents

### 2.3.2.1.4. Fluorous mixture synthesis

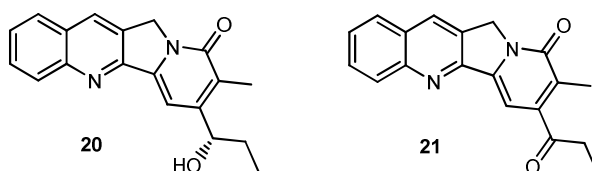
Curran, Zhang *et al.* used the ability of high-performance liquid chromatography combined with fluorous silica to very effectively separate molecules modified by *F*-tags of different perfluoroalkyl chain lengths to develop the first homogeneous solution mixture synthesis methodology that isolates each product from the "library" (Luo *et al.* 2001; Zhang *et al.* 2002b). The general principle of the methodology and amplification principle is presented in Figure 2.19.



**Figure 2.19.** Fluororous mixture synthesis (adapted from (Zhang 2004))

Compounds of the same family are individually modified by *F*-tags whose perfluoroalkyl fragment length varies ( $C_3F_7$ ,  $C_4F_9$ ,  $C_5F_{11}$ ...). The resulting compounds, three in the case presented, are then mixed and can be reacted with a fourth product to produce a mixture of three new products. The mixture can be split in two, then each mixture is reacted with a different product, resulting in two mixtures containing three different products, or six products. The key step will be to carry out a separation on each mixture by means of a preparative fluororous HPLC to isolate each "tagged" product. The products obtained must then be "detached" and the *F*-tag eliminated by *F*-SPE. One of the advantages of this approach is that at each step the mixtures can be analyzed by fluororous HPLC and, if necessary, purified by non-fluororous silica chromatography.

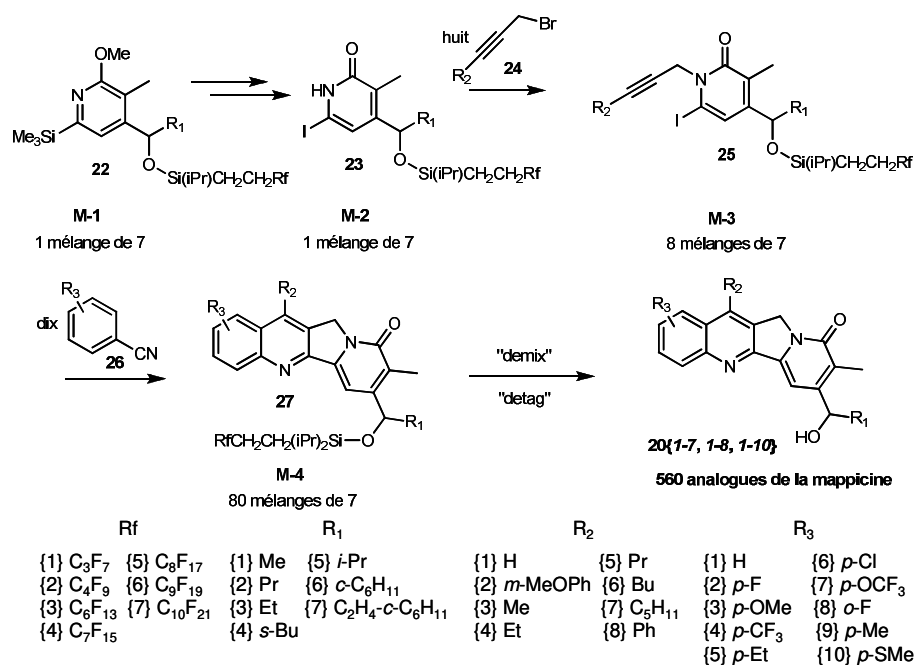
The relevance and efficacy of fluororous mixture synthesis has been demonstrated by the preparation of a "library" of 560 (*S*)-mappicine (**20**) and its analog (**21**), natural products with biological activity against the human herpes virus and cytomegalovirus (Figure 2.20) (Zhang *et al.* 2002b).



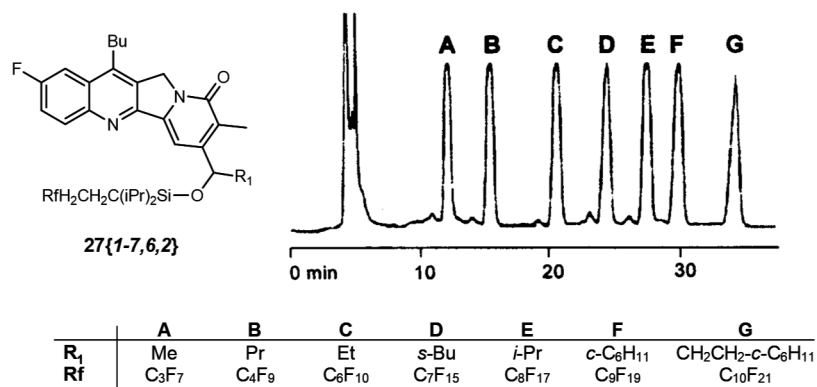
**Figure 2.20.** Structures of (*S*)-mappicine (20) and its analog (21)

The synthesis pathway and protocol used are shown in Figure 2.21. The 7 pyridines 22{1-7} are prepared individually. To each substituent R1 corresponds an *F*-tag, C<sub>3</sub>F<sub>7</sub> for Me, C<sub>4</sub>F<sub>9</sub> for Pr, etc. The 7 pyridines 22{1-7} are mixed in equimolar quantities and reacted with ICl and BBr<sub>3</sub> to produce the product mixture 23{1-7}. Note that a standard silica gel purification step is performed on this mixture. On standard silica, the 7 fluorinated products 23{1-7} will migrate together. The mixture is divided into 8, and each new mixture is reacted with one of the 8 propargyl bromides (24), resulting in 8 mixtures of 7 pyridones 25{1-7,1-8}, or 56 different products. Each of the 8 mixtures is divided into 10, and each of the mixtures obtained is reacted with one of the 10 isonitriles (26), resulting in 80 mixtures each containing 7 tagged mappicines 27{1-7, 1-8,1-10} or 560 compounds. Each of the 80 mixtures is then "demixed" by preparative fluorine HPLC, which allows the 560 products 27{1-7,1-8,1-10} to be isolated. An example of "demixing" on a semi-preparatory scale for tagged mappicines 27{1-7,6,2} is shown in Figure 2.22. All products are perfectly separated, the order of elution always following the increasing order of the total fluorine content. Treatment with HF-pyridine eliminates the silylated protective group and each reaction medium is then processed via chromatography on reverse phase silica gel, allowing the 560 mappicines to be recovered with a purity > 90%. The quantities of mappicine obtained by weight are as follows: 1 to 2 mg for 315 samples (56%), less than 1 mg for 180 samples (32%), and more than 2 mg for 65 samples (12%).



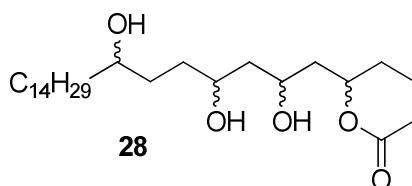


**Figure 2.21.** Fluorous mixture synthesis for the preparation of 560 mappicine analogs (adapted from (Zhang 2004))



**Figure 2.22.** Semi-preparatory HPLC chromatogram corresponding to the separation (demixing) of the product mixture **27{1-7,6,2}**

This concept of fluorous mixture synthesis was subsequently extended to the preparation of stereoisomer "libraries" of natural products such as passiflorin (**28**) (Figure 2.23) (Curran *et al.* 2006). Compared to linear synthesis, this approach significantly reduces the number of chemical reactions that allow access to these compounds.



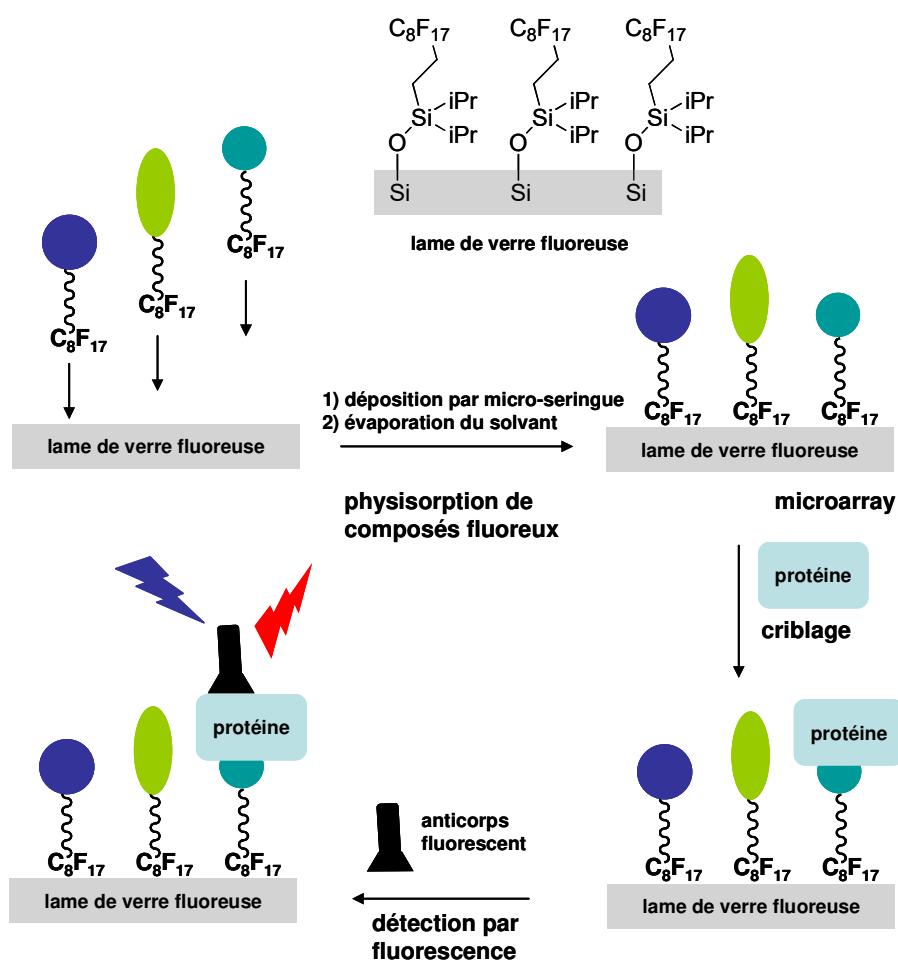
**Figure 2.23.** Structure of *passiflorin*

#### 2.3.2.1.5. Fluorous chemistry for the preparation of *microarrays*

In the field of biotechnology, the development of biochips (or bioarrays) is undergoing considerable growth. A biochip consists of a small support (typically a glass slide with a surface area of one to a few cm<sup>2</sup>) on which very small quantities of a set of DNA molecules (DNA microarray), proteins (protein microarray), oligosaccharides (sugar microarray) or other molecules are fixed on a surface in an ordered and precise manner. These techniques, which are now routinely used, make it possible to identify and study the interactions between biomolecules. The grafting of molecules on the surface is generally done by creating a covalent bond, which avoids losses or migrations on the surface during the hybridization steps. The grafting is carried out by reacting a nucleophilic group already present on the molecule to be grafted or added *via* a tag, onto an electrophilic group present on the surface.

This strategy, although effective, generates many problems related to selectivity, the development of reaction conditions and reproducibility. An important breakthrough was described in 2005 by Pohl *et al.* who showed that it was possible to effectively immobilize monosaccharides non-covalently by exploiting the solvophobic effects generated by *F*-tags (Ko *et al.* 2005). The general principle of fluorous microarrays is shown in Figure 2.24. The validity of this approach was tested by immobilizing monosaccharides or disaccharides tagged with a C<sub>8</sub>F<sub>17</sub> group and showing that it was possible to detect by fluorescence the formation of complexes between some of these sugars and proteins (lectins modified by fluorescent tags). Extended incubation periods and extensive washing to remove non-hybrid proteins do not affect the stability of fluorous microarrays (Mamidyala *et al.* 2006). It was then shown that this type of approach could be used to quantify the binding strength

between sugars and proteins, by measuring the variation in fluorescence intensity as a function of the protein concentration of incubation solutions (Jaipuri *et al.* 2008).

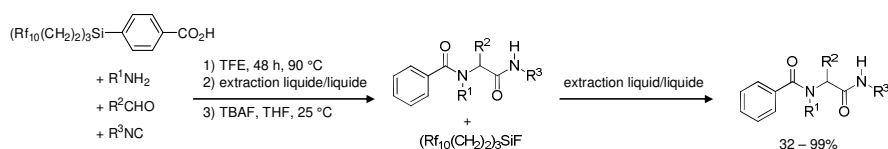


**Figure 2.24.** Fluorous microarrays

### 2.3.2.2. Heavy fluoruous synthesis

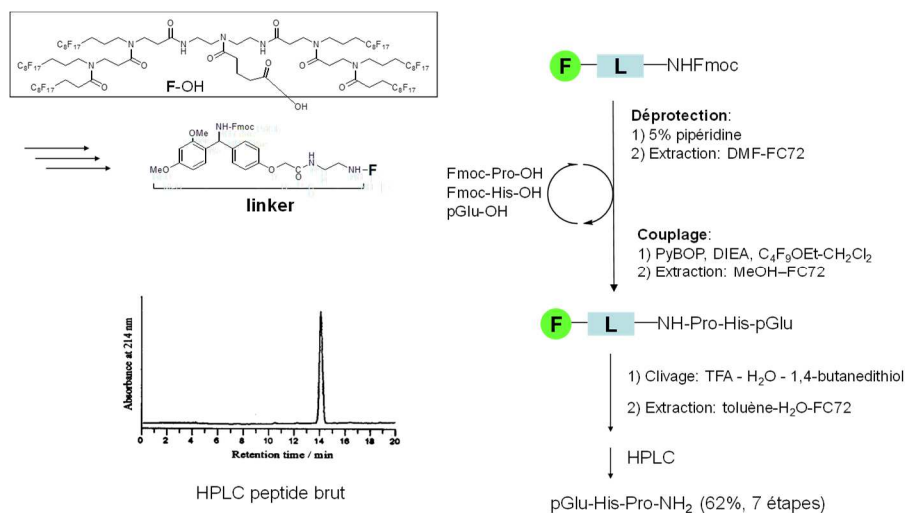
The first fluoruous methodologies developed for synthesis, as early as 1996 by D. Curran *et al.*, concerned so-called "heavy fluoruous" techniques because the reagents used were modified by at least three *F*-tags, thus giving them a high solubility in PFCs. The products, by-products or excess reagent are then removed by liquid/liquid HC/PFC extraction.

In 1997, Curran, Wipf *et al.* developed a fluorous synthesis for the multicomponent condensation of Ugi and Biginelli to obtain functionalized diamides and pyrimidines, respectively (Studer *et al.* 1997a; Studer *et al.* 1997b). An example of Ugi fluorous synthesis is shown in Figure 2.25 (Studer *et al.* 1997b). A heavy fluorous carboxylic acid (15 mol) is reacted for 48 hours at 90°C in trifluoroethanol (TFE, CF<sub>3</sub>CH<sub>2</sub>OH) in the presence of a large excess (17 equivalents each) of amine, aldehyde and isonitrile. The solvent is evaporated, the residue is taken up in benzene and extracted three times by FC-72, which allows the selective and quantitative extraction of fluorous compounds. Desilylation is carried out by tetrabutylammonium fluoride (TBAF) and leads to the formation of desired diamides and fluorosilane which are separated by benzene/FC-72 extraction. The approach is conceptually very interesting and effective. Nevertheless, the use of very expensive solvents (TFE, FC-72) or toxic solvents (benzene) has disadvantages that have led to the development of light fluorous techniques.



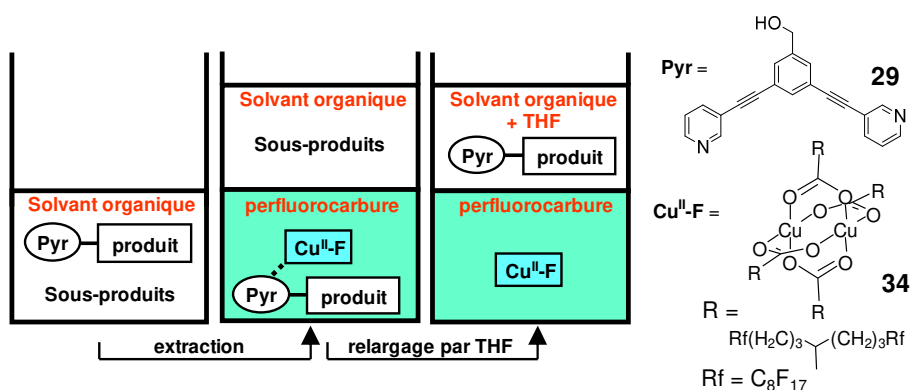
**Figure 2.25.** Fluorous synthesis of Ugi

Inazu *et al.* have developed an original approach based on the use of the heavy fluorous "molecular support" *F*-OH (Figure 2.26) with a dendrimeric structure with 6 *F*-tags -C<sub>8</sub>F<sub>17</sub>. This extremely fluorophilic acid has been successfully used for the solution synthesis of oligopeptides (Mizuno *et al.* 2003) and oligosaccharides (Miura *et al.* 2003; Mizuno *et al.* 2006). The preparation of a biologically active tripeptide (thyrotropin-releasing hormone) was first carried out by grafting a trialkoxybenzhydryl linker commonly used in peptide synthesis on resin. The synthesis uses the Fmoc strategy with deprotection/coupling cycles performed in solution using the usual conditions. Note that for the coupling step, a partially fluorinated ether is used as a co-solvent to promote substrate solubility. A liquid/liquid extraction DMF/FC72 allows the product to be selectively and quantitatively extracted after deprotection. The products obtained after coupling are separated by MeOH/FC72 extractions. The removal of the "molecular support" is carried out in an acidic medium, and the peptide is isolated in the aqueous phase after the three-phase extraction with toluene, H<sub>2</sub>O and FC72. The HPLC chromatogram of the aqueous phase shows that the purity of the crude peptide is very satisfactory. After purification of the aqueous phase by reverse phase HPLC, the peptide is obtained with a yield of 62% for 7 steps and a single purification by chromatography.

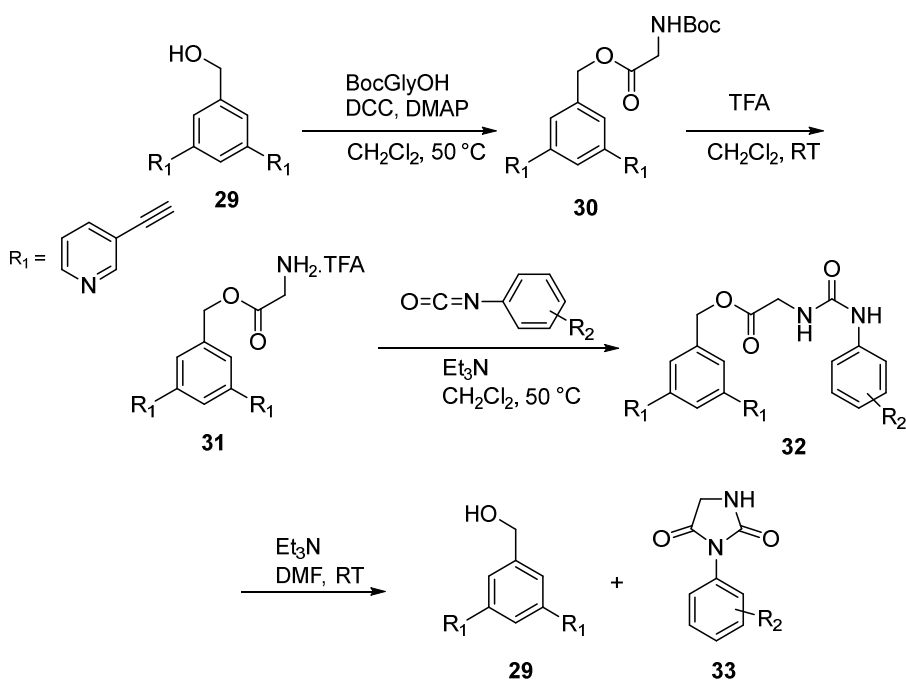


**Figure 2.26.** Use of a heavy fluorinated molecular carrier,  $F-OH$ , for the synthesis of a tripeptide

Finally, Vincent *et al.* developed the concept of reversible extraction of pyridine tag molecules between an organic phase and a PFC (El Bakkari *et al.* 2002), which could be used to facilitate the purification of substrate/products during the multi-step synthesis of a hydantoin (El Bakkari and Vincent 2004). The principle of the liquid/liquid extraction-release system is shown in Figure 2.27. The *bis*-mono-pyridyl tag (29) has a benzyl alcohol function allowing a substrate to be grafted in a manner similar to a Merrifield or Wang type resin. The reaction sequence used for hydantoin synthesis (33) is described in Figure 2.28. Intermediates (30) and (32) are quantitatively extracted from the reaction medium at the end of the reaction by adding a perfluorodecalin solution containing the heavy fluorinated copper dimer (34) soluble only in PFC. After settling, removal of the  $CH_2Cl_2$  phase, (30) and (32) are released into chloroform by the addition of THF. In the last step, the hydantoin and the tag are obtained in equimolar proportions; the addition of the perfluorodecalin solution containing (34) enables to isolate (33) with an overall yield for the 4 steps of 86% (El Bakkari and Vincent 2004).



**Figure 2.27.** Concept of the reversible phase transfer process between an organic solvent and a perfluorocarbon applied to organic synthesis



**Figure 2.28.** Reaction scheme used for the synthesis of hydantoin (33)

## 2.4. Conclusion

Twenty-five years after their appearance in the literature, fluorous techniques offer a very wide range of methodologies to facilitate the purification of complex reaction mixtures. The combination of fluorous molecules and liquid or solid fluorous phases offers an ideal compromise in terms of ease of process implementation, reactivity, efficiency and simplicity of purification. When in a chemical reaction, the purification step is considered as a key step in the process, fluorous techniques are now to be considered as a credible and viable alternative to solid support chemistry. For catalysis applications, fluorous biphasic catalysis is the technique of choice for highly efficient catalyst recycling and has a high potential for industrial applicability. Environmental persistence and therefore the risk of bioaccumulation of PFCs in the environment is a potential problem with these compounds, which must therefore be perfectly contained to avoid any risk of contamination. It should be noted, however, that PFCs are, along with water, the only solvents that are not toxic and can be ingested in large quantities. For synthesis applications, light fluorous techniques are particularly well suited to the preparation of compound libraries *via* automated parallel syntheses. In general, these techniques save time, reduce the use of reagents and significantly reduce the number of chemical reactions required to obtain the target compounds compared to existing techniques. Since 2005, fluorous techniques have successfully entered the field of biotechnology, a rapidly expanding field in which the exceptional physico-chemical properties of perfluorinated tags and phases will continue to be exploited.

## 2.5. Bibliography

- Beier, P., O'Hagan, D. (2002). Enantiomeric partitioning using fluorous biphasic methodology for lipase-mediated (trans)esterifications. *Chem. Commun.*, 1680–1681.
- Betzemeier, B., Lhermitte, F., Knochel, P. (1998). Wacker oxidation of alkenes using a fluorous biphasic system. A mild preparation of polyfunctional ketones. *Tetrahedron Lett.*, 39, 6667–6670.
- Biffis, A., Zecca, M., Basato, M. (2003). A green protocol for the silylation of alcohols using bonded fluorous phase catalysis. *Green Chem.*, 5, 170–173.
- Cavazzini, M., Manfredi, A., Montanari, F., Quici, S., Pozzi, G. (2001). Asymmetric epoxidation of alkenes in fluorinated media, catalyzed by second-generation fluorous chiral (salen)manganese complexes. *Eur. J. Org. Chem.*, 4639–4649.

- Contel, M., Villuendas, P.R., Fernández-Gallardo, J., Alonso, P.J., Vincent, J.-M., Fish, R.H. (2005). Fluorocarbon soluble copper(II) carboxylate complexes with nonfluoroponytailed nitrogen ligands as precatalysts for the oxidation of alkenols and alcohols under fluorous biphasic or thermomorphic modes: Structural and mechanistic aspects. *Inorg. Chem.*, 44, 9771–9778.
- Corrêa da Costa, R., Gladysz, J.A. (2006). Fluorous phase-transfer activation of catalysts: application of a new rate-enhancement strategy to alkene metathesis. *Chem. Commun.*, 2619–2621.
- Crich, D., Zhou, Y. (2004). Recyclable oxidation reagents. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 202–222.
- Croxtall, B., Hope, E.G., Stuart, A.M. (2003). Separation, recovery and recycling of a fluorous-tagged nickel catalyst using fluorous solid-phase extraction. *Chem. Commun.*, 2430–2431.
- Curran, D.P. (1998). Strategy-level separations in organic synthesis: From planning to practice. *Angew. Chem. Int. Ed.*, 37, 1174–1196.
- Curran, D.P. (2008). Fluorous chemistry in Pittsburg: 1996–2008. *J. Fluor. Chem.*, 129, 898–902.
- Curran, D.P., Furukawa, T. (2002). Simultaneous preparation of four truncated analogues of discodermolide by fluorous mixture synthesis. *Org. Lett.*, 4, 2233–2235.
- Curran, D.P., Hadida, J. (1996). Tris(2-(perfluorohexyl)ethyl)tin hydride: A new fluorous reagent for use in traditional organic synthesis and liquid phase combinatorial synthesis. *J. Am. Chem. Soc.*, 118, 2531–2532.
- Curran, D.P., Oderaotoshi, Y. (2001). Thiol additions to acrylates by fluorous mixture synthesis: Relative control of elution order in demixing by the fluorous tag and the thiol substituent. *Tetrahedron*, 57, 5243–5253.
- Curran, D.P., Ogoe, C. (2006). A new fluorous methoxymethyl (<sup>F</sup>MOM) protecting group for alcohols. *QSAR Comb. Sci.*, 25, 732–735.
- Curran, D.P., Hadida, S., He, M. (1997). Thermal allylations of aldehydes with a fluorous allylstannane. Separation of organic and fluorous products by solid phase extraction with fluorous reverse phase silica gel. *J. Org. Chem.*, 62, 6714–6715.
- Curran, D.P., Amatore, M., Guthrie, D., Campbell, M., Go, E., Luo, Z. (2003). Synthesis and reactions of fluorous carbobenzyloxy (<sup>F</sup>CBZ) derivatives of  $\alpha$ -amino acids. *J. Org. Chem.*, 68, 4643–4647.
- Curran, D.P., Moura-Letts, G., Pohlman, M. (2006). Solution-phase mixture synthesis with fluorous tagging en route: total synthesis of an eight-member stereoisomer library of passifloricins. *Angew. Chem. Int. Ed.*, 45, 2423–2426.
- Dandapani, S., Curran, D.P. (2002). Fluorous Mitsunobu reagents and reactions. *Tetrahedron*, 58, 3855–3864.



- Dinh, L.V., Gladysz, J.A. (2005). « Catalyst-on-a-tape »-Teflon: a new delivery and recovery method for homogeneous fluororous catalysts. *Angew. Chem. Int. Ed.*, 44, 4095–4097.
- El Bakkari, M., Vincent, J.-M. (2004). Fluorous phase-switching of pyridyl-tagged substrates/products. *Org. Lett.*, 6, 2765–2767.
- El Bakkari, M., McClenaghan, N., Vincent, J.-M. (2002). The pyridyl-tag strategy applied to the hydrocarbon/perfluorocarbon phase-switching of a porphyrin and a fullerene. *J. Am. Chem. Soc.*, 124, 12942–12943.
- Gladysz, J.A. (2004). Ponytails: Structural and electronic properties. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 41–55.
- Gladysz, J.A., Emnet, C. (2004). Fluorous solvents and related media. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 11–23.
- Gladysz, J.A., Emnet, C., Rábai, J. (2004a). Partition coefficients involving fluororous solvents. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 56–100.
- Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.) (2004b). *Handbook of Fluorous Chemistry*. Wiley-VCH, Weinheim.
- Hobbs, H.R., Thomas, N.R. (2007). Biocatalysis in supercritical fluids, in fluororous solvents, and under solvent-free conditions. *Chem. Rev.*, 107, 2786–2820.
- Hobbs, H.R., Kirke, H.M., Poliakoff, M., Thomas, N.R. (2007). Homogeneous biocatalysis in both fluororous biphasic and supercritical carbon dioxide systems. *Angew. Chem. Int. Ed.*, 46, 7860–7863.
- Hope, E.G., Stuart, A.M. (2004). Synthesis of perfluoroalkylated phosphines. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 247–256.
- Horváth, I.T., Rábai, J. (1994). Facile catalyst separation without water : fluororous biphasic hydroformylation of olefins. *Science*, 266, 72–75.
- Horváth, I.T., Kiss, G., Cook, R.A., Bond, J.E., Stevens, P.A., Rábai, J., Mozeleski, E. (1998). Molecular engineering in homogeneous catalysis: One-phase catalysis coupled with biphasic catalyst separation. The fluororous-soluble  $\text{HRh}(\text{CO})\{\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}_3$  hydroformylation system. *J. Am. Chem. Soc.*, 120, 3133–3143.
- Ishihara, K., Kondo, S., Yamamoto, H. (2001). 3,5-Bis(perfluorodecyl)phenylboronic acid as an easily recyclable direct amide condensation catalyst. *Synlett*, 1371–1374.
- Ishihara, K., Hasegawa, K., Yamamoto, H. (2002). A fluororous super Brønsted acid catalyst: application without fluororous solvents. *Synlett*, 1299–1301.

- Jaipuri, F.A., Collet, B.Y.M., Pohl, N.L. (2008). Synthesis and quantitative evaluation of Glycero-D-manno-heptose binding to concanavalin A by fluorous-tag assistance. *Angew. Chem. Int. Ed.*, 47, 1707–1710.
- Jiao, H., Le Stang, S., Soós, T., Meier, R., Kowski, K., Rademacher, P., Jafarpour, L., Hamard, J.-B., Nolan, P., Gladysz, J.A. (2002). How to insulate a reactive site from a perfluoroalkyl group: Photoelectron spectroscopy, calorimetric, and computational studies of long-range electronic effects in fluorous phosphines  $P((CH_2)_m(CF_2)_7CF_3)_3$ . *Am. Chem. Soc.*, 124, 1516–1523.
- Juliette, J.J.J., Rutherford, D., Horváth, I.T., Gladysz, J.A. (1999). Transition metal catalysis in fluorous media: Practical application of a new immobilization principle to rhodium-catalyzed hydroborations of alkenes and alkynes. *J. Am. Chem. Soc.*, 121, 2696–2704.
- Klmet, I., Lütjens, H., Knochel, P. (1997). Transition metal catalyzed oxidations in perfluorinated solvents. *Angew. Chem. Int. Ed. Engl.*, 36, 1454–1456.
- Ko, K.-S., Jaipuri, F.A., Pohl, N.L. (2005). Fluorous-based carbohydrate microarrays. *J. Am. Chem. Soc.*, 127, 13162–13163.
- Koch, D., Leitner, W.J. (1998). Rhodium-catalyzed hydroformylation in supercritical carbon dioxide. *J. Am. Chem. Soc.*, 120, 13398–13404.
- Lu, Y., Zhang, W. (2006). Fluorous 2,4-Dichloro-1,3,5-triazines (F-DCTs) as nucleophile scavengers. *QSAR Comb. Sci.*, 25, 728–731.
- Luo, Z., Zhang, Q., Odearotoshi, Y., Curran, D.P. (2001a). Fluorous mixture synthesis: a fluorous-tagging strategy for the synthesis and separation mixtures of organic compounds. *Science*, 291, 1766–1769.
- Luo, Z., William, J., Read, R.W., Curran, D.P. (2001b). Fluorous Boc ( $^F$ Boc) carbamates: New amine protecting groups for use in fluorous synthesis. *J. Org. Chem.*, 66, 4261–4266.
- Maillard, D., Pozzi, G., Quici, S., Sinou, D. (2002). Asymmetric hydrogen transfer reduction of ketones using chiral perfluorinated diimines and diamines. *Tetrahedron*, 58, 3971–3976.
- Mamidyala, S.K., Ko, K.-S., Jaipuri, F.A., Park, G., Pohl, N.L. (2006). Noncovalent fluorous interactions for the synthesis of carbohydrate microarrays. *J. Fluor. Chem.*, 127, 571–579.
- Matsugi, M., Curran, D.P. (2005). Synthesis, reaction, and recycle of light fluorous Grubbs-Hoveyda catalysts for alkene metathesis. *J. Org. Chem.*, 70, 1636–1642.
- Matsugi, M., Yamanaka, K., Inomata, I., Takekoshi, N., Hasegawa, M., Curran, D.P. (2006). Synthesis of fluorous-Fmoc reagents and purification of protected dipeptides with fluorous solid phase extraction. *QSAR Comb. Sci.*, 25, 713–715.
- McCormick, R.A., James, K.M., Willets, N., Procter, D.J. (2006). Developing new cleavage strategies in a fluorous phase Pummerer cyclative-capture approach for the synthesis of *N*-heterocycles. *QSAR Comb. Sci.*, 25, 709–712.

- Miura, T., Goto, K., Hosaka, D., Inazu, T. (2003). Oligosaccharide synthesis on a fluorous support. *Angew. Chem. Int. Ed.*, 42, 2047–2051.
- Mizuno, M., Goto, K., Miura, T., Hosaka, D., Inazu, T. (2003). A novel peptide synthesis using fluorous chemistry. *Chem. Commun.*, 972–973.
- Mizuno, M., Goto, K., Miura, T., Inazu, T. (2006). Rapid oligosaccharide and peptide synthesis on a recyclable fluorous support. *QSAR Comb. Sci.*, 25, 742–752.
- Moura-Letts, G., Curran, D.P. (2007). Selective synthesis of (2Z,4E)-dienyl esters by ene-diene cross metathesis. *Org. Lett.*, 9, 5–8.
- Nakamura, Y., Takeuchi, S., Okumura, K., Ohgo, Y., Curran, D.P. (2002a). Recyclable fluorous chiral ligands and catalysts: asymmetric addition of diethylzinc to aromatic aldehydes catalyzed by fluorous BINOL-Ti complexes. *Tetrahedron*, 58, 3963–3969.
- Nakamura, Y., Takeuchi, S., Zhang, S., Okumura, K., Ohgo, Y. (2002b). Preparation of a fluorous chiral BINAP and application to an asymmetric Heck reaction. *Tetrahedron Lett.*, 43, 3053–3056.
- Pearson, W.H., Berry, D.A., Stoy, P., Jung, K.-Y., Sercel, A.D. (2005). Fluorous affinity purification of oligonucleotides. *J. Org. Chem.*, 70, 7114–7122.
- Pozzi, G., Quici, S. (2004). Fluorous nitrogen ligands for oxidation reactions. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 290–298.
- Pozzi, G., Montanari, F., Quici, S. (1997). Cobalt tetraarylporphyrin-catalyzed epoxidation of alkenes by dioxygen and 2-methylpropanal under fluorous biphasic conditions. *Chem. Commun.*, 69–70.
- Richter, B., Spek, A.L., Van Koten, G., Deelman, B.-J. (2000). Fluorous versions of Wilkinson's catalyst. Activity in fluorous hydrogenation of 1-alkenes and recycling by fluorous biphasic separation. *J. Am. Chem. Soc.*, 122, 3945–3951.
- Rocaboy, C., Gladysz, J.A. (2002). Highly active thermomorphic fluorous palladacycle catalyst precursors for the Heck reaction; Evidence for a palladium nanoparticle pathway. *Org. Lett.*, 4, 1993–1996.
- Siedel, F.O., Gladysz, J.A. (2008). Catalysis of intramolecular Morita-Baylis-Hillman and Rauhut-Currier reactions by fluorous phosphines; facile recovery by liquid/solid organic/fluorous biphasic protocols involving precipitation, Teflon® tape, and Gore-Rastex® fiber. *Adv. Synth. Catal.*, 350, 2443–2449.
- Studer, A., Hadida, S., Ferritto, S., Kim, Y., Jeger, P., Wipf, P., Curran, D.P. (1997a). Fluorous synthesis: A fluorous-phase strategy for improving separation efficiency in organic synthesis. *Science*, 275, 823–826.
- Studer, A., Jeger, P., Wipf, P., Curran, D.P. (1997b). Fluorous synthesis: Fluorous protocols for the Ugi and Biginelli multicomponent condensations. *J. Org. Chem.*, 62, 2917–2924.

- Takeuchi, S., Nakamura, Y. (2004). Enantioselective catalysis in non-biphasic conditions. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 316–322.
- Tzschucke, C.C., Markert, C., Glatz, H., Bannwarth, W. (2002). Fluorous biphasic catalysis without perfluorinated solvents: Application to Pd-mediated Suzuki and Sonogashira couplings. *Angew. Chem. Int. Ed.*, 41, 4500–4503.
- Van Vliet, M.C.A., Arends, I.W.C.E., Sheldon, R.A. (1999). Perfluoro-heptadecan-9-one: a selective and reusable catalyst for epoxidations with hydrogen peroxide. *Chem. Commun.*, 263–264.
- Vincent, J.-M., Rabion, A., Yachandra, V.K., Fish, R.H. (1997). Fluorous biphasic catalysis : Complexation of 1,4,7-[C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>3</sub>]-1,4,7-triazacyclononane with [M(C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>)<sub>2</sub>] (M = Mn, Co) to provide perfluoroheptane-soluble catalysts for alkane and alkene functionalization in the presence of *t*-BuOOH and O<sub>2</sub>. *Angew. Chem. Int. Ed. Engl.*, 36, 2346–2349.
- Vincent, J.-M., Lastécouères, D., Contel, M., Laguna, M., Fish, R.H. (2004). Synthesis of fluororous nitrogen ligands and their metal complexes as precatalysts for applications in alkane, alkene, and alcohol oxidation, and atom transfer radical reactions. Dans *Handbook of Fluorous Chemistry*, Gladysz, J.A., Curran, D.P., Horváth, I.T. (dir.). Wiley-VCH, Weinheim, 298–305.
- de Visser, P.C., van Helden, M., Filippov, D.V., van der Marel, G.A., Drijfhout, J.W., van Boom, J.H., Noort, D., Overkleeft, H.S. (2003). A novel, base-labile fluororous amine protecting group: synthesis and use as a tag in the purification of synthetic peptides. *Tetrahedron Lett.*, 44, 9013–9016.
- Wende, M., Gladysz, J.A. (2003). Fluorous catalysis under homogeneous conditions without fluororous solvents: A “Greener” catalyst recycling protocol based upon temperature-dependent solubilities and liquid/solid phase separation. *J. Am. Chem. Soc.*, 125, 5861–5872.
- Wende, M., Meier, R., Gladysz, J.A. (2001). Fluorous catalysis without fluororous solvents: A friendlier catalyst recovery/recycling protocol based upon thermomorphic properties and liquid/solid phase separation. *J. Am. Chem. Soc.*, 123, 11490–11491.
- Werner, S., Curran, D.P. (2003). Fluorous dienophiles are powerful diene scavengers in Diels-Alder reactions. *Org. Lett.*, 5, 3293–3296.
- de Wolf, E., Speets, E.A., Deelman, B.-J., Van Koten, G. (2001). Recycling of; rhodium-based hydrosilylation catalysts; a fluororous approach. *Organometallics*, 20, 3686–3690.
- Xia, J., Johnson, T., Gaynor, S.G., Matyjaszewski, K., DeSimone, J. (1999). Atom transfer radical polymerization in supercritical carbon dioxide. *Macromolecules*, 32, 4802–4805.
- Xiang, J., Orita, A., Otera, J. (2002). Fluorous biphasic esterification directed towards ultimate atom efficiency. *Angew. Chem. Int. Ed.*, 41, 4117–4119.

- Yoshida, A., Hao, X., Nishikido, J. (2003). Development of the continuous-flow reaction system based on the Lewis acid-catalyzed reactions in a fluorous biphasic system. *Green Chem.*, 5, 554–557.
- Zhang, W. (2003). Fluorous synthesis of disubstituted pyrimidines. *Org. Lett.*, 5, 1011–1013.
- Zhang, W. (2004). Fluorous synthesis of heterocyclic systems. *Chem. Rev.*, 104, 2531–2556.
- Zhang, W., Curran, D.P. (2006). Synthetic applications of fluorous solid-phase extraction (F-SPE). *Tetrahedron*, 62, 11837–11865.
- Zhang, W., Hiu-Tung Chen, C. (2003). FluoMar, a fluorous version of the Marshall resin for solution-phase library synthesis. *Org. Lett.*, 5, 1015–1017.
- Zhang, W., Lu, Y. (2003). Fluorous synthesis of hydantoins and thiohydantoins. *Org. Lett.*, 5, 2555–2558.
- Zhang, W., Curran, D.P., Hiu-Tung Chen, C. (2002a). Use of fluorous silica gel to separate fluorous thiol quenching derivatives in solution-phase parallel synthesis. *Tetrahedron* 58, 3871–3875.
- Zhang, W., Luo, Z., Hiu-Tung Chen, C., Curran, D.P. (2002b). Solution-phase preparation of a 560-compound library of individual pure mappicine analogues by fluorous mixture synthesis. *J. Am. Chem. Soc.*, 124, 10443–10450.
- Zhang, W., Hiu-Tung Chen, C., Nagashima, T. (2003). Fluorous electrophilic scavengers for solution-phase parallel synthesis. *Tetrahedron Lett.*, 44, 2065–2068.
- Zoltán, K., Tárkányi, G., Gömöry, A., Kálmán, F., Nagy, T., Soós, T. (2006). Synthesis and application of a fluorous Lawesson's reagent: convenient chromatography-free product purification. *Org. Lett.*, 8, 1093–1095.