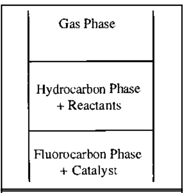
Fluorous phase separation techniques in catalysis



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Fluorous solvents have limited miscibility with conventional organic solvents. Combined with the fact that compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents this can be used to extract fluorous components from reaction mixtures. This review discusses the application and potential of fluorous phase separation techniques for the recovery of soluble metal catalysts.

1 Introduction

Perfluorocarbon fluids, especially perfluoro-alkanes, ethers and amines, have some unique properties which make them attractive alternatives for conventional organic solvents. Among others they are extremely inert, apolar and thermally stable allowing vigorous reaction conditions to be employed.[1] In addition, these fluids and other compounds containing perfluoroalkyl chains often have low surface energies.[2] Technical application of perfluorocarbon fluids benefits from the fact that they are available in a broad range of boiling points, that they are generally not miscible with water, non-toxic and even biocompatible.[3]

Use of perfluorocarbons, however, also may have some disadvantages. Well known are the C_1- and C_2-fluorocarbons (freons) which are greenhouse gases and have become because of their inertness a major environmental problem. These compounds are thought to be responsible for depleting the stratospheric ozone layer. Their boiling points, however, are much lower than the boiling points of the higher perfluoroalkanes. As a consequence of this, higher perfluoroalkanes have lower vapor pressures and might therefore cause less environmental problems than their smaller chain analogues. About the impact, however, of longer perfluoroalkanes on the ozone layer and the greenhouse effect, less is known.

Because of their unique properties perfluorocarbons and perfluoroalkylated compounds have been applied as corrosion

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and oxidation inhibitors for engine oils, hydraulic fluids, lubricants and greases,[4] in polymers (*e.g.* the well-known PTFE)[5] and dendrimers[6] with special surface properties, in perfluorinated monolayers and coatings,[7] supports for immobilization of biomolecules, in biosensors[8] and in preparation of liposomes, vesicles, micelles, emulsions and bilayers.[9] Biphasic mixtures of perfluorocarbon and hydrocarbon fluids have also been employed as media for carrying out suspension polymerization of water sensitive monomers (*e.g.* lauryl methacrylate and styrene).[1]

Perfluorocarbon fluids are usually not miscible with common organic solvents and as a result they display good separation properties with these solvents. Combined with the preferential solubility of perfluoroalkyl-substituted compounds in fluorous (= perfluoro function containing) solvents this feature can be employed for the selective extraction of fluorous compounds from organic reaction mixtures, which is the subject of this review. Although immobilization of biomolecules on fluorous supports has been successfully employed in affinity chromatography and it has been shown that fluorous enzymes immobilized on fluorous supports retain *ca.* 70% of their original activity,[8] the potential of these so called fluorous phase separation and immobilization techniques in transition metal catalysis has only recently received attention after the first report by Horváth *et al.*[10] A brief review on this subject has appeared recently.[11] Below an overview is given on the application of fluorous phase immobilization and separation methods in catalysis. For an overview on steric and electronic effects of perfluoro substituents in organometallics, the reader is referred to an early review by Hughes *et al.*[12]

2 Potential of fluorous phase separation techniques for catalysis

In catalysis, homogeneous catalytic systems are often preferred over heterogeneous ones because of their better product and substrate selectivity. A general problem in homogeneous catalysis, however, is separation and recycling of the catalyst. This has led to the development of several supported catalytic systems, *e.g.* immobilized versions of homogeneous catalysts on inorganic supports[13] and systems connected to polymers or dendrimers,[14] with the combined advantages of both homogeneous and heterogeneous catalysis. Another elegant solution for this separation problem is the aqueous biphasic Ruhrchemie/Rhône-Poulenc process.[15] In this process a water soluble version of the conventional Rh–PPh_3 catalyst is used, *i.e.* TPPTS–Rh (TPPTS = $P(m\text{-}C_6H_4SO_3Na)_3$). The catalytic process is performed under biphasic conditions with the aqueous phase containing the catalyst, and the organic phase containing the products. The catalyst can be easily removed from the products by phase separation. In this way losses of rhodium are kept below 10^{-6} mg kg^{-1} of product produced.

Despite the advantages of aqueous biphasic systems in catalysis, they also have some disadvantages. Some reactants or catalysts hydrolyze when exposed to water, resulting in decreased performance for these systems. Furthermore, due to the two phase nature of the system, the catalyst is not homogeneously mixed with the products. Therefore, the reactants have to cross the phase boundary which could lead to mass flow limitations, resulting in considerably lower reaction rates as compared to single phase homogeneous systems. This effect is enhanced by the often low solubility of organic substrates in water.[10]

The special physical properties of perfluorinated compounds described above and the problem associated with aqueous biphasic catalysis inspired Horváth *et al.* to use fluorous biphase systems in rhodium catalyzed hydroformylation.[10] Here, the fluorous phase, as an alternative to the aqueous phase, denotes a solvent which is rich in C–F bonds. Below a certain temperature the fluorous phase does not mix with an organic phase containing the reactants and products. The principle of fluorous biphase catalysis can be depicted as follows (Fig. 1). At room temperature, the system consists of a fluorous phase, containing a fluorous phase soluble catalyst, and a hydrocarbon phase, containing the reactants. Above a certain temperature, the two phases mix to form one phase allowing efficient homogeneous catalysis to proceed. Catalyst recovery can then be achieved by cooling of the reaction mixture below the temperature where phase separation occurs. Alternatively, if the phase transition temperature of a certain fluorous biphasic system is too high, or if desirable for other reasons, the catalytic reaction can also be performed under biphasic conditions.

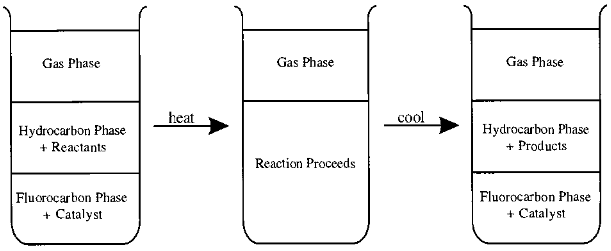


Fig. 1 Principle of fluorous biphase catalysis.

For reactions which cannot be performed in an aqueous biphasic system, *e.g.* due to low solubility of reactants in the aqueous layer, diffusion limitations or water sensitive components, a fluorous biphasic system could be an alternative. Perfluoro solvents do not mix with water and can only contain water at the ppm level.

Fluorous phase separation techniques are of course not limited to applications in catalysis but can also be used in organic synthesis. Fluorous synthesis, developed and recently reviewed by Curran,[16] is based on separation of fluorous reactants and by-product from the desired organic products. Because of its simplicity and speed, fluorous extraction of fluorous side products from the desired organic product is also an attractive purification technique for application in combinatorial synthesis. A library of compounds can be synthesized much faster if the compounds can be purified quickly without the use of time consuming separation techniques like crystallization, distillation or filtration.

3 Applications of fluorous phase separation techniques in catalysis

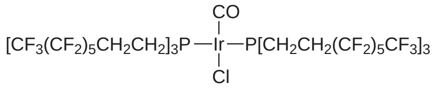
To render a catalyst preferentially soluble in a fluorous phase it is usually functionalized with one or several perfluoroalkyl groups, also sometimes referred to as pony tails. Most often, perfluorohexyl (C_6F_{13}) and perfluorooctyl (C_8F_{17}) groups are used. Branched perfluoroalkyl groups are less common. The length and number of the perfluoroalkyl groups are important, because they influence the solubility of a perfluoroalkylated compound in a fluorous solvent.[17] However, in many cases the distribution of a fluorous catalyst in a fluorous biphasic system has not been optimized. The strongly electron-withdrawing properties of perfluoroalkyl functions could have a dramatic effect on the catalytic activity when compared to the non-substituted system. This can be easily understood from the known high electronegativity of the CF_3 group (3.5 according to Pauling[18]), the reversed polarization of the C–I bond in perfluoroalkyl iodides (which renders the iodine atom rather than the α-carbon susceptible to nucleophilic attack[19]), and the remarkable increase in N_{1s} and $Zn_{2p3/2}$ ionization potential of Zn–porphyrin complexes upon perfluoroalkylation.[20] The strong electron-withdrawing nature of perfluoroalkyl groups was also observed in (trifluoromethyl)cyclopentadienyl transition metal complexes.[12]

Although it is difficult to predict the exact effect of electron-withdrawing perfluoroalkyl groups on catalytic activity since this will depend on the intimate details of each catalytic cycle involved it can be easily understood that a decrease of electron density on the metal center is expected to have a significant effect on, for example, the delicate σ-donation/π-back donation balance in bonding of catalytically important substrates such as CO, H_2 and olefins. In practice the above problem has been solved by using ethylene or propylene spacers that insulate the strongly electron-withdrawing perfluoroalkyl tail from the remainder of the transition metal catalyst. Another type of spacer which has been developed in our own laboratory, is the $-CH_2CH_2SiMe_2$- moiety.[21]

Fluorous biphasic catalysis was first demonstrated in hydroformylation of alk-1-enes using $[HRh(CO)\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_3]$[10,22] in the presence of an excess of $P[CH_2CH_2(CF_2)_5CF_3]_3$. The ratio of normal to branched aldehyde (n/i) obtained was comparable to that for non-fluorous $[HRh(CO)\{PPh_3\}_3]$ (n/i = 2.9) in a conventional solvent. This value was slightly higher than that obtained for the perprotio analogue $[HRh(CO)\{P[(CH_2)_7CH_3]_3\}_3]$ under non-fluorous conditions (n/i = 2.3). Although selectivity was higher the activity of the fluorous catalyst under biphasic conditions was an order of magnitude lower which was explained by the lower solubility of CO and H_2 in the fluorous biphasic solvent system.

Another aspect relevant to recycling of the catalyst is the amount of catalyst that leaches into the organic phase. It was found that losses of rhodium amounted to 4.2% after 9 cycles (corresponding to 0.6 mg of Rh per kg of product) for the above fluorous catalyst. At this point, this fluorous hydroformylation system cannot compete yet with the aqueous biphasic system. As mentioned earlier, the losses of rhodium in the aqueous biphasic system are less than 10^{-6} mg of Rh per kg of product. Although this was not quantified further, judging from the increase in activity and drop of selectivity after each catalyst recycle the authors suggest that the system most probably suffers from leaching of the fluorous phosphine as well.

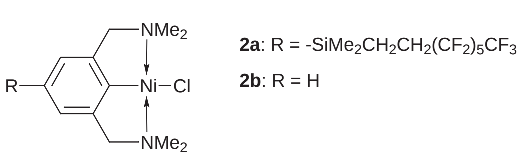
Closely related fluorous rhodium complexes *trans*-$[ClRh(CO)\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_2]$, *trans*-$[ClRh(CO)\{P[C_6H_4(CF_2)_5CF_3\text{-}4]_3\}_2]$,[23] and iridium complex **1**[24] have been prepared although no catalytic activity of those complexes was mentioned. For **1**, a phase distribution constant > 300 in favor of the fluorous phase was found indicating that efficiency of catalyst recovery by a single phase separation could be higher than 99.7%. A fluorous analogue of Wilkinson's catalyst $[ClRh\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_3]$[25] was found to be active in hydroboration of alkenes (turn-over number (TON) = 300–9000, conversion 80–90%).

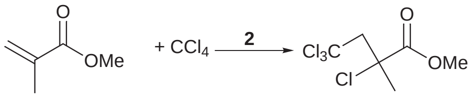


$$[CF_3(CF_2)_5CH_2CH_2]_3P-\underset{Cl}{\overset{CO}{Ir}}-P[CH_2CH_2(CF_2)_5CF_3]_3$$

1

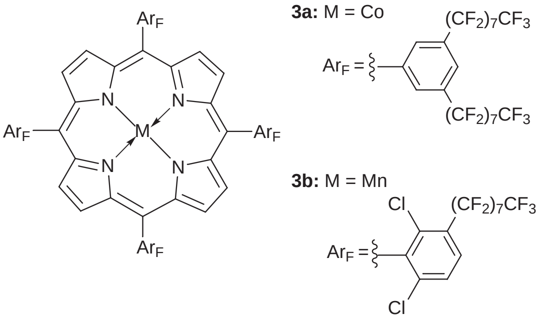
From our own laboratory, the synthesis of **2a** and **2b** was reported, which catalyze the Kharasch addition of CCl_4 with methyl methacrylate (Scheme 1).[21] In CCl_4, selectivity and activity of **2a** were found to be comparable to non-perfluoroalkylated **2b**. Efficient recycling of **2a** by fluorous extraction was, however, hindered by the limited solubility of **2a** in fluorous solvents, which is probably due to the relatively small size of the perfluoroalkyl portion of the catalyst.



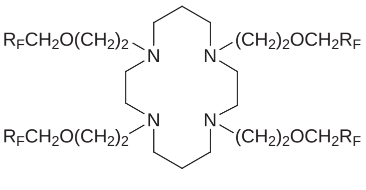


Scheme 1

Several studies on the application of fluorous catalysts for oxidation catalysis have appeared. For instance Pozzi *et al.* prepared among others fluorous tetraarylporphyrin complexes **3a** and **3b**.[26,27] The perfluoroalkyl groups were introduced by cross coupling of the corresponding iodoaryl derivatives and perfluoroalkyl iodides or using FITS [(perFluoroalkyl)phenyl-Iodonium TrifluoromethaneSulfonates] reagents, respectively. Cobalt complex **3a** was found to have good activity and selectivity in fluorous biphasic epoxidation and it was shown by UV–VIS spectroscopy that **3a** was completely partitioned in the fluorous phase. Manganese derivative **3b** was found to be an active epoxidation catalyst under aqueous biphasic conditions.



Copper and cobalt complexes of fluorous tetraazacyclotetradecane **4** are catalysts for alkane and alkene oxidation by t-BuOOH and O_2 under fluorous biphasic conditions.[28] Selectivities of 80% towards ketone, moderate to high yields but modest turn-over numbers (18–330 mol mol^{-1} of catalyst) were found. It was mentioned that the Cu and Co complexes of **4** were only present in the perfluoro solvent (UV–VIS). When the fluorous layers were used for a second run the catalytic activity was retained very well except for the Cu-catalyzed oxidation of cyclohexene, where only 50% of the activity was retained.



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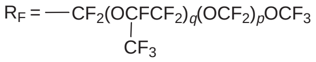

$$R_F = -CF_2(O\underset{CF_3}{C}FCF_2)_q(OCF_2)_pOCF_3$$

$\bar{q} = 3.38$; $\bar{p} = 0.11$

Vincent[29] *et al.* described Mn and Co complexes of 1,4,7-$[C_8F_{17}(CH_2)_3]_3$-1,4,7-triazacyclononane and their activity in fluorous biphasic oxidation of cyclohexene to cyclohex-2-en-1-ol and cyclohex-2-en-1-one in the presence of O_2–t-BuOOH. Overall yields were high, however selectivities were poor. Most importantly, catalyst recovery was successful. Further examples of fluorous oxidation catalysts are Ru and Ni complexes of the fluorinated acetylacetonate anion ($[(C_7F_{15})C(O)CHC(O)(C_7F_{15})]^-$) reported by Klement.[30] They are active in catalytic oxidation of aldehydes, sulfides and epoxidation of cycloalkenes under biphasic conditions. Catalyst recovery was claimed to be easy and no leaching was observed, which was concluded from the fact that the organic layer was colorless.

A fluorous palladium complex [Pd{P($C_6H_4C_6F_{13}$)$_3$}$_4$] turned out to be active in cross-coupling of arylzinc bromides and aryl iodides.[31] The catalyst was recycled several times without a significant drop in reaction yields. The activity of the catalyst was higher than the activity of its non-perfluoroalkylated analogue. This was explained by the lower electron density on the phosphorus atoms, which favors reductive elimination in these cross-couplings.

A few variations on the use of fluorous catalysts and fluorous phase separation techniques were reported. For example, a fluorous phase soluble polymer has been used to remove reagents, catalysts or ligands from a non-fluorous reaction mixture.[32] Also a fluorous analogue of Wilkinson's catalyst,[33] [RhCl{P[*m*-$C_6H_4(CH_2)_2(CF_2)_5CF_3$]$_3$}$_3$] was employed in hydroformylation with supercritical CO_2 as solvent. Here, the perfluoroalkyl tails serve to increase the solubility of the catalyst in this very apolar medium. A conversion of 92% and high selectivity for the *n*-aldehyde (82%) was reached, which is comparable to the selectivity for the non-perfluoroalkylated Wilkinson's catalyst (92%).[22]

4 Phase behavior of fluorous biphasic systems and phase distribution of fluorous catalysts

The special properties of perfluorinated compounds are mainly due to the high electronegativity of the fluorine atom (4.0 on the Pauling scale) and the larger van der Waals radius of fluorine (1.47 Å) as compared to hydrogen (1.2 Å). Although the C–F bond is highly polar,[34] perfluoroalkanes are apolar media and the miscibility with organic solvents is generally low.[35] Because fluorine atoms are very difficult to polarize, the van der Waals interactions between perfluoroalkanes are weak compared to those in alkanes. The weaker van der Waals interactions result in lower boiling points for perfluoroalkanes compared to the corresponding normal alkanes.[36] Also, it is unfavorable for an alkane to mix with a perfluoroalkane, because in terms of energy the gain in van der Waals interactions between perfluoroalkane and alkane molecules upon mixing is not compensated for by the loss of alkane–alkane and perfluoroalkane–perfluoroalkane van der Waals interactions. This leads to low miscibility of organic and perfluoro solvents.

Fluorous biphase catalysis is based on this low miscibility with other organic solvents. One of the most extreme examples is PTFE, which only dissolves in its lower oligomers, *i.e.* long chain perfluoro-*n*-alkanes.[5] The miscibility and critical temperature (T_c) for fluorous biphasic systems, *i.e.* the temperature above which the two liquids are miscible in all ratios, can be determined from a phase diagram like the one depicted in Fig. 2.[36] From this diagram, it can be concluded that also at temperatures below but close to T_c, substantial amounts of perfluorosolvent are dissolved in the organic layer. This could be a potential problem since this may result in some solubility of fluorinated compounds in the organic layer at temperatures close to T_c, leading to, *e.g.*, catalyst loss during phase separation in fluorous biphase catalysis. In general, T_c is close to the phase separation temperature of biphasic systems consisting of equal volumes of each phase.[36] T_c can also be predicted using the Hildebrand–Scatchard Theory, also called Regular Solution Theory[35,36] using eqns. (1) and (2). Here, R is the universal gas

$$T_c \approx \frac{K(v_1 + v_2)}{4R} \tag{1}$$

$$K = (\delta_1 - \delta_2)^2 \tag{2}$$

constant (cal mol^{-1} K^{-1}), v_i the molar volume (cm^3 mol^{-1}), T_c the critical temperature (K) and K (cal cm^{-3}) is a measure of the interaction energy between unlike molecules relative to that of like molecules. The weaker the interaction between two unlike molecules, the higher the value for K. Sufficient large values for K correspond to limited miscibility of the biphasic system. The Hildebrand parameter δ_i (cal$^{1/2}$ cm$^{-3/2}$) of a solvent is defined as the square root of the enthalpy of vaporization (ΔH_i^v) divided by the molar volume (v_i) (eqn. (3)).

$$\delta_i = (\Delta H_i^{v}/v_i)^{1/2} \tag{3}$$

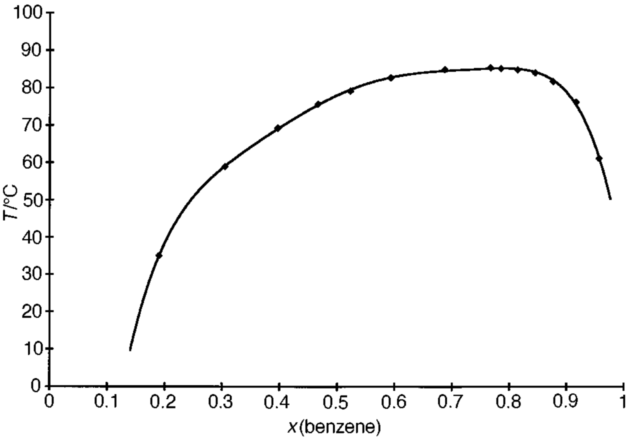

Fig. 2 Phase diagram of perfluoromethylcyclohexane and benzene; x = mole fraction of benzene (redrawn from data in ref. 36).

Values of δ and T_c for specific biphasic systems have been tabulated by Scott[35] and Lo Nostro.[36] Large differences in Hildebrand parameters correspond to large values for K, resulting in low miscibility. Eqn. (1) shows that a large K also corresponds to a high critical temperature. From eqns. (1) and (2), it can be calculated that two liquids are miscible at room temperature when $|\delta_1 - \delta_2|$ is less than 3.5 cal$^{1/2}$ cm$^{-3/2}$ for an average molar volume of 100 ml. The Hildebrand parameters for perfluorocarbons are very low (5.7–6.1), compared to hydrocarbons (>7.0) corresponding to the fact that perfluorocarbons are not completely miscible with organic liquids. For some commonly used solvents δ-values are as follows: *n*-hexane (δ = 7.3), cyclohexane (δ = 8.2) and toluene (δ = 8.9). Especially solvents which have a δ-value around 9 are suitable for use in fluorous biphasic separations since they give phase separation at room temperature. In general, higher polarity solvents also have higher δ-values and consequently give good phase separation with perfluorocarbons.

Explanations given in the literature for experimental deviations from the Hildebrand–Scatchard theory are mainly speculative. For example interpenetration of hydrocarbon molecules, molar volume changes, the polarity of the C–F bond and differences in ionization potential were mentioned.[35,36] Better correlations with experimental data are sometimes obtained with the more complicated Flory–Huggins Theory or Theory of Reed.[36] All these models predict the miscibility of two liquids. Especially relevant for homogeneous catalysis under fluorous biphasic conditions is the partitioning of perfluorinated ligands and metal complexes across a certain fluorous biphasic or multiphasic solvent system. To avoid leaching of catalyst during product separation, the catalyst should be present in the fluorous phase only. However, no models are available which predict the phase distribution of fluorous components in fluorous biphasic systems. A fundamental understanding of factors which govern this distribution, however, is essential for further development of fluorous phase separation and immobilization techniques in catalysis and synthesis.

Also, the role of micelle formation in fluorous biphasic catalysis needs to be considered. For aqueous biphasic systems, the role of micelle formation by, *e.g.* water soluble, surface-active phosphines [P{$C_6H_4(CH_2)_m$-4-$C_6H_4SO_3Na$-4}$_3$] has been proved.[37] It was found that both reaction rate and selectivity of oct-1-ene hydroformylation are improved by micelle formation, probably due to the larger contact surface between the two phases, resulting in less diffusion limitation. Furthermore, it has been reported that addition of amphiphiles to an aqueous chiral rhodium hydrogenation catalyst results in an increase of both the activity and enantioselectivity of the catalyst.[38] The amphiphile, which forms micelles in water, probably increases the solubility of the substrate in water, which increases the activity of the catalyst. It is also known that fluorous surfactants, *i.e.* molecules containing a fluorous part and a hydrophilic part, can form micelles in water above a certain concentration (the critical micelle concentration, cmc).[39] However, no studies dealing with micelle formation and the effect on activity and selectivity in reactions carried out under fluorous multiphasic conditions have appeared.

5 Conclusions and perspectives

Since the first report by Horváth *et al.* in 1994 on the application of fluorous multiphasic separation techniques in catalysis, a number of catalysts have been made fluorous phase compatible by the introduction of perfluoro functions. In cases where comparison has taken place, the activities and selectivities of those catalysts do not differ very much from the non-fluorous analogues. However, often comparisons with non-fluorous systems have not been made, making it difficult to evaluate the effect of the perfluoroalkyl tails and the fluorous biphasic solvent system on the catalyst. Under fluorous biphasic conditions the activity of the fluorous catalyst can be lower compared to both fluorous and non-fluorous single phase conditions as a result of mass transport limitations. Also other important questions remain to be clarified.

For instance the influence of size, structure and number of perfluoro tails attached to a catalyst or other fluorous component will undoubtedly have a significant influence on the phase distribution of these species in fluorous multiphasic systems. However, data on phase distribution of fluorous compounds and the amount of catalyst leaching due to non-zero solubility in the non-fluorous phase are extremely scarce. Also the knowledge of factors which determine the absolute solubility of fluorinated species in perfluorinated solvents is limited. This is a serious handicap in evaluating the possibilities for practical application of fluorous phase separation techniques relative to, *e.g.* aqueous biphasic techniques for catalyst recycling and will have to be addressed in future studies. The distribution is also important from an economic point of view. A fluorous catalyst will be more expensive than a non-fluorous catalyst. However, if the catalyst can be fully recovered it will be cheaper in the long term.

Also, only a limited amount of synthetic methods for connection of perfluoro functions to catalysts have been reported, although a multitude of synthetic routes for perfluoro functionalization is available in the literature. Thus far the types of perfluoro functions employed are mainly limited to perfluoroalkyl groups (with or without a $-CH_2CH_2$- spacer) and there is clearly a need for introduction of other perfluorinated moieties with more diverse structures.

Finally, examples of fluorous phase catalysis now include catalytic hydroformylation, hydroboration, C–C coupling and oxidation but many more fluorous multiphasic catalytic processes could be envisioned. Especially in the area of asymmetric catalysis fluorous phase extraction techniques could have potential for the recycling of the often expensive chiral ligands and/or catalysts. These techniques will undoubtedly be developed in the near future.

It will be clear that the full potential of fluorous separation and immobilization techniques can only be evaluated completely when further information regarding the above aspects has been obtained.

6 Acknowledgements

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