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Review

Fluorous phase transfer catalysts: From onium salts to crown ethers

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ABSTRACT

Fluorous quaternary ammonium and phosphonium salts, as well as fluorous macrocyclic ligands, such as crown and aza-crown ethers, have been gradually emerging as viable alternatives to classical phase transfer catalysts. The major results thus far obtained in this burgeoning field will be the focus of this review.

Contents

1. Introduction

Phase transfer catalysis (PTC) was first introduced in the 1960s, as a tool to efficiently perform reactions between water soluble inorganic reagents and organic substrates, dissolved in mutually immiscible liquid phases [1–3]. Since that period, PTC has received widespread attention, and it still has attracted considerable scientific and practical interest. Moreover, the term PTC encompasses several different techniques characterized by operational simplicity, mild conditions, high reaction rates, high selectivity, and the utilization of inexpensive reagents. These techniques have been widely applied in industry for the synthesis of pharmaceuticals, perfumes, flavorants, dyes, agricultural chemicals, monomers, polymers, and for many other applications [4,5].

PTC processes still have great potential for waste reduction and catalyst reuse. Indeed, removal of traditional phase transfer (PT) catalysts from the reaction mixture can be achieved by solvent extraction, distillation, adsorption, or simply by washing the organic phase with copious amounts of water. In most cases, such PT catalysts have not been recovered from the effluents, or, once recovered, they have not been pure enough, and have been disposed of as waste, thus increasing the process costs and reducing the otherwise remarkable environmental benefits of the PTC approach. Heterogeneous PT catalysts, bound to either an insoluble polymer or an insoluble inorganic support, have been developed in order to overcome these problems [6]. They can be

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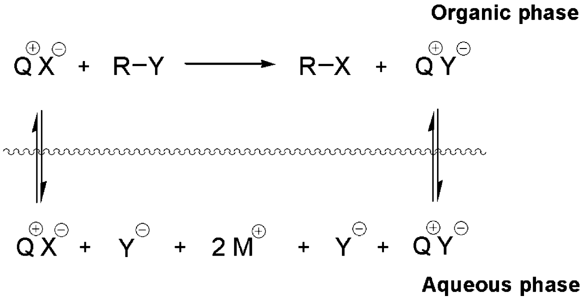
easily separated from reaction products by simple filtration and then reused; but unfortunately, their broad application has been limited by the fact that most PTC reactions are much slower with insoluble catalysts due to mass transfer limitations. More importantly, most solid-bound catalysts have not been found to be mechanically robust enough to survive repeated reaction/separation cycles. As an alternative, immobilization of PT catalysts on soluble polymers, such as poly(ethylene glycol)s (PEGs), has been proposed [7]. Reactions can be performed under standard PTC conditions, after which, selective precipitation of the supported catalyst was induced by thorough dilution of the organic phase with an additional solvent, showing little affinity for the polymer matrix (e.g. Et_2O in the case of PEGs). This method showed some limitations as well, in particular, large amounts of extra solvent have been required in the precipitation step, and also for the efficient washing of the crude precipitate.

In this review, the recent advances on the ease of recovering and recycling PT fluorous catalysts will be discussed. Potential advantages associated with the use of an additional fluorous liquid phase in PTC will also be a focus of this review.

2. Basic PTC concepts

Although the mechanisms and a manifold of applications for PTC were illustrated in detail in several comprehensive books [4,5,8,9] and reviews [10–18], some important key issues are worth further discussions. Many organic reactions entail anionic reactivity, which, especially on the laboratory scale, were enhanced by using dipolar aprotic solvents, such as hexamethylphosphoramide, dimethylsulphoxide, or dimethylformamide. These solvents have been found to be excellent for most organic substrates and, at the same time, they are able to dissolve inorganic salts by selectively solvating the cation, while the unsolvated anion becomes highly reactive [19]. However, dipolar aprotic solvents can be highly toxic and generally exhibit high boiling points and water solubility, making their recovery and the separation of products rather difficult. In PTC, anionic activation was achieved by decreasing the coulombic interaction with the cation, but also through solubilization of the reactive ionic couple in a low polar environment, usually a solution of the organic substrate in a halogenated or hydrocarbon solvent, or the neat liquid substrate itself. The PT catalyst fulfills both functions by forming organophilic ion-pairs, Q^+X^-, in which Q^+ was either a bulky organic cation (e.g. tetraalkylammonium or tetraalkylphosphonium), or the positively charged alkali metal complex of a neutral ligand (e.g. crown ether, PEG), while X^- was the reactive anion. The large size accounts for the low charge density on the surface of the cations: accordingly, interactions with the anion were strongly reduced. The extent of anion extraction into the organic phase, and its reactivity, has depended on a combination of many parameters, including the nature of the anion; for example, charge, size, polarizability, etc. Moreover, the concentration of the inorganic salt in the aqueous phase, the dielectric constant of the organic solvent, the separation between cation and anion in the ion-pair, and the number of water molecules associated with the anion in the organic phase, were also found to be important parameters.

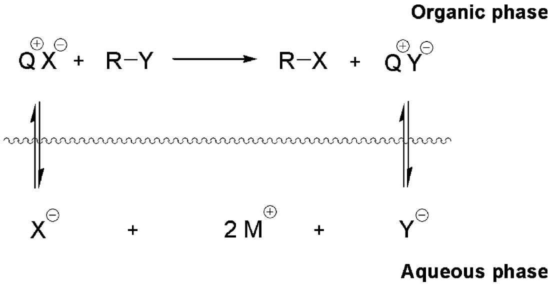
In typical PTC reactions, anions were introduced in a multiphase system under the form of inorganic salts, or they could be generated from an organic precursor possessing an acidic X–H bond under the action of a base. The first general PTC mechanism (Scheme 1) was proposed by Starks, who studied a representative liquid–liquid, aqueous–organic PTC process; namely, the reaction of 1-chlorooctane (RY) and aqueous NaCN (MX) in the presence of $(C_6H_{13})_4N^+Cl^-$ (Q^+Y^-). [3] It was assumed that the PT catalyst, Q^+Y^-, partitioned between the two immiscible liquid phases, should first react in the aqueous phase with CN^- to provide the active species, $(C_6H_{13})_4N^+CN^-$ (Q^+X^-). In this manner, the reacting anion, CN^-, was transferred from the aqueous to the organic phase, where the reaction occurred, and the catalyst was regenerated. The product anion, Cl^-, was then released into the aqueous phase (Scheme 1).



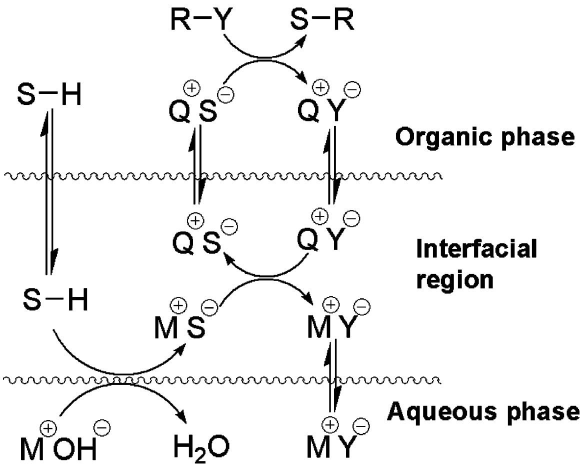
Scheme 1.

It is important to note that this was not the exclusive pathway through which PTC reactions could proceed. Indeed, depending on the nature of the catalyst, the multiphase system employed, and the reaction under investigation, other mechanisms must be taken into account. As an example, Montanari and coworkers demonstrated that under a given set of reaction conditions, the catalytic efficiency of a quaternary onium salt in liquid–liquid PTC increased with its solubility in the organic phase [20]. Based on this observation, and on the independent work of Brändström [21], a revision of the original Starks mechanism was proposed (Scheme 2). Accordingly, the anion transfer does not necessarily require the partitioning of the quaternary cation, while the electroneutrality in the organic and aqueous phase was ensured by the quaternary and the metal cations, respectively [22]. In this case, the anion exchange between the catalyst, Q^+Y^-, and the source of reacting anion, M^+X^-, occurred at the interface, and the following reaction between Q^+X^- and the substrate RY occurred in the bulk organic phase. This modified PTC mechanism can also be applied when lipophilic cyclic and acyclic polyethers were used as catalysts under liquid–liquid PTC conditions.

An interfacial reaction mechanism proposed by Mąkosza was also generally thought possible for liquid–liquid PTC reactions, where aqueous solutions of alkali hydroxides, M^+OH^-, were used to generate the reactive organic anions from weakly acidic substrates, SH (Scheme 3) [23]. As confirmed by extraction experiments, the transfer of OH^- into the organic phase by lipophilic onium salts was hampered by the exceedingly high hydrophilicity of the anion. Alternatively, abstraction of a proton at the aqueous–organic interface was possible, but the resulting ion-pair, M^+S^-, was unable to leave the phase boundary, since M^+ cannot be extracted into nonpolar organic solvents, while solubility of S^- in the concentrated M^+OH^- solution was negligible. The ion exchange with a PT catalyst allowed the formation of a



Scheme 2.



Scheme 3.

lipophilic ion-pair, Q^+S^-, which migrated from the interface to the bulk organic phase, where the anion readily reacted with the electrophilic counterpart, RX.

Detailed mechanistic investigations on several liquid–liquid PTC reactions have demonstrated that the Starks extraction mechanism and the Mąkosza interfacial mechanism could be considered as the two ends of a broad spectrum of possible pathways, and that many liquid–liquid PTC reactions were conducted both at the interface and in the bulk solution [15].

Although most PTC reactions were performed under liquid–liquid (aqueous–organic) conditions, other options were available, which avoid some drawbacks and offer specific advantages. Under classical aqueous–organic PTC, a small amount of water was extracted into the apolar organic phase, mainly as the specific solvation sphere of the anion, thus engendering a reduction of the anionic reactivity. Moreover, the presence of water may lead to undesired side reactions, which reduced the efficiency of the main process and complicated the isolation of the products. In such cases, it was then convenient to use, as the anion source, a solid salt that was suspended in an anhydrous organic solution containing the substrate and the PT catalyst. The latter transfers the anion, as a reactive ion-pair, from the surface of the solid into the organic phase.

As in the case of liquid–liquid PTC, the manifold of mechanistic issues of solid–liquid PTC, such as the way anions could actually be transported from the solid to the organic phase, the nature of the reactive ion-pairs formed by different PT catalysts, the mechanism of exchange of product anions located in the organic phase with reactant anions that are part of the solid phase, and the effects of the particle size on the rate of reaction, have been addressed in the literature [24]. In this review, we also wish to stress the crucial role played by the addition of traces of water in enhancing the rate of several reactions run under solid–liquid PTC conditions. When a slight amount of water was introduced in the system, a thin aqueous layer that coated the surface of the solid reagent was formed, thus allowing the dissolution of the salt and its efficient contact with the PT catalyst [25]. This third liquid phase, interposed between the solid surface and the liquid organic phase, was sometimes referred to as the "omega phase" [24].

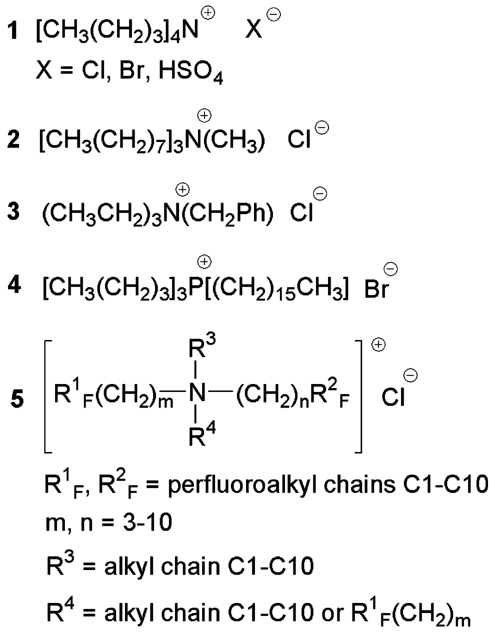
Furthermore, lipophilic crown ethers able to form complexes with metal cations, in particular with Na^+ and K^+, were initially used as catalysts in solid–liquid PTC, because of their efficient interaction with the surface of solid inorganic salts that promote the collapse of the crystal lattice [26]. Subsequently, it was found that acyclic polyethers and quaternary onium salts could work as efficiently as crown ethers in most solid–liquid PTC applications, but crown ethers, which show higher chemical stability in comparison to onium salts, remain the catalysts of choice when forcing reaction conditions were required.

Gas–liquid PTC represents another valid alternative to the liquid–liquid approach [27]. Despite its usual designation, this technique actually involves the use of gas–liquid–solid multiphase conditions, where a continuous flow of vaporized organic reagent passes through a fixed bed of a thermally stable PT catalyst adsorbed onto a solid matrix, which could also act as a source of the desired nucleophile, at a temperature that maintains the catalyst in a molten state. The chemical transformation occurred in the organic microphase of the molten catalyst, and the products were recovered after condensation outside the reactor.

Both solid–liquid and gas–liquid PTC intrinsically generated far less wastewater than liquid–liquid PTC, and usually led to the formation of solid inorganic by-products, which could be easily removed from the organic phase. Moreover, gas–liquid PTC proceeds under solventless conditions, with obvious economic and environmental advantages. The same truth holds for many solid–liquid PTC reactions, where the organic substrates and products were in the liquid state. As far as the recovery of the catalyst was concerned, gas–liquid PTC conditions were particularly appealing. However, the long-term stability of the catalyst remains an issue in view of the forcing temperature conditions required.

3. Quaternary fluorous onium salts

A variety of quaternary ammonium ($R_4N^+Y^-$) and phosphonium ($R_4P^+Y^-$) salts showing diverse hydrophilic/lipophilic character, chemical and thermal stability, and anion activating properties, have been reported as useful PT catalysts. Indeed, the four R groups, which were neither necessarily identical, nor simple alkyl substituents, and the counteranion, Y^-, could be tailored in order to maximize the catalytic efficiency of the onium salt in the reaction of interest. Nevertheless, a few easily accessible compounds, such as tetrabutylammonium halides and hydrogenosulphate, **1**, trioctylmethylammonium chloride, **2**, benzyltriethylammonium chloride, **3**, and hexadecyltributylphosphonium bromide, **4**, were commonly employed, with good results in a broad range of reactions. The synthesis of quaternary ammonium salts of the general formula **5** (Chart 1), which could be thought of as the



1 $[CH_3(CH_2)_3]_4\overset{\oplus}{N}\ \ X^{\ominus}$

$X = Cl, Br, HSO_4$

2 $[CH_3(CH_2)_7]_3\overset{\oplus}{N}(CH_3)\ \ Cl^{\ominus}$

3 $(CH_3CH_2)_3\overset{\oplus}{N}(CH_2Ph)\ \ Cl^{\ominus}$

4 $[CH_3(CH_2)_3]_3\overset{\oplus}{P}[(CH_2)_{15}CH_3]\ \ Br^{\ominus}$

5 $\left[R^1{}_F(CH_2)_m-\underset{R^4}{\overset{R^3}{N}}-(CH_2)_nR^2{}_F\right]^{\oplus} Cl^{\ominus}$

$R^1{}_F, R^2{}_F$ = perfluoroalkyl chains C1-C10

m, n = 3-10

R^3 = alkyl chain C1-C10

R^4 = alkyl chain C1-C10 or $R^1{}_F(CH_2)_m$

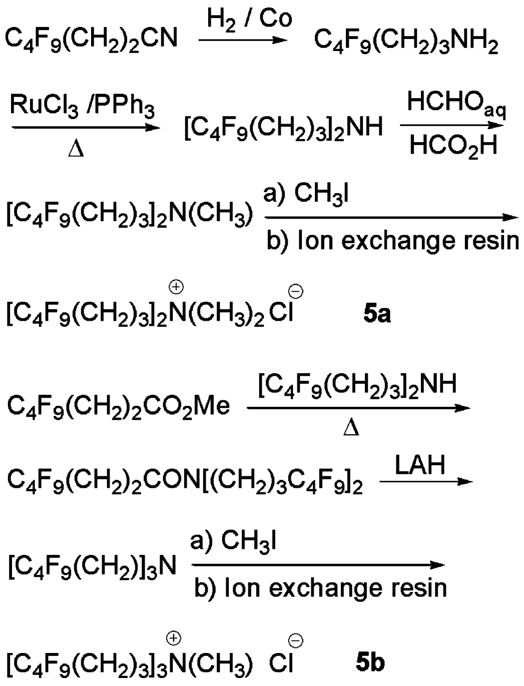
Chart 1.

fluorous analogues of the multipurpose PT catalysts, **1** and **2**, were described in a patent, where the usefulness of these compounds as PTC was also discussed, without being supported by pertinent experimental data [28].

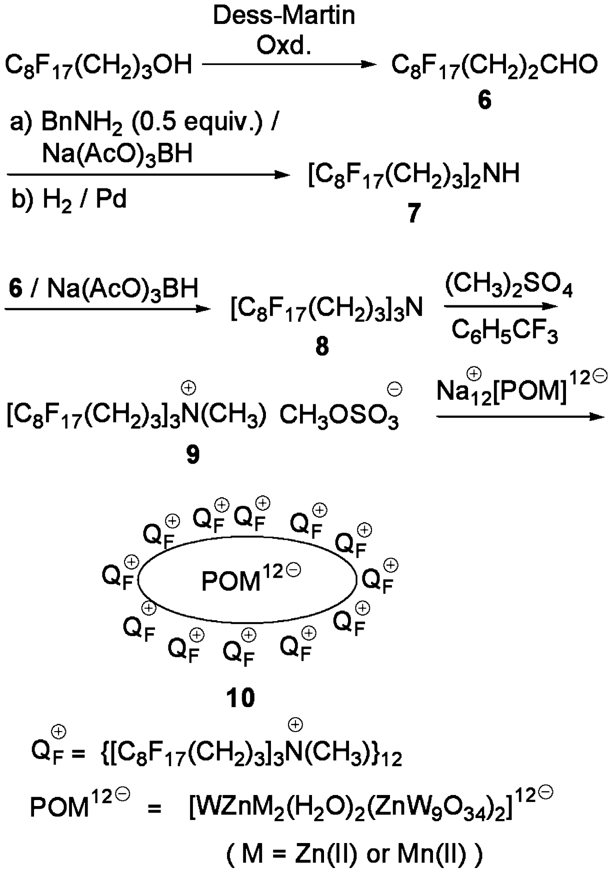
Various synthetic methods were used to generate the onium salts, **5**, including the hydrogenation of a perfluoroalkylated nitrile, $R_F(CH_2)_{n-1}CN$, to the corresponding primary amine, $R_F(CH_2)_nNH_2$, followed by the Ru-catalyzed disproportionation to $[R_F(CH_2)_n]_2NH$, and exhaustive alkylation with $HCHO/HCO_2H$ and/or RX, and then finally anion exchange, if required. Ammonium salts bearing three perfluoalkyl chains were prepared by reacting secondary amines $[R_F(CH_2)_n]_2NH$ with either $R_F(CH_2)_mCOCl$ or $R_F(CH_2)_mCO_2R$ to provide the corresponding tertiary amides, $R_F(CH_2)_mCON[CH_2)_nR_F]_2$, that were reduced to tertiary amines, and then finally alkylated with RX. These two methods are shown in Scheme 4.

A restricted number of structurally simple fluorous ammonium salts were actually used in fluorous catalysis, though not as PT agents [29,30]. Oxidation reactions of alkenes, alkenols and alcohols with H_2O_2 were carried out using the "sandwich"-type polyoxometalate catalyst **10**, which was prepared by mixing one equivalent of the corresponding sodium salt with 12 equivalents of quaternary ammonium salt, **9** (Scheme 5) [29,31]. The introduction of the fluorinated counter cations remarkably affected the solubility properties of **10**. Despite the polyanionic character of its polyoxometalate moiety, and the relatively low 51.5% fluorine content by weight, **10** was found to be freely soluble in perfluorocarbons at room temperature, and it was thus utilized as a recyclable catalyst under fluorous multiphasic conditions. In addition, **10** displays a temperature-dependent solubility profile in common organic solvents, such as ethyl acetate and toluene, where it was insoluble at room temperature, but dissolved upon heating to 60–80 °C. Based on this type of behavior, an alternative reaction protocol without fluorous solvent was also tested, and the recovery and recycling of **10**, by simple precipitation from the organic phase upon cooling, was demonstrated.

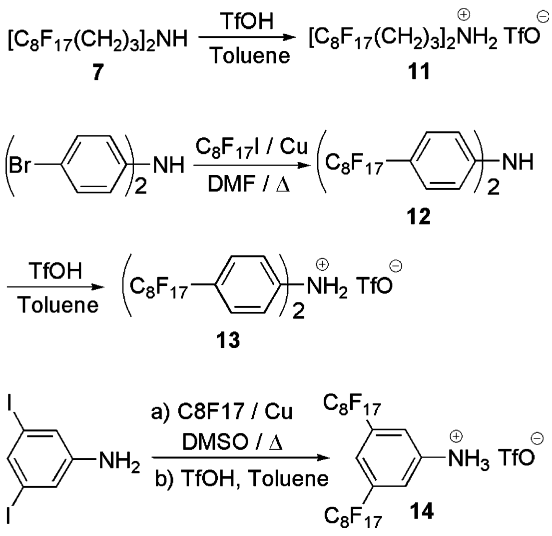
The use of fluorous ammonium triflates, **11**, **13**, and **14** (Scheme 6), as metal-free catalysts for the direct condensation of equimolar amounts of carboxylic acids and aliphatic alcohols was investigated by Mercs et al. [30]. Esterification reactions were conveniently carried out under mild fluorous biphasic conditions, in the presence of 1 mol% of a fluorous catalyst, without recourse to any additional water removal technique. The best results were obtained with the fluorous anilinium salt, **14**, which afforded good to excellent ester yields with a variety of primary and secondary aliphatic alcohols. The fluorous salt was easily recovered by simple phase separation, and reused at least three times without considerable loss of activity.



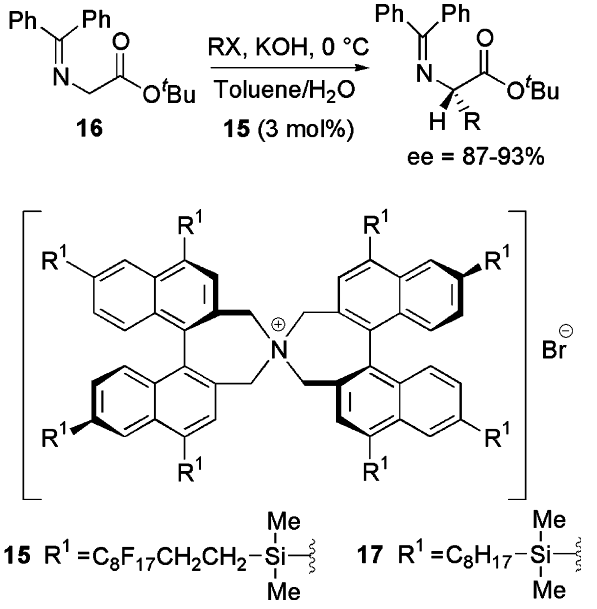
Scheme 4.



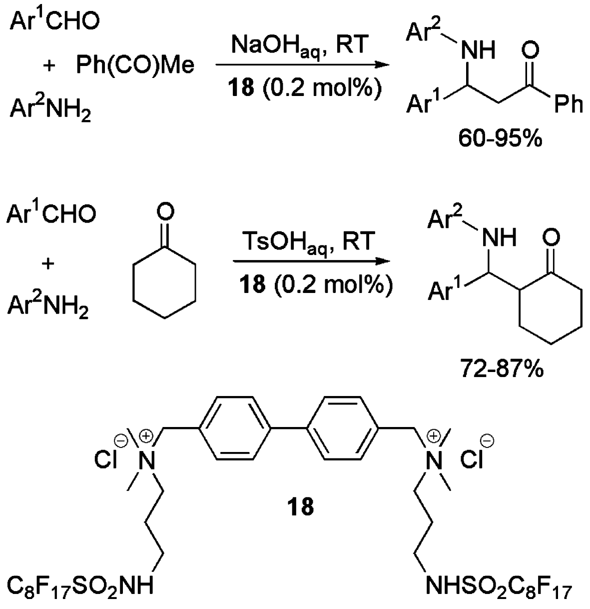
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

Quite amazingly, in light of the preceding discussion, the first example of a recyclable fluorous PT catalyst did not entail a simple onium salt, but the C_2-symmetric quaternary ammonium bromide, **15**, developed by Maruoka and co-workers (Scheme 7) [32]. This synthetically demanding, enantiopure compound was a member of a series of highly lipophilic, *N*-spiro PT catalysts, which were successfully applied to the asymmetric synthesis of both natural and unnatural α-amino acids through enantioselective liquid–liquid PTC alkylation of the protected glycine derivative, **16** [33]. Reactions were conducted at 0 °C in a 50% aqueous KOH/toluene biphasic system, in the presence of 1 mol% of a PT catalyst. Under these conditions, the fluorous compound, **15**, formed a third solid phase and it was thus added in a larger amount (3 mol%). Despite the heterogeneous nature of the catalytic system, the alkylation of **16** with benzyl bromide derivatives or propargyl bromide gave the corresponding products with high yields (81–93%) and enantioselectivity (ee = 90–93%), in 70–140 h. The chiral fluorous catalyst was then easily separated from the organic products by extraction of the reaction mixture with perfluorohexane, and it could be reused at least two times more without any loss of activity and selectivity.

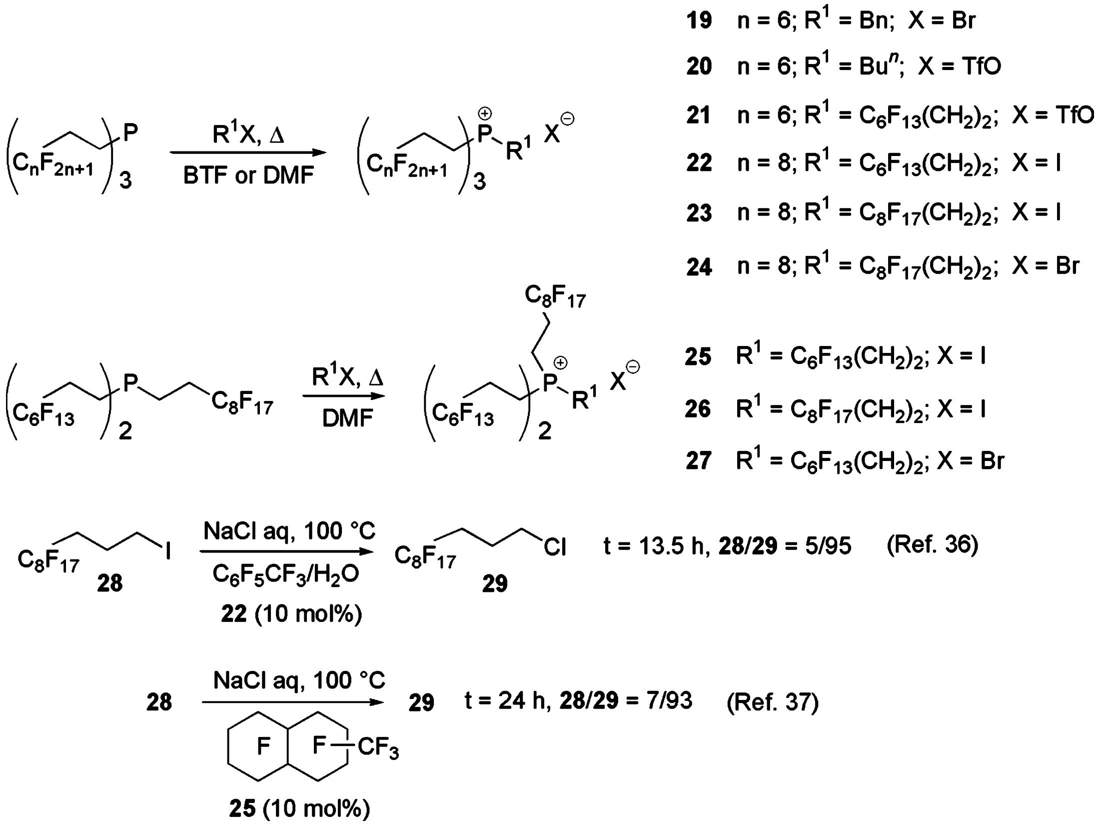
It must be stressed that the most non-fluorous analogues of **15** (e.g. compound **17**, Scheme 7) provided faster reactions, and afforded the alkylated products in slightly better yields and ee values. While the relatively reduced enantioselectivity was found to be directly linked to the influence of the fluoroponytails on the stereoelectronic properties of **15**, its lower catalytic activity might be largely dependent on its poor solubility in toluene, as shown by the results obtained in the alkylation of **16** with EtI catalyzed by **15**, in the presence of $CsOH{\cdot}H_2O$ as a base, and $C_6H_5CF_3$ (BTF) as the solvent. The reaction proceeded in 10 h, affording the product in 83% yield and 87% ee, and could be compared with a 87% yield and 98% ee obtained with catalyst **17** in toluene, during the same reaction time.

As discussed in Section 2, liquid–liquid PTC typically involved the extraction of anionic reactive species from the aqueous phase (or the interfacial region) to the organic solution. However, inverse PTC based on the transport of lipophilic reactants into the aqueous phase by means of suitable amphiphilic PT agents was also possible [34]. One-pot Mannich reactions in water promoted by the bis-perfluoroalkylated ammonium surfactant, **18**, were recently reported (Scheme 8) [35]. Sodium *p*-dodecylbenzenesulphonate (SDBS), a surfactant, which has no PTC activity, was much less effective than **18** and, at the same time, the poor surfactant and good PT catalyst **3** (Chart 1) performed better than SDBS, but worse than **18**. On this basis, it was suggested that the latter could serve as an efficient emulsifying agent, and also as a PT catalyst. Although this mechanistic assumption needs to be confirmed by specific investigations, the experimental approach was quite attractive, since the absence of an organic solvent and the organophobic character of the catalyst allowed a straightforward recovery of the solid products by filtration, while the aqueous phase containing **18** could be reused directly in a new catalytic cycle.

Quaternary phosphonium salts are typically more expensive, and therefore, less utilized as PT catalysts, than the corresponding ammonium salts, but they have the advantage of being more stable at reaction temperatures between 100 and 150 °C, under non-alkaline conditions. Alternatively, tetraalkylphosphonium salts in the presence of strong bases (e.g. NaOH) undergo decomposition at low to moderate temperatures, and were found to be less stable than the ammonium salts.

The potential of fluorous phosphonium salts for PTC was first demonstrated by Stuart and co-workers, who synthesized a series of symmetrically and unsymmetrically substituted phosphonium salts (**19**–**27**), by quaternarization of tertiary fluorous phosphines with primary fluorous and non-fluorous alkylating agents (Scheme 9) [36].

Representative fluorous phosphonium salts were found to be sparingly soluble (**21** and **25**) or even insoluble (**23** and **24**) in perfluoromethylcyclohexane at 20 °C, but complete solubility could be obtained at about 70 °C. Alternatively, octafluorotoluene, $C_6F_5CF_3$, a liquid which was classified as non-fluorous, because of its significant interactions with organic molecules, freely dissolved **21**, **23**, **24**, and **25** at room temperature. More importantly, partition coefficients of these four salts between perfluoro(1,3-dimethylcyclohexane) (PFDMC) or perfluorooctyl bromide, and organic solvents such toluene or CH_2Cl_2, were very biased towards the fluorous phase, with >93% of the salt in the latter. The ability of fluorous phosphonium salts, **19**–**24**, to transfer the highly colored and lipophilic picrate anion from an aqueous phase into BTF or $C_6F_5CF_3$, was also verified. Finally, a solution of the fluorous aliphatic iodide, **28** (Scheme 9), in octafluorotoluene was stirred



Scheme 9.

with an aqueous solution of NaCl at 100 °C. The halide exchange (Finkelstein reaction) between **28** and NaCl did not proceed in the absence of a PT catalyst, while upon addition of **22** (10 mol%), disappearance of **28** and formation of the fluorous aliphatic chloride, **29**, was observed by ^{1}H NMR.

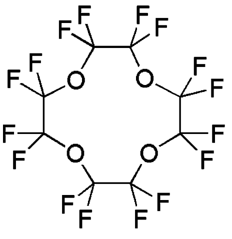
The same Finkelstein reaction catalyzed by 10 mol% of phosphonium salts, **23**, **25**, or **27**, in perfluoromethylcyclohexane or perfluoromethyldecalin, was also reported, as well as, similar halide exchange reactions between fluorous substrates, $C_8F_{17}(CH_2)_nX$, **28**, **30** ($n = 2$ X = I), **31** ($n = 2$, X = Br), and aqueous KI, NaCl, or NaBr, thus showing the feasibility of liquid–liquid PTC processes involving the delivery of inorganic anions stored in an aqueous phase to an extremely nonpolar perfluorocarbon phase, where the fluorous substrate was confined [37]. The recycling of the fluorous phosphonium salt, **25**, was also investigated. Selective precipitation of the catalyst in its resting state, containing the halide ion used as a reagent, was obtained by the addition of hexane to the fluorous phase. The precipitate was washed with hexane and water and reused; after five reaction cycles, 38% of the original catalyst was recovered, while the remaining amount of catalyst loss was due to incomplete precipitation.

Besides **19**–**27**, other fluorous phosphonium salts have been described in the literature and used as catalysts for the cycloaddition of carbon dioxide to propylene oxide under supercritical CO_2 conditions [38], as intermediates in the synthesis of fluorous phosphine ligands [39,40], or investigated as potentially useful ionic liquids [41]. The assessment of their PTC and recycling properties would also deserve consideration.

4. Fluorous crown ethers

As anticipated in Section 2, macrocyclic polyethers such as crown- and aza-crown ethers have important applications in PTC reactions [42], which stem from their ability to form specific complexes with metal cations, M^+, and the consequent activation and transfer of anions from a solid, or less frequently aqueous phase, to a nonpolar, or relatively polar, organic phase. Lipophilic macrocyclic ligands that complex Na^+ and K^+ ions are particularly attractive, since salts of these cations are the most frequently encountered in PTC. It was well known that the relative M^+/binding cavity size plays a large role in determining the thermodynamic stability of the resulting complex, and thus the effective extraction of the MX salt into the organic phase. However, many other factors determine the efficiency of crown ethers and related compounds in PTC, and the exact correspondence between cavity size and ionic diameter has not always been shown to be a critical factor. As an example, salts of hard anions, such as F^- or SO_4^{2-}, have been shown not to be easily transferred into nonpolar medium by crown ethers, while salts of soft anions, such as I^- or SCN^- are easily transferred. Stereoelectronic effects associated with the introduction of substituents in the structure of the macrocyclic ligand should also be significant, especially in connection with the development of fluorous crown ethers and related compounds.

Perfluorinated analogues of 12-crown-4, 15-crown-5 and 18-crown-6 ethers (**32**–**34**, Chart 2) were made available by Lagow and co-workers well before the birth of the fluorous chemistry concept [43]. These and several other perfluorinated macrocyclic polyethers, prepared by direct fluorination of the known organic counterparts under controlled conditions [44], were soluble in chlorofluoro solvents such as $CFCl_2CF_2Cl$ and insoluble in common organic solvents [45]. The Lewis basicity of their oxygen sites was reduced to a significant extent, as a result of the strong electron-withdrawing nature of the $-CF_2-$ units, and they do not form stable complexes with metal cations. However, they do coordinate anions, such as O_2^- and F^-, in the gas phase [46]. Synthetic routes circumventing the direct fluorination step were developed by



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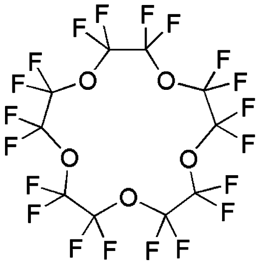

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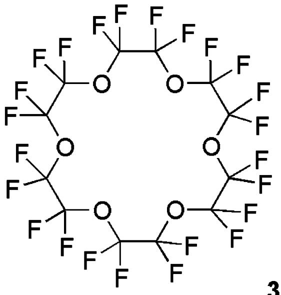

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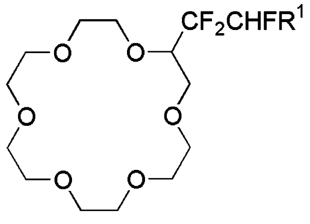
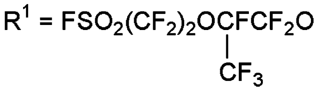
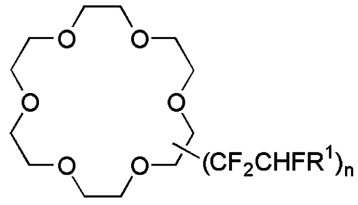


35 $R^1 = C_6F_5CF_2$

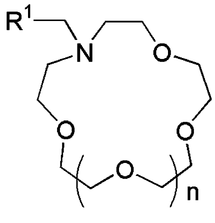


36 $R^1 = FSO_2(CF_2)_2OCF(CF_3)CF_2O$



37 n = 3; $R^1 = CF_3$

38 n = 2; $R^1 = C_6F_5CF_2$



39 n = 0; $R^1 = C_7F_{15}CH_2OCH_2$

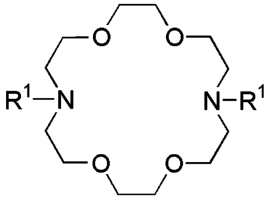
40 n = 1; $R^1 = C_7F_{15}CH_2OCH_2$

41 n = 2; $R^1 = C_7F_{15}CH_2OCH_2$

42 n = 1; $R^1 = C_7F_{15}$

43 n = 1; $R^1 = C_6F_{13}CH_2$

44 n = 1; $R^1 = C_{10}F_{21}(CH_2)_2OCH_2$



45 $R^1 = C_7F_{15}CH_2$

46 $R^1 = C_8F_{17}CH_2CH_2$

47 $R^1 = C_7F_{15}CH_2OCH_2CH_2$

48 $R^1 = C_{10}F_{21}(CH_2)OCH_2CH_2$

49 $R^1 = C_8F_{17}CH_2CH_2CH_2$

50 $R^1 = C_{10}F_{21}CH_2CH_2CH_2$

51 $R^1 = H$

52 $R^1 = C_8H_{17}$

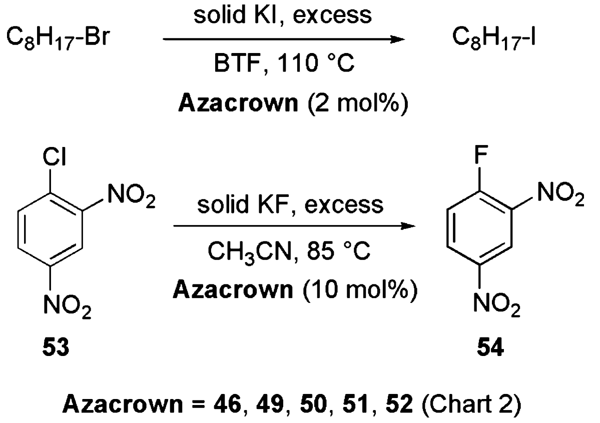
Chart 2.

researchers at DuPont, who obtained poly- and perfluorinated polyethers with oxygen atoms directly linked to $–CF_2–$ units, which were still devoid of any complexation ability towards metal cations [47,48].

Free radical addition of perfluoroalkenes to 18-crown-6 afforded macrocyclic ligands with a variable number of polyfluorinated substituents (e.g. **35**–**38**, Chart 2) depending on the ratio perfluoroalkene/crown [49]. The oxygen atoms in these compounds were somewhat shielded from the electron-withdrawing effect of the polyfluorinated chains, indeed, the mono-substituted crown ethers **35** and **36** were able to form 1/1 complexes with $La(OTf)_3$. This result clearly expanded the scope of highly fluorinated crown ethers in coordination chemistry, but the chosen synthetic pathway made it impossible to control the position where the polyfluorinated substituents were introduced, as shown by the fact that compounds bearing multiple side chains (e.g. **37** and **38**) were obtained as mixtures of isomers.

In order to obtain macrocyclic ligands, which possessed good solubility in perfluorocarbons, while retaining strong metal ion complexation ability, Pozzi and co-workers in Milan, and Fish and co-workers in Berkeley, independently reported on the *N*-alkylation of commercially available polyazamacrocycles with fluoroponytailed alkyl iodides or tosylates in the presence of mild inorganic bases [50,51]. This strategy allowed the introduction of fluoroponytails at specific sites without forming mixtures of isomers, and the ligands thus obtained were found to easily form stable transition metal complexes that were used as catalysts for fluorous biphasic oxidation reactions. Following a similar reasoning, Bartsch and co-workers prepared a set of *N*-substituted mono- and diazacrown ethers with $–(CH_2)_nO(CH_2)_m–$ or $–(CH_2)_n–$ spacer units that separated the nitrogen atoms from the perfluoroalkyl substituents (e.g. **39**–**48**, Chart 2) [52]. The complexation properties of several of these macrocyclic ligands towards alkali metal cations were evaluated by studying the extraction of the corresponding picrate salts from aqueous solutions into chloroform. For each macrocycle, the best extracted alkali metal cation was that which would have been predicted based on the match between the cavity and the cation size; therefore, compound **39**, with a reduced ring size, exhibited selectivity for Li^+, **40** for Na^+, and **41** for K^+, as was similarly found with their non-fluorinated analogues. More interestingly, it was demonstrated that the nature and length of the spacers strongly influenced the efficiency of the extraction process, as evidenced by the results obtained with the aza-15-crown-5 derivatives, **42** ($–CH_2–$ spacer), **43** ($–(CH_2)_2–$), **40** ($–CH_2OCH_2–$), and **44** ($–CH_2O(CH_2)_2–$), which were able to transfer into chloroform 11%, 38%, 49%, and 57% of the sodium picrate originally dissolved in water, respectively.

These investigations paved the way for the use of perfluoroalkylated 4,13-diaza-18-crown-6 ethers as PT catalysts recently disclosed by Stuart and Vidal [53]. Compounds **49** and **50** (Chart 2) were obtained in 52% and 60% yields, respectively, by refluxing 4,13-diaza-18-crown-6 ether **51** in CH_3CN or EtOAc with the appropriate fluorous alkyl iodide in the presence of K_2CO_3 as a base. Potassium picrate extraction studies were performed on these macrocycles, and the results obtained were in agreement with the general conclusion drawn in ref. [52]. In particular, extractions with **49** and **50** featuring longer spacer groups were more efficient than those performed with their analogue, **46**. The



Scheme 10.

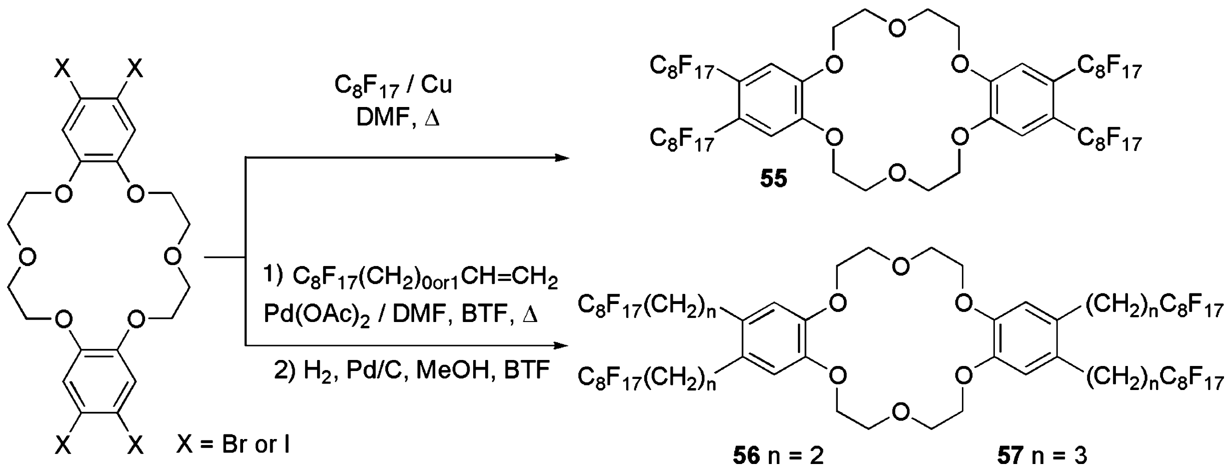
latter was found to extract 11% and 3% of potassium picrate from an aqueous solution into CH_2Cl_2 and BTF, respectively, in contrast to 33% and 22% obtained with macrocycle **49**, bearing the same C_8F_{17} substituents, but with an extra $-CH_2-$ spacer unit. The crucial, but frequently neglected, role of the non-aqueous solvent in this kind of experiments was evidenced by the fact that the extraction of potassium picrate by **46** from water into $CHCl_3$ was much more efficient, with 47% of the salt transferred into the organic phase [52]. Besides halocarbons, other common organic solvents, such as toluene, Et_2O, and EtOAc, were good solvents for the three fluorinated diazacrowns, and their partition coefficients between PFDMC and organic solvents were somewhat biased towards the organic phase, and only in the case of extremely polar, fluorophobic organic solvents like CH_3CN, was there a bias towards the fluorous phase. Due to this behavior, typical of light fluorous compounds, **46**, **49**, and **50**, could only be tested as catalysts under standard PTC conditions. Two substitution reactions were studied; namely, the halide exchange reaction between 1-bromooctane and KI, and the aromatic nucleophilic substitution of the activated chlorobenzene derivative, **53**, with KF (Scheme 10) [53].

In the first model reaction, the three fluorinated azacrowns performed at their best under solid–liquid PTC conditions, while **49** and **50** exhibited higher activities than macrocycle **46**. Compared to their parent compound **51**, and their non-fluorinated *N*,*N*′-bis(*n*-octyl)-4,13-diaza-18-crown-6 ether, **52**, analogue (Chart 2), even **49** and **50** gave slower reaction rates, with maximal conversions and 1-iodooctane yields (>95%) obtained in 5–7 h, in the case of **51** and **52**, while 24 h was required to achieve the same results with **49** and **50**. However, the fluorinated macrocycles could be recovered using fluorous solid-phase extraction, and **49** was reused six times in nucleophilic aliphatic substitution reactions, without any loss of activity. At the end of the recycling experiments, 70% of the original catalyst quantity was recovered.

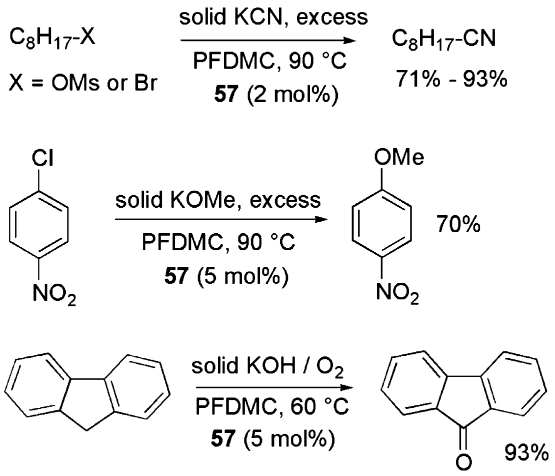
The exchange of chlorine by fluorine on the aromatic substrate **53** was also studied under solid–liquid PTC conditions, but CH_3CN was chosen as the organic solvent instead of BTF. In contrast to the aliphatic nucleophilic substitution reaction, the catalytic activity of the fluorinated macrocycles was completely reversed, with **46** > **49** > **50**. Moreover, both **46** and **50** gave better results than the non-fluorinated ligands, **51** and **52**, providing 2,4-dinitrofluorotoluene, **54**, in 90% and 70% yield, respectively, in 24 h, while the same product was obtained in approximately 50% yield, when **51** or **52** were used as catalysts. The lower activity of diazacrown **50**, compared to **49**, was realistically explained on the basis of its lower solubility in CH_3CN, due to the presence of longer perfluorodecyl groups, but the reasons for the unexpectedly high effectiveness of **46** remained unclear. Once again, excellent recycling results were obtained by fluorous phase extraction in the case of the fluorinated PT catalyst **49**, while the more active catalyst, **46**, was recovered less efficiently, and a severe drop in conversion was observed in the third subsequent run.

We succeeded in preparing fluorous derivatives of dibenzo-18-crown-6 ether by means of metal-catalyzed cross-coupling reactions, as exemplified by the synthetic pathways shown in Scheme 11. [55] In contrast to the above-mentioned polyfluorinated aza-crown ethers, compounds **55**–**57** were found to be almost insoluble in common organic solvents at room temperature, with the exception of CH_2Cl_2 and $CHCl_3$, but totally soluble in perfluorocarbons at temperatures slightly >40 °C, with partial precipitation from their solutions, after standing at room temperature for a few hours. Their partition coefficients between PFDMC and organic solvents, including low polar ones, ranged from >98/2 to 70/30 in the case of **55** (organic solvent = toluene) and **57** (organic solvent = CH_2Cl_2), respectively. We were thus intrigued by the prospect of conducting anion promoted reactions in perfluorocarbons with these fluorous crown ethers, and we proved this concept in the case of the classical Finkelstein reaction, with 1-bromooctane and KI (Scheme 11).

A solution of fluorous crown ether in PFDMC was layered between neat 1-bromooctane and solid KI, thus generating a liquid–liquid–solid triphasic system. It was quickly discovered that PTC activity was possible only for compounds with the two, and the better three methylene spacer, since the powerful electron-withdrawing effect of a C_8F_{17}-group directly bonded to the



Scheme 11.



Scheme 12.

aromatic ring, prevented cation binding to the CE oxygen array. However, iodooctane was obtained in 87% and 96% yields with catalysts **56** (24 h) and **57** (12 h), respectively. Recycle of the liquid fluorous phase containing the crown ethers was a facile process that circumvented the necessity of any post-reaction manipulations, including the use of fluorous solid-phase materials [55].

This approach was successfully applied to other PTC nucleophilic substitution and oxidation reactions, such as the nucleophilic displacement reaction of *n*-octyl methanesulphonate (or *n*-octyl bromide) with solid KCN to provide *n*-octyl cyanide, the challenging nucleophilic aromatic substitution reaction of 4-nitrochlorobenzene with KOMe to give 4-nitroanisole, and the KOH promoted aerobic oxidation of fluorene to fluorenone (Scheme 12) [56].

5. Outlook

Polyfluorinated onium salts and crown ether derivatives with typical light or heavy fluorous characteristics, and yet retaining the ability to transfer reactive anionic species from water or from a solid surface into a second organic or perfluorocarbon phase, have emerged on the fluorous chemistry scene only recently. Therefore, their true potential in PTC reactions has still to be discerned, and the field will be expected to continue to grow in the near future.

The achievement of reactivity and selectivity comparable or even superior to those observed with classical PT agents, without compromising the ease of recovery and the recycling efficiency, has been a primary goal of this research. This will not only demand the broadening of the synthetic options available in order to prepare structurally diverse fluorous PT catalysts, but also the systematic research of optimal reaction conditions and PTC techniques to be employed in association with these particular compounds. Thus far, liquid–liquid and solid–liquid PTC systems have been mainly explored, but fluorous PT catalysts would also offer the opportunity to place alternative approaches into operation, as exemplified by the use of a triphasic system consisting of a fluorous, organic, and an inorganic phase [55]. In analogy to liquid–liquid–liquid PTC systems [54], at the end of the reaction, the immiscible fluorous phase containing the catalyst can be easily recovered and reused without resorting to any specific treatment, such as cumbersome fluorous solvent or solid-phase extraction techniques. Indeed, we have proven this more simplified PTC concept by using tetrafluoroponytailed substituted dibenzo-18-crown-6 derivatives, and the promising results obtained, have been submitted for publication [56]. Another viable option we are currently pursuing can be represented by the use of thermally stable, low melting fluorous polyethers as catalysts in gas–liquid PTC, with the consequences of having environmental and economical advantages that were described in Section 2. Finally, detailed mechanistic and physicochemical studies aimed at a better understanding of the effect of the hydrophobic/organophobic fluorous surroundings on the outcome of PT processes will certainly increase the chances to transform fluorous PTC from a scientific curiosity to a viable synthetic technique.

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