



Syntheses of fluorous quaternary ammonium salts and their application as phase transfer catalysts for halide substitution reactions in extremely nonpolar fluorous solvents

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ABSTRACT

Perfluoromethyldecalin solutions of the fluorous alkyl halides $R_f(\text{CH}_2)_m\text{X}$ ($m=2, 3$; $\text{X}=\text{Cl}, \text{I}$) are inert toward aqueous NaCl, KI, KCN, and NaOAc. However, substitution occurs at 100 °C in the presence of 10 mol % of the fluorous ammonium salts $(R_f(\text{CH}_2)_2)(R_f(\text{CH}_2)_5)_3\text{N}^+\text{I}^-$ (**1**) or $(R_f(\text{CH}_2)_3)_4\text{N}^+\text{Br}^-$ (**2**) (10 mol %), which are fully or partially soluble in perfluoromethyldecalin under these conditions. Stoichiometric reactions of (a) **1** and $R_f(\text{CH}_2)_3\text{Br}$, and (b) **2** and $R_f(\text{CH}_2)_2\text{I}$ are conducted in perfluoromethyldecalin at 100 °C, and yield the same $R_f(\text{CH}_2)_m\text{I}/R_f(\text{CH}_2)_m\text{Br}$ equilibrium ratio (60–65:40–35). This shows that ionic displacements can take place in extremely nonpolar fluorous phases, and suggests a classical phase transfer mechanism for the catalyzed reactions. Interestingly, the non-fluorous ammonium salt mixture $\text{CH}_3(\text{CH}_2)_m)_3\text{N}^+\text{Cl}^-$ (**3**, Aliquat® 336; $m=2:1$ 7/9) also catalyzes halide substitutions, but under triphasic conditions with **3** suspended between the lower fluorous and upper aqueous layers. NMR experiments establish very low solubilities in both phases, suggesting interfacial catalysis.

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1. Introduction

Fluorous liquid phases such as perfluoroalkanes are, by a variety of measures, the least polar known.^{1,2} They are rivaled only by the noble gases, which are liquid over much narrower temperature ranges. Hence, it is not surprising that common inorganic salts and other ionic compounds are insoluble in such media. However, there is a growing recognition that some fluorous salts can dissolve in fluorous liquids, either at room temperature or upon heating, which often dramatically enhances the solubilities of fluorous solutes.³ Some examples are collected in Figure 1, in which R_{fn} denotes a perfluoroalkyl group $(\text{CF}_2)_{n-1}\text{CF}_3$.

Deelman and van Koten have synthesized a series of fluorous BAR_f^- ('Barf') type anions, $\text{B}(4\text{-C}_6\text{H}_4\text{R}_f)_4^-$, $\text{B}(4\text{-C}_6\text{H}_4\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{R}_f)_4^-$, and $\text{B}(3,5\text{-C}_6\text{H}_3(\text{R}_f)_2)_4^-$.⁴ These have been employed to solubilize several cations. For example, the ammonium salt $n\text{-Bu}_4\text{N}^+\text{B}(4\text{-C}_6\text{H}_4\text{-Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{R}_f)_4^-$ (**I**, Fig. 1) exhibits a solubility of 0.000052 M at room temperature in FC-72,^{4b} a medium that consists mainly of perfluorohexane. Note that due to the high molecular weights commonly associated with fluorous molecules, molar solubilities that appear modest translate to mass-based solubilities that are more substantial (0.113 g/L for **I**).

The related rhodium salt $[\text{Rh}(\text{dppe})_2]^+\text{B}(4\text{-C}_6\text{H}_4\text{R}_f)_4^-$ is insoluble in FC-72 (<0.000006 M), but $[\text{Rh}(\text{dppe})_2]^+\text{B}(3,5\text{-C}_6\text{H}_3(\text{R}_f)_2)_4^-$ (**IIa**), which features four additional perfluorohexyl groups in the anion, partitions nearly equally between toluene and perfluoromethylcyclohexane. Bühlmann has reported that the analogous sodium salt **IIb** is quite soluble in perfluorodecalin (0.0011 M), perfluoroperhydrophenanthrene (0.0014 M), and a perfluoroether (0.00091 M).⁵ Not unsurprisingly, distinctly higher solubilities are realized when the cations are also fluorous, as in the rhodium salts **IIIb,c**. In partitioning experiments, these showed much greater affinities for perfluoromethylcyclohexane than toluene.^{4a}

In unpublished work from some time ago, we prepared the fluorous primary ammonium (anilinium) salt $(3,5\text{-C}_6\text{H}_3((\text{CH}_2)_2\text{-R}_f)_2)\text{NH}_3^+\text{Cl}^-$ (**IV**, Fig. 1) and noted a solubility of ca. 10 g/L (0.01 M) in perfluoromethylcyclohexane at room temperature.⁶ Pozzi and co-workers have reported that the related fluorous anilinium triflates **V** and **VI**, as well as the fluorous aliphatic secondary ammonium salt **VII**, exhibit appreciable (and temperature dependent) solubilities in perfluoro-1,3-dimethylcyclohexane.⁷

Neumann and Fish synthesized the fluorous quaternary ammonium salt $(\text{CH}_3)(\text{R}_f(\text{CH}_2)_3)_3\text{N}^+\text{CH}_3\text{SO}_3^-$, and used the cation to render the dodecaanion in **VIII** 'freely soluble in perfluorohydrocarbons'.⁸ Bühlmann combined the same cation with a fluorous BAR_f^- anion to give **IX**, which exhibited solubilities of 0.010 M in FC-72 and perfluoroperhydrophenanthrene.⁵ Maruoka has utilized the chiral fluorous ammonium salt **X** as a phase transfer catalyst for enantioselective

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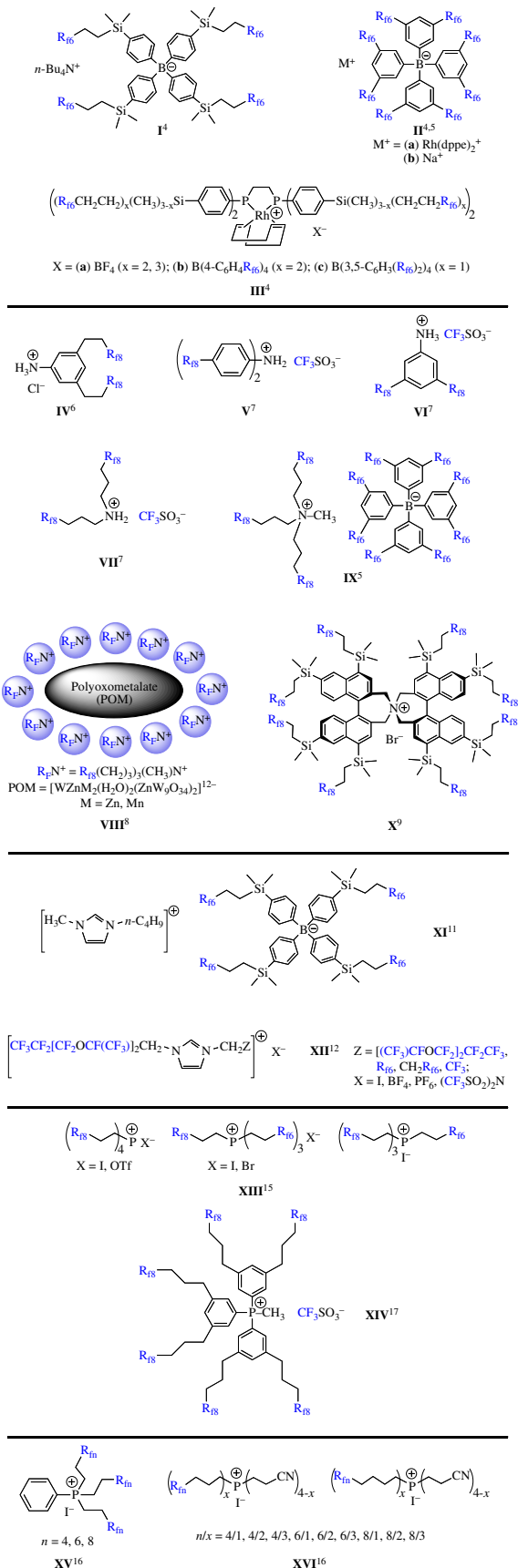


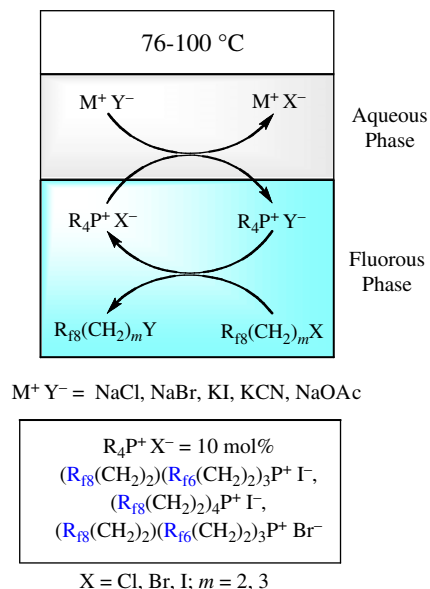
Figure 1. Fluororous salts that have documented solubilities in fluororous liquid phases (**I–IV**), and related species (**XV–XVI**) ($R_{fn} = (CF_2)_{n-1}CF_3$).

alkylations in *organic* media, with subsequent recovery by extraction with FC-72.⁹ Ammonium salts with fewer perfluoroalkyl groups per nitrogen atom have also been described, but no data regarding solubilities in fluororous solvents (which should be lower) are yet available.¹⁰

The ammonium or imidazolium salt **XI**, which features a non-fluororous cation and a fluororous BAR_f^- anion, exhibits a solubility of 0.37 g/L (0.00018 M) in FC-72, and is a room temperature ionic liquid.¹¹ More recently, Kvíčalová has described a large family of liquid salts with fluororous imidazolium cations (**XII**).¹² These are highly soluble in perfluoromethylcyclohexane, exceeding 50 g/L in the best cases, and show much greater affinities for this solvent than toluene. Other fluororous ionic liquids have been described, but solubility data in fluororous solvents have not to our knowledge been reported.¹³

Yasuda, Sakakura, Stuart, Horváth, Bühlmann, and ourselves have prepared a number of fluororous quaternary aliphatic phosphonium halides and triflates (**XIII–XVI**).^{14–17} Those grouped in **XIII** have been shown to be highly soluble in perfluoromethylcyclohexane at elevated temperatures.¹⁵ With the triarylphosphonium salt **XIV**, solubilities exceed 0.014 M in FC-72, perfluoromethylcyclohexane, and perfluoroperhydrophenanthrene at room temperature. Presumably many of **XV–XVI** would also exhibit significant solubilities. Phosphonium salts with a single perfluoroalkyl moiety have also been reported.¹⁸ The manner in which the preceding salts are solvated in fluororous media is an intriguing question that remains to be addressed.

The growing portfolio of fluororous salts that are soluble in fluororous liquid phases offers increased options for introducing polar ions that may interact or react with fluororous solutes. One obvious application would be phase transfer catalysis,¹⁹ whereby an ion of a salt that is insoluble in a fluororous solvent is transported across a phase barrier by a fluororous counter-ion with an appreciable fluororous phase affinity. Indeed, we recently established that fluororous quaternary aliphatic phosphonium salts such as $(R_{f8}(CH_2)_2)(R_{f6}(CH_2)_2)_3P^+ X^-$ ($X = I, Br$) and $(R_{f8}(CH_2)_2)_4P^+ I^-$ catalyze Finkelstein-type²⁰ substitution reactions of fluororous alkyl halides $R_{f8}(CH_2)_mX$ ($m = 2, 3$; $X = Cl, Br, I$) in perfluoromethylcyclohexane ($CF_3C_6H_{11}$) or perfluoromethyldecalin ($CF_3C_{10}H_{17}$) by aqueous NaCl, NaBr, KI, KCN, and NaOAc at 76–100 °C.²¹ These transformations are illustrated in Scheme 1. Other creative approaches to interfacing fluororous chemistry with phase transfer catalysis have also been described.^{9,22–24}



Scheme 1. Phase transfer catalysis of halide substitution reactions in fluororous media using fluororous phosphonium salts.

Additional nucleophiles were tested. An analogous reaction with KCN (entry 3, Table 1) afforded the corresponding fluororous cyanide $R_{\text{FS}}(\text{CH}_2)_5\text{CN}$.²¹ The conversion was 13% after 3.5 h and 72% after 24 h. A similar reaction with NaOAc (entry 4) was much slower, with only 12% conversion after 24 h. The same CN^-/OAc^-

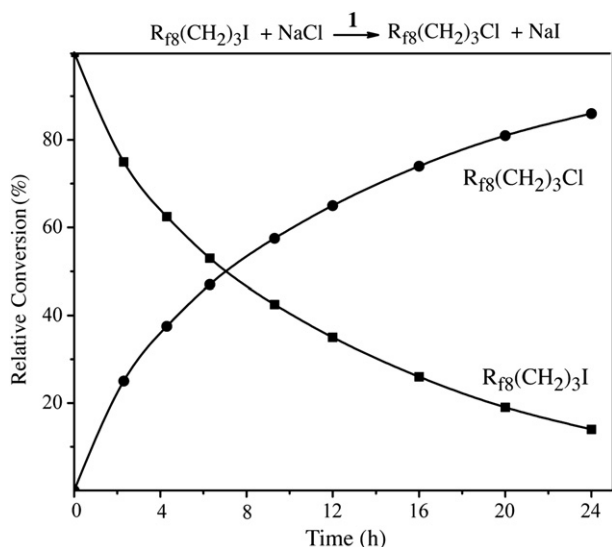


Figure 2. Conversion profile for the reaction of $R_{f8}(CH_2)_3I$ and NaCl catalyzed by **1** in water/perfluoromethyldecalin at 100 °C (entry 1, Table 1).

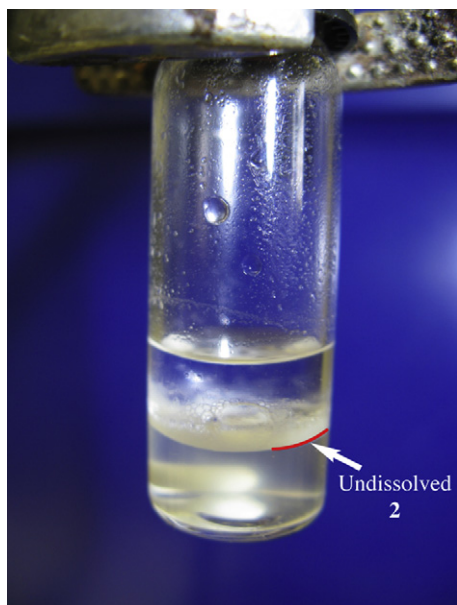


Figure 3. Photograph of the reaction of $R_{f8}(CH_2)_3I$ with NaCl in the presence of **2** at 100 °C (entry 2, Table 1) showing undissolved **2** at the water/perfluoromethyldecalin interface.

nucleophilicity order was found using fluororous phosphonium salt catalysts (Scheme 1).²¹

The reverse of the reaction in entry 1 was investigated. As shown in entry 5, a perfluoromethyldecalin solution of $R_{f8}(CH_2)_3Cl$, excess aqueous KI (1:8 mol ratio), and **1** were similarly combined at 100 °C. Substitution occurred, but at a much slower rate (conversion after 24 h, 22%; 72 h, 48%). Data with fluororous phosphonium salt catalysts established the nucleophilicity order $I^- > Cl^-$.²¹ Thus, the poorer leaving group ability of chloride (or equivalently, the diminished electrophilicity of the alkyl halide) likely plays a key role. However, other factors may also contribute.

Reactions analogous to those in entries 1 and 2 were conducted with the fluororous alkyl iodide $R_{f8}(CH_2)_2I$, which has two methylene spacers instead of three. As shown in entries 6 and 7, substitutions were much slower, with 25–15% conversions to $R_{f8}(CH_2)_2Cl$ after 24 h and 65–41% after 120 h. Parallel trends were observed with the fluororous phosphonium salt catalysts.²¹ All fluororous electrophiles

$R_{f8}(CH_2)_mX$ become less reactive toward nucleophiles as the length of the methylene spacer decreases.³⁰

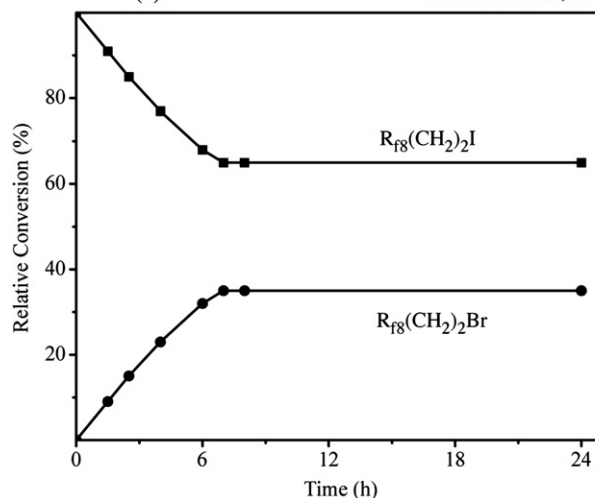
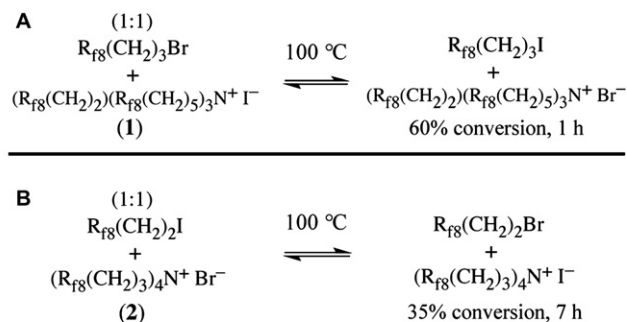
2.3. Phase requirements

An obvious question associated with the preceding data is whether aqueous solutions of nucleophiles are required. When entries 1 or 2 of Table 1 were repeated with solid NaCl, no reaction or apparent dissolution occurred. Thus, solid/liquid phase transfer catalysis does not take place. Fluororous phosphonium salts behaved similarly.²¹

The hybrid solvent $CF_3C_6H_5$ commonly dissolves appreciable quantities of both fluororous and non-fluororous solutes.²⁹ The symmetrically substituted salt **2** exhibited higher solubility in this medium than perfluoromethyldecalin. Thus, a $CF_3C_6H_5$ solution of $R_{f8}(CH_2)_3I$ was combined with **2** and aqueous NaCl at 100 °C in a manner analogous to entry 2 of Table 1. Some **2** remained undissolved, but the quantity was less than in Figure 3. Aliquots were analyzed by 1H NMR, and showed a somewhat slower reaction than in perfluoromethyldecalin, with 31% and 72% conversion after 24 h and 60 h (entry 8, Table 1). A similar reaction in the perfluorinated arene $CF_3C_6F_5$ was comparably slow, with 24% conversion after 24 h at 100 °C (entry 9). The fluororous phosphonium salt catalysts also gave diminished rates in these solvents.²¹

Another obvious question concerns the loci of the reactions in Scheme 3. The preceding results are consistent with substitution occurring in the fluororous phase via a classical phase transfer catalysis mechanism. However, interfacial phenomena might also play a role.³¹ Hence, we sought to confirm that stoichiometric analogs of the preceding reactions could be carried out solely in a fluororous phase.

As depicted in Scheme 4, two reactions (A, B) were conducted with equimolar amounts of fluororous alkyl halides and ammonium salts in perfluoromethyldecalin at 100 °C. The fluororous alkyl



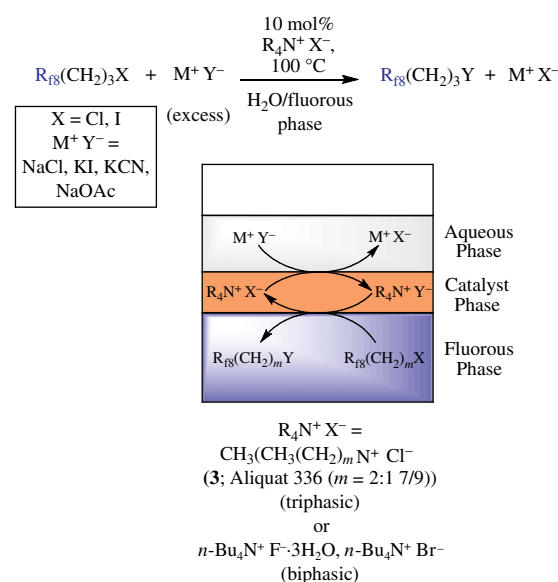
Scheme 4. Reactions of fluororous alkyl halides with equimolar amounts of fluororous quaternary ammonium salts, and conversion data.

bromide $R_8(\text{CH}_2)_3\text{Br}$, which features three methylene spacers, and the ammonium iodide **1** reacted under homogeneous conditions to give the fluoros alkyl iodide $R_8(\text{CH}_2)_3\text{I}$. In less than 1 h, 60% conversion was realized, but no further product formed after a total of 24 h. A transformation approximating the reverse reaction was conducted with the fluoros alkyl iodide $R_8(\text{CH}_2)_2\text{I}$, which features two methylene spacers, and the ammonium bromide **2**. In this case, the catalyst was only partially soluble in perfluoromethyldecalin under the conditions employed. As shown by the rate profile in Scheme 4B, 35% conversion was reached over the course of 7 h. This level, which was replicated in a second experiment, remained constant after a total of 24 h. Hence, despite the differences in the reactants and homogeneities, similar equilibrium constants are reached in both directions.

2.4. Catalyst requirements: non-fluorous ammonium salts

For obvious reasons, we sought to test a comparable non-fluorous quaternary ammonium salt for catalytic activity. Aliquat® 336 (**3**), a commercially available room temperature ionic liquid that is a 2:1 mixture of the octyl- and decyl-substituted species $\text{CH}_3(\text{CH}_3(\text{CH}_2)_7)_3\text{N}^+\text{Cl}^-$ and $\text{CH}_3(\text{CH}_3(\text{CH}_2)_9)_3\text{N}^+\text{Cl}^-$, was selected.³² This cocktail sees extensive use for organic/aqueous phase transfer catalysis.^{19a,24}

Entry 1 of Table 1, corresponding to the protocol in Scheme 3, was repeated using the salt **3**. As shown in entry 1 of Table 2, the fluoros alkyl iodide $R_8(\text{CH}_2)_3\text{I}$ was 85% converted to the chloride $R_8(\text{CH}_2)_3\text{Cl}$ after 24 h. However, the conditions were now triphasic, with **3** layered between the fluoros and aqueous phases to give a liquid/liquid/liquid system as shown in Scheme 5. As summarized in entries 2 and 3 of Table 2, **3** similarly catalyzed reactions of $R_8(\text{CH}_2)_3\text{I}$ with KCN and NaOAc. In both cases, some fluoros alkyl chloride $R_8(\text{CH}_2)_3\text{Cl}$ builds up, derived from the anion of **3**. In this context, entry 4 shows that $R_8(\text{CH}_2)_3\text{Cl}$ is distinctly less reactive toward nucleophiles than $R_8(\text{CH}_2)_3\text{I}$. As compared to the fluoros catalyst **1**, there was a marked rate enhancement with KCN, as



Scheme 5. Phase transfer catalysis of halide substitution reactions using non-fluorous ammonium salts under triphasic conditions.

illustrated in Figure 4. There was also a significant acceleration with NaOAc, but much less difference with NaCl.

NMR experiments involving internal standards (Experimental section) established that **3** has no detectable solubility in perfluoromethyldecalin at room temperature (<0.0006 M) and only a very low solubility at 100 °C (ca. 0.0016 M or 0.001 g/mL). The solubility of **3** in water was low at room temperature (ca. 0.0030 M or 1.3 g in 1000 g), but increased slightly at 100 °C (ca. 0.0039 M or 1.7 g in 1000 g). However, **3** was highly soluble at 100 °C in the neat fluoros alkyl iodide $R_8(\text{CH}_2)_2\text{I}$, which liquefies at 54–58 °C (>191 g in 1000 g, or >25 mol %). Note that the iodide functionality renders this substance more polar than saturated perfluorocarbons.

Table 2

Data for halide substitution reactions catalyzed by non-fluorous ammonium salts at 100 °C under the conditions of Scheme 5 unless noted^a

Entry	Substrate	M ⁺ Y [−]	Product	Catalyst	Time (h)	Product convn (%)	$R_8(\text{CH}_2)_3\text{Cl}$ convn (%) ^b
1	$R_8(\text{CH}_2)_3\text{I}$	NaCl	$R_8(\text{CH}_2)_3\text{Cl}$	Aliquat 336 (3) ^c	3.5 12 24	32 71 85	
2		KCN	$R_8(\text{CH}_2)_3\text{CN}$		1 2	78 91	7 7
3		NaOAc	$R_8(\text{CH}_2)_3\text{OAc}$		1 3 24	18 26 54	11 5 7
4	$R_8(\text{CH}_2)_3\text{Cl}$	KI	$R_8(\text{CH}_2)_3\text{I}$		1 24	5 20	
5 ^d	$R_8(\text{CH}_2)_3\text{I}$	NaCl	$R_8(\text{CH}_2)_3\text{Cl}$	3	4 24	43 93	
6 ^d		KCN	$R_8(\text{CH}_2)_3\text{CN}$		2	98	2
7 ^d		NaOAc	$R_8(\text{CH}_2)_3\text{OAc}$		2 3	73 82	6 5
8 ^e	$R_8(\text{CH}_2)_3\text{I}$	NaCl	$R_8(\text{CH}_2)_3\text{Cl}$	$n\text{-Bu}_4\text{N}^+ \text{F}^- \cdot 3\text{H}_2\text{O}$	24 48 72	26 39 50	
9 ^e	$R_8(\text{CH}_2)_3\text{I}$	NaCl	$R_8(\text{CH}_2)_3\text{Cl}$	$n\text{-Bu}_4\text{N}^+ \text{Br}^-$	24	5	

^a Conditions: $R_8(\text{CH}_2)_3\text{I}$ (0.20 mmol), M⁺ Y[−] (1.60 mmol), perfluoromethyldecalin (0.5 mL), water (0.5 mL), **4** (0.020 mmol).

^b This arises from the chloride counter anion of **3**.

^c $\text{CH}_3(\text{CH}_3(\text{CH}_2)_m)_3\text{N}^+ \text{Cl}^-$, 2:1 m=7/9.

^d As in a but without fluoros solvent; the substrate constitutes the fluoros phase, in which **3** is soluble (biphasic conditions).

^e The catalyst is a water soluble $n\text{-Bu}_4\text{N}^+$ salt (biphasic conditions).

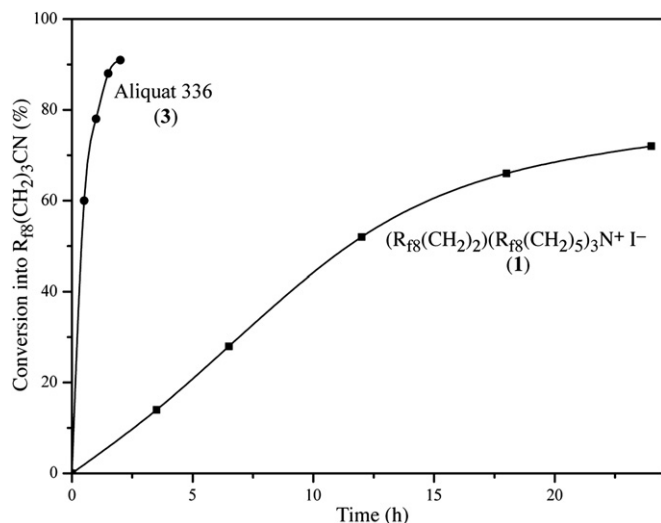


Figure 4. Conversion profiles for the reactions of $R_8(CH_2)_3I$ and KCN catalyzed by **3** (●; entry 2, Table 2) and **1** (■; entry 3, Table 1) in perfluoromethyldecalin/water at 100 °C.

Interestingly, when the fluorosolvent was omitted from the reactions with **3** (entries 5–7, Table 2), conversions were even faster. The alkyl halide now served as its own fluorosolvent phase, and due to the high solubility of **3**, only two phases were present. The reaction with NaCl gave 93% conversion over 24 h, and that with KCN showed complete consumption of the fluorosolvent alkyl iodide within 2 h, with 98% conversion to the fluorosolvent alkyl cyanide. Even in the case of NaOAc, 82% conversion to the fluorosolvent acetate was evident after 3 h, when the experiment was terminated.

To better define the requirements for non-fluorous ammonium salt catalysts, analogous experiments were carried out with shorter-chained tetralkylammonium salts. Thus, entry 1 of Table 2 was repeated using 10 mol % of $n\text{-Bu}_4\text{N}^+\text{F}^- \cdot 3\text{H}_2\text{O}$ or $n\text{-Bu}_4\text{N}^+\text{Br}^-$ in place of **3** (entries 8 and 9). Unlike **3**, these are very water soluble (≥ 600 g/L at 20 °C from vendor data sheets), so the reactions were biphasic. However, much slower conversions were observed (26–5% over 24 h).

3. Discussion

Non-fluorous quaternary ammonium and phosphonium salts can be regarded as the prototype organic/aqueous phase transfer catalysts, dating back to the seminal studies of Starks.³³ In some cases, ammonium salts have been found to be slightly more active catalysts than phosphonium salts,³⁴ but they are also less stable in reactions conducted at higher temperatures (except when hydroxide is the anion).^{19a,33} Similarly, we have now established that fluorosolvent quaternary ammonium and phosphonium salts are excellent aqueous/fluorous phase transfer catalysts for ionic displacements in highly nonpolar fluorosolvents. We have furthermore shown that the phosphonium salts can be recycled, either by precipitation or adsorption onto Teflon® tape.²¹ Similar protocols can likely be developed with **1** and **2**, which exhibit the necessary highly temperature dependent solubilities.

The slower reactions in Table 1 provide unambiguous comparisons with previously reported data. For example, that of $R_8(CH_2)_3I$ and KCN is faster when catalyzed by **1** (entry 3, Table 1) than the fluorosolvent phosphonium salt $(R_8(CH_2)_2)(R_8(CH_2)_3)_3\text{P}^+\text{I}^-$ (72% vs 17% conversion after 24 h).²¹ However, that of $R_8(CH_2)_3I$ and NaOAc is slower when catalyzed by **1** (entry 4, Table 1) than the phosphonium salt (12% vs 56% conversion after 24 h).²¹ Thus, the relative nucleophilicities of the cyanide and acetate anions appear to invert in the two systems.

The stoichiometric transformations in Scheme 4 indicate that fluorosolvent quaternary ammonium halides can effect ionic displacements wholly within a fluorosolvent liquid phase. As similarly

established with the phosphonium salts,²¹ an aqueous/fluorous liquid/liquid interface is not necessary. Therefore, interfacial mechanisms are not required for phase transfer catalysis as in Schemes 1 and 3. However, it should be noted that when simple alkali metal halides are employed, the presence of an aqueous phase is essential. Phase transfer across such fluorosolvent liquid/solid interfaces does not occur at detectable rates.

At the outset of this study, we did not anticipate that related non-fluorous quaternary ammonium or phosphonium salts would be effective phase transfer catalysts for reactions in fluorosolvent media. However, salts in which the heteroatom features at least three long alkyl substituents are active under the triphasic conditions in Scheme 5, in which the molten salt localizes between the lower fluorosolvent and upper aqueous layers. In this study, we have further shown that less lipophilic onium cations, such as $n\text{-Bu}_4\text{N}^+$, afford poor catalysts (entries 8 and 9, Table 2). Given the very low solubility of **3** in perfluoromethyldecalin, we presume that the dominant mode of catalysis involves an interfacial mechanism. Interfacial phenomena can play substantial roles in organic/aqueous phase transfer catalysis, as elegantly summarized in a review.³¹ Although this unexpected observation is most deserving of further study, it is beyond the scope of the present investigation.

Why is chemistry that can be carried out in fluorosolvent solvents of interest? Increasing attention is being given to remediation technologies that would involve sequestering toxic or hazardous compounds in fluorosolvent phases. A secondary objective then becomes the processing of such substances into benign materials, and toward this end the development of a wider vocabulary of reactions that can be applied in very nonpolar fluorosolvent phases is desirable. Note that phase transfer catalysis allows a reactive species to access a new phase, but does not irreversibly introduce new solutes in the usual manner of a reagent. Thus, one avoids increasing the complexity of what is often a 'soup' of hazardous and non-hazardous substances.

Finally, there are several additional ways in which fluorosolvent chemistry can be exploited in phase transfer catalysis, as summarized in a recent review.²⁴ These include (1) the use of fluorosolvent ammonium salt **X** (Fig. 1) as a recoverable catalyst for organic/aqueous phase transfer processes,⁹ (2) the use of fluorosolvent aza/oxa crown ethers to catalyze the reaction of $n\text{-C}_8\text{H}_{17}\text{Br}$ and KI under liquid/solid biphasic conditions using the hybrid solvent $\text{CF}_3\text{C}_6\text{H}_5$,²² and (3) the use of fluorosolvent oxa crown ethers to catalyze the same reaction in both $\text{CF}_3\text{C}_6\text{H}_5$ and chlorobenzene.²³ The last study also described transformations involving perfluoromethylcyclohexane as the host phase for the crown ether catalyst (middle layer), $n\text{-C}_8\text{H}_{17}\text{Br}$ or $n\text{-C}_8\text{H}_{17}\text{OSO}_2\text{CH}_3$ as a second organic phase (neat reactant; upper layer), and KI or KCN as solid phases (lower layer). Effective recovery protocols were established for all of the fluorosolvent crown ether systems.

In summary, this study, together with our previous full paper,^{21b} has opened up unanticipated new vistas for both phase transfer catalysis and fluorosolvent chemistry. Ionic displacement reactions are easily conducted in extremely nonpolar fluorosolvent media at 76–100 °C with either stoichiometric or catalytic quantities of fluorosolvent quaternary onium salts. Related non-fluorous onium salts are even better catalysts, but appear to function interfacially. Future efforts will be directed at expanding the scope of fluorosolvent salts that exhibit significant solubilities in fluorosolvent media (Fig. 1), and other types of applications for such substances.³⁵

4. Experimental section

4.1. General

Reactions were conducted under air unless noted. Chemicals were treated as follows: hexanes, diethyl ether, and $\text{CF}_3\text{C}_6\text{H}_5$ (ABCR, 99%), simple distillation; $\text{CF}_3\text{C}_6\text{H}_5$ (ABCR, 98%), passed through neutral alumina and stored over molecular sieves; DMF, distilled from CaH_2

and freeze/pump/thaw degassed; perfluoromethyldecalin (ABCR, 88%), $R_8(\text{CH}_2)_2\text{I}$ (ABCR, 97%), NaCl (Acros, 99.5%), KCN (Acros, 97%), KI (Acros, 99%), $n\text{-Bu}_4\text{N}^+\text{F}^-\cdot 3\text{H}_2\text{O}$ (Aldrich, 97%), $n\text{-Bu}_4\text{N}^+\text{Br}^-$ (Acros, +99%), Aliquat[®] 336 (Aldrich, $\text{CH}_3(\text{CH}_2)_m\text{N}^+\text{Cl}^-$, $m=2:1\ 7/9$ (**3**)), and resorcinol (Acros, 98%), used as received. For substitution reactions, educts and authentic product samples were purchased (above) or prepared by literature procedures ($R_8(\text{CH}_2)_3\text{I}$,³⁶ $R_8(\text{CH}_2)_3\text{Br}$,³⁷ $R_8(\text{CH}_2)_2\text{Br}$,¹⁵ $R_8(\text{CH}_2)_3\text{Cl}$,^{21b} $R_8(\text{CH}_2)_3\text{CN}$,^{21b} $R_8(\text{CH}_2)_3\text{OAc}$ ^{21b}).

NMR spectra were recorded on Bruker 300 or 400 MHz spectrometers at ambient probe temperatures, and referenced as follows: ^1H , residual internal CHCl_3 , acetone- d_6 , or $\text{C}_6\text{D}_5\text{H}$ (δ 7.24, 2.04, or 7.16 ppm); ^{13}C , internal CDCl_3 or acetone- d_6 (δ 77.0 or 29.8 ppm). The highly coupled ^{13}C signals of the fluorinated carbons are not listed. Mass spectra were recorded on a Micromass Zabspec instrument. Elemental analyses were conducted on a Carlo Erba EA1110 instrument. Melting points were determined using a SRS MPA100 OptiMelt automated melting point system. DSC and TGA data were recorded with a Mettler-Toledo DSC821 instrument and treated by standard methods.³⁸

4.1.1. ($R_8(\text{CH}_2)_2$)($R_8(\text{CH}_2)_5$) $3\text{N}^+\text{I}^-$ (1**).** A Schlenk flask was charged with ($R_8(\text{CH}_2)_5$) 3N (0.815 g, 0.550 mmol),²⁵ $R_8(\text{CH}_2)_2\text{I}$ (0.471 g, 0.821 mmol), and DMF (2 mL). The mixture was stirred at 115 °C for 24 h. The volatiles were removed at 100 °C and 2×10^{-3} mbar. The residue was washed with diethyl ether (2×4 mL) and dried by oil pump vacuum to give **1** as a light yellow solid (0.882 g, 0.43 mmol, 78%). Capillary thermolysis data (OptiMelt monitoring): 110.5 °C (turns red; apparent phase change with some liquefaction), 139.0 °C (clear point). DSC: stronger endotherm with $T_i/T_e/T_p/T_c/T_f$ 81.9/106.1/113.5/116.5/125.0 °C; weaker endotherm with $T_i/T_e/T_p/T_c/T_f$ 138.8/147.2/152.1/158.0/159.7 °C. TGA: onset of 97% mass loss (T_i), 157.9 °C. Anal. Calcd for $\text{C}_{49}\text{H}_{34}\text{F}_{68}\text{IN}$: C, 28.63; H, 1.67; N, 0.68. Found: C, 28.97; H, 1.73; N, 0.87.

NMR (δ): ^1H (acetone- d_6) 3.20 (br s, 6H), 2.33–2.18 (m, 8H), 2.03 (overlapped with acetone- d_6 , m, 8H), 1.89–1.87 (m, 2H), 1.73–1.66 (m, 6H), 1.60–1.54 (m, 6H), ^1H ($\text{CF}_3\text{C}_6\text{F}_5/\text{CDCl}_3$) 3.08 (t, 6H), 2.15–2.04 (m, 8H), 1.94 (br m, 6H), 1.72–1.67 (m, 8H), 1.52 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ (acetone- d_6) 52.7 (CH_2N), 47.0 (CH_2N), 35.0 (t, $^2J_{\text{CF}}=20$ Hz CH_2CF_2), 30.9, 30.4, 26.6, 23.5, 20.3. MS (3-NBA, FAB+) m/z : 1927 ($[(R_8(\text{CH}_2)_2)(R_8(\text{CH}_2)_5)_3\text{N}]^+$, 100%).

4.1.2. ($R_8(\text{CH}_2)_3$) $4\text{N}^+\text{Br}^-$ (2**).** A Schlenk flask was charged with ($R_8(\text{CH}_2)_3$) 3N (1.482 g, 1.06 mmol),²⁵ $R_8(\text{CH}_2)_3\text{Br}$ (0.866 g, 1.60 mmol), and DMF (2 mL) under an inert atmosphere. The mixture was stirred at 115 °C for 24 h. The volatiles were removed at 100 °C and 2×10^{-3} mbar. The residue was washed with hexane (5×4 mL) and diethyl ether (2×4 mL) and dried by oil pump vacuum to give **2** as a cream white solid (1.762 g, 0.909 mmol, 86%). Capillary thermolysis data (OptiMelt monitoring): 115.8 °C (darkening), 138.0 °C (dec; formation of black liquid). DSC: strong endotherm with $T_i/T_e/T_p/T_c/T_f$ 33.9/39.1/42.7/45.8/50.1 °C; medium endotherm with $T_i/T_e/T_p/T_c/T_f$ 116.4/121.1/131.5/134.8/136.0 °C; weak endotherm with $T_i/T_e/T_p/T_c/T_f$ 136.7/137.2/141.7/146.6/148.4 °C. TGA: onset of 99% mass loss (T_i), 149.7 °C. Anal. Calcd for $\text{C}_{44}\text{H}_{24}\text{BrF}_{68}\text{N}$: C, 27.26; H, 1.25; N, 0.72. Found: C, 27.20; H, 1.35; N, 0.76.

NMR (δ): ^1H ($\text{CF}_3\text{C}_6\text{F}_5+\text{CDCl}_3$ (capillary)): 2.71 (br s, 8H, NCH_2), 2.24–2.11 (br m, 8H, CH_2R_8), 1.87 (br m, 8H, $\text{CH}_2\text{CH}_2R_8$); ^1H ($\text{CF}_3\text{C}_6\text{F}_5$ +three drops acetone- d_6 ; external lock CDCl_3 (capillary)): 2.83 (br t, 8H, $^3J_{\text{HH}}=7$ Hz, NCH_2), 2.32 (br m, 8H, CH_2R_8), 1.99 (br m, 8H, $\text{CH}_2\text{CH}_2R_8$); $^{13}\text{C}\{^1\text{H}\}$ (same solvent) 52.0 (s, CH_2N), 28.2 (t, $^2J_{\text{CF}}=22$ Hz, CH_2CF_2), 20.7 (s, $\text{CH}_2\text{CH}_2\text{CF}_2$). MS (3-NBA, FAB+) m/z : 1858 ($[(R_8(\text{CH}_2)_3)_4\text{N}]^+$, 60%), 1398 ($[(R_8(\text{CH}_2)_3)_3\text{NH}]^+$, 100%).

4.1.3. Representative substitution reaction with fluororous catalysts (Scheme 2; Table 1, entry 1). A 4 mL vial was charged with

$R_8(\text{CH}_2)_3\text{I}$ (0.059 g, 0.100 mmol), **1** (0.021 g, 0.010 mmol), perfluoromethyldecalin (0.50 mL), NaCl (0.047 g, 0.80 mmol), and water (0.50 mL). The vial was tightly sealed and the mixture vigorously stirred at 100 °C for 24 h. Aliquots were taken from the fluororous phase hourly and diluted with CDCl_3 , and ^1H NMR spectra were recorded. Data: Figure 2.

4.1.4. Phase requirements. A (reaction without fluororous solvent; Table 2, entry 1). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{I}$ (0.059 g, 0.100 mmol), **1** (0.019 g, 0.010 mmol), NaCl (0.047 g, 0.80 mmol), and water (0.50 mL). The vial was tightly sealed and the homogeneous mixture vigorously stirred at 100 °C for 24 h. The sample was cooled and CDCl_3 was added. A ^1H NMR spectrum of the CDCl_3 layer showed 90% conversion to $R_8(\text{CH}_2)_3\text{Cl}$.

B (reaction with hybrid solvent; Table 1, entry 8). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{I}$ (0.059 g, 0.100 mmol), **2** (0.019 g, 0.010 mmol), $\text{CF}_3\text{C}_6\text{H}_5$ (0.50 mL), NaCl (0.047 g, 0.80 mmol), and water (0.50 mL). The vial was tightly sealed and the heterogeneous mixture vigorously stirred at 100 °C. Aliquots were periodically taken from the $\text{CF}_3\text{C}_6\text{H}_5$ phase and diluted with CDCl_3 , and ^1H NMR spectra were recorded. Data: Table 1.

C (one phase stoichiometric reaction; Scheme 4). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{Br}$ (0.054 g, 0.10 mmol), **1** (0.205 g, 0.10 mmol), and perfluoromethyldecalin (0.25 mL). The vial was tightly sealed and the homogeneous sample vigorously stirred at 100 °C. Aliquots were removed hourly and diluted with CDCl_3 , and ^1H NMR spectra were recorded. Data: Scheme 4. As noted in the text, the corresponding reaction of $R_8(\text{CH}_2)_2\text{I}$ and **2** is not homogeneous.

4.1.5. Representative substitution reactions with non-fluororous catalysts. A (Table 2, entry 1). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{I}$ (0.118 g, 0.201 mmol), **3** (0.010 g, 0.023 mmol), perfluoromethyldecalin (0.50 mL), NaCl (0.095 g, 1.60 mmol), and water (0.50 mL). The vial was tightly sealed and the mixture vigorously stirred at 100 °C for 24 h. Aliquots were periodically taken from the $\text{CF}_3\text{C}_6\text{H}_5$ phase and diluted with CDCl_3 , and ^1H NMR spectra were recorded. Data: Table 2.

B (Table 2, entry 6). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{I}$ (0.118 g, 0.201 mmol), **3** (0.010 g, 0.023 mmol), KCN (0.110 g, 1.69 mmol), and water (0.50 mL). The vial was tightly sealed and the mixture vigorously stirred at 100 °C for 4 h. A ^1H NMR spectrum (CDCl_3) of an aliquot from the $R_8(\text{CH}_2)_3\text{I}$ phase showed a 98:2 $R_8(\text{CH}_2)_3\text{CN}/R_8(\text{CH}_2)_3\text{Cl}$ ratio (δ 2.49/3.65 ppm, t, CH_2X) and essentially no $R_8(\text{CH}_2)_3\text{I}$ (δ 3.23 ppm).

C (Table 2, entry 8). A 4 mL vial was charged with $R_8(\text{CH}_2)_3\text{I}$ (0.118 g, 0.201 mmol), $n\text{-Bu}_4\text{N}^+\text{Br}^-$ (0.006 g, 0.02 mmol), perfluoromethyldecalin (0.50 mL), NaCl (0.094 g, 1.60 mmol), and water (0.50 mL). The vial was tightly sealed and the mixture vigorously stirred at 100 °C for 24 h. Aliquots were periodically taken from the fluororous phase and diluted with CDCl_3 , and ^1H NMR spectra were recorded. Data: Table 2.

4.1.6. Solubility data. A. A flask was charged with **3** (0.030 g, 0.069 mmol), resorcinol standard (0.013 g, 0.118 mmol), and D_2O (1.0 mL). The sample was vigorously stirred at 24 °C for 15 min. Stirring was halted, and an aliquot of the supernatant was removed and diluted with acetone- d_6 . The sample was stirred at 100 °C. An aliquot of the supernatant was similarly removed, and diluted with acetone- d_6 . The ^1H NMR spectra of both aliquots were recorded, and the N -methyl signal of **3** (δ 3.35 ppm, s, 3H) was integrated versus the 2-CH signal of resorcinol (δ 7.16 ppm, t, 1H). Data: see text.

B. A flask was charged with **3** (0.0384 g, 0.089 mmol), $\text{CF}_3\text{C}_6\text{H}_5$ standard (0.0145 g, 0.101 mmol), and perfluoromethyldecalin (0.50 mL). The sample was vigorously stirred at 24 °C. Stirring was

halted, and after the layer of **3** had separated, an aliquot from the lower layer of perfluoromethyldecalin was removed and diluted with C₆D₆. The sample was stirred at 100 °C. An aliquot of the perfluoromethyldecalin layer was similarly removed, and diluted with C₆D₆. The ¹H NMR spectra of the aliquots were recorded, and the *N*-methyl signal of **3** (see A) was integrated versus the CH signals of CF₃C₆H₅ (7.47–7.64 ppm, 5H). No signal was detected for **3** at 24 °C, so a solubility limit was assigned using a noise peak. Data: see text.

C. A flask was charged with **3** (0.0436 g, 0.101 mmol), CF₃C₆H₅ standard (0.0145 g, 0.101 mmol), and R₈(CH₂)₂I (0.2013 g, 0.351 mmol). The sample was stirred at 100 °C, giving a single phase. An aliquot was removed and diluted with CDCl₃. The *N*-methyl signal of **3** (see A) was integrated versus the CH signals of CF₃C₆H₅ (7.47–7.64 ppm, 5H), showing 0.089 mmol of **3** to be present. Data: see text.

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References and notes

- Freed, B. K.; Biesecker, J.; Middleton, W. J. *J. Fluorine Chem.* **1990**, *48*, 63–75.
- Gladysz, J. A.; Emnet, C. Fluorous solvents and related media. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley/VCH: Weinheim, 2004; pp 11–23.
- (a) Temperature controlled catalyst recycling: new protocols based upon temperature-dependent solubilities of fluorous compounds and solid–liquid phase separations. Gladysz, J. A.; Tesevic, V. *Top. Organomet. Chem.* **2008**, *23*, 67–89; (b) Gladysz, J. A. Catalysis involving fluorous phases: fundamentals and directions for greener methodologies. In *Handbook of Green Chemistry*; Anastas, P., Crabtree, R. H., Eds.; Homogeneous Catalysis; Wiley/VCH: Weinheim, 2009; Vol. 1, pp 17–38.
- (a) van den Broeke, J.; de Wolf, E.; Deelman, B.-J.; van Koten, G. *Adv. Synth. Catal.* **2003**, *345*, 625–635; (b) van den Broeke, J.; Lutz, M.; Kooijman, H.; Spek, A. L.; Deelman, B.-J.; van Koten, G. *Organometallics* **2001**, *20*, 2114–2117.
- (a) Boswell, P. G.; Bühlmann, P. J. *Am. Chem. Soc.* **2005**, *127*, 8958–8959; (b) Boswell, P. G.; Lugert, E. C.; Rábai, J.; Amin, E. A.; Bühlmann, P. J. *Am. Chem. Soc.* **2005**, *127*, 16976–16984.
- Rutherford, D. unpublished results, University of Utah (final research report, March 1999).
- Mercs, L.; Pozzi, G.; Quici, S. *Tetrahedron Lett.* **2007**, *48*, 3053–3056.
- Maayan, G.; Fish, R. H.; Neumann, R. *Org. Lett.* **2003**, *5*, 3547–3550.
- (a) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429–1431; (b) Shirakawa, S.; Ueda, M.; Tanaka, Y.; Hashimoto, T.; Maruoka, K. *Chem. Asian J.* **2007**, *2*, 1276–1281; (c) Hashimoto, T.; Sakata, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5014–5017; *Angew. Chem.* **2009**, *121*, 5114–5117.
- (a) Shen, W.; Wang, L.-M.; Tian, H. *J. Fluorine Chem.* **2008**, *129*, 267–273; (b) See also: Qiu, W. US Patent 6054615 (Filed May 27, 1997); *Chem. Abstr.* **2000**, *132*, 264882.
- van den Broeke, J.; Winter, F.; Deelman, B.-J.; van Koten, G. *Org. Lett.* **2002**, *4*, 3851–3854.
- Kysilka, O.; Rybáčková, M.; Skalický, M.; Kvičalová, M.; Cvačka, J.; Kvičala, J. *J. Fluorine Chem.* **2009**, *130*, 629–639.
- (a) Merrigan, T. L.; Bates, E. D.; Dorman, S. C.; Davis, J. H., Jr. *Chem. Commun.* **2000**, 2051–2052; (b) Heitzman, H.; Young, B. A.; Rausch, D. J.; Rickert, P.; Stepinski, D. C.; Dietz, M. L. *Talanta* **2006**, *69*, 527–531; (c) Liu, C.; VanDerver, D.; DesMariseau, D. D. *Org. Lett.* **2008**, *10*, 5565–5568 and references therein; (d) Bara, J. E.; Gabriel, C. J.; Carlisle, T. K.; Camper, D. E.; Finotello, A.; Gin, D. L.; Noble, R. D. *Chem. Eng. J.* **2009**, *147*, 43–50.
- He, L.-N.; Yasuda, H.; Sakakura, T. *Green Chem.* **2003**, *5*, 92–94.
- Emnet, C.; Weber, K. M.; Vidal, J. A.; Consorti, C. S.; Stuart, A. M.; Gladysz, J. A. *Adv. Synth. Catal.* **2006**, *348*, 1625–1634.
- (a) Vláš, G.; Richter, F.; Horváth, I. T. *Org. Lett.* **2004**, *6*, 4559–4561; (b) Vláš, G.; Richter, F.; Horváth, I. T. *Tetrahedron Lett.* **2005**, *46*, 8605–8608.
- Boswell, P. G.; Anfang, A. C.; Bühlmann, P. J. *Fluorine Chem.* **2008**, *129*, 961–967.
- (a) Tindale, J. J.; Na, C.; Jennings, M. C.; Ragogna, P. J. *Can. J. Chem.* **2007**, *85*, 660–667; (b) Tindale, J. J.; Ragogna, P. J. *Chem. Commun.* **2009**, 1831–1833.
- (a) *Phase-Transfer Catalysis*; Starks, C. M., Liotta, C. L., Halpern, M., Eds.; Chapman & Hall: New York, NY, 1994; (b) Makoszka, M. *Pure Appl. Chem.* **1975**, *43*, 439; (c) Yadav, G. D. *Top. Catal.* **2004**, *29*, 145–161.
- Smith, M. B.; March, J. *Advanced Organic Chemistry*, 6th ed.; John Wiley & Sons: New York, NY, 2007; p 574.
- (a) Consorti, C. S.; Jurisch, M.; Gladysz, J. A. *Org. Lett.* **2007**, *9*, 2309–2312; (b) Mandal, D.; Jurisch, M.; Consorti, C. S.; Gladysz, J. A. *Chem. Asian J.* **2008**, *3*, 1772–1782.
- Stuart, A. M.; Vidal, J. A. *J. Org. Chem.* **2007**, *72*, 3735–3740.
- (a) Pozzi, G.; Quici, S.; Fish, R. H. *Adv. Synth. Catal.* **2008**, *350*, 2425–2436; (b) Pozzi, G.; Mihali, V.; Foschi, F.; Penso, M.; Quici, S.; Fish, R. H. *Adv. Synth. Catal.*, in press.
- Review: Pozzi, G.; Quici, S.; Fish, R. H. *J. Fluorine Chem.* **2008**, *129*, 920–929.
- Rocabay, C.; Bauer, W.; Gladysz, J. A. *Eur. J. Org. Chem.* **2000**, 2621–2628.
- (a) Kiss, L. E.; Rábai, J.; Varga, L.; Kövesdi, I. *Synlett* **1998**, 1243–1245; (b) Szilávik, Z.; Tárkányi, G.; Gömöry, A.; Tarcay, G.; Rábai, J. *J. Fluorine Chem.* **2001**, *108*, 7–14; (c) Szabó, D.; Nemes, A.; Kövesdi, I.; Farkas, V.; Hollósi, M.; Rábai, J. *J. Fluorine Chem.* **2006**, *127*, 1405–1414; (d) Szabó, D.; Muhl, J.; Bálint, A.-M.; Bodor, A.; Rábai, J. *J. Fluorine Chem.* **2006**, *127*, 1496–1504.
- (a) Felling, K. W.; Lagow, R. J. *J. Fluorine Chem.* **2003**, *123*, 233–236; (b) Moldavskii, D. D.; Bispfen, T. A.; Kaurova, G. I.; Furin, G. G. *J. Fluorine Chem.* **1999**, *94*, 157–167; (c) Meinert, H.; Fackler, R.; Mader, J.; Reuter, P.; Röhlke, W. *J. Fluorine Chem.* **1992**, *59*, 351–365; (d) Kaplánek, R.; Bříza, T.; Havlík, M.; Martásek, P.; Král, V. *J. Fluorine Chem.* **2007**, *128*, 179–183.
- Rocabay, C.; Hampel, F.; Gladysz, J. A. *J. Org. Chem.* **2002**, *67*, 6863–6870.
- Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. *Top. Curr. Chem.* **1999**, *206*, 79–105.
- Gladysz, J. A. Ponytails: structural and electronic considerations. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley/VCH: Weinheim, 2004; pp 41–55.
- Yang, H.-M.; Wu, H.-S. *Catal. Rev. Sci. Eng.* **2003**, *45*, 463–540.
- Mikkola, J.-P.; Virtanen, P.; Sjöholm, R. *Green Chem.* **2006**, *8*, 250–255.
- Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.
- Landini, D.; Maia, A.; Montanari, F. *J. Am. Chem. Soc.* **1978**, *100*, 2796–2801.
- Mandal, D. work in progress.
- Vincent, J.-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Can. J. Chem.* **2001**, *79*, 888–895.
- Sugiyama, K.; Nemoto, T.; Koide, G.; Hirao, A. *Macromol. Symp.* **2002**, *181*, 135–153.
- Cammenga, H. K.; Eppele, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1171–1187; *Angew. Chem.* **1995**, *107*, 1284–1301.