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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 $R_{f8}(CH_2)_mX$ (m=2, 3; X=Cl, 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 $(R_{f8}(CH_2)_2)(R_{f8}(CH_2)_5)_3N^+ I^-$ (**1**) or $(R_{f8}(CH_2)_3)_4N^+ Br^-$ (**2**) (10 mol %), which are fully or partially soluble in perfluoromethyldecalin under these conditions. Stoichiometric reactions of (a) **1** and $R_{f8}(CH_2)_3Br$, and (b) **2** and $R_{f8}(CH_2)_2I$ are conducted in perfluoromethyldecalin at 100 °C, and yield the same $R_{f8}(CH_2)_mI/R_{f8}(CH_2)_mBr$ 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 $CH_3(CH_3(CH_2)_m)_3N^+ Cl^-$ (**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.

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 $(CF_2)_{n-1}CF_3$.

Deelman and van Koten have synthesized a series of fluorous BAr_f^- ('Barf') type anions, $B(4\text{-}C_6H_4R_{f6})_4^-$, $B(4\text{-}C_6H_4Si(CH_3)_2(CH_2)_2R_{f6})_4^-$, and $B(3,5\text{-}C_6H_3(R_{f6})_2)_4^-$.[4] These have been employed to solubilize several cations. For example, the ammonium salt $n\text{-}Bu_4N^+$ $B(4\text{-}C_6H_4\text{-}Si(CH_3)_2(CH_2)_2R_{f6})_4^-$ (**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 $[Rh(dppe)_2]^+$ $B(4\text{-}C_6H_4R_{f6})_4^-$ is insoluble in FC-72 (<0.000006 M), but $[Rh(dppe)_2]^+$ $B(3,5\text{-}C_6H_3(R_{f6})_2)_4^-$ (**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 $(3,5\text{-}C_6H_3((CH_2)_2\text{-}R_{f8})_2)NH_3^+ Cl^-$ (**IV**, Fig. 1) and noted a solubility of ca. 10 g/L (0.01 M) in perfluoromethylcyclohexane at room temperature.[6] Pozzi and coworkers 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 $(CH_3)(R_{f8}(CH_2)_3)_3N^+ CH_3SO_3^-$, 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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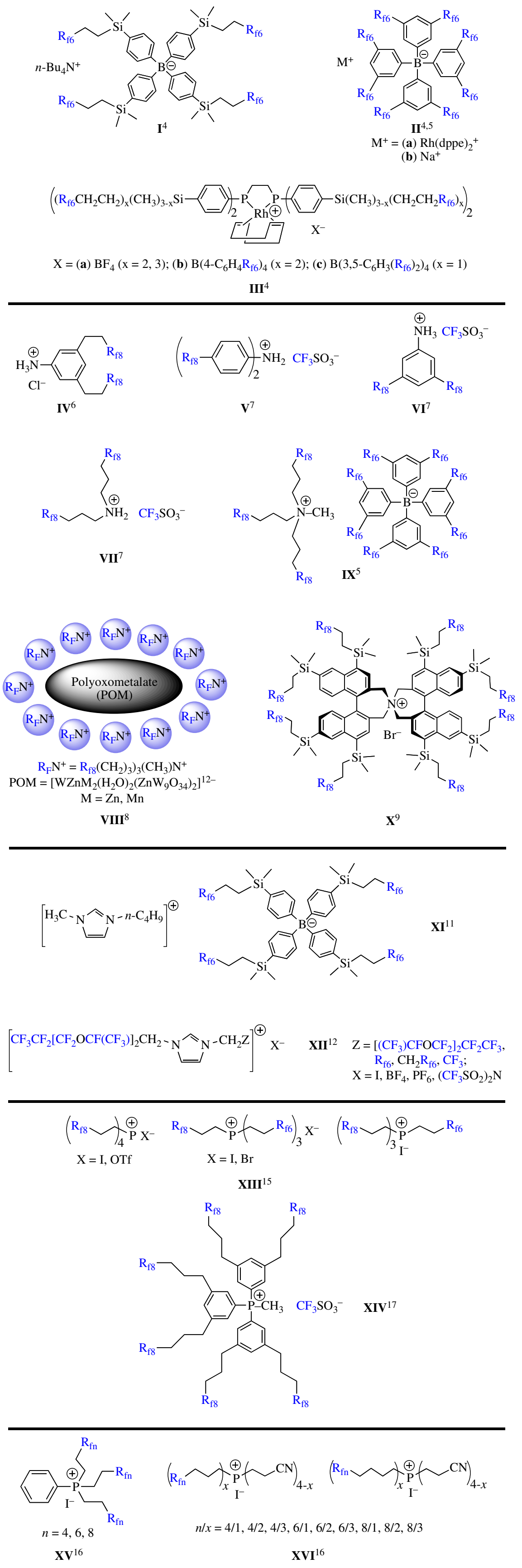


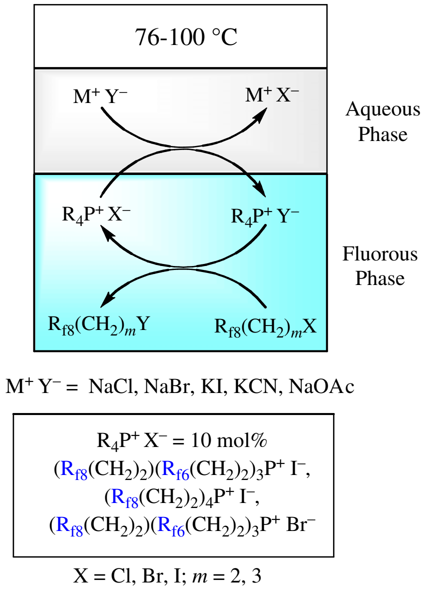
Figure 1. Fluorous salts that have documented solubilities in fluorous liquid phases (**I-XIV**), and related species (**XV-XVI**) (R_{fn}=$(CF_2)_{n-1}CF_3$).

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 fluorous solvents (which should be lower) are yet available.[10]

The ammonium or imidazolium salt **XI**, which features a non-fluorous cation and a fluorous 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 fluorous 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 fluorous ionic liquids have been described, but solubility data in fluorous solvents have not to our knowledge been reported.[13]

Yasuda, Sakakura, Stuart, Horváth, Bühlmann, and ourselves have prepared a number of fluorous 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 fluorous media is an intriguing question that remains to be addressed.

The growing portfolio of fluorous salts that are soluble in fluorous liquid phases offers increased options for introducing polar ions that may interact or react with fluorous solutes. One obvious application would be phase transfer catalysis,[19] whereby an ion of a salt that is insoluble in a fluorous solvent is transported across a phase barrier by a fluorous counter-ion with an appreciable fluorous phase affinity. Indeed, we recently established that fluorous 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-type[20] substitution reactions of fluorous alkyl halides $R_{f8}(CH_2)_mX$ (m=2, 3; X=Cl, Br, I) in perfluoromethylcyclohexane ($CF_3C_6F_{11}$) or perfluoromethyldecalin ($CF_3C_{10}F_{17}$) 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 fluorous chemistry with phase transfer catalysis have also been described.[9,22–24]



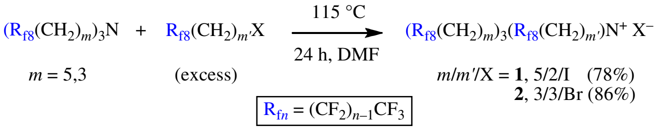
Scheme 1. Phase transfer catalysis of halide substitution reactions in fluorous media using fluorous phosphonium salts.

Quaternary ammonium salts are frequently employed as phase transfer catalysts for ionic displacement reactions in organic/aqueous solvent systems.[19] A variety of fluorous tertiary amines have been reported,[25–27] but to our knowledge, fluorous quaternary ammonium salts have not been previously described, outside of those depicted in **VIII-X** (Fig. 1). In this paper, we report (a) the first fluorous quaternary ammonium salts in which the nitrogen atom features four acyclic fluorous substituents, the iodide and bromide salts $(R_{f8}(CH_2)_2)(R_{f8}(CH_2)_5)_3N^+ I^-$ (**1**) and $(R_{f8}(CH_2)_3)_4N^+ Br^-$ (**2**), (b) their application as phase transfer catalysts for Finkelstein-type ionic displacement reactions of the general type in Scheme 1, and (c) control experiments with the non-fluorous quaternary ammonium salt $CH_3(CH_3(CH_2)_m)_3N^+ Cl^-$ (**3**, Aliquat® 336; m=2:1 7/9). A number of experiments pertaining to the scope, mechanism, and phase where substitution takes place are also presented.

2. Results

2.1. Syntheses and characterization of fluorous quaternary ammonium salts

As shown in Scheme 2, two symmetrically substituted fluorous tertiary amines differing in the number of methylene spacers, $(R_{f8}(CH_2)_5)_3N$ and $(R_{f8}(CH_2)_3)_3N$,[25] were selected. Reactions with the fluorous alkyl halides $R_{f8}(CH_2)_2I$ or $R_{f8}(CH_2)_3Br$, which also differ in the number of methylene spacers, were carried out at 115 °C in DMF. After 24 h, workups gave the fluorous quaternary ammonium salts **1** and **2** in 78% and 86% yields as analytically pure light yellow or cream white solids, respectively. They were characterized by NMR (^1H, ^{13}C) and mass spectrometry, as summarized in Experimental section.



Scheme 2. Syntheses of fluorous ammonium salts.

Both ammonium salts melted at higher temperatures than related fluorous phosphonium salts. With **1**, an apparent phase transition was visually noted prior to melting. DSC measurements confirmed the presence of additional phases, presumably liquid crystals as previously documented for a fluorous pyridinium salt.[28] The salt **1** readily dissolved in the fluorous solvents perfluoromethylcyclohexane ($CF_3C_6F_{11}$, bp 76 °C) and perfluoromethyldecalin ($CF_3C_{10}F_{17}$, bp 160 °C) at elevated temperatures, as well as the hybrid (ambiphilic) solvent $CF_3C_6H_5$ (bp 102 °C).[2,29] However, symmetrically substituted **2** was only sparingly soluble in fluorous solvents under similar conditions. Both **1** and **2** were insoluble in hexane, toluene, diethyl ether, dichloromethane, and water. In contrast, they exhibited appreciable solubilities in acetone at room temperature.

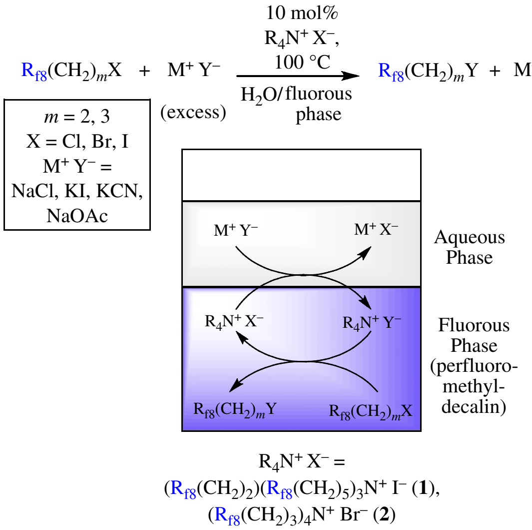
2.2. Ionic displacement reactions

The fluorous alkyl chlorides, bromides, and iodides summarized in Table 1 were treated with NaCl, KI, KCN, and NaOAc under various conditions per the general Scheme 3.

Table 1
Data for halide substitution reactions catalyzed by fluorous ammonium salts at 100 °C under the conditions of Scheme 3 unless noted[a]

Entry	Solvent	Substrate	$M^+ Y^-$	$R_4N^+ X^-$	Product	Time (h)	Convn (%)
1[b]	$CF_3C_{10}F_{17}$[c]	$R_{f8}(CH_2)_3I$	NaCl	**1**	$R_{f8}(CH_2)_3Cl$	4	34
						12	64
						24	86
2				**2**	$R_{f8}(CH_2)_3Cl$	24	70
						48	82
						72	88
3			KCN	**1**	$R_{f8}(CH_2)_3CN$	3.5	13
						24	72
4			NaOAc	**1**	$R_{f8}(CH_2)_3OAc$	4	6
						24	12
5		$R_{f8}(CH_2)_3Cl$	KI	**1**	$R_{f8}(CH_2)_3I$	24	22
						72	48
6	$CF_3C_{10}F_{17}$	$R_{f8}(CH_2)_2I$	NaCl	**1**	$R_{f8}(CH_2)_2Cl$	24	25
						48	37
						120	65
7			NaCl	**2**	$R_{f8}(CH_2)_2Cl$	24	15
						48	26
						120	41
8	$CF_3C_6H_5$[d]	$R_{f8}(CH_2)_3I$	NaCl	**2**	$R_{f8}(CH_2)_3Cl$	24	31
						60	72
9	$CF_3C_6F_5$[d]	$R_{f8}(CH_2)_3I$		**2**	$R_{f8}(CH_2)_3Cl$	5	12
						24	24

[a] Conditions: $R_{f8}(CH_2)_mX$ (0.10 mmol), $M^+ Y^-$ (0.80 mmol), solvent (0.5 mL), water (0.5 mL), $R_4N^+ X^-$ (0.010 mmol, 10 mol %).
[b] For the conversion profile, see Figure 2.
[c] Perfluoromethyldecalin.
[d] Hybrid or non-fluorous solvent.



Scheme 3. Phase transfer catalysis of halide substitution reactions in fluorous media.

First, a 0.10 M perfluoromethyldecalin solution of $R_{f8}(CH_2)_3I$ was prepared. It was treated with a nearly saturated 0.80 M aqueous solution of NaCl to give a sample with a 1:8 $R_{f8}(CH_2)_3I$/NaCl mole ratio. Then 10 mol % of **1** was added. The mixture was rapidly stirred at 100 °C for 24 h. Aliquots were periodically taken and analyzed by ^1H NMR. As indicated in entry 1 of Table 1, 86% conversion to the fluorous alkyl chloride $R_{f8}(CH_2)_3Cl$ was realized. A rate or conversion profile, representative of that made for all entries, is depicted in Figure 2. As illustrated earlier, the ^1H NMR signals of the CH_2X moieties (t) of all fluorous substrates and products are well separated.[21]

The salt **2** also catalyzed this transformation, but the rate was slower, with 70% and 82% conversion after 24 and 48 h (entry 2, Table 1). In contrast to the case with **1**, the reaction mixture was not homogeneous, as shown by the photograph in Figure 3. With **1**, samples often remained homogeneous upon cooling. Note that after reaction, the leaving group and excess nucleophile can both serve as counter-anions for the ammonium cation. No conversion was observed in experiments without **1** or **2**.

Additional nucleophiles were tested. An analogous reaction with KCN (entry 3, Table 1) afforded the corresponding fluorous cyanide $R_{f8}(CH_2)_3CN$.[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^-

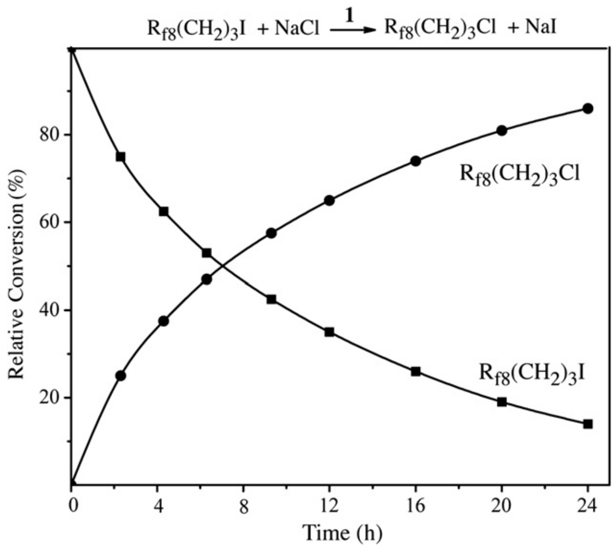


Figure 2. Conversion profile for the reaction of $R_{f8}(CH_2)_3I$ and NaCl catalyzed by **1** in water/perfluoromethyldecalin at 100 °C (entry 1, Table 1).

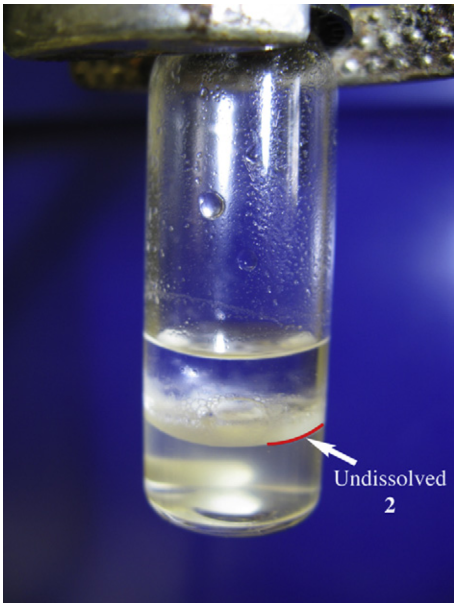


Figure 3. Photograph of the reaction of $R_{f8}(CH_2)_3I$ with NaCl in the presence of **2** at 100 °C (entry 2, Table 1) showing undissolved **2** at the water/perfluoromethyldecalin interface.

nucleophilicity order was found using fluorous 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 fluorous 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 fluorous 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 fluorous phosphonium salt catalysts.[21] All fluorous electrophiles $R_{f8}(CH_2)_mX$ become less reactive toward nucleophiles as the length of the methylene spacer decreases.[30]

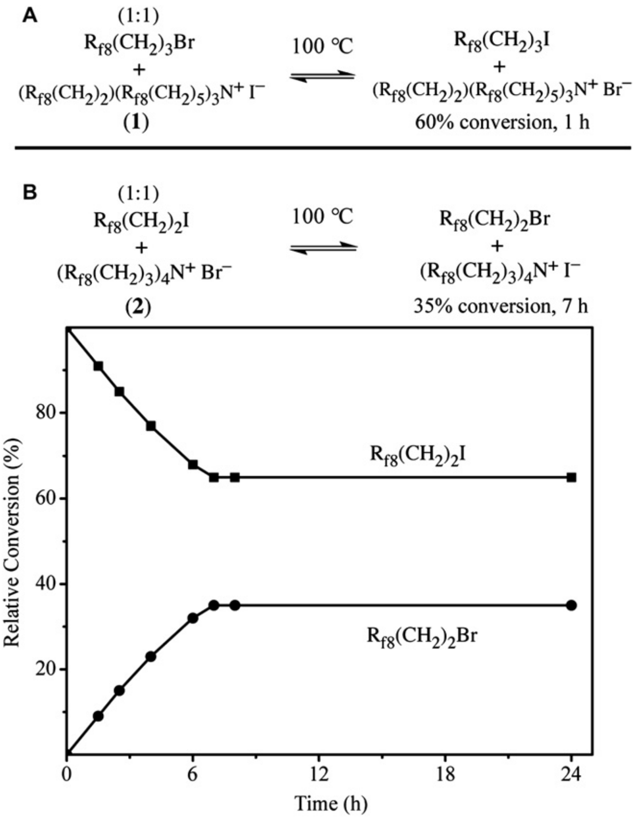
2.3. Phase requirements

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. Fluorous phosphonium salts behaved similarly.[21]

The hybrid solvent $CF_3C_6H_5$ commonly dissolves appreciable quantities of both fluorous and non-fluorous 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 fluorous 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 fluorous 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 fluorous phase.

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



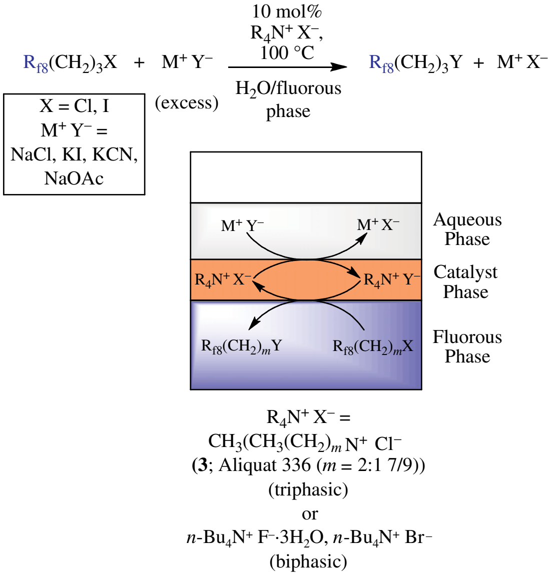
Scheme 4. Reactions of fluorous alkyl halides with equimolar amounts of fluorous quaternary ammonium salts, and conversion data.

bromide $R_{f8}(CH_2)_3Br$, which features three methylene spacers, and the ammonium *iodide* **1** reacted under homogeneous conditions to give the fluorous alkyl iodide $R_{f8}(CH_2)_3I$. 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 fluorous alkyl *iodide* $R_{f8}(CH_2)_2I$, 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 $CH_3(CH_3(CH_2)_7)_3N^+ Cl^-$ and $CH_3(CH_3(CH_2)_9)_3N^+ Cl^-$, 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 fluorous alkyl iodide $R_{f8}(CH_2)_3I$ was 85% converted to the chloride $R_{f8}(CH_2)_3Cl$ after 24 h. However, the conditions were now triphasic, with **3** layered between the fluorous 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 $R_{f8}(CH_2)_3I$ with KCN and NaOAc. In both cases, some fluorous alkyl chloride $R_{f8}(CH_2)_3Cl$ builds up, derived from the anion of **3**. In this context, entry 4 shows that $R_{f8}(CH_2)_3Cl$ is distinctly less reactive toward nucleophiles than $R_{f8}(CH_2)_3I$. As compared to the fluorous catalyst **1**, there was a marked rate enhancement with KCN, as illustrated in Figure 4. There was also a significant acceleration with NaOAc, but much less difference with NaCl.



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

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 fluorous alkyl iodide $R_{f8}(CH_2)_2I$, 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 (%)	$R_{f8}(CH_2)_3Cl$ convn (%)[b]
1	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	Aliquat 336 (**3**)[c]	3.5	32	
					12	71	
					24	85	
2		KCN	$R_{f8}(CH_2)_3CN$		1	78	7
					2	91	7
3		NaOAc	$R_{f8}(CH_2)_3OAc$		1	18	11
					3	26	5
					24	54	7
4	$R_{f8}(CH_2)_3Cl$	KI	$R_{f8}(CH_2)_3I$		1	5	
					24	20	
5[d]	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	**3**	4	43	
					24	93	
6[d]		KCN	$R_{f8}(CH_2)_3CN$		2	98	2
7[d]		NaOAc	$R_{f8}(CH_2)_3OAc$		2	73	6
					3	82	5
8[e]	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	n-$Bu_4N^+ F^- \cdot 3H_2O$	24	26	
					48	39	
					72	50	
9[e]	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	n-$Bu_4N^+ Br^-$	24	5	

[a] Conditions: $R_{f8}(CH_2)_3I$ (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] $CH_3(CH_3(CH_2)_m)_3N^+ Cl^-$, 2:1 m=7/9.
[d] As in a but without fluorous solvent; the substrate constitutes the fluorous phase, in which **3** is soluble (biphasic conditions).
[e] The catalyst is a water soluble n-Bu_4N^+ salt (biphasic conditions).

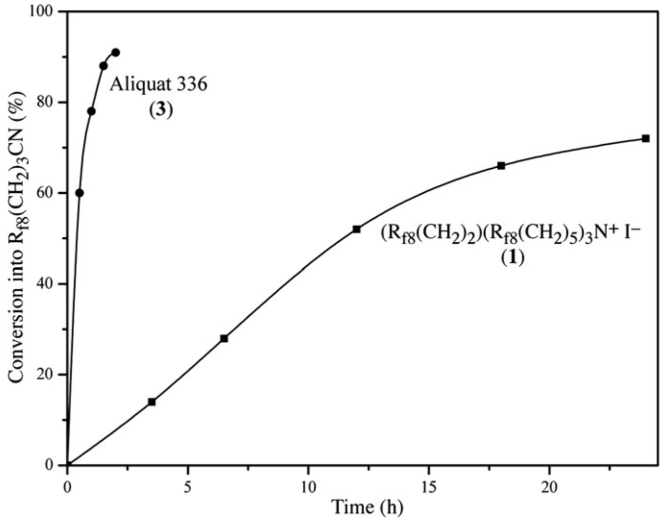


Figure 4. Conversion profiles for the reactions of $R_{f8}(CH_2)_3I$ and KCN catalyzed by **3** (●; entry 2, Table 2) and **1** (■; entry 3, Table 1) in perfluoromethyldecalin/water at 100 °C.

Interestingly, when the fluorous solvent was omitted from the reactions with **3** (entries 5–7, Table 2), conversions were even faster. The alkyl halide now served as its own fluorous liquid 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 fluorous alkyl iodide within 2 h, with 98% conversion to the fluorous alkyl cyanide. Even in the case of NaOAc, 82% conversion to the fluorous 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-$Bu_4N^+F^- \cdot 3H_2O$ or n-$Bu_4N^+ Br^-$ 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 fluorous quaternary ammonium and phosphonium salts are excellent aqueous/fluorous phase transfer catalysts for ionic displacements in highly nonpolar fluorous solvents. 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 $R_{f8}(CH_2)_3I$ and KCN is faster when catalyzed by **1** (entry 3, Table 1) than the fluorous phosphonium salt $(R_{f8}(CH_2)_2)(R_{f8}(CH_2)_3)_3P^+ I^-$ (72% vs 17% conversion after 24 h).[21] However, that of $R_{f8}(CH_2)_3I$ 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 fluorous quaternary ammonium halides can effect ionic displacements wholly within a fluorous 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 fluorous 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 fluorous 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 fluorous and upper aqueous layers. In this study, we have further shown that less lipophilic onium cations, such as n-Bu_4N^+, 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 fluorous solvents of interest? Increasing attention is being given to remediation technologies that would involve sequestering toxic or hazardous compounds in fluorous 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 fluorous 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 fluorous chemistry can be exploited in phase transfer catalysis, as summarized in a recent review.[24] These include (1) the use of fluorous ammonium salt **X** (Fig. 1) as a recoverable catalyst for organic/aqueous phase transfer processes,[9] (2) the use of fluorous aza/oxa crown ethers to catalyze the reaction of n-$C_8H_{17}Br$ and KI under liquid/solid biphase conditions using the hybrid solvent $CF_3C_6H_5$,[22] and (3) the use of fluorous oxa crown ethers to catalyze the same reaction in both $CF_3C_6H_5$ and chlorobenzene.[23] The last study also described transformations involving perfluoromethylcyclohexane as the host phase for the crown ether catalyst (middle layer), n-$C_8H_{17}Br$ or n-$C_8H_{17}OSO_2CH_3$ 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 fluorous 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 fluorous chemistry. Ionic displacement reactions are easily conducted in extremely nonpolar fluorous media at 76–100 °C with either stoichiometric or catalytic quantities of fluorous 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 fluorous salts that exhibit significant solubilities in fluorous 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 $CF_3C_6H_5$ (ABCR, 99%), simple distillation; $CF_3C_6F_5$ (ABCR, 98%), passed through neutral alumina and stored over molecular sieves; DMF, distilled from CaH_2

and freeze/pump/thaw degassed; perfluoromethyldecalin (ABCR, 88%), $R_{f8}(CH_2)_2I$ (ABCR, 97%), NaCl (Acros, 99.5%), KCN (Acros, 97%), KI (Acros, 99%), $n\text{-}Bu_4N^+\ F^-\cdot 3H_2O$ (Aldrich, 97%), $n\text{-}Bu_4N^+\ Br^-$ (Acros, +99%), Aliquat® 336 (Aldrich, $CH_3(CH_3(CH_2)_m)_3N^+\ Cl^-$, 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 ($R_{f8}(CH_2)_3I$,[36] $R_{f8}(CH_2)_3Br$,[37] $R_{f8}(CH_2)_2Br$,[15] $R_{f8}(CH_2)_3Cl$,[21b] $R_{f8}(CH_2)_3CN$,[21b] $R_{f8}(CH_2)_3OAc$[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_5, or C_6D_5H (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. ($R_{f8}(CH_2)_2$)($R_{f8}(CH_2)_5$)$_3N^+\ I^-$ (**1**).* A Schlenk flask was charged with $(R_{f8}(CH_2)_5)_3N$ (0.815 g, 0.550 mmol),[25] $R_{f8}(CH_2)_2I$ (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 $C_{49}H_{34}F_{68}IN$: 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_5, m, 8H), 1.89–1.87 (m, 2H), 1.73–1.66 (m, 6H), 1.60–1.54 (m, 6H), ^1H ($CF_3C_6F_5/CDCl_3$) 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); $^{13}C\{^1H\}$ (acetone-d_6) 52.7 (CH_2N), 47.0 (CH_2N), 35.0 (t, $^2J_{CF}$=20 Hz CH_2CF_2), 30.9, 30.4, 26.6, 23.5, 20.3. MS (3-NBA, FAB+) m/z: 1927 ($[(R_{f8}(CH_2)_2)(R_{f8}(CH_2)_5)_3N]^+$, 100%).

*4.1.2. $(R_{f8}(CH_2)_3)_4N^+\ Br^-$ (**2**).* A Schlenk flask was charged with $(R_{f8}(CH_2)_3)_3N$ (1.482 g, 1.06 mmol),[25] $R_{f8}(CH_2)_3Br$ (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 $C_{44}H_{24}BrF_{68}N$: C, 27.26; H, 1.25; N, 0.72. Found: C, 27.20; H, 1.35; N, 0.76.

NMR (δ): ^1H ($CF_3C_6F_5$+$CDCl_3$ (capillary)): 2.71 (br s, 8H, NCH_2), 2.24–2.11 (br m, 8H, CH_2R_{f8}), 1.87 (br m, 8H, $CH_2CH_2R_{f8}$); ^1H ($CF_3C_6F_5$+three drops acetone-d_6; external lock $CDCl_3$ (capillary)): 2.83 (br t, 8H, $^3J_{HH}$=7 Hz, NCH_2), 2.32 (br m, 8H, CH_2R_{f8}), 1.99 (br m, 8H, $CH_2CH_2R_{f8}$); $^{13}C\{^1H\}$ (same solvent) 52.0 (s, CH_2N), 28.2 (t, $^2J_{CF}$=22 Hz, CH_2CF_2), 20.7 (s, $CH_2CH_2CF_2$). MS (3-NBA, FAB+) m/z: 1858 ($[(R_{f8}(CH_2)_3)_4N]^+$, 60%), 1398 ($[(R_{f8}(CH_2)_3)_3NH]^+$, 100%).

4.1.3. Representative substitution reaction with fluorous catalysts (Scheme 2; Table 1, entry 1). A 4 mL vial was charged with $R_{f8}(CH_2)_3I$ (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 fluorous phase hourly and diluted with $CDCl_3$, and ^1H NMR spectra were recorded. Data: Figure 2.

4.1.4. Phase requirements. A (reaction without fluorous solvent; Table 2, entry 1). A 4 mL vial was charged with $R_{f8}(CH_2)_3I$ (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 $R_{f8}(CH_2)_3Cl$.

B (reaction with hybrid solvent; Table 1, entry 8). A 4 mL vial was charged with $R_{f8}(CH_2)_3I$ (0.059 g, 0.100 mmol), **2** (0.019 g, 0.010 mmol), $CF_3C_6H_5$ (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 $CF_3C_6H_5$ 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 $R_{f8}(CH_2)_3Br$ (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 $R_{f8}(CH_2)_2I$ and **2** is not homogeneous.

4.1.5. Representative substitution reactions with non-fluorous catalysts. A (Table 2, entry 1). A 4 mL vial was charged with $R_{f8}(CH_2)_3I$ (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 $CF_3C_6H_5$ 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 $R_{f8}(CH_2)_3I$ (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 $R_{f8}(CH_2)_3I$ phase showed a 98:2 $R_{f8}(CH_2)_3CN/R_{f8}(CH_2)_3Cl$ ratio (δ 2.49/3.65 ppm, t, CH_2X) and essentially no $R_{f8}(CH_2)_3I$ (δ 3.23 ppm).

C (Table 2, entry 8). A 4 mL vial was charged with $R_{f8}(CH_2)_3I$ (0.118 g, 0.201 mmol), $n\text{-}Bu_4N^+\ Br^-$ (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 fluorous 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), $CF_3C_6H_5$ 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 C_6D_6. The sample was stirred at 100 °C. An aliquot of the perfluoromethyldecalin layer was similarly removed, and diluted with C_6D_6. 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 $CF_3C_6H_5$ (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), $CF_3C_6H_5$ standard (0.0145 g, 0.101 mmol), and $R_{f8}(CH_2)_2I$ (0.2013 g, 0.351 mmol). The sample was stirred at 100 °C, giving a single phase. An aliquot was removed and diluted with $CDCl_3$. The *N*-methyl signal of **3** (see A) was integrated versus the CH signals of $CF_3C_6H_5$ (7.47–7.64 ppm, 5H), showing 0.089 mmol of **3** to be present. Data: see text.

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