Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 9890–9895
Tetrahedron

New fluorous/organic biphasic systems achieved by solvent tuning

Qianli Chu,[a,b] Marvin S. Yu[a,*] and Dennis P. Curran[b]

[a]*Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, USA*
[b]*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Received 23 May 2007; revised 26 June 2007; accepted 27 June 2007

Abstract—Miscibility tests between 60 pairs of fluorous and organic solvents have been performed, and a number of biphasic systems based on hydrofluoroether solvents have been identified. Mutual solubilities of a series of fluorous and organic solvents have been measured to ascertain the compositions of the biphasic systems. A qualitative solvent tuning strategy based on solvent polarity and fluorophilicity/phobicity is introduced. Solvent tuning is then used to modulate the partition coefficients (P) of triarylphosphines with 0–3 fluorous tags. The results lay a foundation for future applications of these and related biphasic systems in catalysis and extraction.

1. Introduction

Liquid–liquid biphasic systems are routinely used in both laboratory research and industrial manufacture for biphasic reactions and for product extractions.[1,2] Traditional aqueous/organic biphasic systems are now being augmented by biphasic systems such as ionic liquid/organic[3] and fluorous/organic,[4,5] among others. Biphasic methods based on fluorous and organic solvents have developed rapidly over the past decade because of their attractive features for reaction, separation, and recycle of the fluorous components.

Most applications of fluorous/organic biphasic systems use perfluoroalkanes (fluorocarbons, FCs) like FC-72 (a mixture of perfluorohexanes), perfluoromethylcyclohexane, or related compounds.[5] These solvents are extraordinarily nonpolar and often do not provide a friendly environment for the organic reaction domain that many fluorous reagents and catalysts possess. A large number of fluorine atoms (as many as 60–120) are typically appended to provide a high partition coefficient for the fluorous component, so the resulting heavy fluorous molecules (MW often >2000) can be complex and hence costly to prepare. In addition, the solubilities of heavy fluorous molecules in standard organic reaction solvents can be low, and this can cause problems at the reaction stage of a chemical process.

Recently, new fluorous/organic biphasic systems that comprise hydrofluoroethers (HFEs, RfOR) as the fluorous phase of a biphasic system have been introduced.[6] HFEs with a wide range of structures, boiling points, and other properties are commercially available and representative examples include HFE-7100 (perfluorobutyl methyl ether, $C_4F_9OCH_3$) and HFE-7500 ($C_3F_7CF(OC_2H_5)CF(CF_3)_2$).[7] The hydrofluoroethers are often less expensive than their fluorocarbon cousins and they are also more environmentally friendly because they are considerably less persistent and have low global warming potential.[8]

The lopsided structure of HFE solvents (fluoroalkyl group on one side of oxygen, alkyl group on the other) imparts increased polarity compared to fluorocarbons. This is a double-edged sword, potentially beneficial by dissolving fluorous components with polar functionalities or fewer fluorines, but potentially detrimental by dissolving organic components and by reducing the range of fluorous/organic biphasic systems that are available. However, hydrofluoroethers and fluorocarbons are generally miscible, so the fluorousness of an HFE phase can be readily adjusted with a fluorocarbon additive.[6c] Further, HFEs are highly hydrophobic, so the fluorophobicity of any organic phase can be increased simply by wetting it.

To understand how these features play out in practice, we undertook a systematic investigation first to identify and then to characterize fluorous/organic biphasic systems based on hydrofluoroethers. We report herein the results of this study. These results lay the foundation for subsequent applications in biphasic reactions and separations as well as for rational design and application of related biphasic systems.

---

[*] Corresponding author. Tel.: +1 412 826 3062; fax: +1 412 826 3053; e-mail: m.yu@fluorous.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.06.092

2. Results and discussion

2.1. Fluorous and organic solvents studied

The fluorous solvents chosen for this study were FC-72, HFE-7100, HFE-7500,[7] and F-626,[6a,b] and their formulas and selected physical properties are summarized in Table 1.[6,8] F-626 is perfluorohexylethyl 1,3-dimethylbutyl ether. Unlike the HFE solvents, F-626 has an ethylene spacer between the ether oxygen and the perfluoroalkyl group. The organic countersolvents selected for this study include common protic and aprotic solvents that range in polarity from non-polar (toluene) through moderately polar (acetone and THF) to polar (methanol, acetonitrile, and DMF). Selected properties of these solvents are listed in Table 2 for comparison.

The FC and HFE solvents are more or less volatile depending on the structure (bps 56–128 °C) and can be readily evaporated. In contrast, the high boiling F-626 (bp 214 °C) is best viewed as a liquid support.[6a,b] While the fluorine content of these solvents (by molecular weight) varies from 55% to 78%, each is miscible with all the others at room temperature. All the solvents have melting points or pour points lower than −78 °C.

Each of the fluorous solvents has a higher density than all of the organic solvents, so the fluorous phase is on the bottom of every biphasic system. To provide a rough proxy for solvent polarity,[9] we calculated the dipole moments of the fluorous ethers with Spartan, and these ranged from 2.3 to 2.7 Debye (D). The calculated dipole moment of FC-72 is 0 D. While these calculated values may not be very accurate, they suffice to place the fluorous ethers in the ballpark of moderately polar solvents like dichloromethane and THF. Comparisons of dielectric constants provide a similar conclusion.

2.2. Miscibility tests

The miscibility of 60 pairs of fluorous solvents and solvent blends with organic solvents was first ascertained with the aid of simple test. The test was performed by shaking sealed vials containing a mixture of 1 mL fluorous solvent and 1 mL organic solvent for 30 min at a speed of 1200 rpm. The vials were allowed to stand for 24 h, and then inspected visually for an interface. The systems that appeared as a single, clear phase without any visible interface, cloudiness or separated droplets were deemed miscible. Other systems were deemed immiscible, and usually exhibited two phases with an obvious interface. The phase separations were usually complete within a few minutes. The results of all miscibility tests shown in Table 3 are divided into three parts: entries 1–4 show all the pairwise combinations of pure

Table 3. Miscibility tests between the fluorous and organic solvent pairings

Entry	Solvents	CH_3CN	THF	DMF	Toluene	MeOH	Acetone
1	FC-72	IM	IM	IM	IM	IM	IM
2	HFE-7100	M	M	M	M	M	M
3	HFE-7500	IM	M	IM	M	IM	M
4	F-626	IM	M	IM	M	IM	M
5	HFE-7100: FC-72 (75:25)	IM	M	IM	M	IM	M
6	HFE-7500: FC-72 (75:25)	IM	M	IM	IM	IM	M
7	F-626:FC-72 (75:25)	IM	M	IM	M	IM	M
8	HFE-7100: FC-72 (50:50)	IM	M	IM	IM	IM	IM
9	HFE-7500: FC-72 (50:50)	IM	IM	IM	IM	IM	IM
10	F-626:FC-72 (50:50)	IM	IM	IM	IM	IM	IM

'M' indicates miscible and 'IM' indicates immiscible.
Solvent pairs (1 mL each) were shaken for 30 min at 1200 rpm then allowed to stand for 24 h.

Table 1. Molecular formulas and selected physical properties of the fluorous solvents used in this work[a]

	FC-72	HFE-7100	HFE-7200	HFE-7500	F-626
Formula	C_6F_{14}	$C_4F_9OCH_3$	$C_4F_9OC_2H_5$	$C_3F_7CF(OC_2H_5)$–$CF(CF_3)_2$	$CF_3(CF_2)_5CH_2CH_2O$–$CH(CH_3)CH_2CH(CH_3)_2$
F-content (%)[b]	78.3	68.4	64.7	66.3	55.1
Mp (°C)[c]	−90	−138	−135	−110	<−78
Bp (°C)	56	61	76	128	214
Density (g/mL)	1.68	1.42	1.51	1.61	1.35
Dipole moment (D)[d]	0	2.4	2.5	2.7	2.3
Dielectric constant	1.8	7.4	7.4	5.8	—

[a] Taken from Refs. 6a and 7.
[b] Percentage by molecular weight.
[c] Melting point or pour point.
[d] Calculated by Spartan'02 (Wavefunction, Inc.) with the MMFF method.

Table 2. Selected properties of organic solvents used in this work[a]

	Acetone	THF	MeOH	CH_3CN	Toluene	DMF
Mp (°C)	−94	−108	−98	−48	−93	−61
Bp (°C)	56	65	65	81	110	153
Density (g/mL)	0.79	0.89	0.79	0.79	0.87	0.94
Dipole moment (D)	2.69 (3.8[b])	1.75 (2.3[b])	2.87 (2.2[b])	3.44 (4.5[b])	0.31 (0.2[b])	3.86 (4.7[b])
Dielectric constant	20.7	7.6	32.6	37.5	2.4	38.3

[a] Taken from 'Burdick and Jackson Solvent Guide'.
[b] Data calculated by Spartan'02 (Wavefunction, Inc.) with the MMFF method are listed in parentheses.

fluorous and organic solvents. In entries 5–7, the fluorous ether solvents are blended with 25% FC-72, while in entries 6–10 they are blended with 50% FC-72.

As expected, the perfluorocarbon FC-72 is not miscible with any of the organic solvents tested (entry 1).[4] At the other extreme, HFE-7100 is miscible with all the organic solvents (entry 2). In the middle, HFE-7500 and F-626 are miscible in the less polar solvents (THF, toluene, and acetone) and immiscible in the more polar solvents (acetonitrile, methanol, and dimethylformamide) (entries 3 and 4). This is sensible since more polar solvents tend to be more fluorophobic.

Addition of 25% FC-72 (entries 5–7) causes phase separation with all three of the polar solvents and HFE-7100, and the toluene phase also separates from the HFE-7500 blend. Increasing the FC-72 content to 50% of the fluorous phase now gives two phases for 17 of the 18 pairings (entries 8–10); the only miscible pair is HFE-7100/FC-72 (50:50) and THF. This is consistent with qualitative observations that THF is the most fluorophilic of all the solvents in Table 1.

Qualitatively, the results in Table 3 demonstrate that the ether solvents merit the ‘fluorous’ descriptor, even if they are not as fluorous as FC-72. Further, they show that the miscibility of fluorous/organic parings can be turned on or off for many blends by adding or removing FC-72. This feature can be handy for controlling phase behavior in various chemical processes.[5a] The results also have implications for tuning partition coefficients, as discussed in more detail below.

2.3. Mutual relative solubility tests

Immiscibility of the two solvent pairs is not the only important feature for biphasic reactions and separations. Because each solvent is partially soluble in the other, the solubilizing properties of a fluorous solvent saturated with the organic countersolvent (or vice versa) can be significantly different from the native solvent. Thus, it is also important to know the approximate mutual solubilities of the solvent pairings in biphasic mixtures.

Experiments were next carried out to measure the mutual relative solubilities of each solvent in the corresponding countersolvent in all the immiscible biphasic systems. Specifically, 1 μL samples were withdrawn (in triplicate) from each layer of an immiscible biphasic system and injected into a GC for analysis. Each sample showed two or three peaks, and the ratio of absolute peak areas of a given solvent in the samples of the two phases was taken to indicate its distribution between these phases.[10]

Table 4 summarizes the quantitative results in a presentation parallel to that of the qualitative data in Table 3. For each immiscible pairing, the number to the left of the backslash represents the percentages of the fluorous solvent in the organic (top) phase in volume while the number to the right represents the percentages of the organic solvent in the fluorous (bottom) phase after mixing. In other words, the compositions (by volume) of the two phases can be readily estimated by the appropriate numbers. For example, in entry 1 and column 3, there was 0.5% of the FC-72 and 99.5% of the CH_3CN in the top organic phase, while 0.2% of the CH_3CN with 99.8% the FC-72 was in the bottom fluorous phase. In the case of fluorous solvent blends, the composite number of the two fluorous solvents is given for simplicity (see Supplementary data for details). As can be seen from the data for the pure solvent pairings, the composite number of a fluorous blend in an organic phase is due mainly to the presence of the more soluble fluorous ether with a small contribution from the less soluble FC-72.

The solubilities of each solvent in the mutually saturated phases range from very small (see example above) to substantial. For example, in the pairing of HFE-7100/FC-72 (75/25) and MeOH (entry 5, column 7), 31.7 vol % of the solvent presented in the fluorous phase is MeOH while 11.4% of the MeOH layer is the fluorous solvents. The volume of organic phase became 1.36 mL and the fluorous became only 0.64 mL after the mixing (see Supplementary data for the calculations). This results in a visually detectable change of relative volumes of the phases.

The data in Table 4 are highlighted to simplify interpretation. The data of those systems <5.0% of each phase distributes to the other are shown in bold, while data for those >5% and <10.0% are in italic. The remainder (>10%) are in bold and italic, and as usual ‘M’ denotes miscible. For the 18 biphasic systems involving the pure hydrofluoroether (HFE) solvents (no FC-72-added, entries 2–4) more than two thirds are miscible, only two fall into the bold category while three are in the intermediate italic category. After blending with 25% FC-72, less than half of pairings are miscible, and five are now in the bold category with one in italic category

Table 4. Percentages of fluorous solvent in a dry organic phase (left) and organic solvent in the fluorous phase (right) after mixing[a,b,c]

Entry	Solvents	CH_3CN	THF	DMF	Toluene	MeOH	Acetone
1	FC-72	**0.5/0.2**	**2.3/3.7**	**0/0.1**	**1.2/2.0**	**0.8/0**	**1.5/2.0**
2	HFE-7100	M[b]	M	M	M	M	M
3	HFE-7500	**3.0/4.5**	M	**0.6/4.4**	M	*5.9/1.5*	M
4	F-626	*0.8/9.0*	M	*3.9/10.0*	M	***11.7/10.1***	M
5	HFE-7100:FC-72 (75:25)	***23.4/14.6***	M	***12.6/11.9***	M	***31.7/11.4***	M
6	HFE-7500:FC-72 (75:25)	**2.3/2.7**	M	**0.6/2.2**	***12.3/14.0***	**4.0/0**	M
7	F-626:FC-72 (75:25)	**4.8/4.9**	M	**2.6/4.7**	M	*5.9/2.0*	M
8	HFE-7100:FC-72 (50:50)	***13.2/2.5***	M	*6.6/3.1*	***18.5/14.5***	***17.8/1.3***	***34.8/32.3***
9	HFE-7500:FC-72 (50:50)	**1.7/1.6**	***14.0/16.5***	**0.4/1.0**	*6.4/7.2*	**2.4/0**	***12.7/12.4***
10	F-626:FC-72 (50:50)	**3.6/2.2**	***34.8/26.0***	**1.7/2.0**	30.6/24.2	**4.0/0**	***31.3/12.6***

[a] Experiments conducted as described for Table 3 with analysis by GC.
[b] ‘M’ stands for miscible.
[c] Bold numbers indicate <5% solvent transfer to the second phase; italic, 5–10%; bold and italic, >10%.

(entries 5–7). For the 50% FC-72 blend, only one system is miscible, six fall into the bold category and two into italic category (entries 8–10). Thus, in a very simple view, the increase of the highlighted entries with the increase of FC-72 in the blend illustrates that the fluorous phase is becoming more fluorous and the organic phase less fluorous.

The mutual solubility data further reinforce the qualitative classification of organic solvents, with acetone, toluene, and (especially) THF being more fluorophilic, and acetonitrile, methanol, and DMF being more fluorophobic.[11]

2.4. A simple solvent tuning strategy

Generally speaking, the miscibilities of various solvents can often be estimated from the Hildebrand solvent scale,[12] which are related to the energy of adsorption of a given solvent on alumina. The further apart two solvents are on the scale, the more likely they are to be immiscible.

In thinking about solvent tuning for fluorous/organic biphasic systems, we use the qualitative two-dimensional model illustrated in Figure 1.[6c] The axes here are ‘fluorophility’ and ‘polarity’, and to emphasize the qualitative nature of the model, we deliberately leave both axes unitless. In principle, various measured or calculated values could be used for either axis.[9,13] Moving away from the origin (lower left corner) in the fluorous direction (up) eventually leads to highly fluorous and extremely non-polar perfluorocarbons like FC-72. Moving in the ‘polar’ direction (right) eventually leads to water. All other solvents are depicted in the triangular space between these two extremes, depending on their polarity and fluorophilicity.

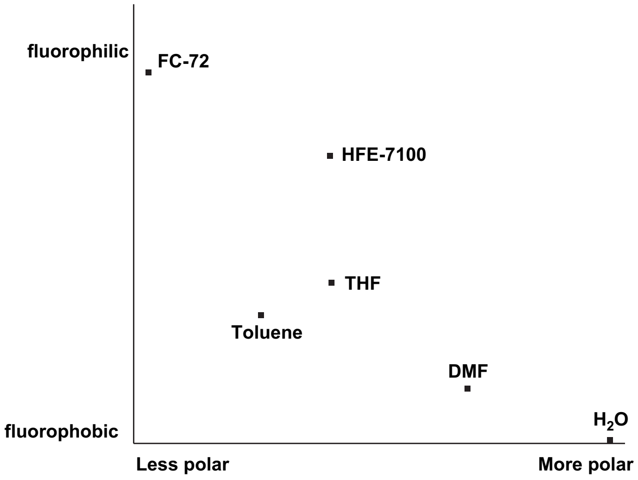

Figure 1. A qualitative model for the general strategy of solvent tuning with various fluorous/organic biphasic systems.

In a qualitative sense, the further apart two solvents are in any direction, the more likely they are to be immiscible. Solvent pairings that are miscible can be rendered immiscible by appropriate increase or decrease of the fluorophilicity or polarity by blending with a cosolvent further out toward one of the two extremes. For example, HFE-7100 and DMF are miscible, but adding some FC-72 renders that medium more fluorophilic and a DMF phase separates, while adding some water renders the medium more fluorophobic and an HFE-7100 phase separates. This two-dimensional view is also useful for modulating partition coefficients, as illustrated in Figure 1.

2.5. Tuning of organic solvents

While the miscibility data in Table 3 already identify a number of interesting biphasic pairings, the mutual solubilities of these pairings are high in some cases with low partition coefficients being the likely result in separation applications. As suggested by Figure 1, water should be an ideal modulator to drive fluorous components out of the organic phase, and indeed this is already known in both extraction (liquid–liquid and solid–liquid) and chromatography applications.[6]

To further understand the effect of water on mutual solubilities, we selected two fluorophobic organic solvents (acetonitrile and DMF) and one fluorophilic organic solvent (THF) for modulation by blending with a small amount (5 vol %) of water. The fluorous solvents used were HFE-7100 and HFE-7500, neat and blended with 25% and 50% FC-72. Mutual solubilities were measured as described above, and the data are shown in the usual way in Table 5. To facilitate comparisons, the data for the ostensibly dry solvents from Table 4 are included in parenthesis. The solubility measurements neglect the partitioning of water, which is not expected to distribute any significant amount in the fluorous phase.

Qualitatively, five of the eight solvent pairings that were miscible with dry solvents are now immiscible, including three of the six pairings with the fluorophilic THF. Quantitatively, decreased mutual solubility was observed in all the pairings that were previously immiscible. In simple terms, the organic layer becomes more fluorophobic. In fluorous SPE and HPLC applications, the saying is that ‘a little water goes a long way’.[14] Not surprisingly, that also applies for liquid–liquid partitions.

Table 5. Approximate percentages of starting fluorous solvent that partitions into a wet (5% water) organic phase (left) and starting organic solvent that partitions into the fluorous phase (right)[a]

Entry	Solvents	CH_3CN with 5% H_2O (CH_3CN)	THF with 5% H_2O (THF)	DMF with 5% H_2O (DMF)
1	HFE-7100	20.8/26.5 (M[b])	M (M)	6.4/15.4 (M)
2	HFE-7500	1.3/3.8 (3.0/4.5)	M (M)	0.2/3.6 (0.6/4.4)
3	HFE-7100+FC-72 (75:25)	13.8/6.9 (23.4/14.6)	M (M)	4.8/7.8 (12.6/11.9)
4	HFE-7500+FC-72 (75:25)	1.0/2.3 (2.3/2.7)	10.3/17.7 (M)	0.3/2.0 (0.6/2.2)
5	HFE-7100+FC-72 (50:50)	8.6/1.8 (13.2/2.5)	23.8/24.1 (M)	3.0/3.0 (6.6/3.1)
6	HFE-7500+FC-72 (50:50)	0.8/1.1 (1.7/1.6)	8.7/11.5 (14.0/16.5)	0.1/1.0 (0.4/1.0)

[a] Experiments conducted as described for Table 3 with analysis by GC.

[b] ‘M’ stands for miscible.

2.6. Partition coefficient tests

These data and the qualitative model that emerges can be used to select biphasic reaction and extraction systems that provide a suitable compromise in partition coefficients for fluorous and organic components, and some of the preliminary data herein have already been used to devise a suitable extraction system for a fluorous Mitsunobu reaction.[6d] Here we illustrate quantitatively the effects of solvent tuning on the partition coefficients of a series of fluorous triarylphosphines.[15] These compounds are used as fluorous equivalents of triphenylphosphines in the Wittig, Staudinger, and Mitsunobu reactions as well as for halogenations of alcohols and acids.[16]

The partition coefficients (*P*) of the phosphines with 0–3 fluorous tags[15] (in *para* positions) have been measured in eight biphasic systems selected from the previous experiments with CH_3CN or DMF as the organic layer and FC-72, HFE-7100, HFE-7500 or mixtures thereof as the fluorous layer (Table 6). The measured partition coefficients (*P*) are shown in the usual way as [% phosphine dissolved in fluorous layer]/[% phosphine dissolved in organic layer].

The heavy fluorous phosphine with three fluorous tags (51 F atoms, far right column) shows little solubility in either phase of the classic biphasic systems (FC-72/CH_3CN and FC-72/DMF, entries 1 and 2). However, it is dissolved in all six new biphasic systems and with a very high partitioning in favor of fluorous layers ($P>100$, entries 3–8). Even the phosphine with two fluorous tags (26 F atoms) exhibits high partition coefficients in favor of the fluorous layer for four of the six tuned systems ($P=42$, 99, 19, and 42, entries 5–8). This is a significant improvement over the starting polar organic/non-polar fluorous systems (entries 1 and 2). Thus, the solvent tuning strategy successfully identifies biphasic systems with high partition coefficients in favor of fluorous layers for phosphines with only two to three fluorous tags.

Importantly, the non-fluorous triphenylphosphine partitions favorably into the organic layer in all the biphasic systems listed in Table 6. Its partitioning is hardly disturbed by the tuning for improving the partition coefficients of the fluorous variants into fluorous phase. This shows the potential of these tuned biphasic systems and the solvent tuning strategy for separating fluorous compounds from organic variants and other organic impurities.

3. Summary

In summary, the general picture of miscibility of novel fluorous/organic biphasic systems shown by the quantitative studies reveals new opportunities for fluorous reactions and separations. The results might be applied in many areas, including industrial processes where cost and efficiency limit the applications of current fluorous separation methods. For example, solvent tuning can be used to identify liquid–liquid biphasic systems suitable for removing light fluorous scavengers, reagents, and catalysts. This in turn reduces the complexity and therefore the cost of the fluorous reaction component. The improved partition coefficients render continuous extraction unnecessary, and the resulting liquid separations may be competitive with or even superior to solid phase extractions.

A rational qualitative strategy for tuning miscibility and mutual solubility of biphasic systems has also been demonstrated. Taken together with other information such as polarity and fluorous content of solutes, this gives a better understanding of the partition coefficient, and facilitates the design and identification of useful fluorous/organic biphasic systems.

4. Experimental

4.1. General

All solvents used in the tests are anhydrous or HPLC grade and commercially available at Aldrich, 3M or Fluorous Technologies, Inc. The miscibility tests were carried out under aerobic atmosphere. GC analyses were performed on a Hewlett-Packard 5890 instrument with split mode (column: 30 m×0.32 mm×0.25 μm HP-1 methyl siloxane).

4.2. Miscibility tests

General procedures for the miscibility tests: the test was performed with a 1 mL:1 mL mixture of fluorous and organic solvent. The mixture was shaken by an IKA® Model MS1 minishaker for 30 min at a speed of 1200 revolutions per min (rpm). The systems whose interfaces disappeared for more than one day were considered miscible.

Table 6. The partition coefficients (*P*) of phosphines with 0–3 fluorous tags in the fluorous/organic biphasic systems[a]

Entry	Biphasic systems		PPh_3	$(C_8F_{17}(CH_2)_2C_6H_4)PPh_2$	$(C_6F_{13}(CH_2)_2C_6H_4)_2PPh$	$(C_8F_{17}(CH_2)_2C_6H_4)_3P$
	Fluorous	Organic				
1	FC-72	CH_3CN	<0.1:>99.9	3.2:96.8	64.7:35.3	—[b]
2	FC-72	DMF	<0.1:>99.9	0.8:99.2	12.9:87.1	—[b]
3	HFE-7500	CH_3CN	3.7:96.3	72.3:27.7	92.6:7.4	>99.9:<0.1
4	HFE-7500	DMF	0.4:99.6	41.9:58.1	87.8:12.2	>99.9:<0.1
5	HFE-7500	CH_3CN with 5% H_2O	4.8:95.2	84.8:15.2	97.7:2.3	>99.9:<0.1
6	HFE-7500	DMF with 5% H_2O	0.9:99.1	79.2:20.8	99.0:1.0	>99.9:<0.1
7	HFE-7100+FC-72 (50:50)	CH_3CN with 5% H_2O	3.6:96.4	61.3:38.7	95.0:5.0	>99.9:<0.1
8	HFE-7100+FC-72 (50:50)	DMF with 5% H_2O	0.5:99.5	41.6:58.4	97.7:2.3	>99.9:<0.1

[a] Phosphine (50 mg) was dissolved in 2 mL biphasic mixture and shaken for 30 min at 1200 rpm then allowed to stand for 24 h. Both the layers were measured by GC.

[b] The phosphine has little solubility in the biphasic system.

4.3. Mutual relative solubility tests

General procedures for the mutual relative solubility tests: for all the immiscible biphasic systems, 1 μL sample was taken from each layer and injected into GC for analysis. The ratio of two absolute peak areas of one solvent in the two samples was utilized as an indicator of its distribution (volume) in the two phases. The data are averages of three consecutive injections.

4.4. Partition coefficient tests

General procedures for the mutual relative solubility tests: for each of the eight selected biphasic systems, 50 mg phosphine was dissolved in a 1 mL:1 mL mixture of fluorous and organic solvent. It was shaken for 30 min at 1200 rpm then allowed to stand for 24 h. 1 μL of sample was taken from each layer and injected into GC for analysis. Each sample showed a peak of the phosphine, and the ratio of absolute peak areas of it in the samples of the two phases was taken to indicate its distribution between the two phases.

Acknowledgements

This work was supported by the National Science Foundation (NSF) SBIR Phase I Grants (2R44GM062717-02 and 2R44GM067326-02) and by the National Institute of General Medical Sciences of the National Institutes of Health. We thank Dr. Tadamichi Nagashima at FTI for assistance with the GC analyses and Prof. Ilhyong Ryu at Osaka Prefecture U. for generous gift of F-626.

Supplementary data

It contains the raw data of the GC analyses and shows how the calculations of mutual solubilities were accomplished (4 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.092.

References and notes

1. *Handbook of Separation Process Technology*; Rousseau, R. W., Ed.; Wiley: New York, NY, 1987.
2. (a) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hill: New York, NY, 1994; (b) Cornils, B. *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer: Berlin, 1999; Vol. 206, pp 133–152; (c) *Green Reaction Media in Organic Synthesis*; Mikami, K., Ed.; Blackwell: Ames, IO, 2005.
3. Dont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
4. (a) *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, 2004; (b) Rábai, J.; Szlavik, Z.; Horváth, I. T. *Handbook of Green Chemical Technology*; Clark, J., MacQuarrie, D., Eds.; Blackwell: Ames, IO, 2002; p 502; (c) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *7*, 1175–1196.
5. Separation strategies: (a) Gladysz, J. A.; Correa de Costa, R. *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 24–40; Fluorous solvents: (b) Gladysz, J. A.; Emnet, C. *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 11–23; (c) Ryu, I.; Matsubara, H.; Emnet, C.; Gladysz, J. A.; Takeuchi, S.; Nakamura, Y.; Curran, D. P. *Fluorous Solvents*; Blackwell: Ames, IO, 2005; Fluorous partition coefficients: (d) Gladysz, J. A.; Emnet, C.; Rabai, J. *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 56–100.
6. (a) Matsubara, H.; Yasuda, S.; Sugiyama, H.; Ryu, I.; Fujii, Y.; Kita, K. *Tetrahedron* **2002**, *58*, 4071–4076; (b) Fukuyama, T.; Arai, M.; Matsubara, H.; Ryu, I. *J. Org. Chem.* **2004**, *69*, 8105–8107; (c) Yu, M. S.; Curran, D. P.; Nagashima, T. *Org. Lett.* **2005**, *7*, 3677–3680; (d) Curran, D. P.; Bajpai, R.; Sanger, E. *Adv. Synth. Catal.* **2006**, 1621–1624; (e) HFEs have also been used as reaction solvents in heavy fluorous synthesis. See, for example, Mizuno, M.; Goto, K.; Miura, T.; Matsuura, T.; Inazu, T. *Tetrahedron Lett.* **2004**, *45*, 3425–3428.
7. HFE solvents are produced by 3M under the tradename Novec: http://www.3m.com/Product/information/Novec-Engineered-Fluid.html. Most solvents are mixtures of isomers. For example, HFE-7100 is a mixture of perfluorobutyl methyl ether and perfluoroisobutyl methyl ether (*n*- and *i*-butyl groups).
8. (a) Wallington, T. J.; Nielsen, O. J. *Handbook of Environmental Chemistry: Organofluorines*; Neilson, A. H., Ed.; Springer: Berlin, 2002; Vol. 3, pp 85–102; (b) Most HFEs are not classified as a volatile organic compound (VOC), and are approved for use under the US EPA Significant New Alternatives Program (SNAP): http://www.epa.gov/ozone/snap/regulations.html.
9. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: New York, NY, 2003.
10. Raw data and details of the calculations can be found in the Supplementary data.
11. Lu, Y.; Zhang, W. Fluorous Technologies, unpublished results.
12. Hildebrand, J. H.; Scott, R. L. *The Solubility of Non-Electrolytes*; Reinhold: New York, NY, 1959.
13. (a) Kiss, L. E.; Kovesdi, I.; Rabai, J. *J. Fluorine Chem.* **2001**, *108*, 95–109; (b) Huque, F. T. T.; Jones, K.; Saunders, R. A.; Platts, J. A. *J. Fluorine Chem.* **2002**, *115*, 119–128; (c) Daniels, S. M.; Saunders, R. A.; Platts, J. A. *J. Fluorine Chem.* **2004**, *125*, 1291–1298; (d) Duchowicz, P. R.; Fernandez, F. M.; Castro, E. A. *J. Fluorine Chem.* **2004**, *125*, 43–48.
14. (a) Curran, D. P. *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 101–127; (b) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865.
15. (a) The fluorous phosphines are commercially available at Aldrich, Wako, and Fluorous Technologies. (b) Prof. Dennis P. Curran owns an equity interest in Fluorous Technologies.
16. (a) Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751–8757; (b) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861–5872; (c) Lindsley, C. W.; Zhao, Z.; Newton, R. C.; Leister, W. H.; Strauss, K. A. *Tetrahedron Lett.* **2002**, 4467–4470.