

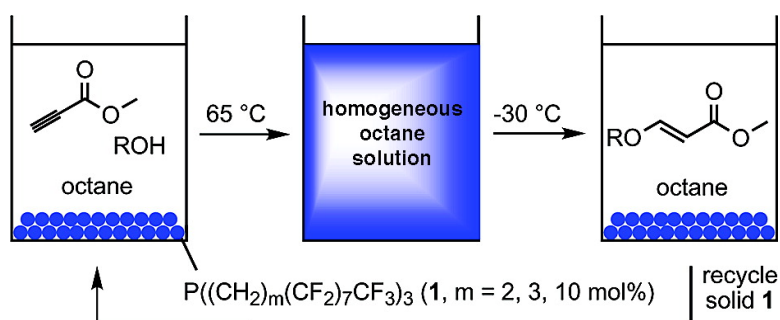
Article

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Fluorous Catalysis under Homogeneous Conditions without Fluorous Solvents: A “Greener” Catalyst Recycling Protocol Based upon Temperature-Dependent Solubilities and Liquid/Solid Phase Separation

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Abstract: The thermomorphic fluorous phosphines $P((CH_2)_m(CF_2)_7CF_3)_3$ ($m = 2$, **1a**; $m = 3$, **1b**) exhibit ca. 600-fold solubility increases in *n*-octane between -20 (**1a** = 0.104 mM) and 80 °C (63.4 mM) and 1500-fold solubility increases between -20 and 100 °C (151 mM). They catalyze conjugate additions of alcohols to methyl propiolate under homogeneous conditions in *n*-octane at 65 °C and can be recovered by simple cooling and precipitation and used again. This avoids the use of fluorous solvents during the reaction or workup, which are expensive and can leach in small amounts. Teflon shavings can be used to mechanically facilitate recycling, and ^{31}P NMR analyses indicate $>97\%$ phosphorus recovery (85.2% **1a**, 12.2% other). ^{19}F NMR analyses show that 2.3% of the $(CF_2)_7CF_3$ moieties of **1a** leach, in some form, into the *n*-octane (value normalized to phosphorus). **1a** similarly catalyzes additions in the absence of solvent. Yield data match or exceed those of reactions conducted under fluorous/organic liquid/liquid biphasic conditions. The extra methylene groups render **1b** more nucleophilic than **1a** and, thus, a more active catalyst. The temperature dependence of the solubility of **1a** is measured in additional solvents and compared to that of the nonfluorous phosphine PPh_3 .

Introduction

Over the last eight years, many new catalysts with high affinities for fluorous solvents have been synthesized.^{1–3} This has been prompted by the development of “fluorous biphasic catalysis”,^{2a} which, as most often practiced, exploits the markedly temperature-dependent miscibilities of organic and fluorous solvents.⁴ As shown schematically in Figure 1A, most combinations give two phases at room temperature. However, with moderate heating, one phase is obtained. Reactions can be catalyzed under monophasic conditions at the high-temperature limit, and the products and catalyst can be separated under biphasic conditions at the low-temperature limit. Most fluorous solvents in current use are saturated perfluorocarbons, but many

other types of fluids are available, encompassing a broad range of molecular weights and phase behavior.⁴

High fluorous liquid-phase affinities can be engineered into catalysts by attaching a number of “pony tails” of the formula $(CH_2)_m(CF_2)_{n-1}CF_3$, abbreviated $(CH_2)_mR_{fn}$, so that n represents the number of fluorinated carbons. This often results in a low-melting solid. In the absence of such groups, most organic molecules of interest show marked affinities for the nonfluorous phase ($>95: <5$). Typical values of m and n are 0–3 and 6–10, respectively. The $(CH_2)_m$ segment can be viewed as an electronic “tuning element”, the length of which modulates the effect of the highly electron-withdrawing perfluoroalkyl groups on the reaction center.

No catalyst recovery method is without potential drawbacks.⁵ Accordingly, the fluorous solvent requirement in Figure 1A has prompted various concerns, the major of which involve cost, solvent leaching, and environmental persistence.⁴ For example, the ether layer of an ether/water liquid/liquid biphasic system contains dissolved water. Small amounts of fluorous solvents are similarly found in the organic layers of fluorous/organic liquid/liquid biphasic systems. This makes losses unavoidable upon phase separation. Although saturated perfluorocarbons appear to have almost infinite half-lives in the environment, it should be emphasized that they do not contribute to ozone

- (1) See: Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823 and the following articles in this special issue entitled “Fluorous Chemistry”.
- (2) (a) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641. (b) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37. (c) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S. *J. Fluorine Chem.* **1999**, *94*, 183. (d) Hope, E. G.; Stuart, A. M. *J. Fluorine Chem.* **1999**, *100*, 75. (e) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (f) Dobbs, A. P.; Kimberly, M. R. *J. Fluorine Chem.* **2002**, *118*, 3.
- (3) Selected full papers with extensive literature background: (a) Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rábai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998**, *120*, 3133. (b) Juliette, J. J. J.; Rutherford, D.; Horváth, I. T.; Gladysz, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 2696. (c) Richter, B.; Spek, A. L.; van Koten, G.; Deelman, B.-J. *J. Am. Chem. Soc.* **2000**, *122*, 3945. (d) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866. (e) Colonna, S.; Gaggero, N.; Montanari, F.; Pozzi, G.; Quici, S. *Eur. J. Org. Chem.* **2001**, 181.
- (4) Survey of practical considerations and underlying physical principles: Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *190–192*, 587.

- (5) For essays on the “ideal recoverable catalyst”, see: (a) Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319. (b) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3214.

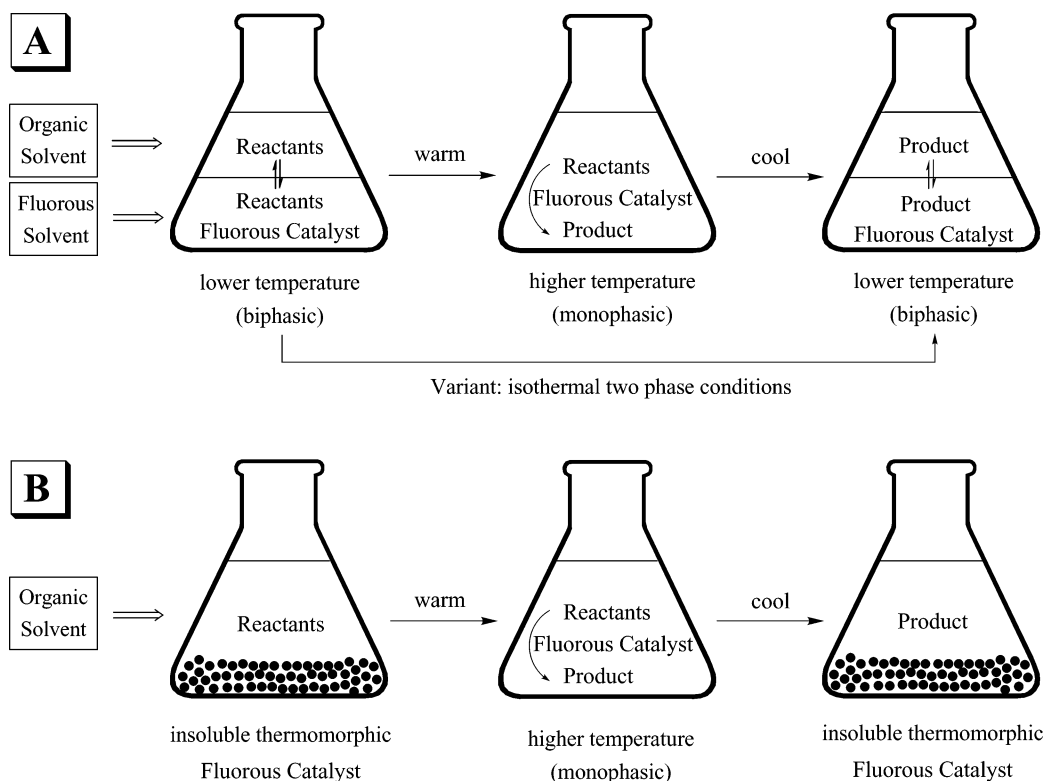


Figure 1. Possible protocols for fluorous biphasic catalysis: (A) recycling by liquid/liquid phase separation; (B) recycling by liquid/solid phase separation.

depletion. Furthermore, there are no known toxicity issues or hazardous properties, consistent with the extensive use of Teflon in household cookware.

We sought a means to eliminate the fluorous solvent requirement for fluorous catalysis. We speculated that the same factors that give highly temperature-dependent organic/fluorous *liquid/liquid* phase miscibilities might also give highly temperature-dependent organic/fluorous *liquid/solid* phase equilibria (e.g., solubilities). In less conceptual terms, as we gained more and more experience with fluorous molecules containing several long pony tails – species that are often essentially insoluble in organic solvents at room temperature – we began to notice marked increases in solubilities with temperature. Of course, above the melting point of a compound, the issue again becomes one of liquid/liquid miscibility.

This suggested that fluorous catalysts might be utilized under one-liquid-phase conditions involving ordinary organic solvents as shown in Figure 1B. The system would first be warmed to achieve monophasic reaction conditions. Subsequent cooling would precipitate the catalyst, and recovery would involve a simple liquid/solid phase separation. Catalysts that exhibit strongly temperature-dependent properties – including but not limited to solubilities – have been termed thermomorph.⁶ This term is also applied to reactions involving reversible phase transitions such as in Figure 1. Several types of polymer-bound catalysts with temperature-dependent solubilities have been developed by Bergbreiter⁷ and exploited in clever reaction/

recovery sequences.^{8,9} However, to our knowledge, this strategy has not been applied to a broad class of *nonmacromolecular* catalysts.

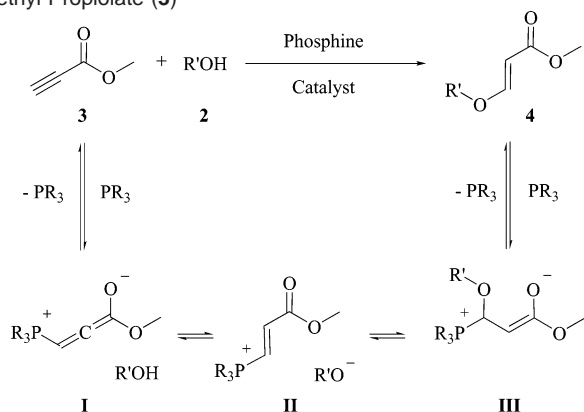
A test reaction to demonstrate the applicability of this concept to fluorous catalysis was required. In the course of our extensive synthetic and physical investigations involving fluorous aliphatic phosphines $P((CH_2)_mR_{in})_3$ (**1**),^{10–12} we noticed that nearly all were very poorly soluble in organic solvents and were solids melting under 100 °C. This drew our attention to the many types of phosphine-catalyzed organic reactions in the literature.^{13,14} We furthermore sought a transformation where the phosphine would represent the catalyst rest state, for – as emphasized elsewhere⁵ – any special property being exploited for catalyst recovery must be associated with the rest state.

Accordingly, the conjugate addition of alcohols (**2**) to methyl propiolate (**3**) shown in Scheme 1 was selected for study.^{14,15}

- (8) Breuzard, J. A. J.; Tommasino, M. L.; Bonnet, M. C.; Lemaire, M. J. *Organomet. Chem.* **2000**, *616*, 37.
- (9) Some relevant recent reviews: (a) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. (b) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345.
- (10) Alvey, L. J.; Rutherford, D.; Juliette, J. J. J.; Gladysz, J. A. *J. Org. Chem.* **1998**, *63*, 6302.
- (11) (a) Alvey, L. J.; Meier, R.; Soós, T.; Bernatis, P.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2000**, 1975. (b) Klose, A.; Gladysz, J. A. *Tetrahedron: Asymmetry* **1999**, *10*, 2665. (c) See also: Soós, T.; Bennett, B. L.; Rutherford, D.; Barthel-Rosa, L. P.; Gladysz, J. A. *Organometallics* **2001**, *20*, 3079.
- (12) Jiao, H.; Le Stang, S.; Soós, T.; Meier, R.; Rademacher, P.; Kowski, K.; Jafarpour, L.; Hamard, J.-B.; Nolan, S. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 1516.
- (13) (a) Ciganek, E. *Org. React.* **1997**, *51*, 201. (b) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (d) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499. (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
- (14) (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241. (b) Baba, Y. Dissertation, 1991. (c) Meier, R. Doctoral Dissertation, Universität Dortmund, 1998.
- (15) The Bayliss–Hillman reaction¹³ would have been another obvious choice, but an efficient fluorous catalyst has not yet been developed.

(6) (a) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058 and references therein. (b) Calhoun, C. D.; Delgado, J. U.S. patent 5,888,650 (filed June 3, 1996); *Chem. Abs.* **1998**, *128*, 62572h.

(7) Selected lead references: (a) Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1987**, *109*, 174. (b) Bergbreiter, D. E.; Zhang, L.; Mariagnanam, V. M. *J. Am. Chem. Soc.* **1993**, *115*, 9295. (c) Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053.

Scheme 1. Phosphine-Catalyzed Addition of Alcohols (**2**) to Methyl Propiolate (**3**)

The mechanism is believed to involve an initial addition of the phosphine to the $\text{C}\equiv\text{C}$ moiety to give a zwitterionic allenolate (**I**), which then deprotonates the alcohol, yielding a vinyl phosphonium salt (**II**).^{14a} An alkoxide addition to give an enolate (**III**), followed by phosphine elimination, gives the product **4** and regenerates the catalyst. Most phosphines do not independently react with **4**. Hence, as more fully documented and analyzed below, intermediate **III** can be excluded as a rest state. Under appropriate conditions, the other intermediates are also unlikely rest states.

In this paper, we describe the successful application of the catalyst recycling protocol in Figure 1B to the addition reaction in Scheme 1, using the thermomorphing fluorous phosphines $\text{P}((\text{CH}_2)_2\text{R}_{18})_3$ (**1a**) and $\text{P}((\text{CH}_2)_3\text{R}_{18})_3$ (**1b**).¹⁰ Catalyst solubility, leaching, and recovery data are reported, as well as extensions to solvent-free conditions and the use of physical supports. A portion of this work has been communicated.¹⁶ Related efforts from Yamamoto's and other laboratories are summarized in the Discussion.^{17–19}

Results

1. Test Reaction Parameters. The four alcohols shown in Table 1 – primary benzylic **2a**, secondary benzylic **2b,c**, and primary aliphatic **2d** – were selected for study. Experiments were first conducted with the catalyst system originally reported, 10 mol % $\text{P}(n\text{-Bu})_3$ in CH_2Cl_2 .^{14a} Preparative reactions with **3** (1.1 equiv, room temperature, 15 min) gave the addition products **4a–d** in 89–72% yields as $\geq 96:\leq 4$ *E/Z* mixtures, after chromatography or distillation (Table 1, entries 1, 4, 6, 10). Although these compounds have been described previously, only one piece of characterization, the ^1H NMR spectrum of **4a**, has been reported.^{14b} Hence, complete analytical data are given in the Experimental Section.

We sought to assay the effectiveness of the fluorous phosphine **1a** as a catalyst. In this compound, *two* methylene groups separate the phosphorus from the perfluoroalkyl moieties. However, **1a** is insoluble in CH_2Cl_2 , precluding rate comparisons. Fortunately, the less polar solvent $\text{CF}_3\text{C}_6\text{H}_5$ is normally able to dissolve both fluorous and nonfluorous compounds.²⁰ Thus, the reaction of **2c** and **3** was repeated in $\text{CF}_3\text{C}_6\text{H}_5$ with

Table 1. Catalysis by Phosphines in Non-Fluorous Solvents: Test Reaction Parameters^a

$$\text{2} + \text{3} \xrightarrow[\text{RT}]{10 \text{ mol\% } \text{PR}_3} \text{4}$$

1a = $\text{P}((\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3)_3$
1b = $\text{P}((\text{CH}_2)_3(\text{CF}_2)_7\text{CF}_3)_3$

entry	R'OH	catalyst	solvent	yield (%)	time (h)
1	2a PhCH ₂ OH	$\text{P}(n\text{-Bu})_3$	CH_2Cl_2	72 ^b	0.25
2		1a	$\text{CF}_3\text{C}_6\text{H}_5$	90 ^c	24 ^d
3		1b	$\text{CF}_3\text{C}_6\text{H}_5$	83 ^c	8
4	2b Ph ₂ CHOH	$\text{P}(n\text{-Bu})_3$	CH_2Cl_2	85 ^b	0.25
5		1a	$\text{CF}_3\text{C}_6\text{H}_5$	78 ^c	48
6	2c PhCH(CH ₃)OH	$\text{P}(n\text{-Bu})_3$	CH_2Cl_2	89 ^b	0.25
7		$\text{P}(n\text{-Bu})_3$	$\text{CF}_3\text{C}_6\text{H}_5$	86 ^c	0.25
8		1a	$\text{CF}_3\text{C}_6\text{H}_5$	81 ^c	24
9		1b	$\text{CF}_3\text{C}_6\text{H}_5$	99 ^c	8
10	2d CH ₃ (CH ₂) ₇ OH	$\text{P}(n\text{-Bu})_3$	CH_2Cl_2	77 ^b	0.25
11		1a	$\text{CF}_3\text{C}_6\text{H}_5$	86 ^c	48

^a The mol ratio of **2**:**3**:catalyst was 1.0:1.1:0.1. ^b Isolated yield ($\geq 98\%$ purity). ^c GC yield (vs internal standard); starting concentrations: 0.3 M (**2b**) or 0.5 M (**2a,c,d**). ^d 95% yield after 96 h reaction time.

both $\text{P}(n\text{-Bu})_3$ and **1a** (Table 1; entries 7, 8). After 15 min, GC analysis of the former addition showed an 86% yield of **4** and no remaining **2c**. The latter addition was slower, with 35%, 52%, and 81% yields of **4** after 3, 8, and 24 h. Phosphine **1a** similarly catalyzed the additions of the other alcohols **2a,b,d** to **3** in $\text{CF}_3\text{C}_6\text{H}_5$ (Table 1; entries 2, 5, 11).

The electronic properties of fluorous phosphines have been studied in detail,¹² and **1a** is distinctly less basic and nucleophilic than $\text{P}(n\text{-Bu})_3$. This should retard the rate of the first step in Scheme 1. However, the slower rate renders this catalyst a more convenient test case for the protocol in Figure 1B. More reactive fluorous phosphines are described below. Control experiments without phosphine catalysts gave no reactions, as further detailed below.

2. Catalysis in Fluorous Solvent Systems. Partition coefficients of many fluorous compounds have been measured in mixtures of perfluoro(methylcyclohexane) ($\text{CF}_3\text{C}_6\text{F}_{11}$) and toluene.⁴ That of phosphine **1a** is very high ($>99.7:<0.3$).¹⁰ Thus, it should be efficiently recovered under the traditional liquid/liquid biphasic conditions in Figure 1A, and recycling protocols involving $\text{CF}_3\text{C}_6\text{F}_{11}$ were investigated. Experiments were first conducted in the ternary solvent system $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene/hexane (3:1:3 v/v/v).^{2a} Reactions with **2a–d**, **3**, and **1a** (1.0:1.1:0.1 mol ratio) proceeded under one-phase conditions at 35–40 °C. After 24–48 h, GC analyses showed the addition products **4a–d** in 88–68% yields. However, when recycling runs were conducted under similar conditions (40–65 °C), the phase behavior varied. More stable systems were sought.

Thus, reactions of **2a,c**, **3**, and **1a** were conducted in the binary solvent system $\text{CF}_3\text{C}_6\text{F}_{11}$ /*n*-octane (5:8 v/v). Mole ratios of 2.0:1.0:0.1 were utilized and maintained for all recycling experiments below. After 8 h under one-phase conditions at 65 °C, samples were cooled. Although two phases were present at room temperature, they were separated via syringe at –30 °C. This represents the temperature of a conveniently located freezer.

- (16) Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490.
 (17) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371.
 (18) Xiang, J.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 84.
 (19) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1299.
 (20) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. *Top. Curr. Chem.* **1999**, *206*, 79.

Table 2. Recycling of Fluorous Phosphine Catalyst **1a** in Fluorous Solvent Systems: Reactions of **2a,c** and **3** To Give **4a,c**^a

entry	reactants (2.0:1.0 mol ratio)	solvent	reaction conditions	recovery conditions	yield 4a or 4c (%)				
					cycle 1	cycle 2	cycle 3	cycle 4	cycle 5
1	2a/3	octane/CF ₃ C ₆ F ₁₁ (8:5)	65 °C one liquid phase	−30 °C two liquid phases	71	82	73	68	66
2	2c/3	octane/CF ₃ C ₆ F ₁₁ (8:5)	65 °C one liquid phase	−30 °C two liquid phases	80	79	76	54	11
3	2a/3	CF ₃ C ₆ F ₁₁	65 °C two liquid phases	−30 °C two liquid phases	81	90	86	87	39

^a 10 mol % of **1a**. Additional relevant conditions are described in the text and Experimental Section.

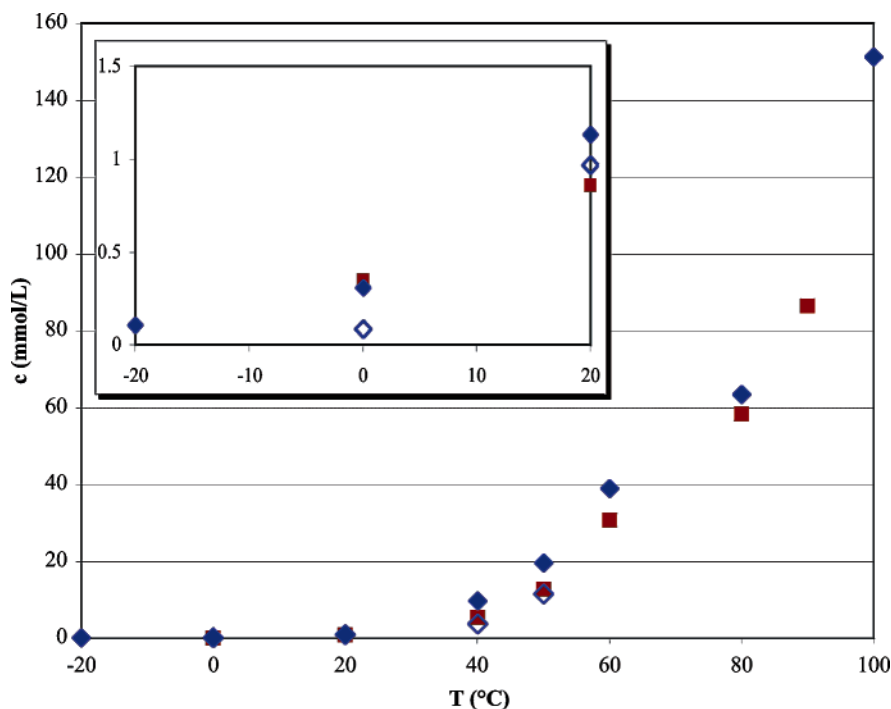


Figure 2. Solubilities of fluoruous phosphines in *n*-octane as a function of temperature. \blacklozenge **1a**, GC assay; \diamond **1a**, ³¹P NMR assay; \blacksquare **1b**, GC assay.

The fluoruous layers were washed once with cold *n*-octane. GC analyses of the *n*-octane layers showed **4a,c** in 80% and 71% yields (Table 2; entries 1 and 2, cycle 1). The fluoruous layers were charged with fresh **2a,c**, **3**, and *n*-octane, and the reaction was repeated. As summarized in Table 2, good yields were maintained for 3–5 cycles, with less deactivation in the case of **2a**. Although yield data do not provide the best measure of catalyst recovery,⁵ quantitative assays and rate data are provided for other systems below.

Because all solvent minimization strategies are of interest, an analogous sequence involving **2a** was conducted in the absence of the *n*-octane organic solvent. As **2a**, **3**, and the product **4a** remain poorly soluble in CF₃C₆F₁₁ at 65 °C, the reaction conditions were biphasic. After reaction, *n*-octane was added to efficiently separate **4a** from the mixture. This was necessary due to the small scale employed (combined mass of **2a/3/1a**, ca. 0.200 g; 31 wt % **1a**). However, when it is not critical to measure the exact yield from each cycle, this can be omitted. As shown in Table 2 (entry 3), yields were somewhat higher than under the two-solvent reaction conditions (entry 1).

3. Temperature-Dependent Solubilities. With the viability of catalyst recycling under organic/fluorous liquid/liquid biphasic conditions for the test reaction established, we sought to probe whether the solubility properties of **1a** were suitable for the fluoruous-solvent-free protocol in Figure 1B. We envisioned

using an aliphatic hydrocarbon solvent, with the idea this would bring greater amounts of a nonpolar fluoruous catalyst into solution than a more polar solvent. To limit the vapor pressure, *n*-octane (bp 126 °C) was selected. Thus, the solubility of **1a** was measured by GC as described in the Experimental Section over the temperature range from −20 to 100 °C. Data are presented in Figure 2.²¹

Indeed, **1a** was strongly thermomorphic. Between 20 and 80 °C, its solubility in *n*-octane increased ca. 60-fold. Between 20 and 100 °C, the increase was 150-fold. More important were the low absolute concentrations at 20 °C and below. Very little **1a** could be detected in solution at −20 or 0 °C (0.104 and 0.308 mM). At 20 °C, millimolar concentration levels were present (1.13 mM). Near the melting point (47 °C), solubilities had risen ca. 20-fold (19.6 mM, 50 °C). To ensure the absence of artifacts, all data were checked in replicate experiments. The results were furthermore verified by ³¹P NMR over the temperature range from 0 to 50 °C, as described in the Experimental Section. These data are also incorporated into Figure 2 (0.084, 0.967, 3.72, and 11.6 mM at 0, 20, 40, and 50 °C, respectively).

4. Fluorous Catalysis without Fluorous Solvents. With the above data in hand, the stage was set for the title experimental

(21) The solubility data are not corrected for any change in solvent volume with temperature.

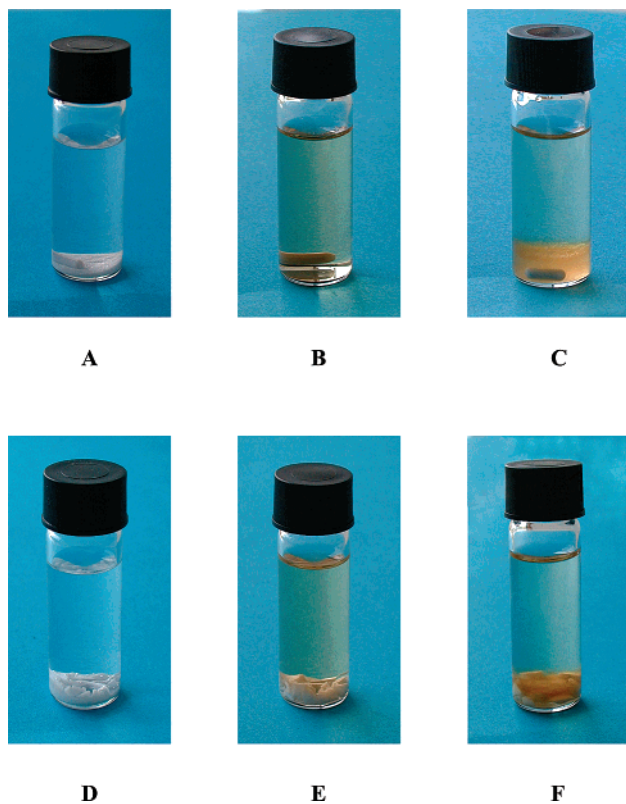


Figure 3. Photographs of recycling sequences. Top row (Table 3, entry 1): (A) room temperature; (B) 65 °C; (C) room temperature. Bottom row (identical, but with added Teflon shavings): (D) room temperature; (E) 65 °C; (F) room temperature.

sequence represented by Figure 1B. Compounds **2a**, **3**, and **1a** (2.0:1.0:0.1 mol ratio) were combined in *n*-octane at room temperature. As would be expected from Figure 2, there was no visually detectable dissolution of **1a** (supernatant 65.0 mM in **3**). The sample was next warmed to 65 °C and became homogeneous (ca. 6.5 mM in **1a**). Photographs of this sequence are given in Figure 3 (panels A and B). After 8 h, the sample was cooled. The catalyst **1a** precipitated, as shown in panel C in Figure 3. In a few cases, the original white color was retained, but most samples were orange and some darkened to red with additional recycling.

The mixture was kept at −30 °C, and the supernatant was removed via syringe. The catalyst residue was washed once with cold *n*-octane. GC analysis indicated an 82% yield of **4a**. As summarized in Table 3 (entry 1), the recovered **1a** was used for four further cycles without deterioration in yield. Multiple runs could be similarly conducted with alcohols **2b–d**, affording comparable yields of **4b–d** (Table 3, entries 2–4). When the reaction with **2c** was conducted at room temperature, **4c** formed in 25% yield. No reaction occurred when **2c** and **3** were similarly kept for 8 h at 65 °C in *n*-octane in the absence of **1a** (<1% **4c**).

To better gauge the extent of catalyst recovery, the rate of the reaction of **2a** and **3** was monitored as a function of cycle. On the first cycle, the maximum yield was reached after ca. 1 h, as illustrated in Figure 4. The second and third cycles were similar. More importantly, when the yields are compared at partial conversion (0.25 h), only modest decreases are noted (67%, 63%, 55%). Thus, ca. 90% of the activity is maintained from cycle to cycle. Both leaching and the composition of

Table 3. Recycling of Fluorous Phosphine Catalysts **1a,b** without Fluorous Solvents: Reactions of **2a–d** and **3** To Give **4a–d** in *n*-Octane at 65 °C, with Catalyst Recovery by Liquid/Solid Phase Separation at −30 °C^a

entry	reactants (2.0:1.0 mol ratio)	catalyst (10 mol %)	yield 4a–d (%)				
			cycle 1	cycle 2	cycle 3	cycle 4	cycle 5
1	2a/3	1a	82	82	80	81	75
2	2b/3	1a	77	84	71		
3	2c/3	1a	90	86	75		
4	2d/3	1a	79	84	66		
5 ^b	2a/3	1a	99	>99	97	95	
6	2a/3	1b	81	89	82	80	77
7	2c/3	1b	92	97	99		

^a Additional relevant data are given in the text. Starting concentration of **2**, 1.25 M; cycle time, 8 h for **1a** and 1 h for **1b**. ^b *n*-Octane solvent omitted.

recovered **1a** are assayed in experiments below that incorporate additional procedural enhancements.

5. Fluorous Catalysis without Solvents. In experiments described above, *either* the organic or the fluorous solvent was eliminated from the traditional recycling protocol in Figure 1A. The logical conclusion to this line of investigation would be to eliminate *all* solvents, a priority in the field of green chemistry.²² Because **2a,c,d**, **3**, and **4a–d** are liquids at room temperature, there are in principle no physical impediments. A solid product could, for example, entrain the catalyst.

Accordingly, **2a**, **3**, and **1a** were reacted as in Table 3, but in the absence of solvent. The catalyst **1a** was insoluble at room temperature, but dissolved as the sample was warmed to 65 °C. Upon cooling, **1a** precipitated as a brown solid, from which most of the liquid phase could easily be removed via syringe. However, on the small scales used (combined mass of **2a/3/1a**, ca. 0.200 g), it was necessary to add some *n*-octane to completely extract the product **4a**. In cases where it is not critical to analyze the exact yield from each cycle, this can be omitted. Data for a four-cycle sequence are given in Table 3, entry 5. The yields (all ≥95%) are the highest realized in this study.

6. Supports for Fluorous/Organic Liquid/Solid Biphasic Recycling. The procedures in the previous two sections require the separation of a solid catalyst from a liquid phase or product. A potential problem, intrinsic to such methodologies, is that the amount of catalyst manipulated can be very small. For example, a thermomorphic fluorous palladacycle that is a highly effective catalyst precursor for the Heck reaction is described below.²³ It can be used at 0.0001 mol % levels. On common laboratory scales, these catalyst quantities can barely be visualized.

One way to increase the mass of recycled material is to use a support. At one extreme, the support could be inert, with only a mechanical function. At another level, the support might provide physical adhesion – for example, for a waxy or gumlike catalyst. At yet another level, the support might provide attractive interactions that would enhance recovery. Although attractive interactions between saturated fluorocarbons are very small,²⁴ we sought to bring them, at least to some degree, into play. Hence, Teflon shavings were selected for initial study.

(22) (a) Poliakov, M.; Fitzpatrick, M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, 297, 807. (b) DeSimone, J. M. *Science* **2002**, 297, 799.

(23) (a) Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, 4, 1993. (b) Rocaboy, C.; Gladysz, J. A. *New J. Chem.* **2003**, 27, 39.

(24) (a) Gross, U.; Rüdiger, S. *Houben-Weyl Methods of Organic Chemistry*; Georg Thieme: Stuttgart, Germany, 1999; Vol. E-10a, pp 18–26. (b) Kiss, L. E.; Kövesdi, I.; Rábai, J. *J. Fluorine Chem.* **2001**, 108, 95.

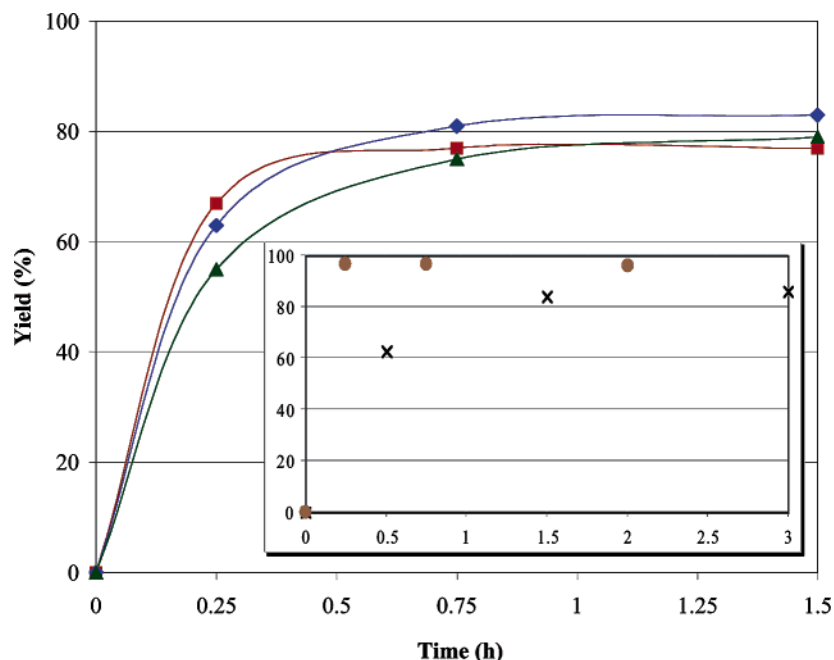


Figure 4. Yield as a function of time for entry 1 in Table 3 (■ cycle 1, ◆ cycle 2, ▲ cycle 3), and (inset) for entries 3 (×) and 7 (●) in Table 3 (first cycle only).

Selected experiments from Table 3 were repeated, but in the presence of Teflon shavings with an average $x/y/z$ dimension of ca. 2 mm. Yield data were comparable, and photographs are provided in panels D–F of Figure 3. This sequence is on the same scale as that in panels A–C. Importantly, the catalyst residues became more compact and firmer, despite the added mass of the Teflon, suggestive of genuine physical adhesion or attraction. The catalyst residues were easier to manipulate, and less leaching occurred, as described in the following section.

Teflon shavings also gave improved results under other types of recycling conditions. For example, the $\text{CF}_3\text{C}_6\text{H}_5$ solvent from reactions similar to those in Table 1 can be removed under reduced pressure, the product **4** can be extracted from the residue with *n*-octane at $-30\text{ }^\circ\text{C}$, and the catalyst residue can be charged with fresh reactants and solvents. This extraction step was much easier, and the yields were higher, when the sequence was conducted in the presence of Teflon shavings (data for five cycles: 90%, 99%, 95%, 97%, 94%).

7. Leaching and Catalyst Recovery. Leaching can be analyzed from the standpoint of both the catalyst (rest state) and the catalyst degradation products. The reactions in entries 1–4 of Table 3 and panels A–C and D–F of Figure 3 involve the separation of an *n*-octane product solution from a **1a** catalyst residue at $-30\text{ }^\circ\text{C}$ and a subsequent *n*-octane extraction. From the quantities employed, the solubility data in Figure 2 predict catalyst leaching of ca. 0.33% per cycle (value calculated at $-20\text{ }^\circ\text{C}$). This rises to 1.0% and 3.6% if phase separations are conducted at 0 and $20\text{ }^\circ\text{C}$.

Leaching was first assayed for reactions conducted in the presence of Teflon shavings (Figure 3, panels D–F). The *n*-octane product solutions from two runs were treated with internal standards for ^{31}P and ^{19}F NMR analysis, as detailed in the Experimental Section. The first showed a barely integratable ^{31}P NMR signal for the oxide of **1a** (41.9 ppm),¹⁰ corresponding to ca. 0.2% leaching. No other signals could be detected.²⁵ The

second showed a much clearer $\text{CF}_3\text{ }^{19}\text{F}$ NMR signal amounting to 2.3% of the **1a** loading (normalized to the three pony tails). Note that all compounds of the formula $\text{X}(\text{CF}_2)_7\text{CF}_3$ give essentially the same CF_3 NMR chemical shift. Hence, the “total number of leached pony tails” can be quite sensitively determined by this method.

The **1a**/Teflon residue from one of the runs was treated with a $\text{CF}_3\text{C}_6\text{H}_5$ solution of a phosphorus-containing internal standard added. A ^{31}P NMR spectrum indicated a 85.2% yield of **1a** (-24.5 ppm) and 12.2% of new phosphorus-containing species (97.4% phosphorus recovery). Of the latter, two were dominant (34.4, 44.4 ppm), and a small amount of the oxide of **1a** was also present. An analogous experiment was conducted with a $\text{CF}_3\text{C}_6\text{H}_5$ solution of a fluorine-containing internal standard added. A ^{19}F NMR spectrum indicated a 97.9% recovery of pony tails.

Some of the new ^{31}P signals could represent alternative catalyst rest states. To help probe this point, **1a** and excess **4a** were combined in $\text{CF}_3\text{C}_6\text{H}_5$. A ^{31}P NMR spectrum showed no reaction other than the formation of some oxide. However, when **1a** and **3** were similarly combined, the sample turned dark black, and ^{31}P NMR spectra showed $>90\%$ reaction. Although the chemical shift of the major product was sometimes close to the one noted above, it varied (46–48 ppm), and many other peaks were present. The multitude of species suggests that the further reaction of intermediate **I** in Scheme 1 with **3** (as opposed to alcohol **2**) provides an avenue for catalyst darkening and decomposition.²⁶ Note that the most nucleophilic alcohol (**2a**) often gives better recycling data (Table 2, entry 1 vs entry 2).

Related experiments were conducted for identical reactions in the absence of Teflon shavings. First, ^{19}F NMR analyses of

(25) Under the conditions of this experiment (which has no *n*-octane extraction), Figure 2 predicts (for phase separation at $-20\text{ }^\circ\text{C}$) ca. 0.17% leaching of **1a** per cycle.

(26) All recycling experiments employ a 2.0:1.0 **2/3** mol ratio. Under these conditions, **I** should be a less long-lived state.

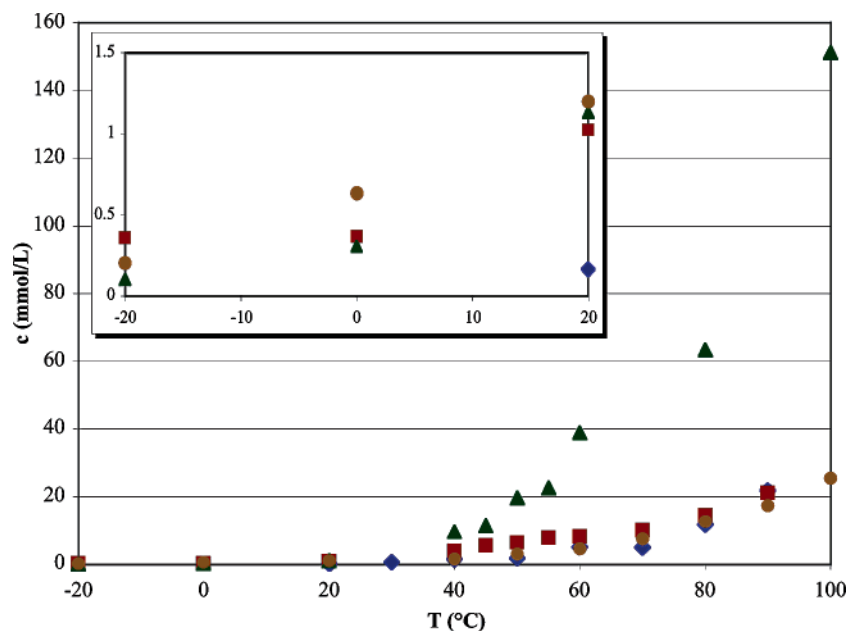


Figure 5. Solubility of **1a** in toluene ■, chlorobenzene ○, dioxane ◆, and *n*-octane ▲ as a function of temperature, as assayed by GC.

the *n*-octane extracts showed a higher level of leached pony tails (first cycle, 7.1%; second cycle, 9.1% based upon **1a** present after first cycle). Second, ^{31}P NMR analysis of the recovered catalyst showed a 90.2:6.0:3.8 ratio of **1a**, the oxide, and other species after the first cycle, and 89.3:6.5:4.2 and 74.5:14.0:11.5 ratios after the second and third cycles. Thus, a gradual degradation of the phosphine **1a** is evident under all recovery conditions.

8. Additional Catalysts. To test the generality of the above phenomena and protocols, the fluorous phosphine **1b**¹⁰ was similarly studied. In this catalyst, *three* methylene groups separate the phosphorus from the perfluoroalkyl moieties. The additional “insulation” renders **1b** considerably more basic and nucleophilic than **1a**, but still far below the levels of tri(*n*-alkyl)-phosphines.¹² It also renders the $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficient slightly lower than that of **1a** (98.8:1.2 vs >99.7: <0.3). However, the melting point is somewhat higher (71.5–72.5 vs 47 °C).

Reactions of **2a,c**, **3**, and **1b** were conducted in $\text{CF}_3\text{C}_6\text{F}_5$ under homogeneous conditions analogous to those used for **1a** and $\text{P}(n\text{-Bu})_3$. As shown in entries 3 and 9 of Table 1, **4a,c** formed in 83% and 99% yields over the course of 8 h at room temperature. The results in entries 7–9, coupled with monitoring data given above, show that **1b** is a much more reactive catalyst than **1a**, but remains less reactive than $\text{P}(n\text{-Bu})_3$.

The solubility of **1b** in *n*-octane as a function of temperature was measured by GC as described for **1a**, and the results are shown graphically in Figure 2.²¹ The solubilities of **1a** and **1b** are strikingly similar. The fact that there is little difference in the region between the melting points (47–72 °C) indicates there is no dramatic solubility increase associated with the solid/liquid phase transition. As would be expected, **1b** gave excellent results in the thermomorphic, fluorous-solvent-free catalytic reactions described above for **1a**. As summarized in Table 3 (entries 6 and 7), high yields of **4a,c** were obtained with much shorter run times (1 h vs 8 h). In the case of **4c**, the data were distinctly better than those with catalyst **1a** (entries 7 vs 3). The relative

rates of these two reactions are compared in the inset in Figure 4 (**1b** \gg **1a**).

9. Additional Solubility Data. Experiments were conducted to provide further context for the above results. First, we were curious about the temperature dependence of the solubility of **1a** in other media. Results for another three solvents that are fairly high boiling and inert to phosphines – toluene, chlorobenzene, and 1,4-dioxane – are given in Figure 5.²¹ Not unsurprisingly, the solubilities of **1a** in these more polar media at ≥ 20 °C are lower than those in *n*-octane. Interestingly, the solubilities in toluene and chlorobenzene at -20 °C are slightly higher (0.360 and 0.205 vs 0.104 mM). In any event, the net result is a lower concentration gradient with temperature.

However, note that from a practicality standpoint, the key issue for the protocol in Figure 1B will usually not be achieving a high catalyst concentration at the high-temperature limit. Any problem in this regard can, in principle, be countered with a more active catalyst. Rather, the critical point is to have a catalyst that is insoluble at the low-temperature limit. Thus, concentration gradients of the types in Figure 5 should often suffice.

Another question regards the extent to which the temperature dependence of the solubilities of fluorous phosphines differs from those of nonfluorous phosphines. Unfortunately, there are no readily available solid tri(*n*-alkyl)phosphines. As a substitute, the solubility of PPh_3 (mp 79–81 °C) in *n*-octane was measured. As shown in Figure 6, a substantial temperature dependence was also observed.²¹ However, note that the solubility remains much higher than that of **1a** at lower temperatures (27.9 vs 0.104 mM, -20 °C). Under the conditions of the reactions in entries 1–4 of Table 3, ca. 89% of the PPh_3 would leach! Furthermore, this solubility would markedly increase in the more polar solvents in Figure 5. Hence, it is the miniscule low-temperature solubilities of appropriate fluorous phosphines in nonfluorous solvents that render them uniquely suitable for recovery via the protocol in Figure 1B.

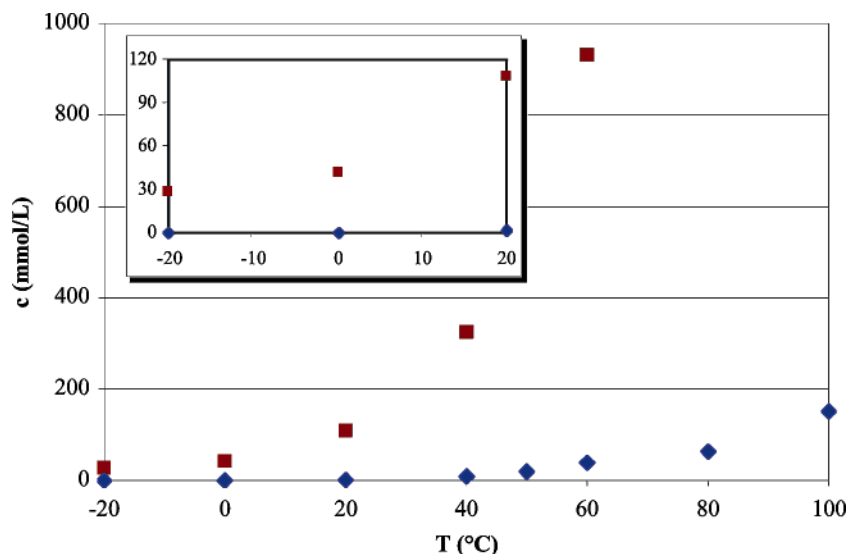


Figure 6. Solubility of **1a** \blacklozenge and PPh_3 \blacksquare in *n*-octane as a function of temperature, as assayed by GC.

Discussion

1. Merits of Methodology. The preceding data clearly demonstrate that fluororous catalysts – here the phosphines **1a,b** – can be applied in single-phase, homogeneous reactions in the absence of fluororous solvents and efficiently recovered via simple liquid/solid phase separations at lower temperatures. This protocol, which is exemplified in Figure 3 and generalized in Figure 1B, significantly expands the scope of fluororous biphasic catalysis as originally formulated (Figure 1A).^{2a} Although an organic solvent (*n*-octane) is utilized under the standard conditions, reactions and catalyst recovery can also be effected under solvent-free conditions.

In anticipation of other applications in which catalyst loadings might be much smaller and therefore less convenient to manipulate, we have also established the viability of using an auxiliary solid support. This remains insoluble during the sequence (Figure 3, panel E) and increases the mass of the recycled material. A support could also be used to provide attractive fluorophilic interactions that would enhance the level of catalyst recovery. Our choice of Teflon shavings was made with this possibility in mind, but there are many other conceivable candidates, such as fluororous reverse phase silica gel.²⁷ Indeed, related methodologies involving fluororous silica gel have recently been reported, as described below.²⁸

Some limitations associated with our protocol merit note. First, insoluble byproducts will interfere with catalyst recovery. Although it would certainly be simple to separate a typical inorganic salt from catalysts such as **1a,b**, this adds an extra manipulation. Second, because heating is required to achieve homogeneity, the method is best suited for reactions normally conducted at elevated temperatures. However, the viability of fluororous catalysis under nonhomogeneous conditions deserves emphasis. For example, there are many examples where reactions of the type in Figure 1A proceed at convenient rates at the biphasic low-temperature limit.^{3b,29,30} Similarly, it will not always be necessary to achieve the homogeneous conditions

depicted in Figure 1B for rapid reaction. Indeed, as noted above, **1a** gives a detectable background reaction of **2c** and **3** in *n*-octane at room temperature.

2. Solubility Considerations. Temperature-dependent solubility is of course a very general phenomenon with respect to all solvents and solutes. Figure 2 provides the first quantitative data for fluororous compounds. The phosphines **1a,b** exhibit ca. 400-, 600-, and 1500-fold solubility increases in *n*-octane between -20 and 60 , 80 , and 100 °C, respectively.²¹ The solubility increases for PPh_3 in Figure 6 appear more dramatic, but in reality that between -20 and 60 °C is only ca. 33-fold. However, as noted above, the degree of temperature dependence is not the critical issue. Nearly all industrially important homogeneous catalysts operate at loadings of much less than 1%, and high solution concentrations are not necessary. Rather, the key point is to design a catalyst with essentially zero solubility at the low-temperature limit.

A number of fluororous compounds with multiple pony tails containing at least eight perfluorinated carbons ($\geq \text{R}_{\text{F}8}$) have been found to exhibit very low solubilities at room temperature, particularly in organic solvents but sometimes also in fluororous solvents. This is often noticed in the course of NMR characterization. Some typical examples which furthermore show markedly enhanced solubilities at higher temperatures are summarized in Figure 7, together with the relevant solvents. Compounds from our group include the sulfoxides **5**,³¹ the aryl iodides and (diacetoxyiodo)arenes **6**,³² and the N-donor and S-donor palladacycles **7,8**.²³ Compounds from other groups include the phenylboronic acid **9**,¹⁷ the distannoxane **10**,¹⁸ and the 1,1-bis(sulfone) **11**.¹⁹ These phenomena are clearly not restricted to any one class of molecule or solvent.

Thus, the fine-tuning of solubility properties is of obvious importance. Figure 2 shows that a one-carbon difference in the methylene spacer segment, $(\text{CH}_2)_2$ versus $(\text{CH}_2)_3$, has little effect upon solubility. However, increasing or decreasing an $\text{R}_{\text{F}8}$

(27) Curran, D. P. *Synlett* **2001**, 9, 1488.

(28) (a) Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4500; *Angew. Chem.* **2002**, *114*, 4678. (b) Schwinn, D.; Glatz, H.; Bannwarth, W. *Helv. Chim. Acta* **2003**, *86*, 188.

(29) Rutherford, D.; Juliette, J. J. J.; Rocaboy, C.; Horváth, I. T.; Gladysz, J. A. *Catal. Today* **1998**, *42*, 381.

(30) Dinh, L. V.; Gladysz, J. A. *Tetrahedron Lett.* **1999**, *40*, 8995.

(31) Rocaboy, C.; Gladysz, J. A. *Tetrahedron* **2002**, *58*, 4007.

(32) Rocaboy, C.; Gladysz, J. A. *Chem.-Eur. J.* **2003**, *9*, 88.

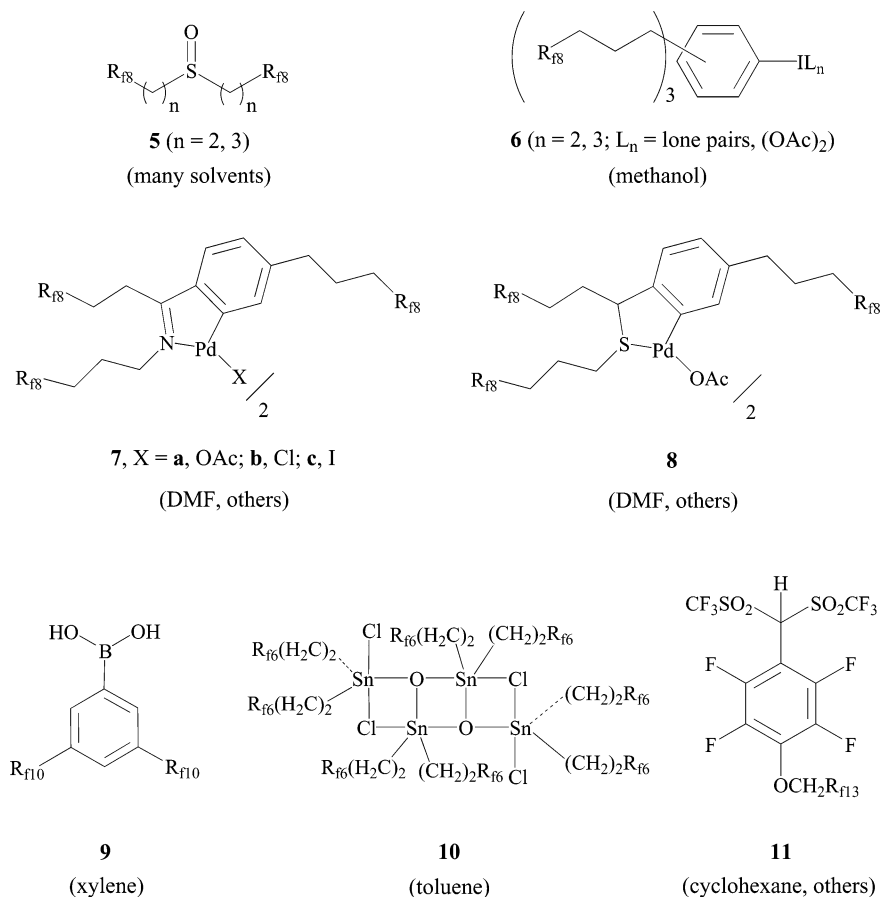


Figure 7. Some fluorous compounds with very low solubilities at room temperature, but much higher solubilities at elevated temperatures.

segment by two carbons can have a profound influence.^{10,33} Longer perfluoroalkyl groups always diminish solubilities, and quantitative data on the phosphines $\text{P}((\text{CH}_2)_3\text{R}_{f6})_3$ (a liquid) and $\text{P}((\text{CH}_2)_3\text{R}_{f10})_3$ (mp 102–103 °C) will be presented in a future report.³⁴ Qualitatively higher solubilities have also been noted for analogues of **11** with shorter pony tails.¹⁹ Fluorous phosphines that are less symmetrically substituted, such as $\text{P}((\text{C}-\text{H}_2)_2\text{R}_{f8})((\text{CH}_2)_3\text{R}_{f8})_2$ (mp 68–69 °C),^{11a} also deserve investigation. None of the compounds in Figure 7 contain branched pony tails, a morphology that is so far somewhat rare³⁵ and would be expected to affect solubilities. Additional pony tails commonly diminish solubilities, although with arenes substitution patterns are often more important (1,4-disubstituted less soluble than 1,3,5-trisubstituted).^{32,33}

When molecular catalysts are covalently bound to polymeric supports, they generally assume the solubility properties of the host polymer. In developing thermomorphic fluorous catalysts as described above, we like to think that we are covalently attaching a small segment of a polymer to a molecular catalyst. In other words, the pony tails can be viewed as short pieces of

Teflon, which impart more of the solubility characteristics of the polymer as they are lengthened. This “inverse immobilization” strategy offers virtually infinite possibilities for engineering the desired physical properties into the catalyst.

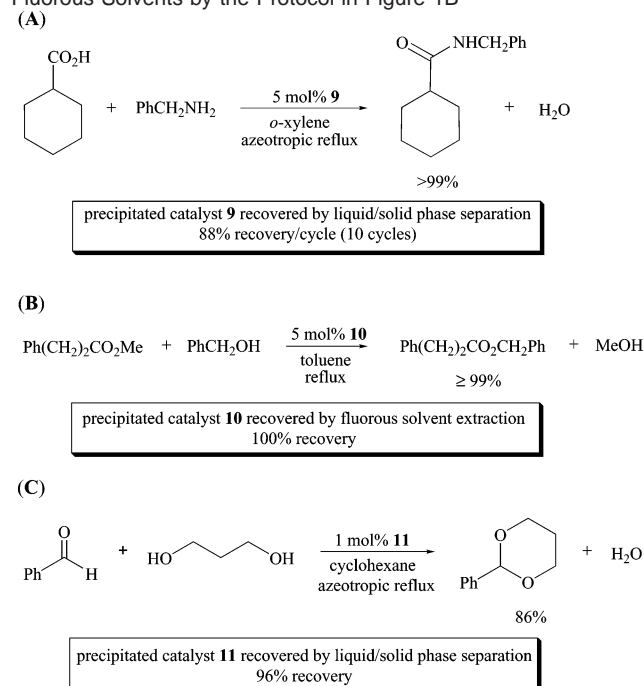
3. Test Reactions. Given our success with the alcohol addition reactions in Scheme 1, appropriate fluorous phosphines can likely serve as recoverable catalysts for other phosphine-catalyzed reactions.¹³ It should be emphasized that no attempt has been made to optimize addition rates. From the order of catalyst activity, $\text{P}(n\text{-Bu})_3 > \mathbf{1b} > \mathbf{1a}$, it is obvious that still faster rates would be obtained with the more highly “insulated” fluorous phosphines $\text{P}((\text{CH}_2)_4\text{R}_{f8})_3$ (mp 44–45 °C)¹⁰ and $\text{P}((\text{CH}_2)_5\text{R}_{f8})_3$ (mp 44 °C).^{11a} Alternatively, reactions might be conducted in more polar solvents such as chlorobenzene. The solubilities of **1a** in chlorobenzene at 60 and 70 °C (4.72 and 7.56 mM; Figure 5) are close to the concentration used for reactions in *n*-octane at 65 °C (6.5 mM). The theoretical maximum leaching of **1a** would be 0.6% per cycle (calculated for phase separation at –20 °C).

Although the catalysts **1a,b** degrade somewhat as they are recycled, no phosphine leaching can be detected by ³¹P NMR. This dramatically illustrates the viability of the recovery protocol in Figure 1B. The more sensitive ¹⁹F NMR assay shows that other materials do leach, but this is significantly decreased in the presence of Teflon shavings (2.7% vs 7.1%). These substances must be either catalyst degradation products or alternative catalyst rest states that are more soluble. In our opinion, there are a number of ways by which the former might be minimized. For example, an alcohol/methyl propiolate or 2/3

(33) Rocaboy, C.; Rutherford, D.; Bennett, B. L.; Gladysz, J. A. *J. Phys. Org. Chem.* **2000**, *13*, 596.

(34) Wende, M.; Gladysz, J. A., manuscript in preparation.

(35) (a) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866. (b) Loiseau, J.; Fouquet, E.; Fish, R. H.; Vincent, J.-M.; Verhac, J.-B. *J. Fluorine Chem.* **2001**, *108*, 195. (c) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y. *Tetrahedron* **2001**, *57*, 5565. (d) Rábai, J.; Szabó, D.; Borbás, E. K.; Kövesi, I.; Kövesdi, I.; Csámpai, A.; Gömöry, A.; Pashinnik, V. E.; Shermolovich, Y. G. *J. Fluorine Chem.* **2002**, *114*, 199. (e) El Bakkari, M.; McClenaghan, N.; Vincent, J.-M. *J. Am. Chem. Soc.* **2002**, *124*, 12942. (f) For silicon-based branches, see: de Wolf, E.; Richter, B.; Deelman, B.-J.; van Koten, G. *J. Org. Chem.* **2000**, *65*, 5424.

Scheme 2. Other Examples of Fluorous Catalysis without Fluorous Solvents by the Protocol in Figure 1B

ratio greater than the 2:1 employed would decrease the lifetime of **I** (Scheme 1), a species that appears to give a multitude of products in the presence of **3** alone. However, a priority from our standpoint was to extend Figure 1B to a broader range of reactions. A parallel investigation of Heck reactions using the fluorous palladacycle catalysts precursors **7,8** (Figure 7) is detailed elsewhere.²³

4. Other Thermomorphic Fluorous Catalysts. Other fluorous catalysts have recently been utilized under homogeneous conditions in nonfluorous solvents and recovered by liquid/solid phase separations. Concurrently with our communication, Yamamoto reported that the phenylboronic acid **9** (Figure 7) efficiently catalyzed condensations of carboxylic acids and amines to give amides.¹⁷ Reactions could be effected in organic/fluorous solvent mixtures, with recovery of **9** by liquid/liquid phase separation. Although **9** was insoluble in aromatic hydrocarbons at room temperature, it exhibited appreciable solubilities as higher temperatures. As shown in Scheme 2A, reactions could be catalyzed under homogeneous conditions in refluxing toluene or xylene, and **9** could be recovered by subsequent precipitation at room temperature. Ten such cycles were conducted, giving the amide product in 96% isolated yield (>99% conversion per cycle) and **9** in 26% yield (88% recovery per cycle).

Otera has reported that fluorous distannoxanes such as **10** (Figure 7) catalyze transesterifications in organic/fluorous solvent mixtures.¹⁸ Although **10** was insoluble in toluene at room temperature, it dissolved at reflux and efficiently catalyzed the transformation in Scheme 2B, as well as others. The catalyst precipitated upon cooling, but a fluorous solvent extraction was utilized for recovery (100%). Most recently, Yamamoto has utilized the bis(sulfone) **11** (Figure 7) as a super Brønsted acid catalyst.¹⁹ This species dissolved in refluxing cyclohexane and catalyzed the acetal formation in Scheme 2C. Cooling precipitated **11**, which was recovered in 96% yield. Benzoylations of alcohols and esterifications of carboxylic acids were similarly

conducted in toluene and methanol, with catalyst recoveries of 70% and 68%.

5. Other Approaches to Catalyst Recovery via Liquid/Solid Phase Separation. Several catalyst recovery protocols related to Figure 1B deserve to be mentioned. For example, the solubilities of fluorous compounds in organic solvents are markedly enhanced by the application of subsupercritical CO₂ pressures (e.g., 20–70 bar).³⁶ Thus, CO₂ gas can be used as a “solubility switch”, complementing the traditional variable of temperature. Although this phenomenon has so far been primarily used for crystallizations, the first application in fluorous catalysis was recently reported.³⁷ This featured a fluorous analogue of Wilkinson’s catalyst, which dissolved under CO₂/H₂ pressures in cyclohexane and could be recovered after hydrogenation with no detectable rhodium leaching.

There is considerable literature on polymer-based thermomorphic catalysts, much of which has originated from the Bergbreiter group.^{7–9} The solubilities of many types of polymers are highly temperature dependent, and Bergbreiter has pursued two orthogonal strategies. The first involves the functionalization of polyethylenes with various ligands and metal fragments.^{7a} These normally insoluble systems can dissolve in hot toluene and xylene and precipitate on cooling. The second involves similar functionalizations of poly(ethylene glycols)^{7b} and polyacrylamides.^{7c} However, the water solubilities of these systems show inverse temperature dependences (less soluble at higher temperature). Bergbreiter has used this both as a recovery strategy and as a control element to precipitate catalysts when the desired temperature range of a reaction has been exceeded.

While this manuscript was being reviewed, Bannwarth described the adsorption of palladium complexes of fluorous phosphines onto fluorous reverse phase silica gel.²⁸ The resulting free-flowing powders were effective catalyst precursors for Suzuki and Sonogashira reactions, which were conducted at 80–100 °C. They could be recovered by decantation at 0 °C with <2% palladium loss and reused. Although it is not yet clear whether adsorbed or dissolved palladium species are primarily responsible for these reactions, this obviously represents another creative and useful approach to fluorous catalysis without fluorous solvents.

6. Additional Considerations. As emphasized above, any property being exploited for catalyst recovery must be associated with the rest state.⁵ Several special challenges in this regard are best analyzed in retrospect. First, when a catalyst or catalyst precursor is covalently bound to a polymer support, it can be assumed (under idealized conditions and with an appropriate mode of attachment) that all intermediates and the rest state remain covalently bound. All local energy minima assume the general physical properties of the host polymer. In contrast, for all types of liquid/liquid biphasic recovery protocols involving *molecular* catalysts, all species are free to partition with different affinities between phases. The same obviously holds for liquid/solid biphasic recovery methods.

Note that catalysts can have a distribution of rest states and that the dominant one *during* a reaction (recovery from a continuous process) can differ from that after the consumption

(36) Jessop, P. G.; Olmstead, M. M.; Ablan, C. D.; Grabenauer, M.; Sheppard, D.; Eckert, C. A.; Liotta, C. L. *Inorg. Chem.* **2002**, *41*, 3463.

(37) (a) Eckert, C. A.; Jessop, P. G.; Liotta, C. L. U.S. Patent 2002096550; *Chem. Abstr.* **2002**, *138*, 26344. (b) Jessop, P. G., oral presentation, “Green Solvents for Catalysis”, Bruchsal, Germany, October 15, 2002.

of the limiting reagent (recovery from a batch process). Hence, the efficient recovery of molecular catalysts under biphasic conditions requires that a number of conditions are simultaneously fulfilled. One simplifying advantage of the test reaction in Scheme 1 is that a high fraction of the original phosphine catalyst is present after the reaction has gone to completion, representing the dominant rest state.

It is also important not to blur the distinction between a catalyst and a catalyst precursor. In particular, many metal-containing catalysts – including fluororous systems employed for hydrogenations,²⁹ hydrosilylations,³⁰ and Heck arylations²³ – feature induction periods. An induction period usually indicates an irreversible transformation that must occur to access the catalytically active species. In such cases, the composition and properties of the catalyst rest state are likely to significantly differ from those of the catalyst precursor. Thus, in the development of additional metal-containing fluororous catalysts for recovery according to Figure 1B, highly relevant solubility data will not always be available. Intuition and luck must therefore play correspondingly larger roles.

Conclusion

To our knowledge, there have been no previous attempts to develop a broad class of *molecular* catalysts that have temperature-dependent solubilities, such that they can be applied under homogeneous conditions at elevated temperatures and efficiently recovered by simple liquid/solid phase separations at lower temperatures.³⁸ The above data, coupled with those of other investigators in Scheme 2, clearly establish the applicability of appropriately designed fluororous molecules to such recycling protocols (Figure 1B). There is every reason to predict the evolution of a new general method for catalyst recovery – “fluorous catalysis without fluororous solvents” – that removes many objections to the organic/fluorous liquid/liquid biphasic procedure in Figure 1A.

The practicality of this recovery technique is critically dependent upon a very low catalyst solubility at the low-temperature limit, and toward this end there is a broad palette of structural variables that can be used for optimization and fine-tuning (e.g., number, length, branching, and substitution pattern of perfluoroalkyl segments). There is also the tantalizing possibility that fluororous solid supports could be used to further enhance catalyst recovery, as demonstrated by our first-generation experiments with Teflon shavings and Bannwarth's recent data with fluororous reverse phase silica gel.²⁸ These and other refinements are under active investigation and will be reported in due course.

Experimental Section

General. Reactions were conducted under inert atmospheres. Methyl propiolate (**3**; Aldrich, 99%), benzyl alcohol (**2a**; Fluka, ≥99%), 1-phenylethanol (**2c**; Fluka, 96%), 1-octanol (**2d**; Fluka, ≥99.5%), *n*-undecane, and *n*-tetradecane (2× Aldrich, ≥99%) were freeze–pump–thaw degassed (3×). Diphenylcarbinol (**2b**; Aldrich, 99%), P(*n*-Bu)₃ (Fluka, 95%), PPh₃ (ABCR, 99%), and C₆F₆ (Aldrich, 99%) were

used as received. The phosphines P((CH₂)_m(CF₂)₇CF₃)₃ (*m* = 2/3, **1a**/**1b**) were prepared as described earlier.¹⁰ Solvents were distilled as follows and then freeze–pump–thaw degassed (3×): *n*-octane (Lancaster), 1,4-dioxane, and toluene, from Na/benzophenone; CH₂Cl₂, from CaH₂; chlorobenzene, CF₃C₆H₅, and CF₃C₆F₁₁ (ABCR), from P₄O₁₀; hexanes and ethyl acetate (for chromatography), simple distillation. NMR spectra were recorded on Bruker or JEOL 400 MHz instruments at ambient probe temperature and referenced to residual internal CHCl₃ (¹H, δ 7.27) or CDCl₃ (¹³C, δ 77.2). Gas chromatography was conducted on a ThermoQuest Trace GC 2000 instrument. Elemental analyses were conducted with a Carlo Erba EA1110 instrument.

Phosphine-Catalyzed Additions: Authentic Samples. A Schlenk flask was charged with the alcohol (**2a–d**, 5.00 mmol), P(*n*-Bu)₃ (0.124 mL, 0.500 mmol), and CH₂Cl₂ (5 mL), and placed in a 10–15 °C bath. Next, **3** (0.490 mL, 5.50 mmol) was added with stirring over the course of 5 min. The mixture turned deep red-brown and then black. After 10 min, air was introduced to oxidize and facilitate separation of the P(*n*-Bu)₃. After 1 h, the volatiles were removed by oil pump vacuum. Next, 10:1 v/v hexanes/ethyl acetate (ca. 10 mL) was added to the black tar. The sample was filtered through a short plug of silica, which was washed with hexanes/ethyl acetate (150 mL). Solvents were removed from the filtrate to give crude **4a–d** as viscous yellow oils. Further purification: **4b**, silica gel column chromatography, 4:1 v/v hexanes/ether; **4a,c,d**, Kugelrohr distillation (6–8 × 10^{−3} Torr, fraction between 90 and 130 °C). This gave **4a–d**^{14a,b} as colorless oils, some of which turned light tan overnight, even when stored in a refrigerator under N₂.

C₆H₅CH₂OCH=CHCO₂CH₃ (4a). 0.692 g, 3.60 mmol, 72%, >99: <1 *E/Z*. NMR (CDCl₃): ¹H (400 MHz) δ = 7.64 (d, *J* = 12.2 Hz, =CHO), 7.37–7.24 (m, C₆H₅), 5.31 (d, *J* = 12.7 Hz, =CHC), 4.87 (s, CH₂), 3.68 (s, CH₃); ¹³C (125 MHz) δ = 168.0, 162.0, 135.1, 128.7, 128.5, 127.6, 97.0, 72.8, 51.1. MS (positive FAB, 3-NBA, *m/z*): 193 (M⁺, 100%). Anal. Calcd for C₁₁H₁₂O₃: C, 68.74; H, 6.29. Found: C, 68.74; H, 6.48.

(C₆H₅)₂CHOCH=CHCO₂CH₃ (4b). 1.140 g, 4.25 mmol, 85%, 96:4 *E/Z*. NMR (CDCl₃, *E* isomer unless noted): ¹H (400 MHz) δ = 7.64/7.73 (2d, *J* = 12.7/12.5 Hz, *E/Z* =CHO), 7.37–7.27 (m, 2C₆H₅), 5.95 (s, CHO), 5.34 (d, *J* = 12.7 Hz, =CHC), 3.64 (s, CH₃); ¹³C (125 MHz) δ = 168.1, 161.3, 139.5, 128.7, 128.3, 126.8, 98.9, 85.5, 51.1. MS (positive FAB, 3-NBA, *m/z*): 267 (M⁺, 5%), 167 ([Ph₂CH]⁺, 100%). Anal. Calcd for C₁₇H₁₆O₃: C, 76.10; H, 6.01. Found: C, 75.76; H, 6.05.

C₆H₅CH(CH₃)OCH=CHCO₂CH₃ (4c). 0.918 g, 4.45 mmol, 89%, >99: <1 *E/Z*. NMR (CDCl₃): ¹H (400 MHz) δ = 7.51 (d, *J* = 12.5 Hz, =CHO), 7.37–7.27 (m, C₆H₅), 5.23 (d, *J* = 12.5 Hz, =CHC), 5.01 (q, *J* = 6.6 Hz, CHCH₃), 3.62 (s, OCH₃), 1.57 (d, *J* = 6.6 Hz, CCH₃); ¹³C (125 MHz) δ = 168.2, 161.4, 141.2, 128.8, 128.2, 125.7, 98.0, 80.5, 51.0, 23.4. MS (positive FAB, 3-NBA, *m/z*): 207 (M⁺, 100%).

CH₃(CH₂)₇OCH=CHCO₂CH₃ (4d). 0.825 g, 3.85 mmol, 77%, >99: <1 *E/Z*. NMR (CDCl₃): ¹H (400 MHz) δ = 7.55 (d, *J* = 12.5 Hz, =CHO), 5.15 (d, *J* = 12.8 Hz, =CHC), 3.79 (t, *J* = 6.6 Hz, OCH₂), 3.66 (s, OCH₃), 1.66 (OCH₂CH₂), 1.39–1.21 (m, 5CH₂), 0.84 (t, *J* = 6.8 Hz, CCH₃); ¹³C (125 MHz) δ = 168.3, 162.7, 95.9, 71.2, 51.0, 31.7, 29.13, 29.10, 28.8, 25.7, 22.6, 14.0. MS (positive FAB, 3-NBA, *m/z*): 215 (M⁺, 100%), 183 ([M – OMe]⁺, 20%). Anal. Calcd for C₁₂H₂₂O₃: C, 67.25; H, 10.35. Found: C, 67.23; H, 10.53.

Catalyst Recycling. A. A 4 mL screw-top vial was charged with a stir bar, **1a** (0.0686 g, 0.050 mmol), *n*-undecane GC standard (0.3–0.5 mmol added gravimetrically), **2a** or **2c** (1.00 mmol), **3** (0.0421 g, 0.500 mmol), *n*-octane (0.80 mL), and CF₃C₆F₁₁ (0.50 mL). The sample was stirred at 65 °C for 8 h (monophase conditions) and stored at −30 °C overnight. The light yellow upper organic phase was carefully removed from the lower fluororous phase by syringe. The fluororous phase was shaken with cold *n*-octane (0.8 mL, −30 °C), and the *n*-octane layer was similarly separated. The organic phases were combined. An

(38) Because the homogeneous catalysis literature is so vast, and electronic search methods are not capable of systematically retrieving such data, there are likely precedents that have escaped our attention. For example, considering the numerous amine-catalyzed reactions, many of which are conducted at elevated temperature, it would not be surprising to find scattered examples. However, we are confident that for whatever cases that might exist, there would be little chance of developing a general family of catalysts encompassing the breadth of molecules represented by **1a,b** and Figure 7.

aliquot (0.2 mL) was filtered through a silica gel plug (0.5 × 1 cm) with ethyl acetate/hexanes (10 mL, 1:10 v/v). The filtrate was analyzed by GC (0.0010 mL autoinjection). The vial with the fluororous phase was again charged with *n*-undecane, **2a** or **2c**, **3**, and *n*-octane, and the procedure was repeated. Data: Table 2, entries 1–2.

B. An analogous series of experiments was conducted without CF₃C₆F₁₁ using catalysts **1a** and **1b** and alcohols **2a–d**. The organic phase was separated by syringe from the solid or gumlike **1a** or **1b**. The solid was washed with cold *n*-octane (0.8 mL, –30 °C), which was added to the organic phase. The vial was again charged with *n*-undecane, **2a–d**, **3**, and *n*-octane, and the procedure was repeated. Data: Table 3, entries 1–4, 6, and 7.

C. A 4 mL screw-top vial was charged with a stir bar, **1a** (0.0686 g, 0.050 mmol), *n*-undecane GC standard (0.3–0.5 mmol added gravimetrically), **2a** (0.1081 g, 1.000 mmol), and **3** (0.0421 g, 0.500 mmol). The sample was stirred at 65 °C for 8 h (solvent-free conditions). *n*-Octane (0.8 mL) was then added, and the sample was stored at –30 °C overnight. The light yellow liquid phase was carefully removed from the catalyst residue by syringe. The residue was treated with cold *n*-octane (0.8 mL, –30 °C), and the liquid phase was similarly separated. The liquid phases were combined. An aliquot (0.2 mL) was filtered through a silica gel plug (0.5 × 1 cm) with ethyl acetate/hexanes (10 mL, 1:10 v/v). The filtrate was analyzed by GC (0.0010 mL autoinjection). The vial with the gumlike catalyst was again charged with *n*-undecane, **2a**, and **3**, and the procedure was repeated. Data: Table 3, entry 5.

D. A solution of **3** (0.4235 g, 5.000 mmol) and *n*-undecane GC standard (0.4689 g, 3.000 mmol) in *n*-octane (5.6240 g) was prepared. Three 4 mL screw top vials (A', B', C') were charged with a stir bar, **1a** (0.0686 g, 0.050 mmol), **2a** (0.1081 g, 1.000 mmol), and a portion of the *n*-octane solution (0.6516 g delivered gravimetrically; 0.500 mmol of **3**, 0.300 mmol of *n*-undecane). The samples were stirred at 65 °C for 8 h, and aliquots (0.050 mL) were periodically removed from vial A' (0.25, 0.75, 1.5, 3.0, 5.0, 8.0 h) and diluted with CF₃C₆H₅ (0.5 mL). The aliquots were filtered through a silica gel plug (0.5 × 1 cm) with ethyl acetate/hexane (10 mL, 1:10 v/v) and analyzed by GC (0.0010 mL autoinjection). The reaction mixtures were stored at –30 °C overnight. The light yellow upper organic phase was carefully separated by syringe from the solid **1a**. The solid was washed with cold *n*-octane (0.8 mL, –30 °C), which was added to the organic phase. Vials B' and C' were charged again with **2a** (0.1081 g, 1.000 mmol) and a portion of the *n*-octane solution of **3** (0.6516 g delivered gravimetrically; 0.500 mmol of **3**, 0.300 mmol of *n*-undecane). Aliquots from vial B' were analyzed analogously to the first cycle. A third cycle was similarly conducted, and aliquots from vial C' were analyzed. Data: Figure 4.

Catalyst Recovery. A. A 4 mL screw-top vial was charged with a stir bar, **1a** (0.0653 g, 0.0476 mmol), **2a** (0.1081 g, 1.000 mmol), **3** (0.0421 g, 0.500 mmol), and *n*-octane (0.8 mL). The sample was stirred at 65 °C for 8 h, and Teflon shavings (ca. 0.3 g, average *x/y/z* dimension ca. 2 mm) were added. The sample was kept at –30 °C overnight. The light yellow liquid phase was carefully removed from the catalyst/Teflon residue by a syringe fitted with a filter. A solution of PPh₃ (0.0619 g, 0.236 mmol) in CF₃C₆H₅ (3.5231 g) was prepared, and a portion was added gravimetrically (0.1287 g, 0.00874 mmol of PPh₃). The solid residue was treated with a solution of PPh₃ (0.0581 g, 0.222 mmol) in CF₃C₆H₅ (2.0 mL). Both samples were analyzed by inverse-gated ³¹P NMR (pulse delay = 12 s), and the signals were integrated against that of PPh₃.³⁹ Data: see text.

B. A solution of C₆F₆ (0.0576 g, 0.310 mmol) in hexanes (3.3033 g) was prepared. An experiment identical to procedure A was conducted, and a portion was added gravimetrically (0.0761 g, 0.00701 mmol of C₆F₆) to the filtered liquid phase. A solution of C₆F₆ (0.0847 g, 0.455 mmol) in CF₃C₆H₅ (4.0077 g) was prepared, and a portion was added gravimetrically (2.0074 g, 0.223 mmol of C₆F₆) to the solid residue. Both samples were analyzed by ¹⁹F NMR. The total intensities of all (CF₂)₇CF₃-based CF₃ triplets were integrated against the C₆F₆ signal. Data: see text.

C. The light yellow upper layers from vials B' and C' of recycling experiment D above were, after separation from catalyst **1a**, treated with C₆F₆ (0.007720 (B') and 0.008789 (C') mmol; delivered as in recovery experiment B). The samples were similarly analyzed by ¹⁹F NMR (vial B' after cycle 1, vial C' after cycle 2). Data: see text.

D. The catalyst residues from vials A', B', and C' of recycling experiment D were dissolved in CF₃C₆H₅. Analysis by inverse-gated ³¹P NMR (pulse delay = 12 s) gave the relative amounts of phosphorus-containing species in the recovered catalyst.³⁹ Data: see text.

Temperature-Dependent Solubilities. A. The following is representative. A solution of *n*-tetradecane (0.1414 g, 0.7127 mmol) in *n*-octane (2.1841 g) was prepared. A portion of this solution (0.1184 g delivered gravimetrically) was added to a solution of *n*-undecane (0.1002 g, 0.6410 mmol) in *n*-octane (7.0843 g). A 2 mL round-bottom flask was fitted with a septum and a stir bar, and charged under argon with **1a** (0.250 g, 0.182 mmol) and ca. 1.0 mL of the second solution (0.7155 g delivered gravimetrically; 0.06283 mmol of *n*-undecane, 0.003556 mmol of *n*-tetradecane). The flask was placed in a thermostated bath and stirred at –20.0 °C for 2 h. Stirring was discontinued, and the suspension was allowed to settle. After 10 min, a 0.002 mL aliquot was removed from the clear supernatant for GC analysis. Samples were similarly taken after 20 min equilibration periods at higher temperatures. Aliquots taken at or above 40 °C (0.008 mL) were diluted with degassed CF₃C₆H₅ (0.100 mL) to avoid gel formation (see text). Data: Figure 2.²¹

B. A solution of PPh₃ (0.0697 g, 0.266 mmol) in *n*-octane (4.2416 g) was prepared. A screw-capped NMR tube was then charged under argon with a portion of this solution (0.5530 g delivered gravimetrically; 0.0346 mmol of PPh₃), **1a** (0.0813 g, 0.0592 mmol), and a capillary filled with toluene-*d*₈. The sealed tube was immersed in a water bath (first run: 0 °C, then 20, 40, and 50 °C) and vigorously shaken for 15 min. It was transferred to a NMR probe and spun at the corresponding temperature for an additional 10 min. Spinning was ceased, and the suspension/emulsion was allowed to settle. After 20 min, an inverse-gated ³¹P NMR spectrum was recorded (without spinning; pulse delay = 12 s). The concentration of **1a** was calculated from the integral ratio.³⁹ Data: Figure 2.

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(39) This technique is known to give accurate ³¹P NMR signal integrals. A calibration run gave a PPh₃/**1a** response factor of 0.999.