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Fluorous Catalysis without Fluorous Solvents: A Friendlier Catalyst Recovery/Recycling Protocol Based upon Thermomorphic Properties and Liquid/Solid Phase Separation

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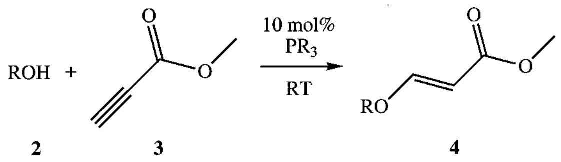
Over the last 6 years, many new catalysts with high affinities for fluorocarbon (fluorous) solvents have been synthesized.[1,2] This has been prompted by the development of "fluorous biphase catalysis",[1a] which as most often practiced exploits the markedly temperature-dependent miscibilities of organic and fluorous solvents. At room temperature, most combinations give two phases.[3] 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 separated under biphasic conditions at the low-temperature limit.

No catalyst recovery method is without potential drawbacks.[4] Accordingly, the fluorous solvent requirement in this protocol has mobilized a vocal contingent of nay-sayers, the major objections from which involve cost and environmental persistence.[3] However, a way to eliminate any such problems has been overlooked. High fluorous-phase affinities are achieved by appending a number of "pony tails" $(CH_2)_m(CF_2)_{n-1}CF_3$ (typically $m = 0-3$, $n = 6-10$) to the catalyst, often giving a low-melting solid. What has not been appreciated is that the same factors that give highly temperature-dependent organic/fluorous *liquid/liquid* phase miscibilities can also give highly temperature-dependent organic/fluorous *liquid/solid* phase miscibilities (e.g., solubilities). In less conceptual terms, as we gained more and more experience with pony-tail-containing fluorous compounds in our laboratory, we began to notice marked increases in solubilities with temperature, particularly near melting points.

A case in point is the easily prepared fluorous phosphine $P((CH_2)_2(CF_2)_7CF_3)_3$ (**1**), which melts at 47 °C.[5] As part of a study involving many related phosphines,[5,6] we began to probe various types of phosphine-catalyzed organic reactions already in the literature.[7,8] The addition of alcohols **2** to methyl propiolate (**3**) shown in Chart 1 was selected for emphasis.[8] Good yields of addition products **4** were obtained at room temperature with both a previously reported catalyst system, $P(n\text{-}Bu)_3$ in CH_2Cl_2, and **1** in $CF_3C_6H_5$. The latter solvent was selected for its ability to dissolve both fluorous and nonfluorous compounds.[9] The mechanism is believed to involve initial 1,4-addition of the phosphine to give a zwitterionic allenolate, which then deprotonates the alcohol.[8a] An alkoxide addition/phosphine elimination sequence gives the product and regenerates the catalyst. Reactions should be slower in less polar solvents, consistent with the data in Chart 1. $P(n\text{-}Bu)_3$ was also an effective catalyst in $CF_3C_6H_5$ and gave faster rates than **1**, consistent with its greater basicity and nucleophilicity.[6d]

Chart 1. Phosphine-Catalyzed Addition Reaction



1 = $P((CH_2)_2(CF_2)_7CF_3)_3$

ROH (0.9 equiv)		Catalyst	Solvent	Yield (%)	Time (h)
2a	$PhCH_2OH$	**1**	$CF_3C_6H_5$	90 [a]	24
				95 [a]	96
		$P(n\text{-}Bu)_3$	CH_2Cl_2	72 [b]	0.5
2b	Ph_2CHOH	**1**	$CF_3C_6H_5$	78 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	85 [b]	0.5
2c	$PhCH(CH_3)OH$	**1**	$CF_3C_6H_5$	81 [a]	24
		$P(n\text{-}Bu)_3$	CH_2Cl_2	89 [b]	0.5
2d	$CH_3(CH_2)_7OH$	**1**	$CF_3C_6H_5$	86 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	77 [b]	0.5

[a] GC yield (vs internal standard); starting concentrations: 0.3 M (**2b**) or 0.5 M (**2a**, **c**, **d**). [b] Isolated yield after Kugelrohr distillation (≥98% purity); starting concentrations: 1.5 M (**2b**) or 1.0 M (**2a**, **c**, **d**).

We were able to recycle catalyst **1** using standard liquid biphase (e.g., $CF_3C_6F_{11}$/octane) and monophase ($CF_3C_6H_5$) conditions, as will be detailed in a full paper. Of particular novelty and the emphasis of this communication is the thermomorphic[10] behavior shown in Figure 1. Between 20−80 and 20−100 °C, **1** exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dissolving nonpolar fluorous compounds, little **1** could be detected at 0 °C by GC (0.31 mM) or ^{31}P NMR. At 20 °C, millimolar concentration levels were present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility was observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C).

Such a dramatic solubility/temperature dependence suggests an obvious catalyst recycling method. As shown in Chart 2, **1** (0.1 equiv), **2a** (2.0 equiv), and **3** were combined in octane (65.0 mM in **3**). The sample was kept at 65 °C (8 h) and cooled to −30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) was isolated by decantation. GC analysis of the supernatant indicated a 82%

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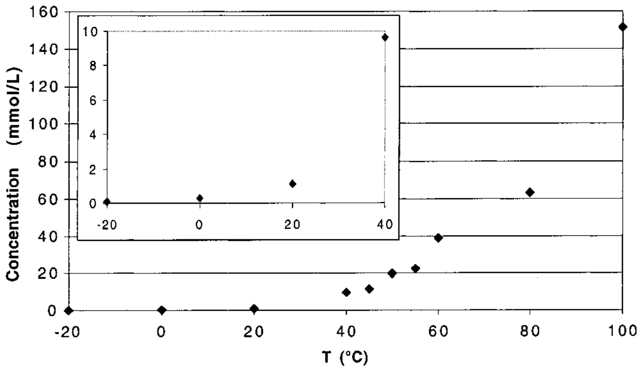


Figure 1. Temperature-dependent solubility of $P((CH_2)_2(CF_2)_7CF_3)_3$ (**1**) in octane (GC vs internal standard; ≥15 min stirring at each temperature and ≥5 min settling period with no stirring).

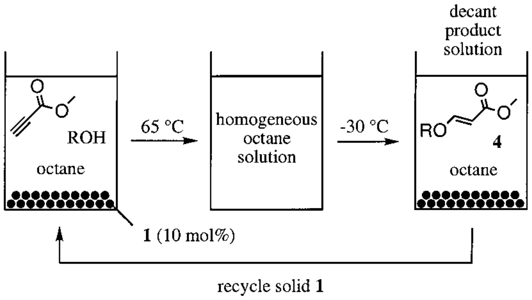
yield of **4a**. The recovered catalyst was used for four further cycles without deterioration in yield, as summarized in Chart 2. Similar results were obtained with alcohols **2b-d**. No background reactions were detected at 65 °C in the absence of **1**, and rates were much slower at lower temperatures.

In a procedural variation, identical reactions were conducted in the presence of Teflon beads or shavings. This provided an adsorbant for the precipitated catalyst, and physically facilitated recycling. The Teflon/catalyst residue from such an experiment (synthesis of **4a**) was extracted with $CF_3C_6H_5$, and a known amount of PPh_3 was added. A ^{31}P NMR spectrum indicated a 89.5% recovery of **1** and 7.8% of two new phosphorus-containing species (possibly educt-derived alternative rest states). The octane solution of the product showed a barely integratable signal for the oxide of **1** (0.4% leaching).[5]

In a further refinement, **2a** and **3** were reacted as in Chart 2, but in the absence of solvent. Toluene was added to efficiently separate **4a** from solid **1**, which was then reused. Yields for a four-cycle sequence were 99, >99, 97, and 95%. The temperature dependence of the solubility of **1** in toluene was also probed. At 0 and 20 °C, concentrations were similar to those in octane. However, solubilities were reduced by half at 40 and 45 °C (4.00 and 5.56 mM), and rose to only 14.4 M at 80 °C. We view this as a logical consequence of the higher solvent polarity and speculate that more dramatic gradients can be achieved with shorter pony tails.

We believe that one-solvent protocols of the type described above will be applicable to a wide variety of fluorous catalysts. It is probably not always necessary to traverse a melting point to achieve a sufficient solubility gradient. Nonetheless, one would expect that the melting points of fluorous compounds can be engineered by shortening, lengthening, or branching the pony tails and by increasing/decreasing their numbers. The phase properties of a catalyst family could be optimized and tailored to a broad portfolio of solvents. However, it must be emphasized that the solubility characteristics of the *catalyst rest state*—not the catalyst precursor—are critical for recycling. In Charts 1 and 2, phosphine **1** represents the dominant rest state, but transition-metal catalyst precursors often exhibit induction periods or are otherwise transformed under reaction conditions. In any event, we have unequivocally shown that fluorous catalysts can be utilized under one-phase conditions in ordinary organic solvents and recovered by low-temperature liquid/solid-phase separation[11] and without recourse to fluorous solvents. There are obvious further refinements of our methodology, and these will be reported in due course.

Chart 2. Fluorous Catalyst Recycling Based upon Liquid/Solid Phase Separation



ROH (2.0 equiv)[a]	Cycle	Yield (%)
2a	1	82
	2	82
	3	80
	4	81
	5	75
2b	1	77
	2	84
	3	71
2c	1	90
	2	86
	3	75
2d	1	79
	2	84
	3	66

[a] Starting concentration of **2**: 1.25 M; reaction time: 8 h; reaction temperature: 65 °C.

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