

## Phase-Vanishing Reactions that Use Fluorous Media as a Phase Screen. Facile, Controlled Bromination of Alkenes by Dibromine and Dealkylation of Aromatic Ethers by Boron Tribromide

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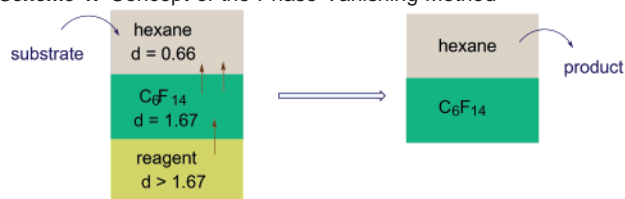
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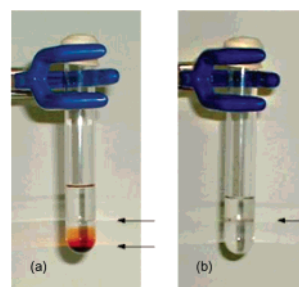
Ongoing work in the fluorous field focuses on the reaction and separation features of fluorous reagents, catalysts, substrates, and other fluorous reaction components.<sup>1</sup> Herein we report a new synthetic technology founded on the unusual properties of fluorous media. We use no fluorous reaction components. We simply capitalize on the physical phenomena that most organic and fluorous media are immiscible, that fluorous media are generally heavier than most organic media, but that many useful organic and inorganic reagents are even heavier than fluorous media.

The concepts of the “phase-vanishing method” are illustrated in Scheme 1. When a fluorous solvent such as perfluorohexanes ( $d = 1.67$ ) is mixed with a heavier reagent, two phases result with the reagent on the bottom. When an organic solvent containing a substrate is added, the fluorous solvent then locates in the middle, screening the two otherwise miscible phases containing the substrate and the reagent from each other. In this triphasic reaction,<sup>2</sup> the fluorous “phase screen” is a liquid membrane that prevents mixing but permits passive transport of reagents from the bottom layer to the top layer and thereby regulates the reaction. As the reagent is consumed, the bottom phase vanishes. Our preliminary experiments suggest that this phase-vanishing method based on spontaneous reaction control by gravity and diffusion is indeed useful for typical synthetic reactions such as bromination of alkenes and dealkylation of aromatic ethers by boron tribromide.

**Scheme 1.** Concept of the Phase-Vanishing Method



We examined phase-vanishing bromination of alkenes as a model. Standard bromination requires careful control of addition rate and temperature to avoid undesirable side reactions.<sup>3,4</sup> FC-72 (perfluorohexanes) was placed in a test tube, and then bromine was introduced slowly by using a glass pipet. The heavier bromine sank to the bottom, forming two layers. A hexane solution of cyclohexene was then slowly added. This floated on top of the FC-72 layer, thus forming a triphasic system (Figure 1). The color of FC-72 gradually turned to wine red, and after 2 days the bromine layer disappeared. The hexane layer was decanted, washed with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , and dried over  $\text{MgSO}_4$ . Purification by short column



**Figure 1.** Phase-vanishing bromination of cyclohexene. The arrows indicate the interface of phases. (a) Triphasic system (from the bottom: bromine, FC-72, hexane solution of cyclohexene). (b) After 2 days, the bromine layer disappeared.

**Table 1.** Phase-Vanishing Bromination of Alkenes

entry	substrate	method <sup>a</sup>	product	yield, <sup>b</sup> %
1		A		81 %
2		B		90 %
3 <sup>c</sup>		B		88 %
4		A		86 %
5		A		81 %
6		A		86 %
7		B		91 % (1/2) <sup>d</sup>
8		A		88 % (13/1) <sup>d</sup>
9		A		97 %
10		A		68 %

<sup>a</sup> Conditions: alkene (2 mmol), hexane (1.5 mL),  $\text{Br}_2$  (2 mmol), FC-72 (1.5 mL), room temperature, with aluminum foil protection from light. Method A, 2 days without stirring; Method B, 4 h (5 h for entry 3) with gentle stirring. <sup>b</sup> Isolated yield for product from hexane layer by silica gel chromatography. <sup>c</sup> Reaction was conducted on an 11 mmol scale. <sup>d</sup> Refer to the ratio of  $2R^*3R^*$  to  $2R^*3S^*$ . Estimated by  $^1\text{H NMR}$ .

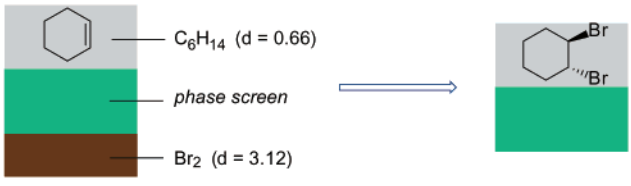
chromatography on silica gel with hexane gave *trans*-1,2-dibromocyclohexane in 81% yield (Table 1, entry 1).

Table 1 demonstrates the generality of the phase-vanishing bromination of alkenes. Gentle stirring of the bromine layer, taking

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**Table 2.** Comparison of "Phase Screen" Ability for Bromination


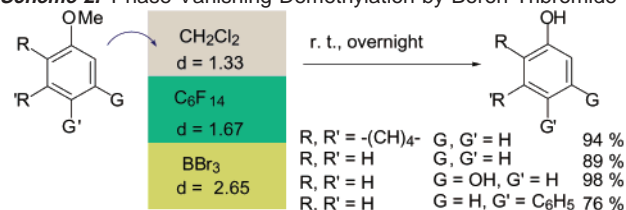
phase screen	density (g/cm <sup>3</sup> )	method <sup>a</sup>	yield <sup>b</sup>
H <sub>2</sub> O	1.0	A	3%
CH <sub>3</sub> CN	0.79	A	32% <sup>c</sup>
C <sub>6</sub> F <sub>14</sub>	1.67	A	81%

<sup>a</sup> Conditions: cyclohexene (4 mmol), hexane (1.5 mL), Br<sub>2</sub> (2 mmol), phase screen (1.5 mL), room temperature, 2 days (method A) or 4 h with gentle stirring (method B) with aluminum foil protection from light.  
<sup>b</sup> Isolated yield for product from hexane layer by silica gel chromatography.  
<sup>c</sup> Acetonitrile layer contained 37% yield of dibromocyclohexane.

care not to mix the three layers, proved to considerably accelerate the reaction. For example, bromination of cyclohexene was complete within 4 h, giving *trans*-1,2-dibromocyclohexane in 90% isolated yield (entry 2).<sup>5</sup> Without shielding the reaction from light, cyclohexyl bromide was generated in 36% yield along with *trans*-1,2-dibromocyclohexane in 60% yield. Not only cyclic alkenes (entries 1–5) but also aliphatic alkenes (entries 6–10) underwent bromination to give the corresponding dibromides in high yields. In every case, completion of the reaction was noticed by the disappearance of the bromine phase and recovery of the transparency of the fluoruous layer.<sup>6</sup>

The ability of the fluoruous phase to act as a phase screen was compared with that of acetonitrile and water, because these solvents can also create three phase systems with bromine and hexane (Table 2). The use of water as a middle layer was inefficient without stirring to give *trans*-1,2-dibromocyclohexane in a very poor yield (3%), suggesting that the diffusion of bromine in water is sluggish. In the case of acetonitrile, dibromocyclohexane was obtained in 32% from the upper hexane layer, but a comparable amount of the product was found to be dissolved in the middle acetonitrile layer. These observations suggest that features of reagent transportation and extrusion of organic products are superior for fluoruous media.

To show that the fluoruous phase screening method is applicable to other exothermic reactions, we focused on boron tribromide (BBr<sub>3</sub>), which is a powerful reagent for dealkylation of ethers and is heavier than FC-72. BBr<sub>3</sub> dealkylations are highly exothermic, and low temperatures (−78 and 0 °C) are typically employed.<sup>7</sup> A dry, inert atmosphere is required because BBr<sub>3</sub> is highly moisture sensitive, so water and acetonitrile are not potential phase screens. We found that the present phase-vanishing method is advantageous for reactions using boron tribromide (Scheme 2). A triphasic mixture consisting of a dichloromethane layer containing  $\alpha$ -methoxynaphthalene, FC-72, and boron tribromide was kept overnight at room temperature. The bottom phase vanished, and  $\alpha$ -naphthol was obtained from the dichloromethane layer in 94% yield. Demethyl-

**Scheme 2.** Phase-Vanishing Demethylation by Boron Tribromide

ation of anisole and two substituted anisoles also produced the corresponding phenols in 76–98% yield.

In summary, we have demonstrated that a fluoruous phase can screen two otherwise miscible heavier and lighter organic phases in the bromination of alkenes and the dealkylation of aromatic ethers by boron tribromide. The fluoruous phase acts as a liquid membrane regulating the exchange between the two organic phases by passive diffusion. The method may be suitable for controlling heat evolution in exothermic reactions, especially on a large scale. This is usually done by cooling and/or by slow addition of one of the components. Cooling consumes energy, and both cooling and slow addition can require complex engineering solutions. In contrast, heat evolution in these fluoruous phase screening reactions is regulated by the rate of transport of the reagent, which in turn depends on readily tunable features including its solubility in the fluoruous phase, the volumes and surface areas of the phases, and mixing method. Further applications of this method will be reported in due course.

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**Supporting Information Available:** Experimental details and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) Like all slow addition techniques (for example, syringe pump additions), the maximum benefits are reaped when the reaction is much faster than the transport as in the case of the present bromination. Because reagents have some solubility in the fluoruous phase, the disappearance of the bottom phase may not strictly correspond to the end of the reaction even for fast reactions. Yet it is a good qualitative guide that the reaction is approaching completion.
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