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Fluorous Solvent as a New Phase-Screen Medium between Reagents and Reactants in the Bromination and Chlorination of Alcohols

Hiroyuki Nakamura,*,† Taikou Usui,† Hirokazu Kuroda,† Ilhyong Ryu,‡ Hiroshi Matsubara,‡ Shinji Yasuda,‡ and Dennis P. Curran§

Department of Chemistry, Faculty of Science, Gakushuin University,
Mejiro, Tokyo 171-8588, Japan, Department of Chemistry, Faculty of Arts and
Sciences, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan, and
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

hiroyuki.nakamura@gakushuin.ac.jp

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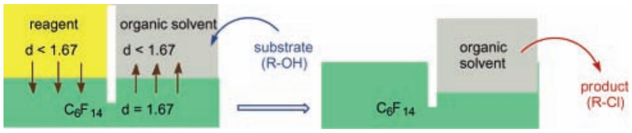
ABSTRACT



A perfluorohexane layer regulates the rate of reagent transport in the bromination and chlorination of alcohols. A fluorous triphasic U-tube method is effective for lighter reagents; the thionyl chloride layer (yellow) vanishes, and the chlorides are obtained from the right top organic layer in the chlorination of alcohols.

Since fluorous biphasic reactions were introduced to organic synthesis,[1] much attention has been paid to the strategic new option of a fluorous technique for conducting organic reactions and for separating the reaction mixtures.[2] Fluorous biphasic reactions are based upon an interaction among fluorous solvents and fluorous compounds such as catalysts, reagents, and reactants; unfluorinated products are usually extracted from a fluorous phase into an organic phase, and fluorinated compounds are recovered from a fluorous phase at the end of reactions.[3,4] As another use for the fluorous technique, we recently found that a fluorous solvent acts as a phase-screen medium in the bromination of alkenes and in the demethylation of aromatic methyl ethers for regulation of the rate of reagent addition.[5] This is important for controlling heat evolution in exothermic reactions, especially

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† Gakushuin University.
‡ Osaka Prefecture University.
§ University of Pittsburgh.

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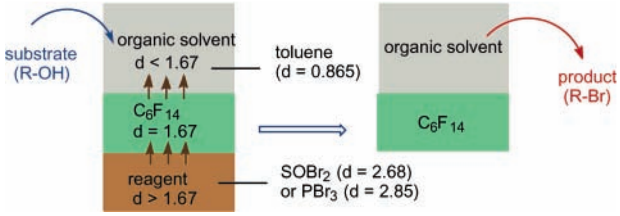
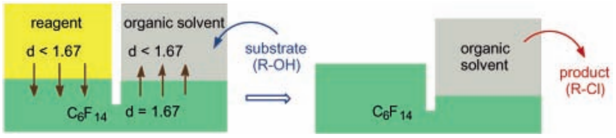
on a large scale. The concept of this *Phase-Vanishing* (PV) reaction is based upon the density of three layers: organic (top), fluorous (middle), and organic and inorganic (bottom). There is passive transport of heavier reagents ($d > 1.67$) from the bottom layer to the top layer ($d < 1.67$) through the fluorous layer (C_6F_{14}; $d = 1.67$).

We applied this method to the bromination of alcohols and found that thionyl bromide ($d = 2.68$) and phosphorus tribromide ($d = 2.85$) are effective for the PV bromination (Scheme 1). Furthermore, we have now succeeded in the extension of the original PV method not only to heavier reagents but also to lighter reagents by introducing the *triphasic U-tube system*, as shown in Scheme 2.[6] A U-tube holds a lower fluorous phase that serves as a phase-screen to separate the upper reagent and organic phases ($d < 1.67$). The substrate added in the organic phase reacts with the reagent regularly transported through the fluorous phase to afford a product, and the reagent phase vanishes as it is consumed. In this paper, we report the chlorination of alcohols using thionyl chloride ($d = 1.63$) and phosphorus trichloride ($d = 1.57$) as a lighter reagent as well as the bromination of alcohols using thionyl bromide and phosphorus tribromide as a heavier reagent.

Scheme 1. Concept of the Phase-Vanishing Method for Heavier Reagents



Scheme 2. Triphasic U-Tube System for Light Reagents



$$\mathrm{R{-}OH} \xrightarrow{\text{halogenation reagent}} \mathrm{R{-}X} \qquad (1)$$

1a: R = benzyl
b: R = 4-methoxybenzyl
c: R = cinnamyl
d: R = 1-naphthylmethyl
e: R = diphenylmethyl
f: R = 1-phenylpentyl
g: R = 1-adamantyl
h: R = cholesteryl

2a-h: X = Br
3a-h: X = Cl

We first examined the bromination of alcohols[7] using the PV method. FC-72 (perfluorohexane, 2 mL) was placed in a test tube, and thionyl bromide (1.5 mmol) was introduced slowly using a glass pipet. The heavier thionyl bromide sank to the bottom, forming two layers. The slow addition of benzyl alcohol **1a** (0.5 mmol) dissolved in toluene (2 mL) formed a triphasic system. The reaction progress in the upper toluene layer was monitored by GC or TLC analysis. Benzyl alcohol **1a** was consumed for 14 h, and the toluene layer was decanted, washed with water, dried over anhydrous $MgSO_4$, and then concentrated. Purification by short column chromatography on silica gel with hexane gave benzyl bromide **2a** in 97% yield (entry 1 in Table 1). Alcohols **1d**−**f** containing aromatic substituents also underwent the bromination under the same conditions, giving the corresponding bromides **2d**−**f** in 96−99% yields (entries 3−5), although the reaction of cinnamyl alcohol **1c** gave **2c** in 50% yield (entry 2). The reaction of 1-adamantanol **1g** proceeded very smoothly to afford **2g** in 96% yield (entry 6); however, cholesterol **1h** needed a longer reaction time (3 days) to give **2h** in 68% yield (entry 7). We also examined the bromination of alcohols using phosphorus tribromide as shown in Table 1. The reaction proceeded, and the bromides were obtained in 81−96% yields under the PV reaction conditions except for **1h** (34% yield).

Table 1. Phase-Vanishing Bromination of Alcohols **1** with $SOBr_2$[a] and PBr_3[b]

			$SOBr_2$		PBr_3	
entry	alcohol	bromide	time	yield (%)[c]	time	yield (%)[c]
1	**1a**	**2a**	14 h	97	12 h	89
2	**1c**	**2c**	6 h	50	24 h	84
3	**1d**	**2d**	7 h	99	12 h	81
4	**1e**	**2e**	24 h	98	15 h	80
5	**1f**	**2f**	6 h	99	13 h	96
6	**1g**	**2g**	22 h	96	12 h	87[d]
7	**1h**	**2h**	3 days	68	24 h	34

[a] Amount of reagents used in the bromination with thionyl bromide is as follows: alcohol **1** (0.5 mmol), $SOBr_2$ (1.5 mmol), FC-72 (1 mL), toluene (2 mL). [b] Amount of reagents used in the bromination with phosphorus tribromide is as follows: alcohol **1** (2.0 mmol), PBr_3 (1.0 mmol), FC-72 (3 mL), toluene (3 mL). The PBr_3 layer vanished within 2 h. [c] Isolated yields based on **1**. [d] Conditions: **1g** (0.66 mmol), PBr_3 (0.4 mmol), FC-72 (3 mL), 1,2-dichloroethane (3 mL) instead of toluene.

Next, we examined a chlorination of alcohols[8] with thionyl chloride as a lighter reagent using the triphasic U-tube system (Scheme 2). A toluene solution of benzyl alcohol **1a** was added to FC-72 held on the U-tube from one side ("the reactant layer"), and thionyl chloride was floated on the other side. The reaction progress in the reactant layer was

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(7) For the established procedures of bromination of alcohols using $SOBr_2$ and PBr_3, see: (a) *Organic Syntheses*; Gilman, H., Ed.; Wiley: New York, 1941; Collect. Vol. I, p 36. (b) *Organic Syntheses*; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. II, p 358.

(8) For the established procedures of chlorination of alcohols using $SOCl_2$ and PCl_3, see: (a) *Organic Syntheses*; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 110. (b) *Organic Syntheses*; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. II, p 136.

monitored by GC or TLC analysis. The possibility of the transport of toluene or **1a** from the reactant layer to the reagent layer through the fluorous layer was considered; however, the thionyl chloride layer vanished within 3 h and benzyl bromide **3a** was obtained from the toluene reactant layer in 95% yield (entry 1 in Table 2). 4-Methoxybenzyl alcohol **1b** was also transformed into the corresponding chloride **3b** in 98% yield (entry 2). In both cases, the addition of 1-hydroxybenzotriazole (HOBt) into the reactant layer was effective for obtaining the chlorides in high yields.[9] The reaction of cinnamyl alcohol **1c** and 1-naphthyl alcohol **1d** also proceeded smoothly, giving **3c** and **3d** in 94 and 98% yields, respectively (entries 3 and 4). Not only primary alcohols but also secondary and tertiary alcohols such as diphenylmethanol **1e**, 1-phenylpentan-1-ol **1f**, 1-adamantanol **1g**, and cholesterol **1h** underwent the chlorination to afford the corresponding chlorides **3e**−**h** in 80−94 yields (entries 5−8). As the other lighter chlorination reagent, we chose phosphorus trichloride and examined the chlorination of alcohols under the same conditions. The chlorination of alcohols proceeded, although the yields of the corresponding chlorides were not necessarily high (28−86% yields in Table 2) in all cases.

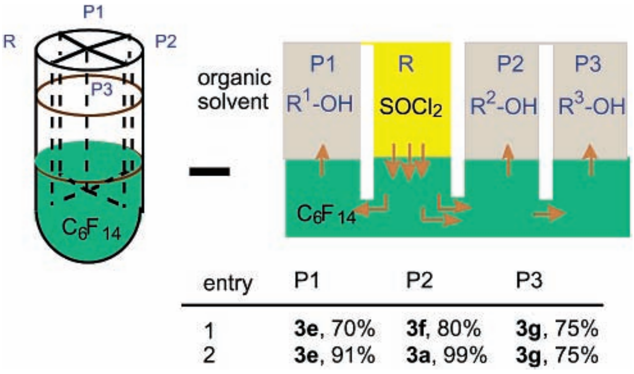
Table 2. Triphasic U-Tube Chlorination of Alcohols **1** with $SOCl_2$[10] and PCl_3[a]

			$SOCl_2$		PCl_3	
entry	alcohol	chloride	time	yield (%)[b]	time	yield (%)[b]
1[c]	**1a**	**3a**	4 h	95	12 h	62
2[c]	**1b**	**3b**	12 h	98	12 h	86
3	**1c**	**3c**	6 h	94	27 h	52
4	**1d**	**3d**	12 h	98	21 h	36
5	**1e**	**3e**	20 h	93	25 h	70
6	**1f**	**3f**	13 h	80	27 h	58
7	**1g**	**3g**	13 h	83	50 h	30
8	**1h**	**3h**	3 days	94	3 days	28

[a] Conditions: **1** (0.3 mmol), PCl_3 (1.2 mmol), FC-72 (3 mL), toluene (1 mL). [b] Isolated yields based on **1**. [c] Addition of HOBt (3 equiv relative to **1**) accelerated the reaction progress. Dichloromethane was used instead of toluene. Without the addition of HOBt, **3a** was obtained in 28% yield.[9]

It was envisioned that the triphasic U-tube system would be suitable for a parallel synthesis. We designed the multislit apparatus with an open bottom, as shown in Scheme 3. The figure at the left of Scheme 3 depicts the designed multislit apparatus for the parallel synthesis, and FC-72 to this apparatus as the phase-screen layer. Each toluene solution of **1e**, **1f**, and **1g** was added to FC-72 from each slit (P1−P3), and thionyl chloride was floated on the slit R. The figure at the right of Scheme 3 depicts the concept of the parallel synthesis using the multislit system. Thionyl chloride was transported through the FC-72 layer into the reactant layer of each slit (P1−P3). After 24 h, the chlorination reactions of alcohols in each slit were complete and the corresponding chlorides **3e**, **3f**, and **3g** were obtained in 70, 80, and 75% yields, respectively, without any contamination of products. The combination of the alcohols **1a**, **1e**, and **1g** was also examined under the same conditions, and **3e** and **3g** were obtained in 91 and 75% yields, respectively, after 24 h. Interestingly, 24% of **1a** was converted into **3a** at this moment; however, the addition of another equivalent of thionyl chloride to the slit (R2) and removal of other reactant layers (P1 and P3) accelerated the chlorination of **1a** to give **3a** in 99% yield.

Scheme 3. Parallel Chlorination Using The Triphasic Multislit Apparatus



entry	P1	P2	P3
1	**3e**, 70%	**3f**, 80%	**3g**, 75%
2	**3e**, 91%	**3a**, 99%	**3g**, 75%

We have demonstrated that a fluorous solvent acts as a phase screen between reagent and reactant phases and regulates the bromination and the chlorination of alcohols. The triphasic U-tube system was efficient for regulation of the lighter reagent transport in the PV reaction. In this system, it is essential that the rate of the passive transport of unfluorinated reagents to the reactant layer through fluorous media should be higher than that of reactant and product transport from the reactant layer to the reagent layer. The parallel chlorination of alcohols has been achieved using the multislit apparatus without any contamination. It is now possible to conduct reactions with controlled addition rates of various unfluorinated reagents by the fluorous phase screen independent of whether the reagent is more or less dense than the phase screen.

Supporting Information Available: Detailed experimental procedures and characterization data for compounds **1f**, **2f**, **2h**, and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763.

(10) Typical procedure is as follows: a solution of **1** (0.5 mmol) in toluene (1 mL) was put into one side of the U-tube, in which FC-72 (3 mL) was placed, and $SOCl_2$ (0.15 mL, 2 mmol) was put into the other side of the U-tube. The $SOCl_2$ layer vanished after 3−5 h. The reaction progress was monitored by GC or TLC analysis. After the reaction was completed (between 4 h and 3 days), the toluene layer was decanted and poured into water. The mixture was extracted with ether, washed with a saturated NaCl aqueous solution, and concentrated. The residue was purified by column chromatography on silica gel with hexane (or ether) to give **3**.