Phase-Vanishing Methodology for Efficient Bromination, Alkylation, Epoxidation, and Oxidation Reactions of Organic Substrates
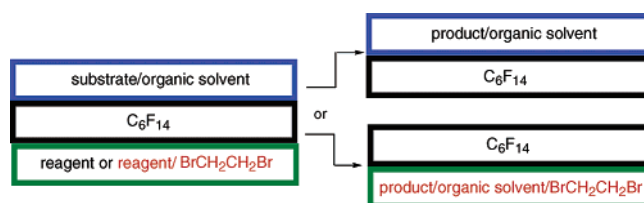
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ABSTRACT

In cases where both reactants in a phase-vanishing reaction are less dense than the fluorous phase, an alternative to the U-tube method is to employ a solvent with greater density than the fluorous phase, such as 1,2-dibromoethane. This modification has been successfully applied to the methylation of a phenol derivative with dimethyl sulfate and to the m-CPBA-induced epoxidation of alkenes, N-oxide formation from nitrogen-containing compounds, and S-oxide or sulfone formation from organic sulfides.

Fluorous-phase chemistry is currently a topic of considerable interest.[1,2] The use of a fluorous solvent as a phase screen for maintaining temporary separation between two reactive organic phases allows so-called phase vanishing reactions[3] to occur. A significant advantage of such reactions is that exothermic transformations normally carried out below room temperature (typically −78 to 0 °C) can be carried out at room temperature because heat is released to the environment in a slow and controlled manner. Energy savings incurred in fluorous phase vanishing reactions are therefore advantageous for potential large-scale production in industry.

In the usual phase-vanishing reaction environment, the density of the fluorous solvent is less than that of one of the reactant phases but is greater than that of the other. In such cases, the top phase consists of one reactant in an organic solvent, a fluorous solvent comprises the more dense middle phase, and a second reactant (a liquid) functions as the bottom phase. When both reactants are less dense than the fluorous phase, the fluorous phase can be contained in a U-tube with a reactant phase in each arm floating on the fluorous phase. Here, we present an alternative to the U-tube method in which one of the phases can be dissolved in a high-density solvent (1,2-dibromoethane in the present instance) to form the bottom phase.

The more usual phase-vanishing technique has recently been applied by Ryu et al. to the bromination of alkenes,[3a] the dealkylation of aromatic ethers by boron tribromide,[3a] the acylation of aromatic compounds,[3b] and the bromination of alcohols using PBr_3 or $SOBr_2$ as the bottom liquid phase.[3c] These workers have also applied the U-tube approach to the chlorination of alcohols using $SOCl_2$, PCl_3 as the top liquid phases.[3c] Here we describe the use of phase-vanishing

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Scheme 1. Bromination of Aromatic Compounds with Bromine Using the Phase-Vanishing Technique
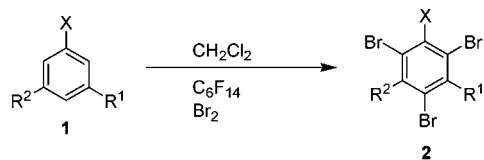
			yield (%)	literature yield (%)
2a	X= OH,	$R^1 = R^2 = H$	90	45- 98[4b,c,e,h]
2b	X= OH,	$R^1 = R^2 = Me$	92	45-97[4e,f]
2c	X= NH$_2$,	$R^1 = R^2 = H$	85	65-93[4d,g]
2d	X= NHMe,	$R^1 = R^2 = H$	78	65-93[4d,g]

Scheme 2. Bromination of Unsaturated Alcohols with Phosphorus Tribromide Using the Phase-Vanishing Technique

				yield (%)	literature yield (%)
4a	$R^3 =$	HC≡C-	$R^4 = H$	80	41.5-72[5a-b]
4b	$R^3 =$	HC≡C-	$R^4 = Me$	78	42-78[5a-c]
4c	$R^3 =$	$H_2C=CH-$	$R^4 = H$	75	46-95[5d-e]
4d	$R^3 =$	$CH_3HC=CH-$	$R^4 = H$	80	86-98[5f-g]

reactions for the bromination of phenols and anilines by elemental bromine, the bromination of allylic and propargylic alcohols with phosphorus tribromide, the alkylation of a phenol derivative by dimethyl sulfate, the epoxidation of several alkenes by *m*-CPBA, and *N*-oxide formation from nitrogen-containing compounds with *m*-CPBA and *S*-oxide or sulfone formation of some organic sulfides with *m*-CPBA. For all but the first two types of reactions, 1,2-dibromoethane is used as a solvent of highest density to dissolve the liquid dimethyl sulfate and the solid *m*-CPBA for constituting the bottom solution phase. The utilization of a solvent more dense than the fluorous phase in phase vanishing reactions does not seem to have been reported. In all cases, perfluorohexane was used as the screening middle phase and all the reactions were carried out at room temperature.

During the reaction of bromine (bottom layer) with phenols **1a,b** and anilines **1c,d** (in dichloromethane as the top layer) the bromine phase was seen to vanish when the reaction was complete. Although the yields shown in Scheme 1 are not as good as the corresponding maximum values found in the literature, each of the yields is substantially above the middle of the corresponding literature range.[4]

In literature reports describing various reagents for the bromination of alcohols,[5] the use of PBr$_3$[5b] requires controlled addition of this reagent as well as low temperature. In our protocol, a propargyl, allyl, or crotyl alcohol in ether constitutes the top phase and phosphorus tribromide forms the stirred bottom phase (Scheme 2). In this scheme, it is seen that after disappearance of the bottom phase, the product yield is higher than the maximum[5a,c,e,g] and lower than the minimum[5b,d,f] observed for **4a** and **4c**, respectively, seen in the literature range. The yields for **4b** and **4d** are as good as

the maximum and higher than the middle, respectively, of the corresponding ranges recorded in the literature.

In literature investigations of classical alkylations of phenols,[6] those utilizing dimethyl sulfate normally require reflux conditions.[6a] In our experiment, dimethyl sulfate dissolved in dibromoethane formed the stirred bottom phase and an equimolar mixture of salicyclic acid and triethylamine in acetone made up the top phase. After the top phase had vanished into the bottom phase, the selectively monoalkylated product **5** was obtained in considerably better yield (90%) than the maximum of the range reported in the literature (56−72%[6a−e]).
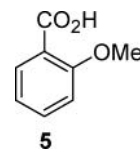
Among the variety of approaches available for the epoxidation of alkenes,[7] the use of *m*-CPBA normally requires temperatures of 0 °C or below. In the present protocol, *m*-CPBA in 1,2-dibromoethane forms the stirred bottom phase and styrene in dichloromethane is the top phase that vanishes into the bottom phase. The epoxide yields shown in Table 1 are in each case at or beyond the maximum yield reported in the literature, except for cyclohexene oxide, for which the yield is still well beyond the middle of the literature range.
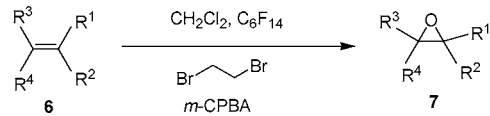
N-Oxide preparations from amines using a variety of oxidizing agents is well documented in the literature,[8] and the same is true for the oxidation of sulfides to sulfoxides
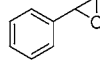
(4) (a) Fuson, R. C. *Reaction of Organic Compounds*; Wiley: New York, 1962; Vol. 58, p 98. (b) Vona, J. A.; Merker, P. C. *J. Org. Chem.* **1949**, *14*, 1048. (c) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Chem. Lett.* **1987**, 627. (d) Kajigaeshi, S.; Kakinami, T. Inoue, K.;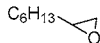 Kondo, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 597. (e) Kakinami, T.; Suenaga, H.; Yamaguchi, T.; Okamoto, T.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3373. (f) Goud, B. S.; Desiraju, G. R. *J. Chem. Res.* **1995**, 244. (g) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K. *Tetrahedron Lett.* **1998**, *39*, 8163. (h) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R. Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247. (i) Smith, M. B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; LaChapelle, E. *Org. Lett.* **2002**, *4*, 2321. (j) Deacon, G. B.; Farquharson, G. J. *Aust. J. Chem.* **1976**, *29*, 627. (k) Deacon, G. B.; Farquharson, G. J. *Aust. J. Chem.* **1977**, *30*, 293.

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Table 1. Epoxidation of Alkenes with *m*-CPBA Using the Phase-Vanishing Technique[a]

entry	alkene	epoxide	yield(%)[b]	literature yield (%)
1	(styrene)	**7a**	96	5-89[7f,g,k]
2	(cyclohexene)	**7b**	78	46-91[7f,g,k-n]
3	(cycloheptene)	**7c**	92	48-91[7f,k-m]
4	(cyclooctene)	**7d**	95	78-96[7e,g,i,k-m,o]
5	C$_6$H$_{13}$ (terminal alkene)	C$_6$H$_{13}$ **7e**	86	59-67[7m,o]

[a] 1,2-Dibromoethane (2.0 mL), *m*-CPBA (3.0 mmol), perfluorohexane (1.5 mL), alkene (2.0 mmol), dichloromethane (1.5 mL), bottom layer stirred at room temperature for 2 days. [b] Isolated yields.

Figure 1. Oxidation of amines and sulfides with *m*-CPBA using the phase-vanishing technique.

or sulfones.[9] The use of *m*-CPBA in both types of oxidation normally requires a temperature of 0 °C or below. In our procedure for both transformations, *m*-CPBA in 1,2-dibromoethane constituted the stirred bottom layer and the substrate dissolved in dichloromethane was the vanishing top layer. Pyridine gave pyridine *N*-oxide (**8a**) in excellent yield

(92%) although this value is not quite at the maximum of the literature range (76−99%[8c−h]). 8-Hydroxyquinoline gave the corresponding *N*-oxide **8b** in reasonable yield (75%) which was well above the average of the literature range (20−84%[8d,e]) (Figure 1).

Because of the ease with which the parent sulfoxide of **9** was oxidized to **9** with *m*-CPBA under our conditions, the use of only 1 equiv of *m*-CPBA produced about 0.5 equiv of **9** (44%). We therefore used 2 equiv of *m*-CPBA for the parent sulfides of **9**−**11**, which afforded excellent and above-average yields in the first two instances and a yield very nearly as good as the maximum literature yield in the third case. Similar treatment of 3-(thiophenoxy)cyclohexanone, however, gave only a 40% yield of sulfone **12** along with a 47% yield of the corresponding sulfoxide (**13**) which to the best of our knowledge is a compound that has not been reported. Under our mild conditions, steric hindrance posed by the phenyl ring probably reduces the reactivity of the parent sulfide.

In conclusion, the types of transformations preliminarily explored in this work provide product yields that in the majority of instances are quite comparable to and in several

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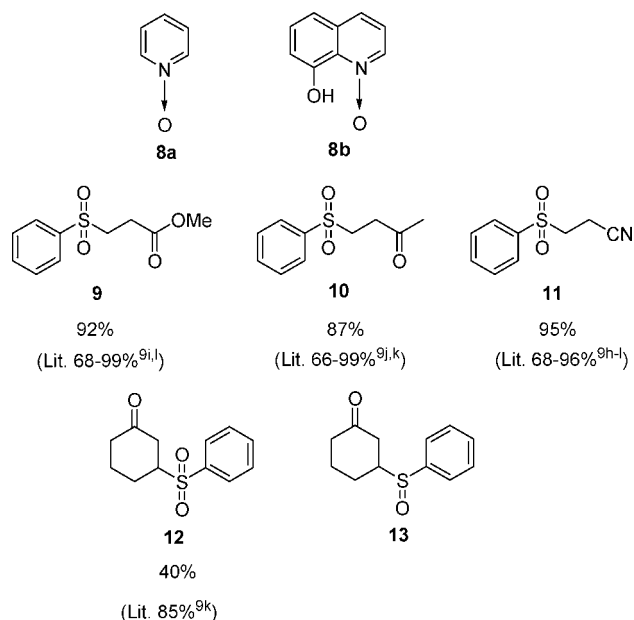
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cases in excess of maximum yields reported in the literature. Advantages associated with the protocols for the reactions described herein are savings in energy, the recyclable nature of the perfluorohexane phase screen and, as reported in this publication, the use of dimethyl sulfate and *m*-CPBA in phase-vanishing reactions (and presumably other reactants of lower density than the fluorous phase) by dissolving such a reactant in an appropriate solvent more dense than perfluorohexane. Broadening the scope of transformations of the type reported here will be the subject of a future publication.

Supporting Information Available: Experimental details, NMR (^{1}H and ^{13}C) spectroscopic data for compounds prepared, and characterization of the sulfoxide derivative of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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