

Quadruphase Phase-Vanishing Method: Application to Bromination Reactions that Produce Acidic By-Products

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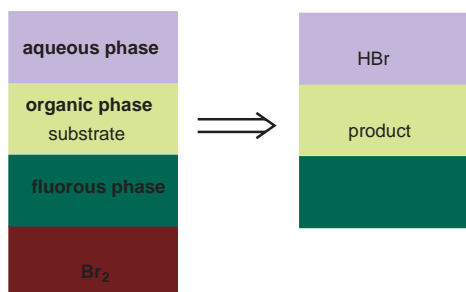
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Abstract: A quadruphase phase-vanishing method was developed that employs water as the fourth phase acting as an 'acid scavenger phase'. This protocol worked well for bromination of acetophenones giving high yields of the corresponding α -bromo ketones.

Key words: fluoruous solvent, quadruphase, phase-vanishing method, bromination of acetophenones, acidic by-products

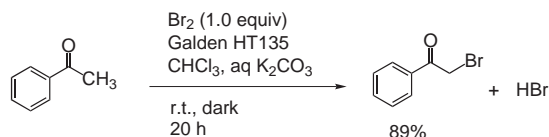
Fluorous-phase chemistry has opened a new frontier in organic synthesis and separation.¹ The organic and fluorous media generally constitute immiscible layers at room temperature. Phase-vanishing methods are based on this typical property of the fluorous media, where the fluorous phase acts as an inert liquid membrane to divide and connect the reactant and reagent phases.² The fluorous phase controls the gentle mixing of the reactants and the reagents by either (i) slow diffusion of the reagent through the fluorous media towards the reactant phase^{2a-c} or (ii) slow extraction of the reactant towards the reagent phase.^{2e,f}



Scheme 1 Concept of quadruphase phase-vanishing bromination: aqueous phase traps an acidic by-product: HBr

In the phase-vanishing method, exothermic reactions, which generally require (1) slow addition of the reactant (using a dropping funnel or a syringe pump) and (2) maintenance of low temperature ($-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$), can be carried out at room temperature without using any special apparatus or equipments for the addition of the reagents or temperature control.

Bromination of ketones is among the most basic transformations in synthetic chemistry.³ The most commonly



Equation 1

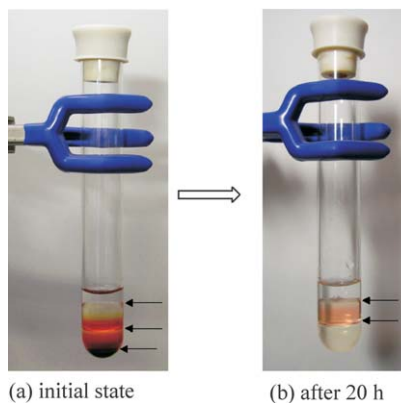


Figure 1 Quadruphase phase-vanishing bromination of acetophenone (Equation 1). The arrows indicate the interface of the phases. (a) Four-phase system: bromine, Galden[®] HT135, CHCl_3 solution of acetophenone, aq solution of K_2CO_3 (from the bottom). (b) After completion of the reaction (r.t., 20 h), the bromine layer disappeared giving three phases: Galden[®] HT135, CHCl_3 phase, aqueous phase (from the bottom)


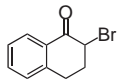
used reagent for this purpose is molecular bromine and in many cases the bromination is conducted in the presence of a protic or Lewis acid catalyst.⁴ α -Bromination of ketones, benzylic bromination of arylalkanes and electrophilic aromatic bromination all have a common feature, i.e., HBr is generated as a by-product.⁵ This acidic by-product can be problematic and in this study we wanted to address this problem by adding an additional 'scavenger phase' to the original triphasic phase-vanishing method. The concept is illustrated in Scheme 1. As the reaction proceeds, HBr is produced which would diffuse through the reactant phase towards the alkaline aqueous phase. Thus, removal of the HBr from the reaction system with concomitant neutralization would be accomplished.

In this study, we used Galden[®] HT135⁶ (bp $135\text{ }^{\circ}\text{C}$), polyether-type perfluorinated solvent as a phase screen, which is less volatile and less expensive than FC-72 (bp $51\text{--}59\text{ }^{\circ}\text{C}$). We examined the phase-vanishing bromination of acetophenone as a model.^{7,8} Liquid bromine ($\rho = 3.12\text{ g/mL}$) was overlaid by Galden[®] HT 135 ($\rho = 1.72\text{ g/mL}$)

which in turn was overlaid by a chloroform solution of acetophenone. Since the slightly basic aqueous phase is less dense than chloroform, it made the fourth layer at the top acting as a trap for HBr (Figure 1). At the end of the stoichiometric reaction, the bottom phase had disappeared resulting in a triphasic system, and the product was located in the middle organic phase. The organic phase was collected and after flash column chromatography on silica gel α -bromo acetophenone was obtained in 89% yield (Equation 1). It should be noted that diffusion of bromine was much faster through Galden[®] HT135 than that through FC-72.

The generality of this quadruphase method was examined with several acetophenone derivatives (Table 1). With the exceptions of entries 2 and 6, monobromination took place selectively. Bromination of 1-tetralone gave high yield of the desired α -brominated product (entry 10). Dibromination was achieved by simply using two equivalents of bromine with respect to the acetophenones (entries 8 and 9).

Table 1 Phase-Vanishing α -Bromination of Acetophenones^a

Entry	Substrate	Time	Products (yield, %) ^b
1	PhCOCH ₃	20 h	PhCOCH ₂ Br (89)
2	4-MeC ₆ H ₄ COCH ₃	18 h	4-MeC ₆ H ₄ COCH ₂ Br (80) + 4-MeC ₆ H ₄ COCHBr ₂ (3)
3	4-MeOC ₆ H ₄ COCH ₃	20 h	4-MeOC ₆ H ₄ COCH ₂ Br (92)
4	4-ClC ₆ H ₄ COCH ₃	18 h	4-ClC ₆ H ₄ COCH ₂ Br (90)
5	4-BrC ₆ H ₄ COCH ₃	18 h	4-BrC ₆ H ₄ COCH ₂ Br (92)
6 ^c	PhCOCH ₂ CH ₃	13 h	PhCOCHBrCH ₃ (90) + PhCOCHBr ₂ CH ₃ (8)
7	PhCOCH(CH ₃) ₂	3 d	PhCOCHBr(CH ₃) ₂ (93)
8 ^d	PhCOCH ₃	46 h	PhCOCHBr ₂ (97)
9 ^d	PhCOCH ₂ CH ₃	48 h	PhCOCHBr ₂ CH ₃ (94)
10		48 h	 (92)

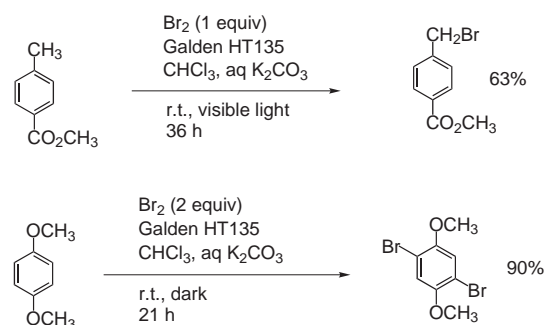
^a Reaction conditions: substrate (2 mmol), CHCl₃ (1.5 mL), Br₂ (2 mmol), Galden HT135 (1.5 mL), aq K₂CO₃ solution (1.0 mL), with aluminum foil protection from light, kept at r.t. without stirring.

^b Isolated yields.

^c Br₂ (2.2 mmol).

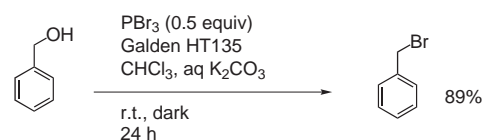
^d Br₂ (4 mmol).

We also tested the present quadruphase system for some other bromination reactions, such as benzylic and aromatic brominations, which also produce HBr as a by-product (Scheme 2). Previously benzylic bromination used an anhydrous solvent, a radical initiator such as AIBN and photoirradiation.⁹ Phase-vanishing bromination of methyl 4-methylbenzoate under visible-light gave the desired benzyl bromide in 63% yield. Dibromination of 1,4-dimethoxybenzene also gave the corresponding dibromo derivative in 90% yield.^{10,11}



Scheme 2 Phase-vanishing benzylic and aromatic bromination

The present quadruphase phase-vanishing method can also be applied to some other reactions which produce acidic materials other than HBr. Bromination of alcohols with PBr₃ produces the acidic by-product, P(OH)₃.¹² Even though PBr₃ is sensitive to water, bromination of benzyl alcohol was achieved using the quadruphase method, giving benzyl bromide in very good yield (Scheme 3). We assumed that the reaction took place mainly at the chloroform/Galden interface and the aqueous phase had no detrimental effect on the course of the reaction.



Scheme 3 Phase-vanishing bromination of benzyl alcohol

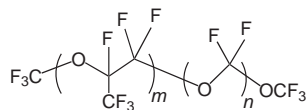
In summary, the modified phase-vanishing protocol using an aqueous phase as the fourth layer proved to be useful for the α -bromination of acetophenones and some other bromination reactions, in which slightly basic aqueous top layer well functions as an effective acid scavenger. The new entry of an aqueous phase to create a quadruphase system for phase-vanishing methods should help to extend this method to include an in situ work up system.

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- (6) Galden® HT135 is a polyether-type perfluorinated solvent, which is commercially available as a heat transfer liquid (Solvay Solexis Inc.). Bp 135 °C, density = 1.72 g/mL at 25 °C, average molecular weight = 610. The general structure is shown in Figure 2.
- (7) **Typical Experimental Procedure for Bromination of Acetophenones.**
 Galden® HT 135 (1.5 mL) was placed in a test tube, and then bromine (320.0 mg, 2.0 mmol) was introduced slowly by using a glass pipette. Since bromine is more dense than the fluorine phase, bromine sank to the bottom, forming two layers. A CHCl₃ solution (1.5 mL) of 4-chloroacetophenone (309.0 mg, 2.0 mmol; Table 1, run 4) was then slowly added, which made the third layer. Then, 1.0 mL of 1 M aq solution of K₂CO₃ was added on the top, forming a four-phasic system. Then the test tube was covered with aluminum foil to protect from light and left overnight without stirring at r.t. After the bromine layer had disappeared and the fluorine phase became colorless, the upper two phases (aqueous and organic) were decanted. The organic phase was separated, washed with aqueous solution of Na₂SO₃, dried over MgSO₄ and concentrated. The residue was purified by a short column chromatography (silica gel, eluted with hexane–EtOAc) to give 420.4 mg (yield 90%) of 2-bromo-1-(4-chlorophenyl)ethanone as colorless microcrystals.
- (8) In a triphasic system (aqueous phase being omitted) bromination of acetophenone derivatives proceeded, however, pungent HBr gas evolved from the top layer.
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Galden® HT135

Figure 2