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A Photo-Irradiative Phase-Vanishing Method: Efficient Generation of HBr from Alkanes and Molecular Bromine and its Use for Subsequent Radical Addition to Terminal Alkenes

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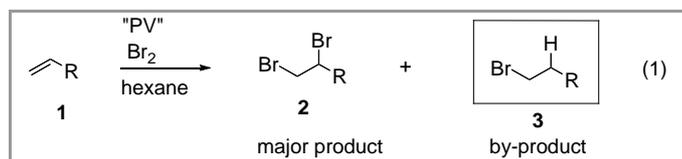
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Abstract: A triphasic phase-vanishing (PV) system comprised of an alkane, perfluorohexanes, and a bromine was successfully combined by photo-irradiation to efficiently generate hydrogen bromide, which underwent radical addition with 1-alkenes in the hydrocarbon layer to afford terminal bromides in high yields.

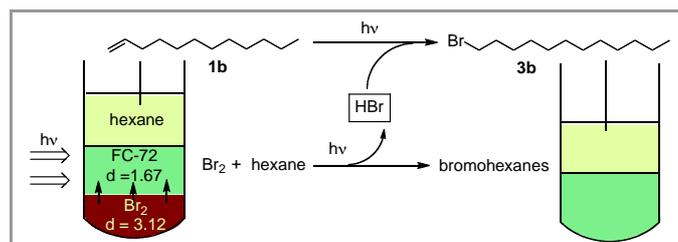
Key words: fluoros solvent, phase-vanishing, photo-irradiation, bromination, hydrogen bromide

Reduction or elimination of the use of hazardous organic solvents is one of the major issues of the green chemistry, and in this regard fluoros solvents represent workable alternatives of the organic solvents.^{1,2} Fluoros solvents are generally immiscible with common organic solvents, while exhibit thermomorphic nature to give homogeneous solution upon heating. Thus far we developed recyclable organic/fluoros amphiphilic solvents, such as F-626³ and fluoros DMF.⁴ In our recent work, we also reported that fluoros chiral amines can be used repeatedly for enantioselective desymmetrization of ketones.⁵

In a different direction of utilizing fluoros media for organic synthesis, multi-phasic reactions appear promising. The Curran group and we have jointly developed phase-vanishing (PV) methods, which utilizes triphasic reactions based on the phenomenon that fluoros media act as liquid membranes to transport reagents to organic layers containing substrates.⁶ Since the first demonstration of the PV method,⁷ which is used for room temperature bromination of alkenes with molecular bromine to give vic-dibromoalkanes, a number of applications to various reagents other than bromine have been developed by us⁸ and the others.⁹ Recent advances in phase-vanishing bromination include a quadruphase PV bromination of ketones and aromatic compounds,^{8c} in which an aqueous “scavenger” phase was added to the original triphasic PV method to remove HBr. In a related study using a related triphasic system, Iskra and co-workers reported benzylic bromination under irradiation conditions,^{9d} and Dragojlovic and co-workers employed Teflon tape as the fluoros phase screen.^{9h, 9i} Weiss and co-workers carried out stereoselective bromination of alkenes using an ionic liquid as the phase screen of the PV method.^{9g}



Looking back to the original procedure of PV bromination of alkenes with bromine, shielding the test tube from sunlight with aluminium foil is important for the prevention of the formation of 1-bromoalkane **3** as a by-product (eq 1).⁶ The formation of **3** was puzzling, however we hypothesized that hydrogen bromide would form in this system by sunlight-irradiative reaction of the hydrocarbon solvent with molecular bromine. This led us to examine the “photo-irradiative” phase vanishing reaction as a means for the generation of dry HBr. In this Letter, we report on the efficient in situ generation of HBr and the use for the synthesis of terminal alkyl bromides via anti-Markovnikov addition to terminal alkenes.



Scheme 1 Photo-irradiative phase-vanishing bromination of 1-dodecene (**1b**) leading to 1-bromododecane (**3b**).

With 1-dodecene (**1b**) as the substrate and hexane as the solvent, PV bromination was carried out under a variety of conditions using a Xenon lamp as the light source (Table 1). When FC-72 (perfluorohexanes, 3 mL) was placed in a test tube (Pyrex, $\phi = 13$ mm) to which bromine (1.05 equiv) was slowly introduced, the heavier bromine sank to the bottom, forming two layers. A hexane (1.5 mL) solution containing 1-dodecene (2 mmol) was then added; this floated on top of the FC-72 layer, forming a triphasic system (Picture A). The test tube was then irradiated with a 500 W Xenon lamp. The FC-72 layer gradually turned milky and small bubbles of hydrogen bromide gas began to evolve (Picture B). As the bromine layer disappeared in 45 min, the evolution of small bubbles ceased gradually and after 1.5 h the FC-72 layer recovered transparency (Picture C). The hexane layer was then taken, washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$, and dried over Na_2SO_4 . After aqueous work-up, purification by short column chromatography on silica gel with hexane gave a mixture of 1,2-dibromododecane (**2b**) and 1-bromododecane (**3b**) in 68% and 32% yields, respectively (Table 1, entry 1).

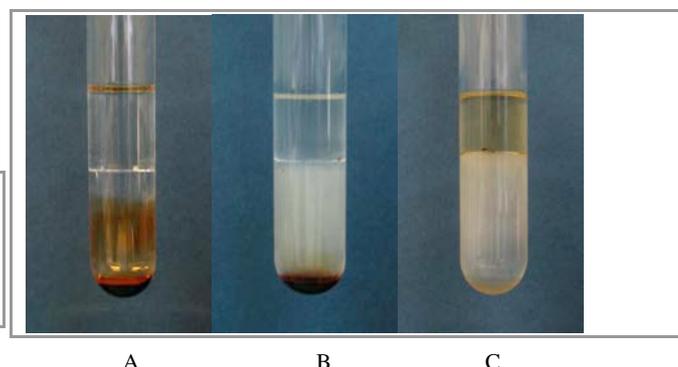
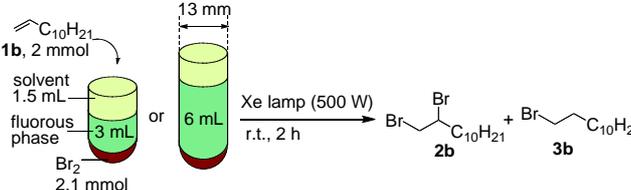


Fig. 1 Pictures of the photo-irradiative phase-vanishing bromination of 1-dodecene with bromine. A: Before irradiation. B: With irradiation, the FC-72 layer turned milky. C: After ca. 1.5 h, the bromine layer disappeared and the FC-72 layer recovered transparency.

The formation of 1-bromododecane (**3b**) was the result of two consecutive radical reactions: (i) generation of HBr *via* a photo-

induced radical reaction of molecular bromine with the hydrocarbon solvent, hexane, and (ii) the photo-induced free-radical addition of the resulting HBr to **1b** to give **3b** (Scheme 1). Consistent with this proposed mechanism, bromohexanes were detected by GC-MS analysis of the crude reaction mixture. As we expected, the use of isooctane and 2,4-dimethylpentane, having tertiary C-H bonds, as the top solvent raised the yield to 61% and 77%, respectively (entries 3 and 6).¹⁰ The use of perfluorinated polyether Galden HT135 also works well to give a better yield of **3a** (entry 5). Since HBr is supposed to be generated by the reaction of alkanes partially dissolved in the fluorous phase with diffusing bromine, we hypothesized that simply increasing the length of the fluorous phase would give the bromine a greater chance for reaction with isooctane. Indeed, the simple manipulation to double the fluorous phase (22 mm to 44 mm by length, 3 mL to 6 mL by volume) in volume, yielded 1-bromodecane **3b** as the sole product (96%) (entry 4).

Table 1 Control experiments for photo-irradiative phase-vanishing bromination of **1b**



entry	solvent	fluorous phase	light	yield ^a	
				2b	3b
1	hexane	FC-72, 3 mL	+	68%	32%
2	hexane	FC-72, 3 mL	- ^b	90%	- ^c
3	isooctane	FC-72, 3 mL	+	39%	61%
4	isooctane	FC-72, 6 mL	+	trace	96%
5	isooctane	GALDEN HT-135, 3 mL	+	10%	90%
6	2,4-dimethylpentane	FC-72, 3 mL	+	22%	77%

^aIsolated yield from organic layer after silica gel column chromatography. ^bWith aluminium foil and gentle stirring. ^cNot detected.

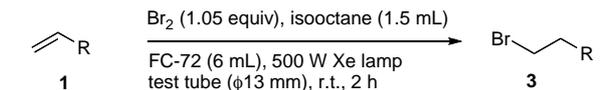
Under these optimal conditions obtained for entry 4, we examined the generality of the hydrobromination of alkenes under irradiative PV-bromination conditions. As shown in Table 2, a variety of terminal alkenes **1a-f**, some of which have a functional group, were converted to the corresponding 1-bromoalkanes **3a-f** in high yields (entries 1-6). Dienes **1g-i** were also examined as substrates. The reaction of 1,9-decadiene (**1g**) with bromine (2.5 mol equiv) yielded 92% yield of 1,10-dibromoalkane (**3g**) (entry 7). Under similar conditions, 1,11-dodecadiene (**1h**) and 1,13-tetradecadiene (**1i**) yielded the corresponding dibromoalkanes **3h** (93%) and **3i** (97%), respectively. On the other hands, the reaction of these dienes with equimolar amounts of bromine gave a mixture of 1:1 and 1:2 products. For example, the reaction of **1h** gave a mixture of 12-bromododec-1-ene (**3h'**) (13%) and **3h** (36%) together with a large amount of unreacted **1h** (41%) (entry 9). It is interesting to note that the major formation of dibromide may suggest that after the first HBr addition, a bromine radical forms in a reaction cage, which might undergo addition to another alkene terminus. The reactions were also tested for endo and exo-cyclic alkenes, **1j** and **1k**, (entries 11 and 12). While **1j** gave mono-bromide **3j** in good yield (entry 11), in the case of **1k**, ionic HBr addition competed to give a mixture of an anti-Markovnikov product **3k** and a Markovnikov product **3k'** (entry 12).

Somewhat tedious indirect methods exist for the synthesis of 1-bromoalkanes from terminal alkenes, which employ initial conversion of alkenes to organometallic species such as organoboron,¹¹ organosilicon¹² or organo-groups (IV)¹³ and (XIII)^{11,14} compounds. Irradiative PV bromination involving in situ generation of HBr provided a simple method for preparation of 1-bromoalkanes from

terminal alkenes using molecular bromine and appropriate hydrocarbons.¹⁵ It should also be noted that this methodology provided a spontaneous "molecular-level" flow reaction system in which two successive photo-radical reactions occurred in just one test tube: formation of hydrogen bromide from hydrocarbon solvent and molecular bromine, and addition of hydrogen bromide to olefins. Many useful synthetic methodologies, based on *in situ* generation of fresh HBr and its use for additional transformations, may therefore be possible.¹⁶

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Table 2 Photo-irradiative phase-vanishing reaction of terminal alkenes **1** leading to bromoalkanes **3**



entry	alkene 1	product 3	yield ^a
1	1a R = C ₉ H ₁₉	3a	89%
2	1b R = C ₁₀ H ₂₁	3b	96%
3	1c R = C ₁₂ H ₂₅	3c	94%
4	1d R = C ₉ H ₁₈ OMe	3d	84%
5	1e R = C ₈ H ₁₆ CO ₂ Me	3e	80%
6	1f R = C ₉ H ₁₈ Cl	3f	86%
7 ^b	1g	3g	92%
8 ^b	1h	3h	93%
9 ^c	1h	3h 36%, 3h' 13%	
10 ^b	1i	3i	97%
11	1j	3j	96%
12	1k	3k 31%, 3k' 17%	

^aIsolated yield from organic layer after silica gel column chromatography. ^bBr₂ (2.5 mol equiv). ^cBr₂ (1.05 mol equiv).

Typical Procedure for Photo-Irradiative Phase-Vanishing Hydrogen Bromide Addition to Alkenes (Table 2, entry 2):

FC-72 (6 mL) was placed in a Pyrex test tube (13 mm ϕ x 105 mm) to which bromine (2.1 mmol, 340 mg) was added slowly using a glass pipette. Isooctane (1.5 mL) solution of 1-dodecene (2.0 mmol, 340 mg) was then added slowly, forming three layers. The test tube was irradiated with a 500W Xenon lamp for 2 h. The isooctane layer was taken up with a pipette. Then, additional hexane (4 mL x 4) was placed on the residual FC-72 layer, followed by decanting off. The combined organic layer was washed

with aqueous 10% Na₂S₂O₃ (30 mL) and saturated brine (30 mL), dried over Na₂SO₄, and concentrated. Purification by a short column chromatography on silica gel with hexane gave 1-bromododecane (480 mg, 96%).

Notes and references

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- (10) ¹H-NMR of the concentrated reaction mixture in entry 6 of shows peaks assigned to 2-bromo-2,4,4-trimethylpentane as the product, suggesting that hydrogen abstraction from isooctane would occur selectively at the tertiary position of isooctane.
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- (15) The reaction without fluorine phase gave an inferior result. For example, irradiation of a mixture of bromine (1.16 mmol) and isooctane (6 mL) with a 500 W Xe lamp for 30 min, followed by addition of 1-dodecene (1 mmol) at rt, gave 1-bromododecane in 79% yield together with unreacted 1-dodecene (11%). Probably some HBr generated would outgas during the reaction.
- (16) For an example to use HBr during sequential reactions, see: W. Zhang, Y. Hua, S. J. Geib, G. Hoge, P. Dowd, *Tetrahedron* **1994**, *50*, 12579.