Headline Articles

Radical Reaction by a Combination of Phosphinic Acid and a Base in Aqueous Media

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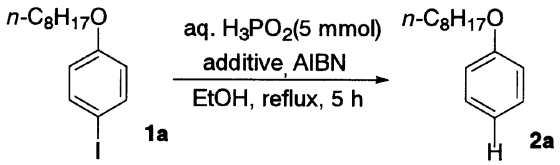
Treatment of various organic halides with phosphinic acid (hypophosphorous acid) in aqueous ethanol in the presence of a radical initiator and a base gave the corresponding reduced products in high yields. Addition of a base is indispensable for the reduction of halides by phosphinic acid. Allylic ether of *o*-iodophenol or 2-haloalkanal allylic acetal underwent radical cyclization under the same conditions to afford the corresponding cyclic product in excellent yield. Deuterated phosphinic acid was found to be an efficient chain carrier for the radical deuteration of organic halides. For example, a deuterium oxide solution of deuterated phosphinic acid, potassium carbonate, 2,2′-azobis(isobutyramidine) dihydrochloride as an initiator, and *p*-iodobenzoic acid was heated at reflux to give *p*-deuteriobenzoic acid in 94% yield. A mixed dioxane/D_2O solvent system combined with DBU and potassium peroxodisulfate was crucial to deuterate hydrophobic substrates in high yields and with high deuterium incorporation. Complete deuterium incorporation was accomplished only by the reaction in D_2O without an organic cosolvent and an organic base.

1. Reduction of Organic Halides with Phosphinic Acid in Aqueous Ethanol

During the recent dramatic development of radical methodology in organic synthesis, tin hydride has played a leading role.[1] However, it is difficult to remove highly toxic organotin compounds from the desired product. For this reason, the use of tin hydride for the purpose of synthesis of medicines, drugs, and food additives is avoided, and efficient alternatives to tin hydride have been actively investigated.[2,3] Among them, Barton's[4] and other[5] groups reported phosphinic acid (hypophosphorous acid, H_3PO_2) as a cheap, much less toxic and easily removable chain carrier in various reduction reactions, although toxic solvents such as dioxane and benzene were used.[6] To reduce total toxicity in a radical reaction, it is of importance to pay attention to the solvent employed where the radical reaction is carried out. We wish to report herein[7] the details of the radical reduction of various halides using a combination of phosphinic acid and a base in aqueous ethanol. Radical cyclization of allylic ether of *o*-iodophenol or 2-haloalkanal allylic acetal is also described.

1-1. Simple Reduction of Organic Halides. We chose **1a** as a model substrate to examine radical reduction by phosphinic acid in ethanol (Scheme 1). A solution of **1a** (0.50 mmol), phosphinic acid (50% aqueous solution, 0.55 mL, 5.0 mmol), and AIBN (0.10 mmol) in ethanol (5 mL) was heated at reflux for 5 h. Contrary to our expectations, the desired product **2a** was obtained in only 14% yield and 85% of **1a** remained unchanged. Then this reaction was performed in the presence of sodium hydrogencarbonate (6.0 mmol). Surprisingly, the yield improved sharply up to 98%. Potassium hydroxide or triethylamine was also highly effective to furnish **2a** in 79% or 96% yield, respectively.[8] On the other hand, addition of hydroiodic acid suppressed the reaction completely.[9] These facts clearly show that a base is essential to carry out the phosphinic-acid-mediated radical reduction of organic halides smoothly and suggest that the actual chain carrier would be a phosphinate anion.[10,11]



None	14% (85% recovery)
6 mmol $NaHCO_3$	98%
6 mmol KOH	79%
6 mmol Et_3N	96%
5 mmol aq. HI	<1% (90% recovery)

Scheme 1.

The results of reduction using an aq H_3PO_2/$NaHCO_3$/EtOH

system are summarized in Table 1, 2, and 3. Alkyl iodides **1b** and **1c** were quantitatively reduced within 30 min to give **2b** and **2c**, respectively (Table 1, entry 1 and 2). Three equimolar amounts of phosphinic acid could be used to complete the reduction within 1 h (entry 4). Reduction did not finish when a smaller amount of phosphinate was used (entry 5 and 6). As described above, the reduction was again sluggish without a base, and no reduced product was obtained in the presence of hydroiodic acid (entry 7 and 8). Triethylborane, instead of AIBN, acted effectively as a radical initiator at room temperature (entry 9).[12,13] Reduction did not occur in the absence of a radical initiator.

A wide range of functional groups survived even in basic refluxing aqueous ethanol, including hydroxy, carbonyl, and nitro groups, which react under ionic reduction conditions (Table 2). In the case of acetate **1g**, the ester bond was partly

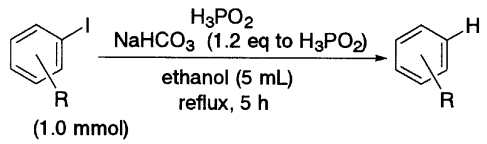
Table 1. Reduction of 1-Iodododecane and 6-Iodohexyloxybenzene under Various Conditions[a)]

n-$C_{12}H_{25}$-X **1b**: X=I, **2b**: X=H PhO$(CH_2)_6$X **1c**: X=I, **2c**: X=H

Entry	Substrate	H_3PO_2	$NaHCO_3$	Time	Yield[b)]
		mmol	mmol	h	%
1	**1b**	10	12	0.5	100
2	**1c**	10	12	0.5	100
3	**1b**	5.0	6.0	0.5	97
4	**1b**	3.0	3.5	1	97
5	**1b**	2.0	2.4	6.5	78 (6)
6	**1b**	1.0	1.2	6.5	38 (57)
7	**1c**	10	0	0.5	31 (69)
8	**1c**	10	0[c)]	0.5	<1 (81)
9	**1b**	5.0	6.0	3	95[d)]

a) Substrate (1.0 mmol) was subjected to reduction in ethanol (5 mL) at reflux. AIBN (0.10 mmol) was used unless otherwise noted. b) The yields of the recovered starting material are in parentheses. c) HI (5.0 mmol) was added. d) Triethylborane (1.0 mmol) was employed at room temperature.

Table 2. Reduction of Various Aryl Iodides



(1.0 mmol)

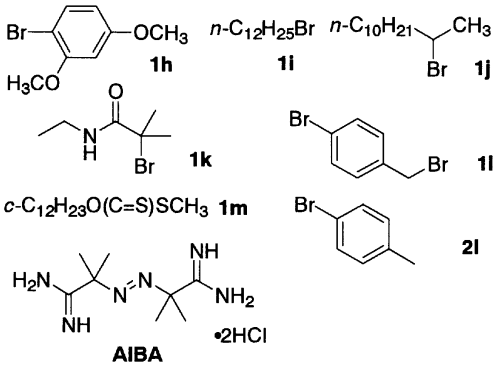
1d: R=*o*-CH_2OH **1e**: R=*o*-NO_2

1f: R=*p*-COO-*n*-C_4H_9 **1g**: R=*o*-CH_2OCOCH_3

Entry	Substrate	Product	H_3PO_2	AIBN	Yield
			mmol	mmol	%
1	**1d**	**2d**	10	0.10	85
2	**1d**	**2d**	5.0	0.50	100
3	**1e**	**2e**	10	0.50	73
4	**1f**	**2f**	10	0.10	95
5	**1g**	**2g**	5.0	0.10	70[a)]
6	**1g**	**2g**	10	2.0[b)]	83

a) Benzyl alcohol (23%) was obtained. Reaction time was 3 h. b) Et_3B was used instead of AIBN at room temperature.

Table 3. Reduction of Other Compounds[a)]



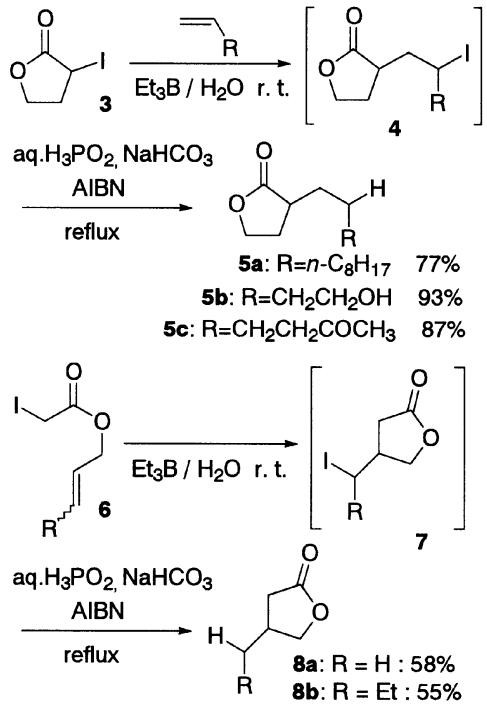
Entry	Substrate	Product	AIBN	Time	Yield[b)]
			mmol	h	%
1	**1h**	**2h**	0.50 × 2	5	9 (91)
2	**1i**	**2b**	0.20	5	17 (30)
3	**1i**	**2b**	0.20[c)]	5	84
4	**1j**	**2b**	0.10[c)]	3	80
5	**1k**	**2k**	0.10	2	89
6[d)]	**1l**	**2l**	0.30	2.5	8 (39)
7	**1m**	**2m**	0.20	0.5	100
8	**1m**	**2m**	1.0 × 4[e)]	24	69

a) Substrate (1.0 mmol), H_3PO_2 (10 mmol), $NaHCO_3$ (12 mmol), and EtOH (5 mL) were used. b) Isolated yield. The yield of the recovered starting material is in parentheses. c) 2,2′-Azobis(isobutyramidine) dihydrochloride (AIBA) was used instead of AIBN. d) H_3PO_2 (5.0 mmol) and $NaHCO_3$ (6.0 mmol) were employed. e) Et_3B was used instead of AIBN.

cleaved, which was overcome by using Et_3B as an initiator at room temperature (entry 6).

Disappointingly, aryl bromide resisted reduction (Table 3, entry 1). Alkyl bromide was less reactive than alkyl iodide and dodecane was obtained in only 17% yield (entry 2). We found that 2,2′-azobis(isobutyramidine) dihydrochloride (AIBA) was more effective than AIBN in reducing alkyl bromide (entry 3 and 4). Reduction of reactive α-bromo carbonyl compound **1k** was facile, employing AIBN as an initiator (entry 5). Reduction of benzylic bromide was inefficient, probably because of the stronger P–H bond relative to a Sn–H bond (entry 6). Dithiocarbonate **1m** smoothly underwent deoxygenation under the same conditions to furnish cyclododecane (**2m**) without hydrolysis of the thiocarbonyl moiety (entry 7). Deoxygenation was slow when the reaction was carried out with Et_3B at room temperature (entry 8).

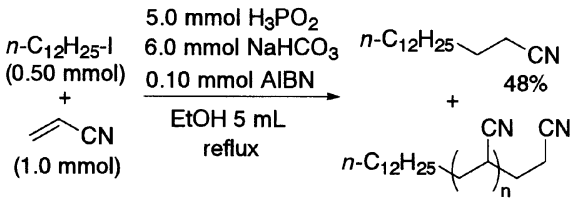
We recently demonstrated that iodine atom transfer radical reactions proceeded more effectively in water, especially in the case of the cyclization of allyl iodoacetate.[12c] Reduction of the product resulting from iodine atom transfer radical process in water was achieved in the same pot with phosphinate as shown in Scheme 2. The unique solvent effect of water offered direct radical lactonization, for example, starting from allyl iodoacetate (**6**), which is difficult to carry out in organic solvents such as benzene and hexane. The subsequent one-pot reduction of **7** by phosphinate gave β-methyl-γ-butyrolactone (**8a**) in 58% yield.[14] In these cases, ethanol was not used.



Scheme 2.

However, reductive radical addition of 1-iododododecane to acrylonitrile did not give a satisfactory result. The best result was obtained when 1-iododododecane (0.50 mmol), acrylonitrile (1.0 mmol), H_3PO_2 (5.0 mmol), $NaHCO_3$ (6.0 mmol), AIBN (0.10 mmol), and ethanol (5 mL) were used to give pentadecanenitrile in 48% yield (Scheme 3). The low yield is attributed to the low reactivity of the P–H bond. Donating hydrogen to the cyano-stabilized carbon-centered radical was slow and a further competitive radical addition of the radical to another acrylonitrile occurred.

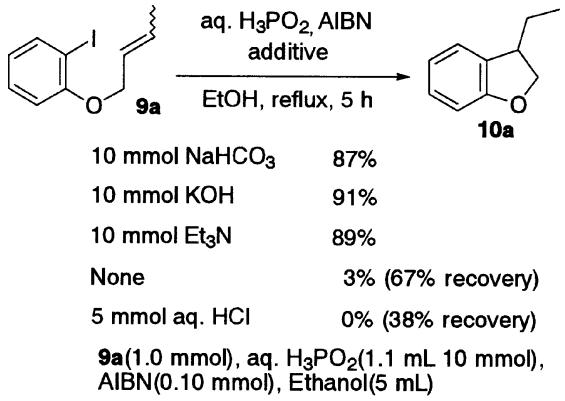
Although these reactions were carried out in nontoxic aqueous ethanol, it is necessary to use organic solvents such as ethyl acetate and hexane in extracting and purifying the products. In order to clear up the contradiction, isolation by distillation was performed. After **1b** (50 mmol) was subjected to the reduction, water was added to the aqueous ethanol solution of **2b** in the reaction flask. The homogeneous solution separated into two layers, and the organic layer, mainly consisting of **2b**, floated on the aqueous layer. The upper layer was collected with a Pasteur pipette in a flask. Distillation under reduced pressure gave pure **2b** in 84% yield. No toxic solvent was used in this process and the phosphinic-acid-mediated reaction could be applied to a large scale reaction.



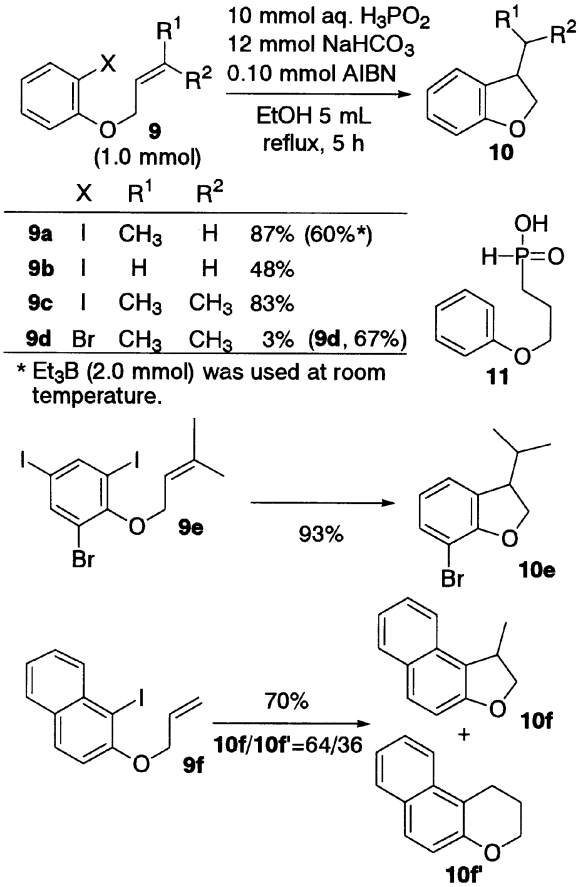
Scheme 3.

1-2. Radical Cyclization of Allylic Ether of *o*-Iodophenol or 2-Haloalkanal Allylic Acetal in Aqueous Ethanol. The model substrate, 2-butenyl ether of *o*-iodophenol **9a**, was treated with phosphinic acid solution and sodium hydrogencarbonate in the presence of AIBN in refluxing ethanol. The reaction proceeded cleanly to give the desired dihydrobenzofuran derivative **10a** in 87% yield. Effects of additives are shown in Scheme 4, which shows similar results to Scheme 1.

Scheme 5 shows the results of radical cyclization using an aq H_3PO_2/$NaHCO_3$/EtOH system. Allyl ether **9b** afforded **10b** in moderate yield, due to its volatility as well as the formation



Scheme 4.

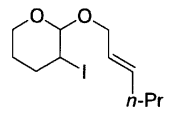
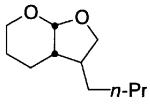
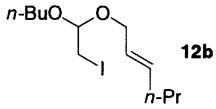
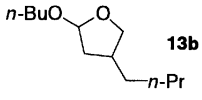
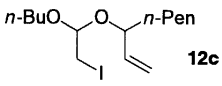
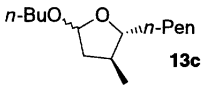
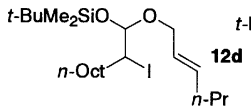
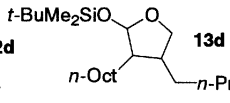
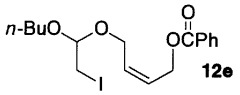
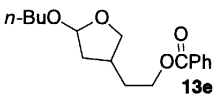
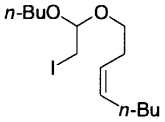
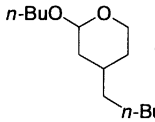
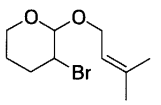
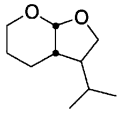
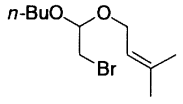
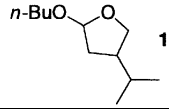


Scheme 5.

of by-product **11**[15] (15%). Radical cyclization proceeded with triethylborane as a radical initiator at room temperature. Although aryl bromide **9d** hardly reacted, selective cyclization of **9e** could be achieved in excellent yield.[16] When allyl ether of iodonaphthol **9f** was employed as a substrate, 6-endo cyclization was observed[17] in addition to 5-exo cyclization.

Next, we focused on radical cyclization of halo acetals[18] (Table 4). For example, a solution of phosphinic acid, sodium hydrogencarbonate (1.5 molar amounts to H_3PO_2), and AIBN in ethanol was added to iodo acetal **12a** and the resulting mixture was heated at reflux. The reaction was completed within 30 min to give bicyclic acetal **13a** in 98% yield. Some comments are worth noting. (1) *tert*-Butyldimethylsilyl ether **12d** as well as benzoate ester **12e** was tolerant under the basic conditions. (2) Decreasing the amounts of H_3PO_2 and $NaHCO_3$ led to slightly lower yet good yields (**13c** and **13d**). (3) A slow addition of an aqueous solution of H_3PO_2, $NaHCO_3$ and 4,4′-azobis(4-cyanopentanoic acid) to **12f** afforded six-membered **13f** in 79% yield.[19] (4) Bromo analogs **12g** and **12h** underwent cyclization with longer reaction time and a larger amount of AIBN. On the other hand, AIBA was more effective in the reaction of bromo acetals.

Table 4. Radical Cyclization of Halo Acetals Using H_3PO_2/$NaHCO_3$/EtOH System[a)]

 **12a**	 **13a**	98% (74/26) 82% (81/19)[b)]
 **12b**	 **13b**	97% (76/24)
 **12c**	 **13c**	96% (51/49) 74% (50/50)[c)]
 **12d**	 **13d**	100% (39/33/19/9) 96% (39/39/15/7)[c)]
 **12e**	 **13e**	100% (70/30) 80% (66/34)[b)]
 **12f**	 **13f**	79% (70/30)[d)]
 **12g**	 **13g**	83% (61/39)[e)] 88% (60/40)[f)]
 **12h**	 **13h**	64% (63/37)[e)] 86% (63/37)[f)]

a) **12** (1.0 mmol), H_3PO_2 (10 mmol), $NaHCO_3$ (15 mmol) and AIBN (0.10 mmol) in ethanol (5 mL) was heated at reflux for 30 min unless otherwise noted. The diastereomer ratios are in parentheses. b) Et_3B was used instead of AIBN. Reaction time was 3 h. c) **12** (1.0 mmol), H_3PO_2 (5.0 mmol), $NaHCO_3$ (7.5 mmol) and AIBN (0.20 mmol) in ethanol (5 mL) was heated at reflux for 3 h. d) To a solution of **12f** in refluxing ethanol was added a solution of H_3PO_2 (10 mmol), $NaHCO_3$ (15 mmol) and 4,4′-azobis(4-cyanopentanoic acid) (0.10 mmol) in water over 5 h. e) AIBN (0.30 mmol × 2) was used and the reaction completed within 10 h. f) AIBA (0.10 mmol) was used instead of AIBN. Reaction time was 3 h.

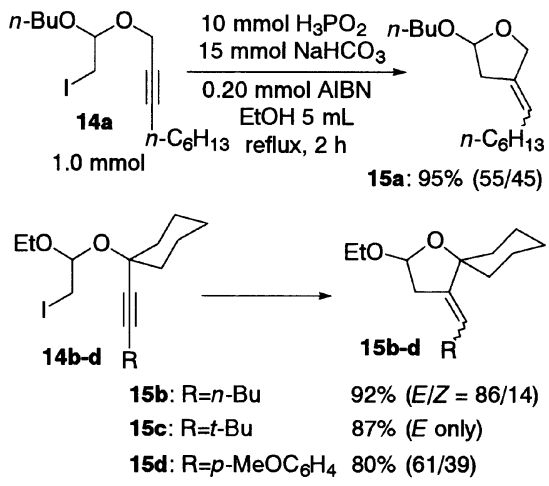
Finally, radical cyclization to carbon-carbon triple bonds was examined (Scheme 6). Cyclization of **14a** was not stereoselective. Introduction of the pentamethylene group at propargylic position resulted in improving stereoselectivity (**15b**, *E*/*Z* = 86/14). Furthermore, the acetal **14c** bearing the *tert*-butyl group instead of the butyl group afforded a single isomer. The stereochemistry of **15c** was found to be *E* configuration by using deuterated phosphinic acid (vide infra). Cyclization onto the aryl acetylenic linkage afforded both stereoisomers without selectivity.

In summary, we have demonstrated the phosphinic-acid-mediated radical reaction in aqueous ethanol. Ethanol is cheap and a far less toxic organic solvent than other organic solvents. Phosphinic acid and sodium hydrogencarbonate are probably the cheapest combination for radical reduction, avoid suffering from troublesome tin residues, and permit large scale preparation.

2. Deuterium Labeling Using Deuterated Phosphinic Acid in D_2O via a Radical Pathway

Recent progress in the fields of NMR spectroscopy and mass spectrometry has allowed stable isotope labeling to become an important technique in metabolic research for determining the biological behavior of small molecules. Stable isotopomers are more easily prepared and handled than their radioisotope analogs.[20] The development of synthetic methods for the preparation of compounds labeled with non-radioactive isotopes such as deuterium has therefore gained in importance.

Common methods for incorporating deuterium into organic molecules include ionic reactions using metal deuterides such as $NaBD_4$ and $LiAlD_4$, and radical methods involving *n*-Bu_3SnD.[21] However, radical reactions using tin deuterides have serious drawbacks when used in the synthesis of biologi-

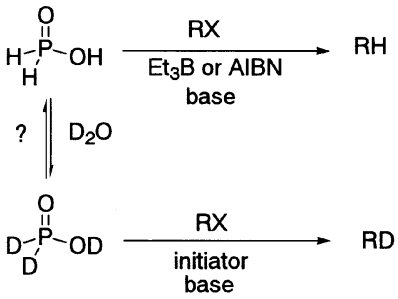


Scheme 6.

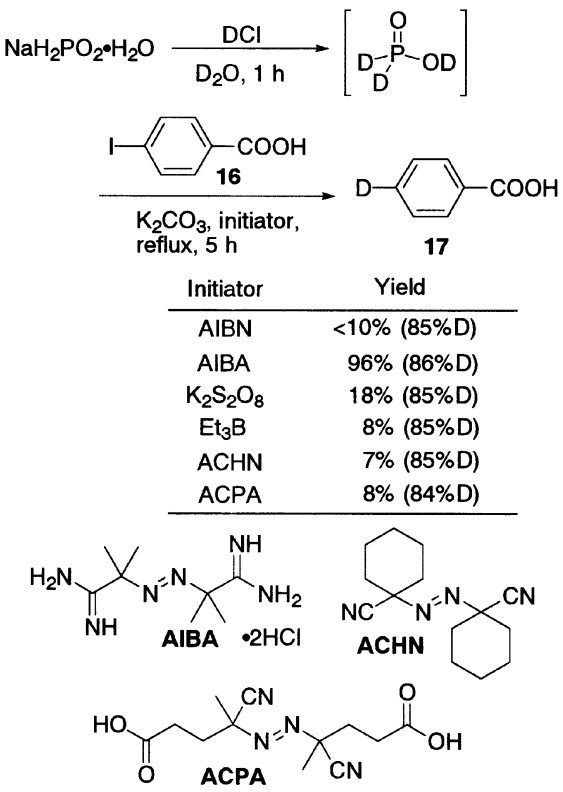
cally active compounds, because the inherent toxicity of organotin derivatives and the difficulty of removal of residual tin compound often prove fatal.

We[7] and others[5,6] have reported radical cyclizations employing non-toxic and easily removed phosphinic acid (H_3PO_2) in aqueous solvents. A logical extension of this methodology utilizes deuterium oxide, the most inexpensive deuterium source, as solvent. After deuterium exchange of the hydrogens on phosphorus with D_2O, the deuterated phosphinic acid acts as a chain carrier in this new method for the incorporation of deuterium via a radical process in D_2O or dioxane/D_2O solvents systems (Scheme 7).

We examined the reduction of *p*-iodobenzoic acid (**16**) in D_2O as a model reaction (Scheme 8). Sodium phosphinate monohydrate ($NaH_2PO_2{\cdot}H_2O$, 5.0 mmol) was treated with DCl (37 wt% solution in D_2O, 0.80 mL, 10 mmol) in D_2O (5 mL). After stirring for 1 h, K_2CO_3 (8.0 mmol) was added to the solution to give the deuterated potassium phosphinate, and then



Scheme 7.



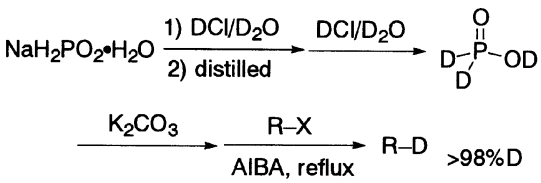
Initiator	Yield
AIBN	<10% (85%D)
AIBA	96% (86%D)
$K_2S_2O_8$	18% (85%D)
Et_3B	8% (85%D)
ACHN	7% (85%D)
ACPA	8% (84%D)

Scheme 8.

AIBN (0.10 mmol) and **16** (0.50 mmol) were added. The resulting mixture was refluxed for 5 h to give benzoic acid (**17**). The deuterium incorporation at the para position was 85%,[22,23] although the yield was miserable (< 10%). In order to improve the yield of **17**, we investigated several radical initiators. We found that 2,2′-azobis(isobutyramidine) dihydrochloride[24] (AIBA) gave an excellent result. Other initiators such as $K_2S_2O_8$, Et_3B, azobis(cyclohexanecarbonitrile) (ACHN), and 4,4′-azobis(4-cyanopentanoic acid)[24] (ACPA) were far inferior to AIBA.

The reason for the uniqueness of AIBA as a radical initiator for deuteration is not clear. In the previous section, AIBN was effective in refluxing aqueous ethanol. Et_3B also acted as an initiator at 25 °C. In the present case, it is obvious that kinetic isotope effects would operate in the initiation step. The radical generated from AIBA is stabilized with the amide group resulting from hydrolysis of the amidine group. The amide-stabilized radical would be more unstable than the radicals produced from AIBN, ACHN, and ACPA, which cyano groups stabilize and would be more reactive in deuterium abstraction.[25] Et_3B produces a more reactive ethyl radical, which has no delocalization of the unpaired electron. However, when Et_3B is used in a polar protic solvent under heated condition, the efficiency of Et_3B declines, probably because of its volatility or its lack of thermal stability. $K_2S_2O_8$ generates an oxygen–centered radical, which has the highest reactivity among the radical examined. We cannot explain the fact that $K_2S_2O_8$ was not effective in D_2O. On the other hand, $K_2S_2O_8$ worked efficiently in a mixed dioxane/D_2O solvent (vide infra).

The exchange reaction of hydrogen with deuterium on the phosphorus center is reversible. Because of this equilibrium, the deuteration of phosphinic acid was not perfect. To complete the exchange, the solvent was removed by distillation in vacuo from the solution of deuterated phosphinic acid, and DCl solution was added again. This procedure accomplished almost complete incorporation of deuterium into the phosphinic acid. Using deuterated phosphinic acid prepared in this fashion afforded products with > 98% deuterium incorporation (Scheme 9). The use of commercially available phosphinic acid-d_3[26] (50 wt% in D_2O, 5.0 mmol, 0.50 mL) gave the same results.



R–X	Yield[a] of R–D
p-iodobenzoic acid	91% (94%)
o-iodobenzoic acid	99% (98%)
o-iodobenzyl alcohol	93% (92%)

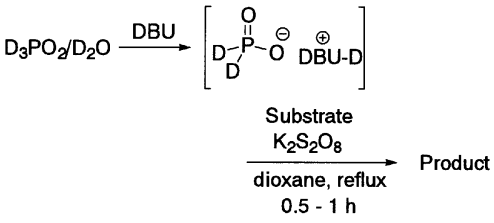
a) The yields using commercially available D_3PO_2 are shown in parentheses

Scheme 9.

We also explored the reduction of various hydrophobic organic halides in organic solvents (Table 5). Phosphinic acid-d_3 (10 M solution in D_2O) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[27] and the mixture was stirred for 10 min. A dioxane solution of substrate[28] and $K_2S_2O_8$[29] were added and the mixture was stirred under reflux. Extractive workup and silica gel chromatography provided the desired deuterated product. One noteworthy feature of this radical reaction is the construction of tertiary carbon centers bearing deuterium in high yields (entry 3 and 4). Deuterated lactone **21** was obtained by Jones oxidation of the crude acetal prepared from radical cyclization of iodo acetal **12c** (entry 5).

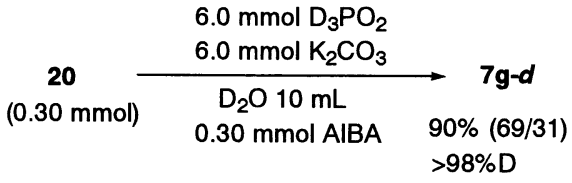
In each case in Table 5, deuteration was not perfect because the intermediary radicals can abstract a hydrogen atom from dioxane, DBU, or both. A molecule of water has no active hydrogen atom to be abstracted under usual radical conditions. To obtain higher deuterium incorporation, the reaction of **20** was performed in D_2O without organic cosolvent (Scheme 10). A solution of D_3PO_2 (6.0 mmol), K_2CO_3 (6.0 mmol), AIBA (0.30 mmol) in D_2O (10 mL) was added to **20** (0.30 mmol) and

Table 5. D_3PO_2-Mediated Radical Reaction in Dioxane/D_2O[a)]



Entry	Substrate	Product	Yield
1	I–$(CH_2)_{12}$–I **18** 0.40 mmol	D–$(CH_2)_{12}$–D **19**	94% 91% D
2	O-*n*-C_8H_{17} **1a** 0.50 mmol	O-*n*-C_8H_{17} **2a-*d***	95% 88% D
3	**20** 0.70 mmol	**7g-*d***	84% (68/32) 88% D
4	**9c** 0.50 mmol	**10c-*d***	90% 87% D
5	*n*-BuO, *n*-C_5H_{11} **12c** 0.70 mmol	*n*-C_5H_{11}, CH_2D **21**	85%[b)] 93% D

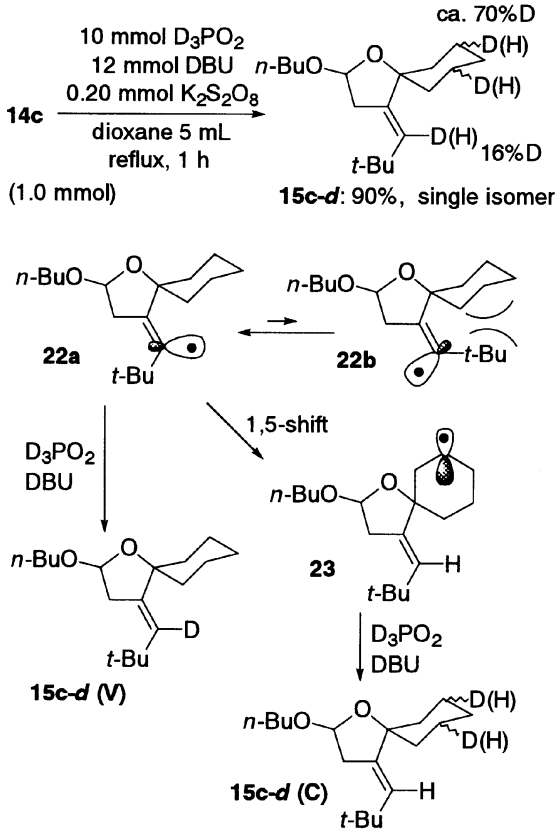
a) Reaction conditions: D_3PO_2 (10 M solution in D_2O, 0.50 mL, 5.0 mmol), DBU (0.90 mL, 6.0 mmol), substrate, dioxane (5 mL), $K_2S_2O_8$ (0.20 mmol). b) Overall yield after Jones oxidation.



Scheme 10.

heated for 2 h at reflux with vigorous stirring to afford **7g-*d*** in 90% yield (> 98% D).[30] Although a large amount of solvent is necessary for the cyclization reaction, D_2O is easily recovered by distillation of the aqueous phase after workup.

Deuteration by D_3PO_2 was successfully applied to the stereochemical assignment of **15c** (Scheme 11). Treatment of **14c** with deuterated phosphinic acid in dioxane/D_2O to give **15c-*d*** as a single stereoisomer, which was similar to the reaction with H_3PO_2 in aqueous ethanol. However, deuterium was incorporated in only 16% at the vinylic position. Deuterium was found in the cyclohexane ring instead. This result indicates that 1,5-hydride shift to the vinylic position occurred after the 5-exo-dig radical cyclization. 1,5-Hydride shift must give the intermediate **23**, whose stereochemistry at the double bond is defined as shown in Scheme 11. Deuteration of **23** gave **15c-*d*(C)** with *E* configuration. On the other hand, direct deuteration of the vinyl radical afforded **15c-*d*(V)**, which has the identical stereochemistry with **15c-*d*(C)**. Thus, the stereochemistry of **15c** could be determined. Steric repulsion be-



Scheme 11.

tween the *tert*-butyl group and the cyclohexane ring would play a key role in explaining the selectivity.

In conclusion, D_3PO_2 is an attractive alternative to *n*-Bu_3SnD for radical deuteration of organic halides. The reduction of organic halides with D_3PO_2 in D_2O or dioxane/D_2O allows the preparation of labeled compounds to be assayed in vivo. In this case, D_2O is the best solvent for quantitative labeling.

Experimental

^1H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. Mass spectra were recorded on a JEOL JMS-700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The analyses were carried out at the Elemental Analysis Center of Kyoto University. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Dioxane was dried over slices of sodium. DBU was distilled from KOH and stored under argon. Halo acetals were prepared according to the literature.[18]

General Procedure for Reduction Using Phosphinic Acid: A mixture of 2-iodobenzyl alcohol (**1d**, 0.23 g, 1.0 mmol), phosphinic acid (50% aqueous solution, 1.1 mL, 10 mmol), $NaHCO_3$ (1.0 g, 12 mmol) in ethanol (5 mL) in the presence of AIBN (16 mg, 0.10 mmol) was heated at reflux under argon for 5 h. After cooling, the mixture was poured into brine (20 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Silica-gel column chromatography of the crude oil provided 92 mg of benzyl alcohol (**2d**, 85% yield). When a substrate is acid-labile, **1m** for example, a basic solution was prepared first. Phosphinic acid solution and sodium hydrogencarbonate was added to ethanol and the resulting mixture was vigorously stirred for 30 min. Then, **1m** was placed in another flask and the prepared mixture and AIBN were added. After the reaction mixture was refluxed for 30 min under argon, usual workup furnished cyclododecane (**2m**) in 100% yield.

Procedure for Radical Reaction Using Triethylborane as a Radical Initiator: In our laboratory, an ethanol solution of triethylborane (1.0 M, 1 M = 1 mol dm^{-3}) was prepared and was used as a radical initiator in order to perform radical reactions in aqueous media. Under argon atmosphere, to ethanol (26 ml) was added triethylborane (4.3 mL, 30 mmol) at 0 °C. Triethylborane was stable in this solution at ambient temperature under inert gas and could act as an initiator for a few months or longer.

Triethylborane in ethanol (1.0 mL, 1.0 mmol) was added to a mixture of 1-iodododecane (**1b**, 0.30 g, 1.0 mmol), phosphinic acid (0.55 mL, 5.0 mmol) and $NaHCO_3$ (0.50 g, 6.0 mmol) in ethanol (5 mL) under argon, and the resulting mixture was stirred under air for 3 h. **Caution** : *When an ethanol solution of triethylborane was added to the reaction mixture under air, it flared up*. Extraction with hexane, concentration and purification afforded 162 mg of dodecane (**2b**) in 95% yield.

Representative Procedure for Sequential Atom Transfer Radical Reaction and Reduction: α-Iodo-γ-butyrolactone (**3**, 0.21 g, 1.0 mmol) and 1-decene (0.14 g, 2.0 mmol) were suspended in water (10 mL) with vigorous stirring. An ethanol solution of triethylborane (0.10 mL, 0.10 mmol) was added to the reaction mixture. The mixture was stirred for 1 h, and the complete consumption of **3** was checked by TLC analyses. Phosphinic acid (0.55 mL, 5.0 mmol), $NaHCO_3$ (0.50 g, 6.0 mmol), and AIBN (16 mg, 0.10 mmol) were added and the whole mixture was heated at reflux for 1 h. Acidification with 1 M HCl (20 mL), extraction with ethyl acetate, concentration, and silica-gel column purification gave α-decyl-γ-butyrolactone (**5a**) in 77% yield.

Large Scale Reaction without an Extraction Step: In a 500 mL flask, 1-iodododecane (**1b**, 14.8 g, 50.0 mmol) was dissolved in ethanol (200 mL) and $NaH_2PO_2{\cdot}H_2O$ (26.5 g, 250 mmol), AIBN (1.64 g, 10.0 mmol), and water (50 mL) were added. The resulting solution was heated at reflux for 30 min and then cooled down to room temperature. Water (200 mL) was added to the aqueous ethanol solution of dodecane in the reaction flask. After stirring for 3 min, the reaction mixture stood undisturbed for 3 min. The homogeneous solution separated into two layers, and the organic layer, mainly consisting of dodecane, floated on the aqueous layer. The upper layer was collected with a Pasteur pipette in a flask. Distillation under reduced pressure gave pure dodecane in 84% yield.

Typical Procedure for Radical Cyclization: 3-Methyl-2-butenyl ether of 2-iodophenol (**9c**, 0.29 g 1.0 mmol) was dissolved in ethanol (5 mL) and phosphinic acid solution (1.1 mL, 10 mmol), sodium hydrogencarbonate (1.0 g, 12 mmol) and AIBN (16 mg, 0.10 mmol) were successively added. The resulting mixture was heated at reflux under argon for 5 h. Extractive workup followed by silica gel column purification gave **10c** (135 mg, 83%). In the case of radical cyclization of halo acetals, a basic solution was prepared in advance as described.

Typical Procedure for Deuteration in D_2O with $NaH_2PO_2{\cdot}H_2O$: Deuteration of *p*-iodobenzoic acid (**16**) is representative. Sodium phosphinate monohydrate ($NaH_2PO_2{\cdot}H_2O$, 0.53 g, 5.0 mmol) was treated with DCl (37 wt% solution in D_2O, 0.80 mL, 10 mmol) in D_2O (3 mL) under argon. After stirring for 1 h, the solvent was removed in vacuo. D_2O (3 mL) and DCl (0.25 mL, 3.0 mmol) were added and stirred for additional 30 min. Then, K_2CO_3 (1.1 g, 8.0 mmol), 2,2′-azobis(isobutyramidine) dihydrochloride (27 mg, 0.10 mmol) and **16** (0.12 g, 0.50 mmol) were added. The resulting mixture was heated at reflux for 5 h. After being cooled to room temperature, the mixture was washed with ethyl acetate (5 mL × 2). The organic layer was removed and 1 M HCl solution (10 mL) was added to the aqueous layer. The mixture was extracted with 1 : 1 ethyl acetate/hexane (10 mL × 2). Concentration of the combined organic layer gave pure *p*-deuteriobenzoic acid (56 mg) in 91% yield (> 98% D).

Procedure for Deuteration in D_2O with Commercially Available Phosphinic Acid-d_3: A solution of phosphinic acid-d_3 (50 wt% in D_2O, 0.50 mL, 0.50 mmol), K_2CO_3 (0.69 g, 5.0 mmol), 2,2′-azobis(isobutyramidine) dihydrochloride (27 mg, 0.10 mmol) and **16** (0.12 g, 0.50 mmol) was heated for 5 h at reflux. Workup as above provided *p*-deuteriobenzoic acid (58 mg) in 94% yield (> 98% D).

General Procedure for Deuteration in Dioxane/D_2O with Commercially Available Phosphinic Acid-d_3: Radical cyclization of **12c** was representative. Phosphinic acid-d_3 in D_2O (50 wt%, 0.50 mL, 0.50 mmol) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.90 mL, 0.60 mmol) at room temperature and the mixture was stirred for 10 min. The substrate **12c** (0.25 g, 0.70 mmol) in dioxane (5 mL) and $K_2S_2O_8$ (54 mg, 0.20 mmol) were added and the mixture was stirred vigorously at reflux for 30 min. Extractive workup followed by concentration afforded colorless oil. The residue was dissolved in acetone (10 mL) and Jones reagent was dropped until the color of the solution turned

brown from pale green. Ether (20 mL) and water (20 mL) were added to the reaction flask and the organic layer was washed with brine. Evaporation and silica gel column purification (hexane/ethyl acetate = 5/1) yielded 73 mg of **21** (85% overall, 93% D). The deuterium incorporation was determined by examining the integration of the CH_2D protons by contamination with the CH_3 protons (δ 1.10–1.05, multiplet, 2.07H) and that of the CH_3 protons (δ 0.90, triplet, 3H) in the pentyl group in the fine ^{1}H NMR chart. In the case of **7g**, which consisted of two diastereomers (6/4), the integration of the methyl protons in the $(CH_3)_2CH$ group and that of the $(CH_3)_2CD$ group were indirectly compared. One of two methyl groups in the deuterated major diastereomer appeared a singlet at δ 0.80. For nonlabeled **7g**, the corresponding methyl group appeared a doublet at δ 0.80 and 0.82. Thus, the deuterium incorporation (% D) was calculated as [Area(δ 0.82) − Area(δ 0.80)]/[Area(δ 0.82) + Area(δ 0.80)] × 100.

Radical Cyclization of 20 with Deuterated Phosphinic Acid in D_2O: A solution of D_3PO_2 (6.0 mmol), K_2CO_3 (6.0 mmol), AIBA (0.30 mmol) in D_2O (10 mL) was prepared under argon in advance. The solution was added to **20** (0.30 mmol) in a 20-mL pear-shaped flask and heated for 2 h at reflux with vigorous stirring. Extraction with ethyl acetate (10 mL × 3) and concentration, followed by silica gel column purification afforded 46 mg of **7g** (90%, > 98% D).

Characterization Data. Spectral data for most of the compounds shown in this paper are well known or can be found in the literature.[12,17,31]

α-(4-Hydroxybutyl)-γ-butyrolactone (5b): IR (neat): 3260, 2924, 2856, 1744, 1461, 1379, 1148, 1023, 953 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.43–1.75 (m, 6H), 1.85–2.05 (m, 2H), 2.36–2.47 (m, 1H), 2.48–2.61 (m, 1H), 3.67 (t, J = 6.3 Hz, 2H), 4.20 (ddd, J = 6.6, 9.0, 9.6 Hz, 1H), 4.36 (ddd, J = 3.0, 9.0, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.24, 28.25, 29.72, 32.00, 39.01, 61.98, 66.50, 179.88. HRMS Found: *m/z* 158.0899. Calcd for $C_8H_{14}O_3$: 158.0943.

α-(5-Oxohexyl)-γ-butyrolactone (5c): IR (neat): 2932, 2860, 1767, 1713, 1460, 1412, 1375, 1211, 1172, 1147, 1024, 964, 941 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34–1.53 (m, 3H), 1.56–1.67 (m, 2H), 1.80–2.01 (m, 2H), 2.15 (s, 3H), 2.35–2.59 (m, 4H), 4.20 (dt, J = 6.6, 9.0 Hz, 1H), 4.35 (dt, J = 3.0, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.11, 26.56, 28.46, 29.81, 29.89, 38.91, 43.10, 66.42, 179.51, 208.90. HRMS Found: *m/z* 184.1101. Calcd for $C_{10}H_{16}O_3$: 184.1099.

2-Bromo-4,6-diiodophenyl 3-Methyl-2-butenyl Ether (9e): IR (neat): 2842, 1462, 1377, 1236, 937, 852, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 3H), 1.82 (s, 3H), 4.50 (d, J = 7.5 Hz, 2H), 5.65 (t, J = 7.2 Hz, 1H), 7.83 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.18, 25.76, 70.10, 88.25, 94.40, 118.07, 119.14, 140.11, 141.69, 146.17, 155.84. HRMS Found: *m/z* 491.8087. Calcd for $C_{11}H_{11}{}^{79}BrOI_2$: 491.8083.

3-Isopropyl-7-bromo-2,3-dihydrobenzofuran (10e): IR (neat): 2956, 2924, 2868, 1602, 1582, 1479, 1447, 1388, 1370, 1257, 1218, 1161, 1127, 1052, 954, 764, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H), 0.95 (t, J = 6.9 Hz, 3H), 1.92–2.04 (m, 1H), 3.44 (quintet, $J \approx$ 5 Hz, 1H), 4.47 (dd, J = 5.1, 9.3 Hz, 1H), 4.62 (t, J = 9.3 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.17, 19.62, 31.53, 48.98, 74.19, 102.60, 121.59, 124.09, 131.05, 131.26, 154.63. HRMS Found: *m/z* 240.0100. Calcd for $C_{11}H_{13}{}^{79}BrO$: 240.0149.

Allyl 1-Iodonaphthyl Ether (9f): IR (neat): 2924, 2850, 1499, 1463, 1267, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.73 (d, J = 2.4 Hz, 2H), 5.32 (dd, J = 10.8, 1.5 Hz, 1H), 5.56 (dd, J = 17.1, 1.5 Hz, 1H), 6.04–6.18 (m, 1H), 7.15 (dd, J = 8.7, 3.3 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.75 (dd, J = 15.3, 8.1 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 70.41, 88.59, 114.28, 117.67, 124.36, 127.99, 128.12, 129.89, 130.13, 131.17, 132.74, 135.58, 155.66. HRMS Found: *m/z* 309.9840. Calcd for $C_{13}H_{11}OI$: 309.9855.

4-Butyl-2-*tert*-butyl(dimethyl)siloxy-3-octyltetrahydrofuran (13d) was treated with tetrabutylammonium fluoride in THF followed by Jones oxidation to give β-butyl-α-octyl-γ-butyrolactone (mixture of diastereomers, 80/20) in 78% yield. IR (neat): 2920, 2852, 1776, 1467, 1379, 1164, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84–0.98 (m, 6H), 1.20–1.78 (m, 20H), 2.13–2.31 (m, 1.6H), 2.42–2.58 (m, 0.4H), 3.82 (dd, J = 9.0, 7.8 Hz 0.8H), 4.07 (dd, J = 9.0, 3.6 Hz, 0.2H), 4.21 (dd, J = 9.0, 6.0 Hz, 0.2H), 4.38 (dd, J = 9.0, 7.5 Hz, 0.8H); ^{13}C NMR ($CDCl_3$): major diastereomer, δ 13.72, 13.91, 22.49, 22.56, 26.61, 29.09 (2C), 29.22, 29.24, 29.48, 31.70, 32.56, 40.70, 45.24, 71.61, 179.69. minor diastereomer, δ 13.75, 13.91, 22.56, 24.72, 26.17, 26.61, 27.34, 29.18, 29.24, 29.40, 31.70, 32.56, 38.49, 43.05, 70.53, 179.26. Found: C, 75.70; H, 12.13%. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%.

2-Iodoethanal 4-Benzoyloxy-2-butenyl Butyl Acetal (12e): IR (neat): 3030, 2956, 2932, 2870, 1720, 1603, 1453, 1272, 1100, 1039, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 3H), 1.34–1.46 (m, 2H), 1.53–1.63 (m, 2H), 3.24 (d, J = 5.7 Hz, 2H), 3.50 (dt, J = 9.0, 6.6 Hz, 1H), 3.62 (dt, J = 9.0, 6.6 Hz, 1H), 4.23–4.36 (m, 2H), 4.67 (t, J = 5.7 Hz, 1H), 4.91 (d, J = 4.5 Hz, 2H), 5.85 (t, J = 3.9 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 8.05 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 4.88, 13.63, 19.10, 31.52, 60.51, 61.76, 66.33, 101.43, 126.78, 128.35 (2C), 129.60 (2C), 130.02, 130.41, 133.01, 166.31. Found: C, 48.79; H, 5.64%. Calcd for $C_{17}H_{23}IO_4$: C, 48.82; H, 5.54%.

4-(2-Benzoyloxyethyl)-2-butoxytetrahydrofuran (13e): (66/34 diastereomers mixture) IR (neat): 2954, 2932, 2868, 1721, 1604, 1453, 1316, 1273, 1177, 1112, 1071, 1027, 927, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, J = 7.5 Hz, 1.02H), 0.92 (t, J = 7.5 Hz, 1.98H), 1.29–1.43 (m, 2H), 1.49–1.73 (m, 3H), 1.87 (q, J = 6.9 Hz, 0.68H), 1.95 (q, J = 6.6 Hz, 1.32H), 2.12 (dd, J = 12.9, 4.5 Hz, 0.34H), 2.27–2.40 (m, 1.32H), 2.54–2.65 (m, 0.34H), 3.32–3.42 (m, 1H), 3.58 (t, J = 8.4 Hz, 1H), 3.63–3.72 (m, 1H), 4.04 (t, J = 7.8 Hz, 0.66H), 4.13 (t, J = 7.8 Hz, 0.34H), 4.27–4.41 (m, 2H), 5.11–5.14 (m, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): major diastereomer, δ 13.66, 19.20, 31.69, 32.05, 35.57, 38.76, 63.99, 67.31, 71.47, 104.24, 126.38, 129.55, 130.27, 132.94, 166.57. minor diastereomer, δ 13.66, 19.17, 31.63, 32.69, 34.38, 39.13, 63.90, 66.90, 72.11, 103.82, 126.38 (2C), 129.55 (2C), 130.27, 132.94, 166.57. Found: C, 70.07; H, 8.48%. Calcd for $C_{17}H_{24}O_4$: C, 48.82; H, 5.54%.

2-Iodoethanal Butyl 3-Octenyl Acetal (12f): IR (neat): 3004, 2954, 2926, 2866, 1465, 1415, 1379, 1346, 1176, 1111, 1042, 1007, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 6.6 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H), 1.25–1.47 (m, 6H), 1.52–1.63 (m, 2H), 2.05 (dt, J = 6.9, 6.9 Hz, 2H), 2.35 (dt, J = 6.9, 6.9 Hz, 2H), 3.22 (d, J = 5.4 Hz, 2H), 3.44–3.57 (m, 2H), 3.58–3.66 (m, 2H), 4.63 (t, J = 5.7 Hz, 1H), 5.33–5.53 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 5.12, 13.69, 13.81, 19.18, 22.17, 26.91, 27.73, 31.61, 31.65, 66.08, 66.33, 101.91, 125.10, 132.35. Found: C, 47.38; H, 7.58%. Calcd for $C_{14}H_{27}IO_2$: C, 47.46; H, 7.68%.

2-Butoxy-4-pentyltetrahydropyran (13f): (70/30 stereoisomers mixture) IR (neat): 2922, 2856, 1459, 1380, 1341, 1256, 1186, 1129, 1077, 1035, 989 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84–0.97

(m, 6H), 1.02–1.44 (m, 12H), 1.48–1.88 (m, 5H), 3.32–3.90 (m, 3.7H), 3.97–4.04 (m, 0.3H), 4.33 (dd, J = 9.3, 2.1 Hz, 0.3H), 4.79 (d, J = 2.1 Hz, 0.7H); ^{13}C NMR ($CDCl_3$): major isomer, δ 13.80, 13.90, 19.37, 22.52, 25.80, 28.95, 31.73, 31.98, 32.18, 36.97, 37.07, 59.59, 66.65, 97.00; minor isomer, δ 13.76, 13.90, 19.19, 22.52, 25.97, 31.80, 31.83, 31.94, 34.29, 36.42, 38.19, 65.28, 68.52, 102.01. Found: C, 73.37; H, 12.55%. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36%.

2-Iodoethanal Butyl 2-Nonynyl Acetal (14a): IR (neat): 2924, 2856, 1461, 1379, 1264, 1107, 1035, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 1.22–1.64 (m, 12H), 2.22 (tt, J = 6.9, 2.1 Hz, 2H), 3.26 (d, J = 5.1 Hz, 2H), 3.48–3.56 (m, 1H), 3.61–3.69 (m, 1H), 4.25 (t, J = 2.1 Hz, 2H), 4.78 (t, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 5.06, 13.67, 13.88, 18.59, 19.12, 22.39, 28.35, 28.40, 31.17, 31.54, 54.39, 66.67, 75.24, 87.51, 100.42. HRMS Found: m/z 239.2042, Calcd for $C_{15}H_{27}IO_2$ – I: 239.2011.

2-Butoxy-4-heptylidenetetrahydrofuran (15a): (55/45 stereoisomers mixture) IR (neat): 2904, 2848, 1460, 1344, 1181, 1097, 1068, 1031, 997, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 1.20–1.42 (m, 10H), 1.50–1.60 (m, 2H), 1.85–2.04 (m, 2H), 2.36–2.70 (m, 2H), 3.37–3.45 (m, 1H), 3.63–3.73 (m, 1H), 4.26–4.42 (m, 2H), 5.15 (d, J = 5.7 Hz, 0.45H), 5.22 (d, J = 5.1 Hz, 0.55H), 5.25–5.37 (m, 1H); ^{13}C NMR ($CDCl_3$): major isomer, δ 13.70, 13.93, 19.22, 22.50, 28.84, 29.18, 29.81, 34.64 (2C), 35.80, 66.96, 69.12, 103.86, 120.22, 136.05. minor isomer, δ 13.70, 13.93, 19.22, 22.50, 28.81, 29.22, 29.66, 31.64 (2C), 38.91, 66.83, 66.90, 103.27, 121.18, 135.89. HRMS Found: m/z 240.2066, Calcd for $C_{15}H_{28}O_2$: 240.2089.

2-Iodoethanal Ethyl 1-(1-Hexynyl)cyclohexyl Acetal (14b): IR (neat): 2922, 2854, 2230, 1446, 1412, 1372, 1338, 1297, 1176, 1116, 1043, 1002, 938, 905, 614 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 6.9 Hz, 3H), 1.37–1.74 (m, 12H), 1.78–1.86 (m, 1H), 1.91–2.00 (m, 1H), 2.26 (t, J = 6.9 Hz, 2H), 3.20–3.31 (m, 2H), 3.60 (dq, J = 9.3, 6.6 Hz, 1H), 3.74 (dq, J = 9.3, 6.9 Hz, 1H), 5.06 (dd, J = 6.6, 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 8.34, 13.41, 14.86, 18.20, 21.82, 23.05 (2C), 25.10, 30.67, 38.55, 39.07, 61.34, 74.8, 80.64, 88.12, 97.67. Found: C, 51.03; H, 7.21%. Calcd for $C_{16}H_{27}IO_2$: C, 50.80; H, 7.19%.

5-Ethoxy-2,2-pentamethylene-3-(pentylidene)tetrahydrofuran (15b): (84/16 stereoisomers mixture) IR (neat): 2896, 2848, 1760, 1447, 1372, 1345, 1210, 1185, 1145, 1119, 1093, 1048, 977, 909, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85–0.97 (m, 3H), 1.14–1.42 (m, 10H), 1.52–2.18 (m, 9H), 2.46–2.87 (m, 2H), 3.40–3.52 (m, 1H), 3.74–3.86 (m, 1H), 5.04 (d, J = 5.1 Hz, 0.16H), 5.11–5.19 (m, 1.68H), 5.26 (t, J = 8.1 Hz, 0.16H); ^{13}C NMR ($CDCl_3$): major isomer, δ 13.80, 14.94, 22.11, 22.56, 22.79, 25.39, 29.30, 31.52, 36.55, 38.59 (2C), 61.90, 83.84, 101.55, 119.84, 144.83. minor isomer, δ 13.80, 14.94, 22.25, 22.31, 22.72, 27.70, 32.35, 36.02, 36.43, 38.58, 41.65, 61.78, 83.06, 100.93, 121.54, 142.66. HRMS Found: m/z 252.2080, Calcd for $C_{16}H_{28}O_2$: 252.2090.

2-Iodoethanal Ethyl 1-(3,3-Dimethyl-1-butynyl)cyclohexyl Acetal (14c): IR (neat): 2920, 2856, 2224, 1445, 1411, 1363, 1338, 1301, 1261, 1205, 1177, 1099, 993, 939, 905, 889, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.2 Hz, 3H), 1.25 (s, 9H), 1.46–1.74 (m, 8H), 1.78–1.85 (m, 1H), 1.92–2.00 (m, 1H), 3.19–3.23 (m, 2H), 3.55 (dq, J = 9.3, 7.2 Hz, 1H), 3.77 (dq, J = 9.3, 7.2 Hz, 1H), 5.02 (dd, J = 3.3, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 8.27, 14.79, 23.02, 23.06, 25.03, 27.14, 30.83 (3C), 38.43, 39.02, 62.01, 74.38, 78.90, 96.62, 97.75. Found: C, 50.83; H, 7.44%. Calcd for $C_{16}H_{27}IO_2$: C, 50.80; H, 7.19%.

4-(2,2-Dimethylpropylidene)-2-ethoxy-1-oxaspiro[4.5]decane (15c): IR (neat): 2926, 2856, 1447, 1362, 1322, 1210, 1189, 1146, 1120, 1095, 1056, 1021, 988, 889, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H), 1.15–1.39 (m, 6H), 1.51–1.71 (m, 6H), 1.81–1.88 (m, 1H), 2.71–2.88 (m, 2H), 3.47 (dq, J = 9.9, 6.9 Hz, 1H), 3.80 (dq, J = 9.9, 7.2 Hz, 1H), 5.10 (t, J = 2.4 Hz, 1H), 5.16 (dd, J = 5.1, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.00, 22.77, 22.93, 25.45, 30.37 (3C), 32.65, 36.62, 38.80, 38.85, 62.00, 85.22, 101.99, 130.47, 141.57. Found: C, 75.92; H, 11.45%. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18%.

2-Iodoethanal Ethyl 1-[2-(4-Methoxyphenyl)ethynyl]cyclohexyl Acetal (14d): IR (neat): 2854, 2218, 1606, 1571, 1511, 1444, 1413, 1372, 1337, 1290, 1248, 1175–938 (broad), 905, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19–1.34 (m, 5H), 1.56–1.80 (m, 6H), 1.90–2.14 (m, 2H), 3.24–3.37 (m, 2H), 3.60 (dq, J = 9.3, 7.2 Hz, 1H), 3.74–3.84 (m, 1H), 3.82 (s, 3H), 5.14 (dd, J = 3.9, 6.6 Hz, 1H), 6.88–6.88 (m, 2H), 7.36–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 8.33, 14.97, 23.15 (2C), 25.14, 38.53, 38.93, 55.24, 62.15, 75.16, 87.46, 88.43, 97.96, 114.00 (2C), 114.68, 133.15 (2C), 159.84. Found: C, 53.50; H, 5.93%. Calcd for $C_{19}H_{25}IO_3$: C, 53.28; H, 5.88%.

4-[(4-Methoxyphenyl)methylene]-2-ethoxy-1-oxaspiro[4.5]-decane (15d): (6/4 stereoisomers mixture) IR (neat): 2928, 1608, 1575, 1511, 1445, 1301, 1246, 1175, 1118, 1094, 1037, 982, 919, 867, 823, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88–1.77 (m, 12.6H), 1.92 (d, J = 13.2 Hz, 0.4H), 2.66 (d, J = 16.2 Hz, 0.6H), 2.88–3.10 (m, 1.4H), 3.42–3.53 (m, 1H), 3.75–3.88 (m, 4H), 5.11 (d, J = 5.4 Hz, 0.6H), 5.26 (d, J = 5.1 Hz, 0.4H), 6.15 (t, J = 2.4 Hz, 0.4H), 6.47 (s, 0.6H), 6.81–6.88 (m, 2H), 7.13 (d, J = 8.1 Hz, 1.2H), 7.22 (d, J = 8.7 Hz, 0.8H); ^{13}C NMR ($CDCl_3$): major isomer, δ 14.97, 22.18, 22.47, 25.09, 36.36, 37.12, 42.50, 55.01, 61.91, 83.59, 100.43, 113.12 (2C), 121.26, 130.01, 130.19 (2C), 146.35, 158.18. minor isomer, δ 14.94, 22.56, 22.84, 25.35, 38.30, 38.35, 38.65, 55.09, 62.08, 85.34, 101.87, 113.66 (2C), 119.50, 129.37 (2C), 130.64, 145.05, 158.15. Found: C, 75.20; H, 8.81%. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67%.

4-Deuteriophenyl Octyl Ether (2a-*d*, 88%D): IR (neat): 3032, 2924, 2852, 1599, 1493, 1470, 1389, 1294, 1246, 1172, 1035, 840, 752, 690, 598 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (s, J = 6.6 Hz, 3H), 1.20–1.52 (m, 10H), 1.78 (quintet, J = 6.6 Hz, 2H), 3.95 (t, J = 6.6 Hz, 2H), 6.84–6.96 (m, 2.1H), 7.24–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 13.96, 22.55, 25.98, 29.16, 29.22, 29.29, 31.74, 67.81, 114.52(2C), 120.2 (t, J = 24.8 Hz, 0.9C), 120.48 (s, 0.1C), 129.33 (1.8C), 129.44 (0.2C), 159.28. Found: C, 81.19; H+D, 10.86%. Calcd for $C_{14}H_{21.1}D_{0.9}O$: C, 81.14; H+D, 11.13%.

7-(1-Deuterio-1-methylethyl)-2,9-dioxabicyclo[4.3.0]nonane (7g-*d*, > 99%D): (6/4 diastereomers mixture) IR (neat): 2928, 2864, 1467, 1402, 1254, 1226, 1148, 1093, 1073, 1043, 1018, 997, 952, 897, 871 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.80 (s, 1.8H), 0.87 (s, 1.2H), 0.92 (s, 1.8H), 0.94 (s, 1.2H), 1.32–2.00 (m, 5.6H), 2.06–2.17 (m, 0.4H), 3.43 (dt, J = 2.1, 11.1 Hz, 0.4H), 3.62–3.80 (m, 2.2H), 3.85–3.98 (m, 1H), 4.19 (t, J = 8.7 Hz, 0.4H) 4.99 (d, J = 3.3 Hz, 0.4H) 5.30 (d, J = 3.3 Hz, 0.6H); ^{13}C NMR ($CDCl_3$): major isomer, δ 18.65, 20.69, 21.45, 23.12, 25.69 (t, J = 19.4 Hz), 35.57, 48.71, 60.60, 68.89, 102.03; minor isomer, δ 19.16, 20.57, 21.18, 23.34, 29.39 (t, J = 18.8 Hz), 41.18, 44.09, 64.20, 70.93, 102.42. Found: C, 69.89; H, 9.99%. Calcd for $C_{10}H_{17}DO_2$: C, 70.13; H, 10.00%.

3-(1-Deuterio-1-methylethyl)-2,3-dihydrobenzofuran (10c-*d*, 87% D): IR (neat): 3044, 3028, 2866, 1610, 1595, 1482, 1463, 1454, 1387, 1368, 1325, 1222, 1163, 1099, 1017, 958, 812, 744,

724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.95 (s, 3H), 3.28–3.38 (m, 1H), 4.37 (dd, J = 5.1, 9.0 Hz, 1H), 4.52 (t, J = 9.0 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.85 (dt, J = 0.9, 7.2 Hz, 1H), 7.09–7.21 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 18.18, 19.57, 31.11 (t, J = 19.4 Hz), 47.87, 73.80, 109.36, 120.11, 125.13, 128.19, 129.51, 160.40; HRMS Found: *m/z* 163.1107, Calcd for $C_{11}H_{13}DO$: 163.1108.

4-Deuteriomethyl-5-pentyl-4,5-dihydro-2(3*H*)-furanone (21, 93% D): IR (neat): 2926, 2856, 1779, 1462, 1424, 1263, 1206, 1170, 1121, 1072, 1002, 946 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 6.6 Hz, 3H), 1.10–1.15 (m, 2.07H), 1.26–1.74 (m, 8H), 2.13–2.28 (m, 2H), 2.67 (q, J = 12.0 Hz, 1H), 3.98–4.05 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 13.71, 16.90 (t, J = 19.4 Hz, 0.9C), 17.19 (s, 0.1C), 22.24, 25.17, 31.33, 33.74, 35.77 (0.9C), 35.85 (0.1C), 36.87, 87.32, 176.67; HRMS Found: *m/z* 171.1365, Calcd for $C_{10}H_{17}DO_2$: 171.1370.

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8 When commercially available sodium phosphinate monohydrate ($NaH_2PO_2{\cdot}H_2O$) was used instead of the combination of aqueous phosphinic acid and a base, an addition of water was essential to proceed the reaction smoothly. Treatment of **1a** with $NaH_2PO_2{\cdot}H_2O$ in anhydrous ethanol afforded **2a** in 3% yield and **1a** was recovered (94%), whereas the reaction in aqueous ethanol ($EtOH/H_2O$ = 5 mL/1 mL) gave **2a** in 95% yield. These facts were due to the poor solubility of $NaH_2PO_2{\cdot}H_2O$ in ethanol. Crystalline $NaH_2PO_2{\cdot}H_2O$ apparently remained insoluble in refluxing anhydrous ethanol. Adding water gave a clear solution.

9 The use of other initiators such as $K_2S_2O_8$ or di-*tert*-butyl peroxide was not effective at all.

10 In the previous reports using phosphinic acid, reactions were carried out with a base necessarily to protect acid-sensitive functionalities (see Refs. 4 and 5) or to solve a substrate with a carboxylic group into water (see Ref. 6). However, it was reported that the reduction of thionocarbonates of (*R*,*R*)-tartarates with H_3PO_2 gave enantiopure (*R*)-malates in the absence of a base. Therefore, the halogen abstraction step would be unfavorable without a base. See, D. O. Jang and S. H. Song, *Tetrahedron Lett.*, **41**, 247 (2000).

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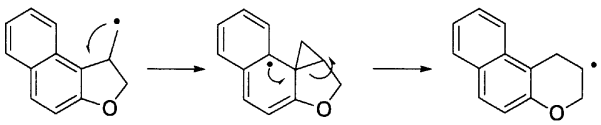
13 The reaction did not go to completion when a catalytic amount of Et_3B was used. The hydrogen abstraction step would be slow at room temperature because of the strong P–H bond.

14 Triethylborane was superior to AIBN in the lactonization step because the reaction at high temperature led to the hydrolysis of the ester bond. On the other hand, the reduction step proceeded faster with AIBN at 100 °C than with Et_3B at 25 °C.

15 Phosphorus-centered radical easily adds to terminal olefin (see Ref. 4).

16 We checked whether *n*-Bu_3SnH also has the ability to discriminate between aryl iodide and aryl bromide. Treatment of **9e** with exactly 2.0 molar amounts of *n*-Bu_3SnH and a catalytic amount of AIBN in refluxing benzene afforded **10e** in 66% yield exclusively after removal of the tin residue with aqueous KF.

17 Slow addition of H_3PO_2 and $NaHCO_3$ to a solution of **9f** and AIBN gave **10f** and **10f′** in the same ratio. This result means that direct 6-endo cyclization occurred, that is, the reaction path as below would be improbable under the present conditions.



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19 Treatment of **12f** under the standard conditions gave **13f** in 52% yield in addition to the direct reduction product (38% yield).

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21 For recent examples of *n*-Bu_3SnD-mediated radical deuteration, see: a) E. Kawashima, Y. Aoyama, T. Sekine, M. Miyahara, M. F. Radwan, E. Nakamura, M. Kainosho, Y. Kyogoku, and Y.

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22 The deuterium incorporation was determined by the integration of ^{1}H NMR.

23 The exchange between hydrogen in H_3PO_2 and deuterium in D_2O proceeds more rapidly in acidic conditions than in neutral and basic conditions. When a mixture of $NaH_2PO_2{\cdot}H_2O$, *p*-iodobenzoic acid, and AIBN in D_2O was heated at reflux for 5 h, a trace amount of the reduced product was obtained. The deuterium incorporation of the product at the para position was 18%. Most of the starting material was recovered. Addition of potassium carbonate is crucial to obtain benzoic acid in quantitative yield; however, almost no deuterium was incorporated in the product. For the exchange reaction, see: W. A. Jenkins and D. M. Yost, *J. Chem. Phys.*, **20**, 538 (1952).

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26 Deuterated phosphinic acid is available from Aldrich Chemicals and is sold as "Hypophosphorous acid–d_3".

27 DBU was the most effective among the bases we examined. Pyridine, 4-dimethylaminopyridine, Li_2CO_3 and 1,10-phenanthroline did not give the desired product. Use of n-Bu_3N in the reaction of **20** afforded **7g** in 58% yield.

28 The reaction in ethanol-*d* gave **7g** in 13% yield along with recovered **20** (69%). The reaction did not go to completion when dimethoxyethane (**7g**: 70% and **20**: 12%) or benzene (16% and 68%) was employed as a reaction solvent. Heating at about 100 °C seems necessary to perfect the reaction.

29 Contrary to the reaction in D_2O, $K_2S_2O_8$ is effective in dioxane/D_2O. Although the reaction initiated by AIBA proceeded smoothly, deuteration was not satisfactory (73% D).

30 Reductive deuteration of **12c** under the same reaction conditions resulted in failure and **12c** remained unchanged.

31 a) R. Inoue, J. Nakao, H. Shinokubo, and K. Oshima, *Bull. Chem. Soc. Jpn.*, **70**, 2039 (1997). b) A. Inoue, H. Shinokubo, and K. Oshima, *Org. Lett.*, **2**, 651 (2000). Compound **5i** was subjected to oxidation by Jones oxidant to give known β-isopropyl-γ-butyrolactone. See, c) S. S. C. Koch and A. R. Chamberlin, *J. Org. Chem.*, **58**, 2725 (1993).