Studies on Radical Reactions in Aqueous Media

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Contents

Introduction and General Summary

1. Organoborane-induced Radical Chain Reactions

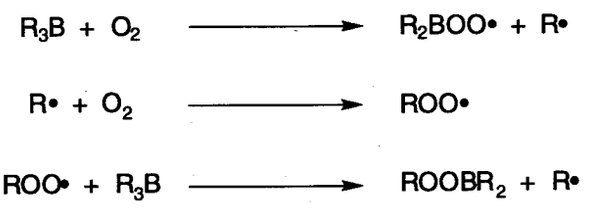
Carbon-carbon bond formation is the central issue of organic synthesis. Numerous organic chemists have dedicated themselves to creating new, efficient, and selective methods for the construction of carbon-carbon bonds. Ionic reactions have been powerful tools from the beginning of organic synthesis. The Grignard reaction, aldol reaction, and Friedel–Crafts reaction, for example, represent reliable methods for selective carbon-carbon bond constructions in industrial processes as well as in laboratories. Modern polar reactions are often mediated by transition metals such as palladium, nickel, copper, chromium, titanium, zirconium and lanthanides. Polar reaction processes are still growing to pursue higher efficiency and selectivities. Pericyclic reactions, including the Diels–Alder reactions and Claisen rearrangement, also offer a promising route to construct complex skeletons. Many efforts have been made to control pericyclic reactions. As a result, high levels of stereo- and regioselectivity are now available.

On the other hand, radical reactions in organic synthesis had been undeveloped because of the prejudice that radical reactions are unmanageable and proceed violently without selectivity. Radical processes were hence employed mostly in polymer chemistry. However, organic radical chemists noticed that radical reactions could be controllable.[1] Careful arrangement of reaction systems proved to be important for the success of radical reactions. Especially, the use of radical mediators such as organotin hydride and organomercury hydride largely enhanced the development of synthetic radical chemistry. The choice of a radical initiator is also important because it decides the outcome of the reaction in the initiation step. The conventional azo compounds and peroxides are frequently used in conducting a radical reaction. In these cases, elevated temperatures are usually necessary. A hexabutylditin/UV system generates reactive tin-centered radicals and was applied to atom transfer radical reactions.[2] One drawback arises from the residual tin compounds that are toxic and troublesome to remove. Efficient and user-friendly initiators were awaited.

In general, organoboranes are very sensitive to oxidation and are normally handled under argon or nitrogen. Examples of conjugate addition of trialkylborane to α,β-unsaturated carbonyl compounds under inert atmosphere were found in the 1960s, and these were initially thought to be

polar reactions.[3a–3d] However, Brown's group established in 1970 that conjugate addition of trialkylborane is a radical reaction.[3e,3f] A trace amount of oxygen in the reaction medium reacts with trialkylborane to produce an alkyl radical as shown in Scheme 1.[4] Although the synthetic utility of conjugate addition had been well documented, new reaction patterns of trialkylborane via a radical process had not been discovered. In 1987, triethylborane-induced hydrostannylation of alkynes[5] had opened up new possibilities for using trialkylborane, especially Et_3B, as a radical initiator in organic synthesis. Compared with other initiators such as azobis(isobutyronitrile) (AIBN) and benzoyl peroxide (BPO), Et_3B-induced radical reactions have several characteristic features. In this section, the usefulness of Et_3B as an excellent radical initiator is reviewed.[6]

Scheme 1

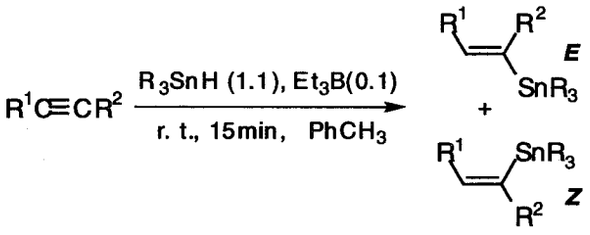


1.1 Triethylborane-induced Radical Reaction at Low Temperature

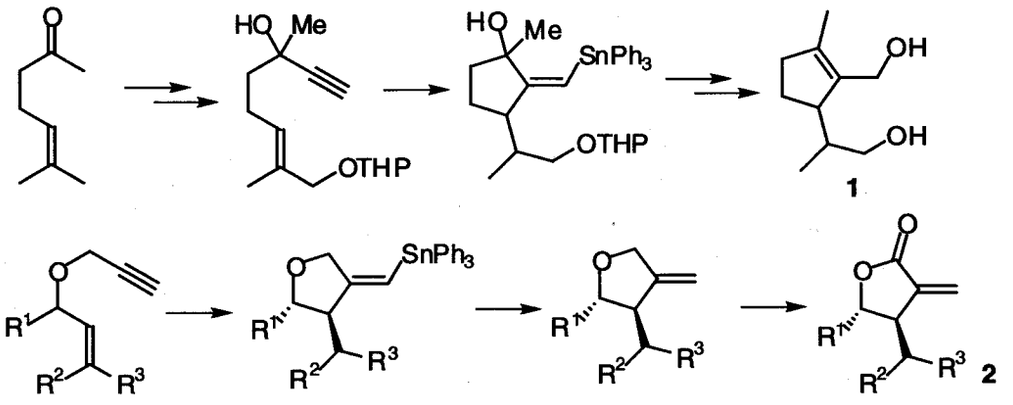
Triethylborane can act as a radical initiator in the presence of a trace of oxygen even at –78 °C, where Et_3B is decidedly superior to AIBN and BPO. Reactions at lower temperatures allow us to control stereoselectivity, to employ thermally unstable substrates and to save troubles and energy in heating.

Et_3B as a simple radical initiator was first discovered in hydrostannylation of alkynes.[5] The reactions were performed at room temperature or below in the presence of a trace amount of oxygen (Scheme 2). Hydrostannylation was applied to the synthesis of dehydroiridodiol (**1**) and α-methylene-γ-butyrolactone **2**. Triethylborane-induced radical addition reactions of triphenylgermane,[7] tris(trimethylsilyl)silane,[8] and benzenethiol[9] to alkynes were also reported. In the case of triphenylgermane, both (*E*)- and (*Z*)-alkenylgermanes could be selectively obtained by changing reaction conditions (Scheme 3).

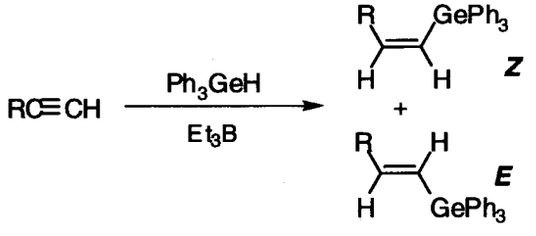
Scheme 2



R^1	R^2	R_3SnH	Yield	*E/Z*
n-$C_{10}H_{21}$	H	Ph_3SnH	80%	79/21
		n-Bu_3SnH	40%	80/20
$HOCH_2CH_2$	H	Ph_3SnH	87%	82/18
Ph	H	Ph_3SnH	75%	100/0
Me_3Si	H	Ph_3SnH	83%	100/0
n-C_5H_{11}	*n*-C_5H_{11}	Ph_3SnH	86%	0/100



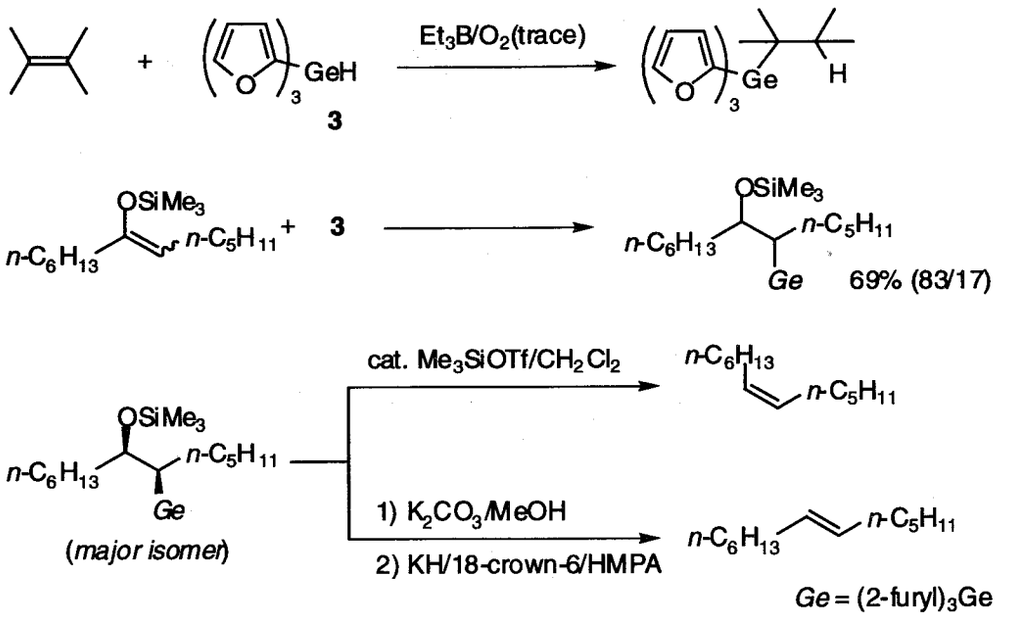
Scheme 3



R	Temp.	Yield	*Z/E*
n-$C_{10}H_{21}$	–78°C	76%	>20/1
	60°C	99%	<1/20
$HOCH_2CH_2$	–78°C	80%	>20/1
	60°C	75%	<1/20
$EtOOC(CH_2)_9$	–78°C	64%	>10/1
	60°C	93%	<1/20

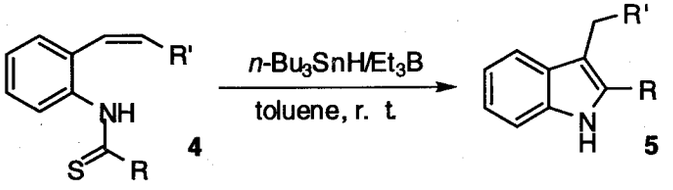
Recently, it was demonstrated that tri-2-furylgermane (**3**) added to various alkenes, including not only disubstituted alkenes but also tri- and tetrasubstituted alkenes at room temperature.[10] Stereoselective olefination reaction was achieved by the radical addition of tri-2-furylgermane to silyl enolate followed by treatment of the adduct with Me_3SiOTf or with 1) K_2CO_3/MeOH and 2) KH (Scheme 4). This sequential reaction provides a new route for the conversion of ketones into alkenes.

Scheme 4



Fukuyama's group illustrated that 2,3-disubstituted indole **5** was prepared under mild conditions starting with 2-alkenylthioanilide **4** (Scheme 5).[11] Labile β-lactam could be introduced at the indole 2-position.

Scheme 5

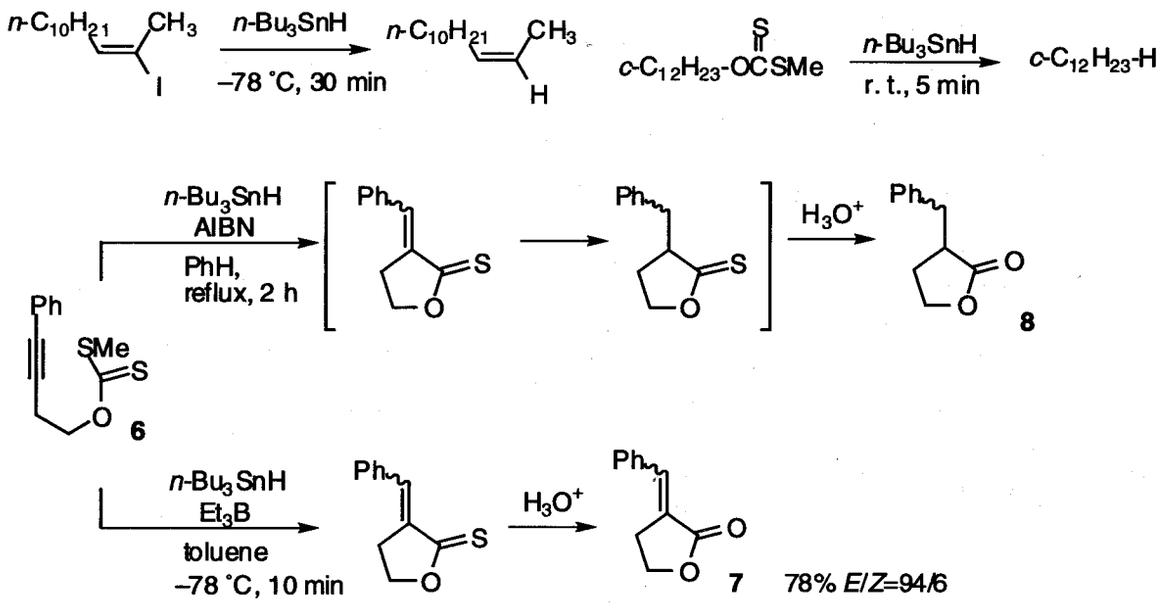


R	R'	Yield
Me	CH_2OAc	89%
NTBS	CH_2OTHP	98%
NHCbz, Me	CH_2OAc	82%

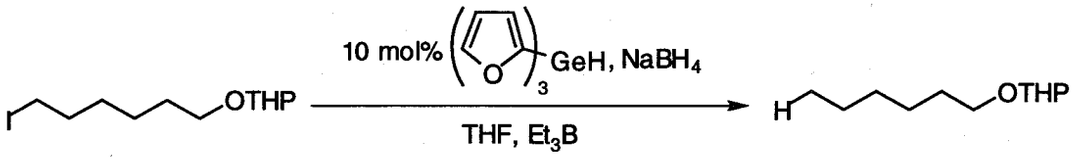
Alkyl iodides and bromides were reduced at –78 °C with *n*-Bu_3SnH within 30 min.[12] Alkenyl halides were also dehalogenated easily (Scheme 6). Moreover, Et_3B lowered the temperature at which the reduction of dithiocarbonate was performed.[13] The radical reaction of **6** showed a clear contrast between AIBN and Et_3B. Treatment of **6** with *n*-Bu_3SnH in the presence of Et_3B at –78 °C for only 10 min in toluene afforded α-benzylidene-γ-butyrolactone **7** in high yield, whereas saturated γ-lactone **8** was obtained when AIBN was employed in refluxing benzene. Tri-2-furylgermane-mediated reduction of organic halides proceeded at room temperature with Et_3B/O_2.[14] Catalytic reduction by a tri-2-furylgermane/$NaBH_4$ system was also successful

(Scheme 7).

Scheme 6



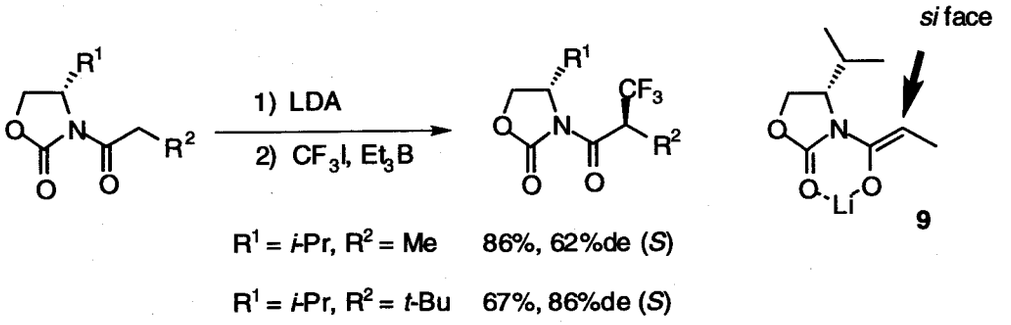
Scheme 7



Stereoselective radical reactions have been actively investigated. Et_3B has contributed largely toward improving stereoselectivity because one can examine at lower temperature. Many excellent diastereoselective and enantioselective works were reported, and most of them are mentioned elsewhere in detail.[15] Some limited examples are shown here.

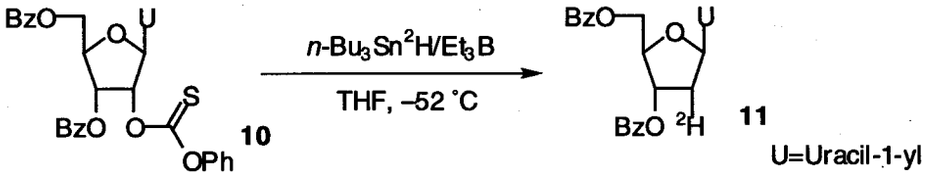
Diastereoselective trifluoromethylation of chiral imide enolate with iodotrifluoromethane was performed at –78 °C to produce α-trifluoromethyl carboximide.[16] The attack of trifluoromethyl radical to the lithium-chelated enolate **9** would proceed with C(α)-*si*-face preference (Scheme 8).

Scheme 8



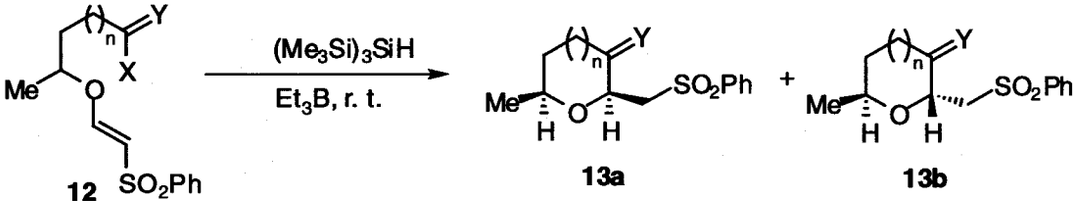
Preparative synthesis of 2'-deoxy[2'-^{2}H]ribonucleoside **11** with high stereoselectivity was achieved by reduction of the corresponding thionocarbonate **10** with *n*-Bu_3Sn^2H/Et_3B.[17] Stereoselectivity was not controllable when AIBN was used in benzene at reflux (Scheme 9).

Scheme 9



Treatment of **12** with $(Me_3Si)_3SiH$ and Et_3B predominantly afforded cyclic ethers with *cis* stereochemistry.[18] Construction of oxepines (n = 2) proceeded at low concentration. Additionally, the reaction at low temperature was effective to suppress decarbonylation of the intermediary acyl radical derived from acyl selenide (Scheme 10).

Scheme 10

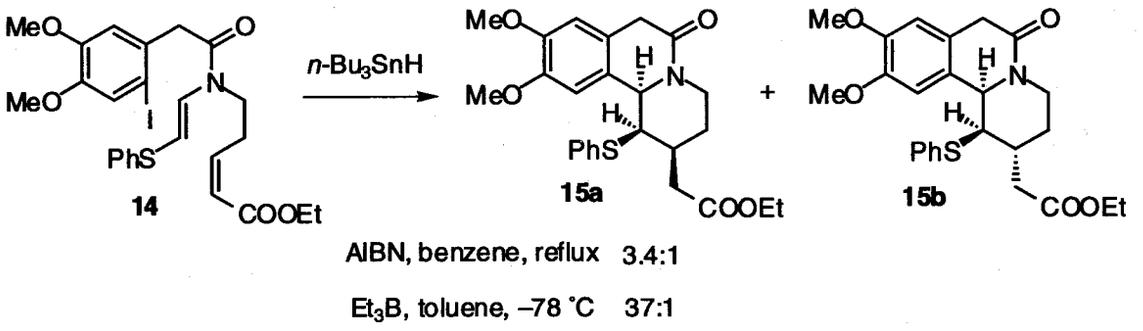


n=0	X=Br	Y=H_2	0.02 M	99% (>19:1)
n=0	X=SePh	Y=O	0.02 M	87% (17:1)
n=1	X=SePh	Y=O	0.01 M	83% (8:1)
n=2	X=SePh	Y=O	0.005 M	63% (17:1)

Stereoselective radical cascade approach to benzo[a]quinolizidines utilizing Et_3B was highly effective.[19] When **14** was treated with *n*-Bu_3SnH in the presence of AIBN in boiling benzene, the

radical cascade products **15a** and **15b** were obtained in a ratio of 3.4:1 and in 36% combined yield. A similar reaction with Et_3B at –78 °C in toluene afforded **15a** and **15b** in a ratio of 37:1 in a 46% yield. Recrystallization of the obtained mixture gave the pure isomer **15a** (Scheme 11).

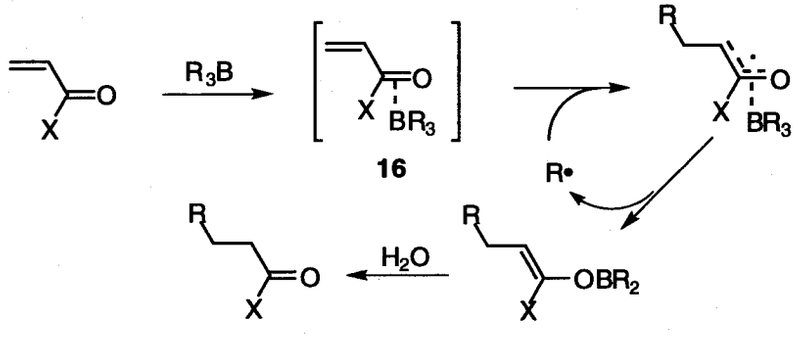
Scheme 11



1.2 Lewis Acidic Trialkylborane: Radical Mediator and Terminator as Well as Initiator

Stoichiometric organoboranes are well known to undergo conjugate addition to various α,β-unsaturated carbonyl compounds such as methyl vinyl ketone.[3a–3d] It was later discovered that galvinoxyl inhibited the reaction, suggesting a radical mechanism.[3e,3f] Very recently, spectroscopic analyses clarified that the reaction of α,β-unsaturated carbonyl compounds with Et_3B under free radical conditions would involve the prior formation of an 'α,β-unsaturated carbonyl compound-organoborane' complex **16** (Scheme 12).[20]

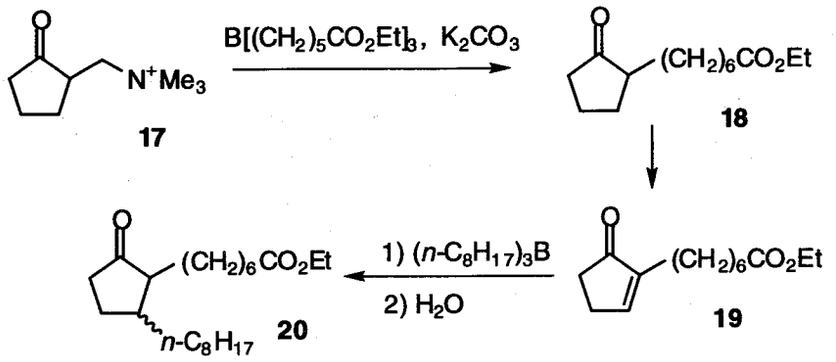
Scheme 12



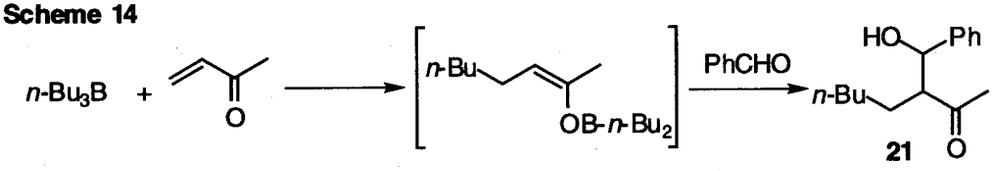
Among many examples of conjugate addition reported, the synthesis of a prostaglandin model **20** is exemplified in Scheme 13.[21] Trialkylborane containing an ester moiety added to enone generated *in situ*. The second conjugate addition gave α,β-dialkylcyclopentanone **20**. Another example is successive conjugate addition of alkyl radical and aldol reaction with aldehyde.[22]

Subsequent addition of aldehyde, instead of water, to the reaction mixture resulted in aldol addition to form β-hydroxy ketone **21** (Scheme 14).

Scheme 13

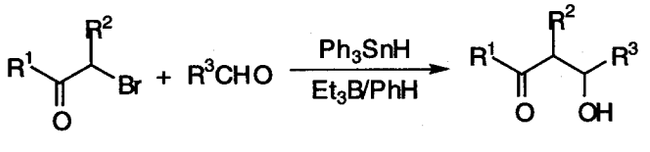


Scheme 14

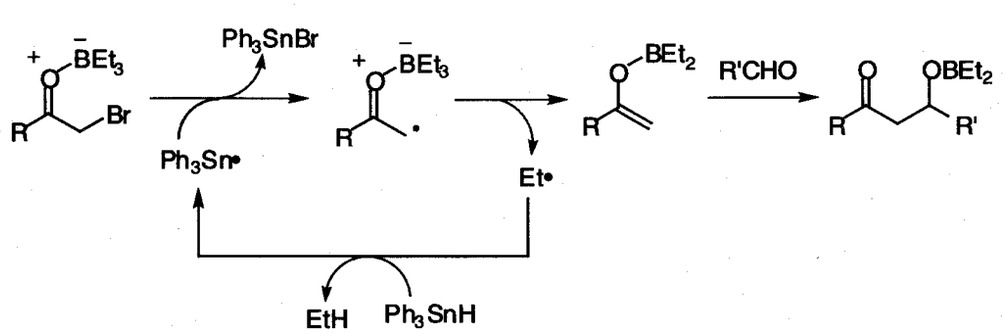


Reformatsky-type reaction mediated by Ph_3SnH/Et_3B provided β-hydroxy ketone.[23] In the case of cyclic ketone, *threo* isomer was selectively obtained, which indicated the formation of boron enolate and cyclic transition state. The plausible mechanism is shown in Scheme 15. According to the recent study,[20] Et_3B would first coordinate to a carbonyl moiety to trap alkoxy radical.

Scheme 15



R^1	R^2	R^3CHO	yield (%)	
Ph	H	PhCHO	88	
		n-$C_8H_{17}CHO$	77	
		cyclohexanone	81	
-$(CH_2)_4$-		n-$C_6H_{13}CHO$	82	(*erythro*/*threo*=2/98)
		t-BuCHO	82	(*erythro*/*threo*=0/100)



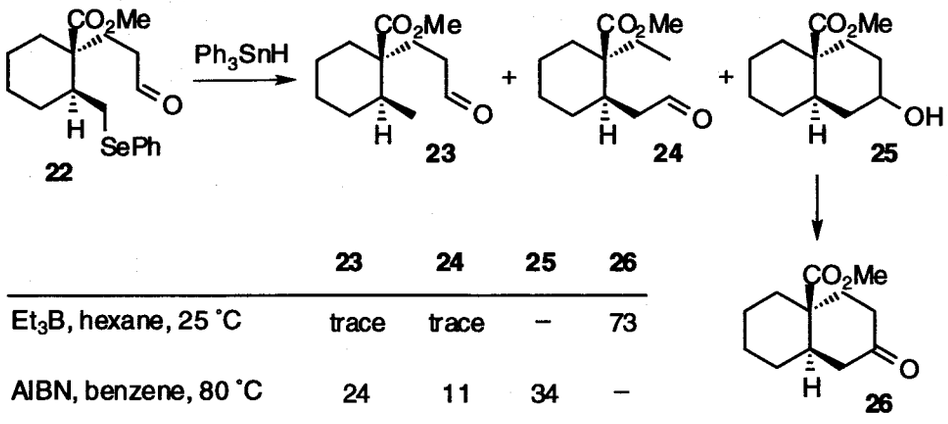
The intramolecular addition of radicals to carbonyl moieties is difficult because radical addition to a carbonyl group is reversible whereas addition to alkene is normally irreversible (Scheme 16).[24] This is because an oxygen-centered radical is unstable and β-fragmentation of cyclopentyloxy or cyclohexyloxy radical occurs.

Scheme 16

In order to overcome the reversibility, the coordination of Et_3B to a carbonyl group has been utilized. The Et_3B-stannane-air system is highly effective for intramolecular radical addition to aldehyde.[25] Ph_3SnH and Et_3B were added simultaneously to aldehyde **22** in hexane. Oxidation of the crude product afforded bicyclic ketone **26** in good yield. The directly reduced product **23** and the product **24** that was formed by the β-fragmentation of the cyclohexyloxy radical were obtained when AIBN was employed as an initiator at 80 °C (Scheme 17). Malacria's recent study has provided a new method to obtain cycloalkanols in high yield via radical cyclization to carbonyl group.[26] Treatment of **27a** or **27b** with *n*-Bu_3SnH and an excess amount of Et_3B at –78 °C to 0 °C furnished methylenecyclopentanol **28a** or methylenecyclohexanol **28b** in good yield, respectively (Scheme 18). Cyclization of **29a** in the presence of *n*-Bu_3SnH and an excess of Et_3B gave a quantitative yield of **30a**. Furthermore, satisfactory yield of **30a** was obtained without stannane mediator. It is crucial in this tin-free reaction that Et_3B produces an ethyl radical. An ethyl radical is much more reactive than a 2-cyano-2-propyl radical derived from AIBN because no resonance stabilization exists in an ethyl radical. It is disfavored for a resonance-stabilized radical to abstract an iodine atom from alkyl iodide. However, an ethyl radical can abstract iodine reversibly to produce the corresponding alkyl radical without the help of stannanes, which is another characteristic feature of Et_3B as an initiator (see the following section). They also investigated the cyclization of ketone **29c**. With 1.3 equimolar amount of tin hydride, only the reduced product was formed. However, tertiary alcohol **30c** was obtained in excellent yield in the absence of tin hydride. These investigations were applied to the synthesis of 2-

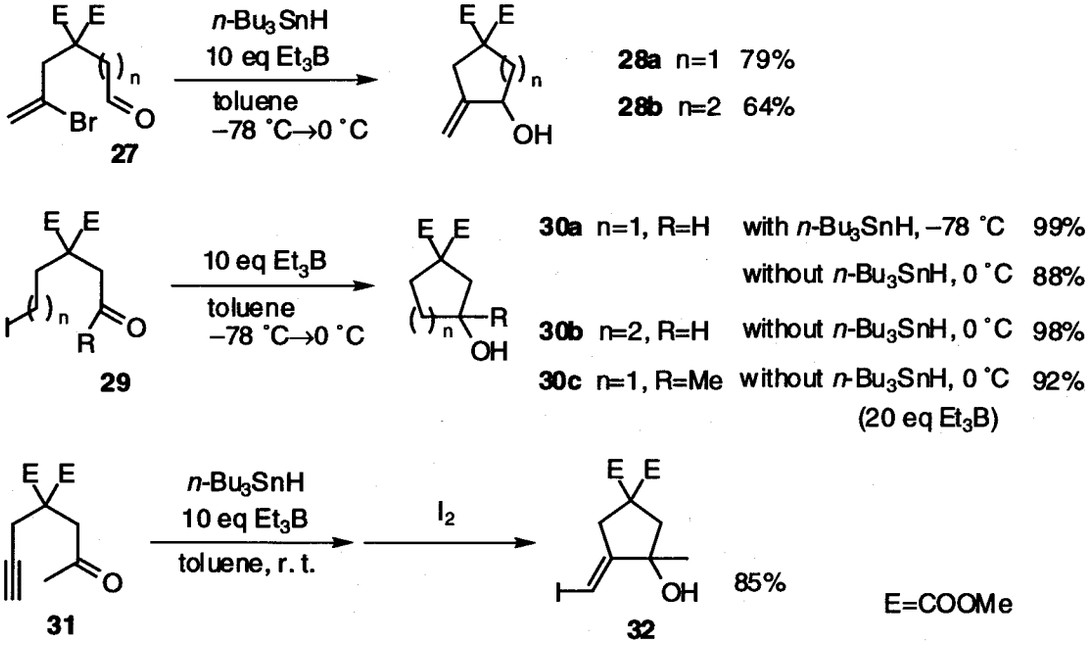
iodomethylenecycloalkanols. The stannyl radical addition-cyclization cascade was successful, giving 2-iodomethylenecyclopentanol **32** stereoselectively after the crude vinylstannane was treated with iodine. The explanation proposed for these results was that Et_3B acts as a radical quencher of the intermediary alkoxy radical to prevent the β-scission pathway.

Scheme 17



	23	24	25	26
Et_3B, hexane, 25 °C	trace	trace	–	73
AIBN, benzene, 80 °C	24	11	34	–

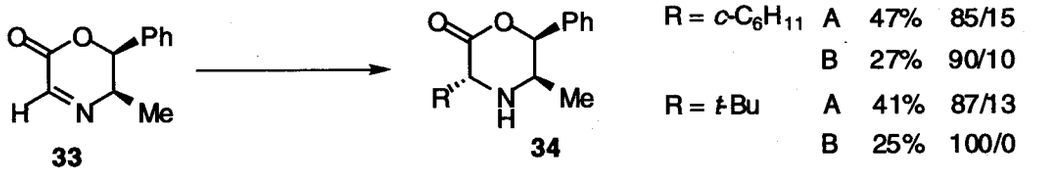
Scheme 18



Et_3B has also worked in radical addition to C=N bonds. Bertrand et al. reported diastereoselective radical addition to glyoxylate imines **33**.[27] Compared with the *n*-Bu_3SnH /AIBN system, the stereoselectivity of the products is higher when Et_3B and no *n*-Bu_3SnH were

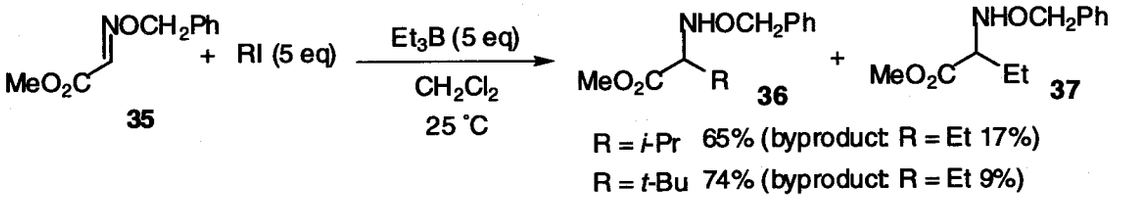
employed at –40 °C (Scheme 19). Naito's group demonstrated that intermolecular radical addition to glyoxylic oxime ether **35** proceeded effectively using alkyl iodide and Et_3B.[28] Treatment of **35** with excess RI and Et_3B afforded the corresponding adduct **36** in good yield in addition to a small amount of the ethyl radical adduct **37**. Both groups pointed out that Et_3B acts as a radical initiator, a Lewis acid and a radical terminator as shown in Scheme 20.

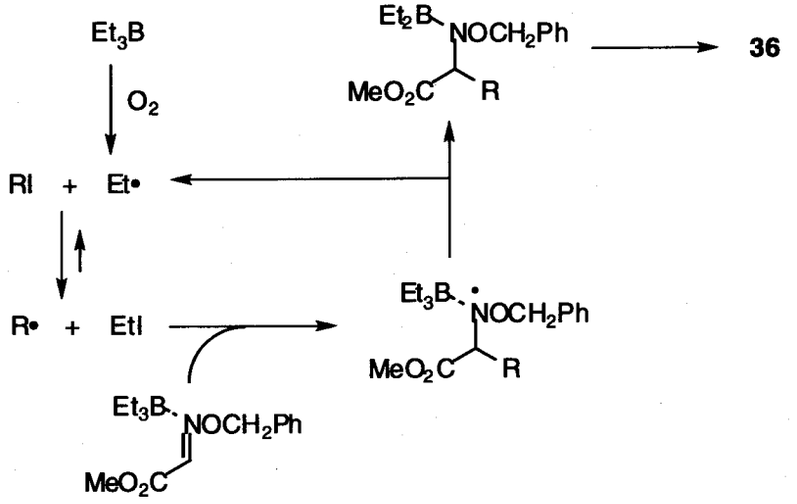
Scheme 19



Conditions A: RI (0.95 eq), *n*-Bu_3SnH (1.05 eq.), AIBN, benzene, 80 °C
Conditions B: RI (6 eq), Et_3B (3 eq.), CH_2Cl_2, –40 °C

Scheme 20





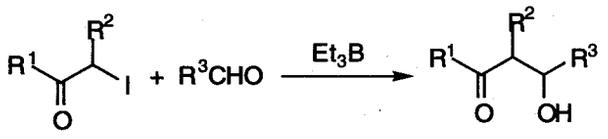
1.3 Triethylborane as a Source of Reactive Ethyl Radical

As mentioned above, Et_3B produces an ethyl radical that is reactive enough to abstract iodine atom from alkyl iodide without the help of radical mediators such as *n*-Bu_3SnH. A carbon-iodine

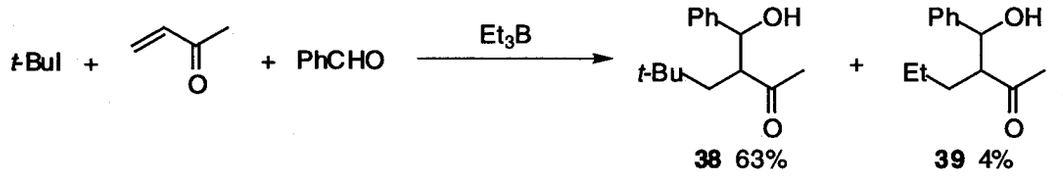
bond in secondary alkyl, tertiary alkyl and carbonylmethyl iodide is easily cleaved homolytically by an ethyl radical. Newly formed radical species adds to an olefinic moiety intermolecularly or intramolecularly to afford the corresponding radical species.

Treatment of α-iodo ketone and aldehyde with an equimolar amount of Et_3B yielded the Reformatsky-type adduct in the absence of Ph_3SnH (Scheme 21), different from α-bromo ketone as shown in Scheme 15.[23] An ethyl radical abstracts iodine to produce carbonylmethyl radical, which would be trapped by Et_3B to give the boron enolate and regenerate an ethyl radical. The boron enolate reacts with aldehyde to afford the adduct. Three component coupling reaction of *tert*-butyl iodide, methyl vinyl ketone and benzaldehyde proceeded to give the corresponding adduct **38** with the contamination of the ethyl radical addition product **39**. The order of stability of carbon centered radical is carbonylmethyl radical > *t*-Bu• > *i*-Pr• > Et• > Me•. Compound **38** was hence predominantly formed.

Scheme 21



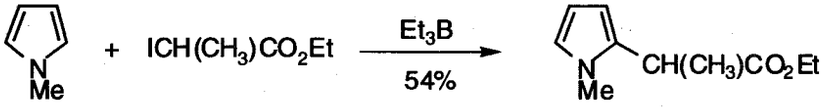
R^1	R^2	R^3CHO	yield (%)
Ph	H	*n*-$C_6H_{13}CHO$	72
		cyclohexanone	77
-$(CH_2)_3$-		*n*-$C_6H_{13}CHO$	64 (*erythro*/*threo*=6/94)
		t-BuCHO	70 (*erythro*/*threo*=0/100)



38 63% **39** 4%

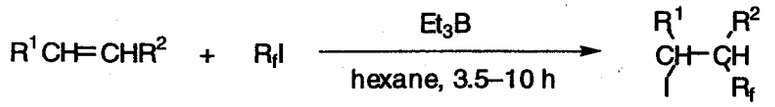
Electron-deficient carbon-centered radical generated by the action of Et_3B underwent homolytic aromatic substitution of five-membered heteroaromatics.[29] The 2-position was selectively substituted to yield 2-heteroarylacetic acid derivatives (Scheme 22).

Scheme 22

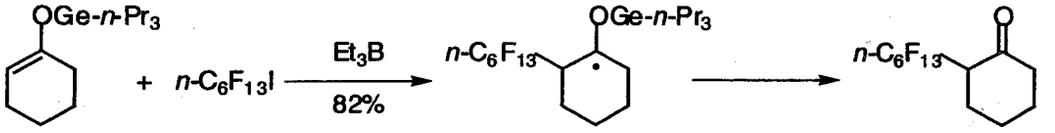


iodide,[30] α-halo nitrile, and α-halo ester[31] added to alkenes and alkynes at low temperature. Not only terminal alkenes but also internal alkenes can be employed to furnish iodine atom transfer adducts (Scheme 23). Furthermore, addition to silyl and germyl enolate provided α-perfluoroalkyl ketones.[32] The reaction would involve elimination of a trialkylgermyl radical from the intermediate **41**.

Scheme 23



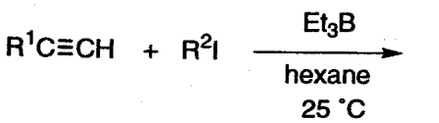
R^1	R^2	R_fI	Temp. (°C)	Yield (%)
$MeOOC(CH_2)_8$	H	n-$C_6F_{13}I$	25	90
n-$C_{10}H_{21}$	H	$(CF_3)_2CFI$	25	87
n-C_5H_{11}	n-C_5H_{11}	CF_3I	–24	61



40 **41** **42**

Intermolecular radical addition of alkyl iodide is generally difficult. However, it was realized with satisfactory yields especially in the case that trimethylsilylacetylene, ethyl propiolate, or phenylacetylene was used (Scheme 24).[33]

Scheme 24

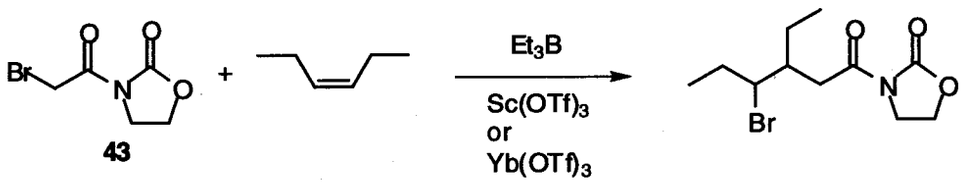


R^1	R^2	yield (%)	*E*/*Z*
Me_3Si	Et	84	0/100
COOEt	*i*-Pr	88	34/66
Ph	*i*-Pr	81	21/79

The $Sc(OTf)_3$- and $Yb(OTf)_3$-promoted atom transfer radical addition reaction of *N*-bromoacetyl-2-oxazolidinone (**43**) proceeds smoothly not only with terminal alkenes but also 1,2-disubstituted alkenes (Scheme 25).[34] The reaction occurs at ambient temperature. Bromine

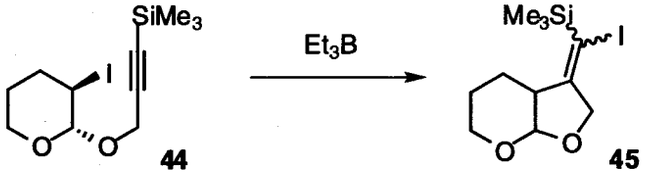
atom transfer reaction usually requires higher temperature than iodine atom transfer. The addition of a Lewis acid made the bromine atom transfer reaction easier.

Scheme 25

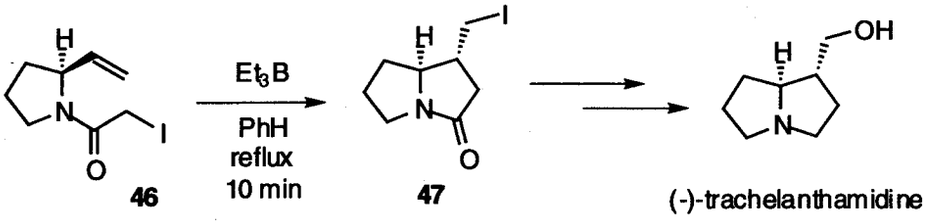


Et_3B-induced halogen atom transfer radical cyclization is a successful application. Cyclization of iodo acetal **44** afforded tetrahydrofuran derivative **45** in almost quantitative yield (Scheme 26).[33] Et_3B also induced radical cyclization of *N*-allylic α-iodoacetamide to give β-iodomethyl-γ-lactam via an atom transfer process.[35] The reaction of **46**, prepared from 2-prolinol, proceeded smoothly within 10 min in boiling benzene in the presence of Et_3B to yield (1*R*, 8*S*)-1-iodomethylpyrrolidin-3-one **47**, which can be readily converted into (–)-trachelanthamidine (Scheme 27).

Scheme 26



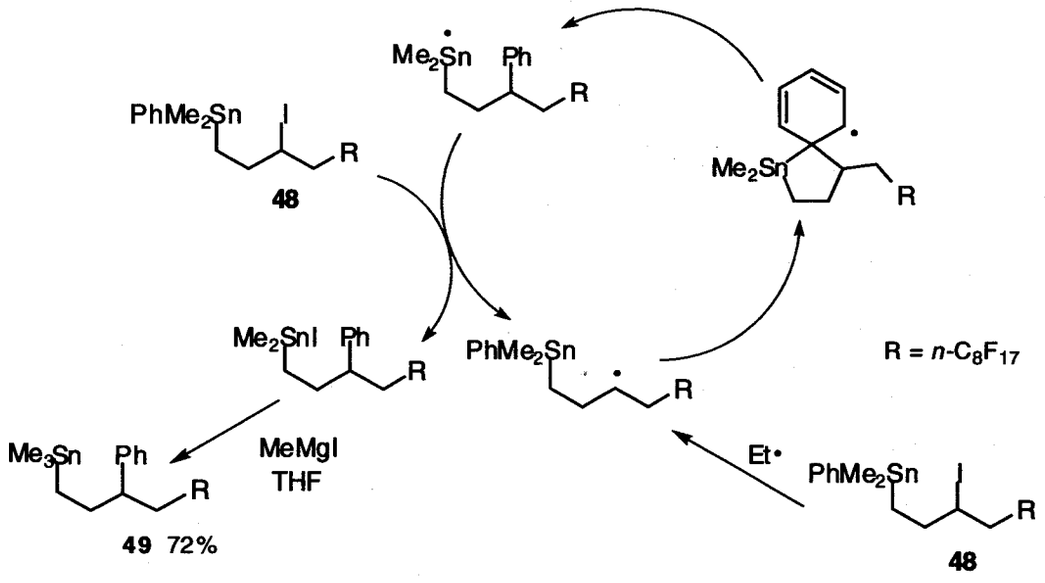
Scheme 27



An intramolecular ipso substitution reaction took place when Et_3B was added to a solution of 3-iodoalkylaryldimethylstannane in benzene at reflux to migrate the aryl group from tin to carbon via an atom transfer process.[36] In this case, reactive ethyl radical would play an important role in abstracting iodine from the substrate. For example, treatment of **48** with Et_3B followed by

addition of methylmagnesium iodide provided 3-phenylalkyltrimethylstannane **49** in good yield (Scheme 28). On the other hand, AIBN could not initiate the reaction, and **48** remained unchanged.

Scheme 28



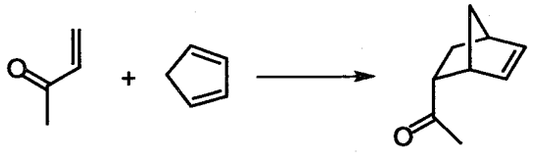
2. Organic Reactions in Aqueous Media

Organic reactions are generally carried out in organic solvents. Little attention has been paid for reactions in aqueous media, although water is a cheap, inflammable and nontoxic solvent. This is mostly because (1) the majority of organic compounds does not dissolve in water, and (2) organometallic reagents that are employed for carbon-carbon bond formation are usually unstable in water. Despite these disadvantages, water has been attracting much attention as an appealing reaction medium in organic synthesis. Although excellent reviews for reactions in aqueous media were available,[37] interesting examples and very recent reports are described here.

In 1980, Breslow and Rideout found that the Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone was remarkably accelerated in water, although cyclopentadiene is almost insoluble in water (Scheme 29).[38] They attributed the rate enhancement to hydrophobic interaction. This report strongly promoted following new researches on modern organic reactions in aqueous media.[37] Other pericyclic reactions such as hetero-Diels–Alder reaction,[39] Claisen rearrangement,[40] and 1,3-dipolar cycloaddition reaction[41] were found to proceed faster in water

than those in organic solvents.

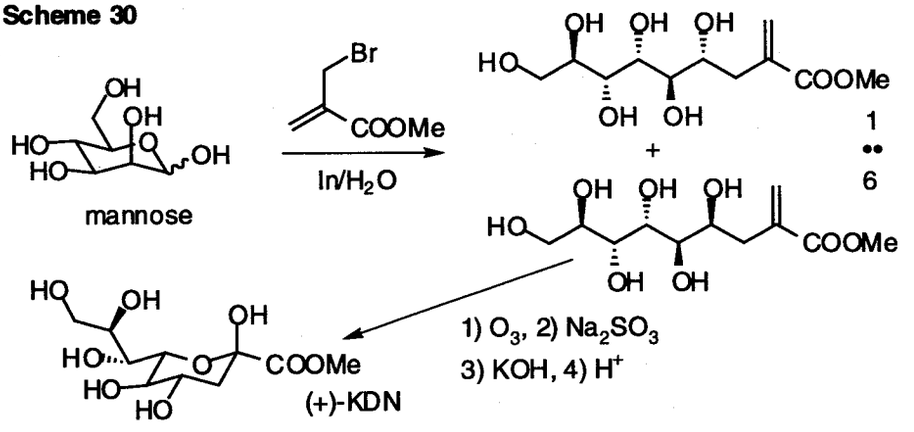
Scheme 29



solvent	Kinetics / $10^5 M^{-1}s^{-1}$
isooctane	5.94
methanol	75.5
water	4400

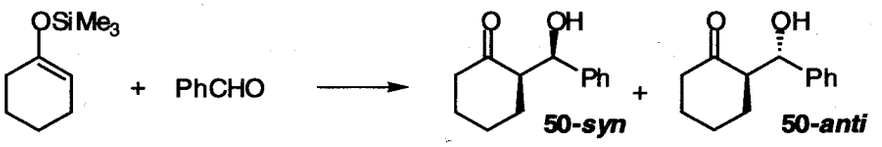
Metal-mediated reactions in aqueous media are not only possible but also powerful tools in organic synthesis. In 1983, Nokami and Otera reported that tin-mediated allylation of aldehyde was accelerated in the presence of water and hydrobromic acid.[42] Chan and Li found that allylation of carbonyl compounds with indium and allyl bromide in water proceeded smoothly.[43] Allylation with indium metal was applied to short synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) starting from allylation of unprotected mannose in water (Scheme 30).[44]

Scheme 30



Lubineau reported a noteworthy phenomenon in the Mukaiyama aldol reaction carried out in aqueous solvents without any acid catalyst.[45] The crossed aldol products **50** showed slight syn diastereoselectivity, which was the same as when this reaction was carried out in an organic solvent under high pressure (Scheme 31).

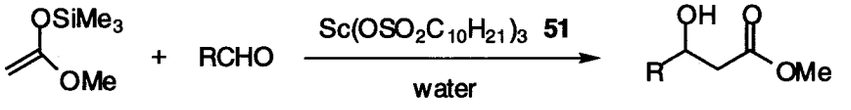
Scheme 31



Conditions	Yield, *syn/anti*
$TiCl_4$, CH_2Cl_2	82%, 25/75
10 kbar, CH_2Cl_2	90%, 75/25
Urtrasound, MeOH	30%, 57/43
Urtrasound, H_2O/THF	76%, 74/26

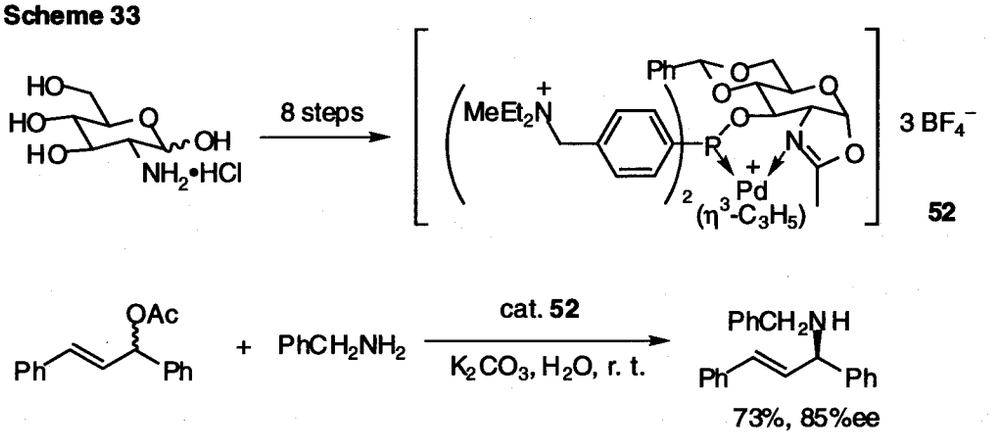
Lanthanide triflates are special Lewis acids that are active in the presence of water. Kobayashi has exploited lanthanide triflates as catalysts of the Mukaiyama aldol reaction in water.[46] His group also observed the acceleration of the reaction in the presence of a certain surfactant. Furthermore, he developed Lewis-acid-surfactant-combined catalysts such as **51** that enable aldol reaction of ketene silyl acetal in water (Scheme 32).[47]

Scheme 32



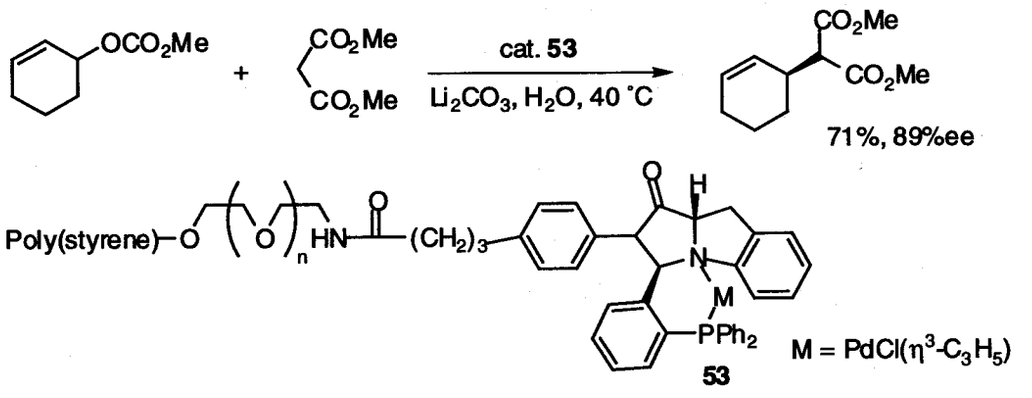
Uemura and Ohe developed an amphiphilic chiral ligand derived from D-glucosamine (Scheme 33).[48] This ligand was applied to palladium-catalyzed asymmetric allylic substitution reaction in an aqueous medium as well as in an organic medium. This catalytic system allows recycling of the catalyst by simple extraction procedure.

Scheme 33



On the other hand, Uozumi has reported an alternative approach, a resin-supported amphiphilic *P, N*-chelate chiral ligand (Scheme 34).[49] The palladium complex **53**, immobilized by the ligand, catalyzed asymmetric allylic substitution in water. The catalyst could be recovered by filtration and could be reused without loss of catalytic activity.

Scheme 34



As above, water as a solvent or a cosolvent dramatically enhances reaction rates or changes a reaction path in some concerted reactions and ionic reactions. However, the solvent effect of water is complicated to reveal clearly due to its unique character such as very strong hydrogen bonds. Water is therefore expected to offer undisclosed interesting, dramatic and useful solvent effects and remains to be studied as a reaction medium.

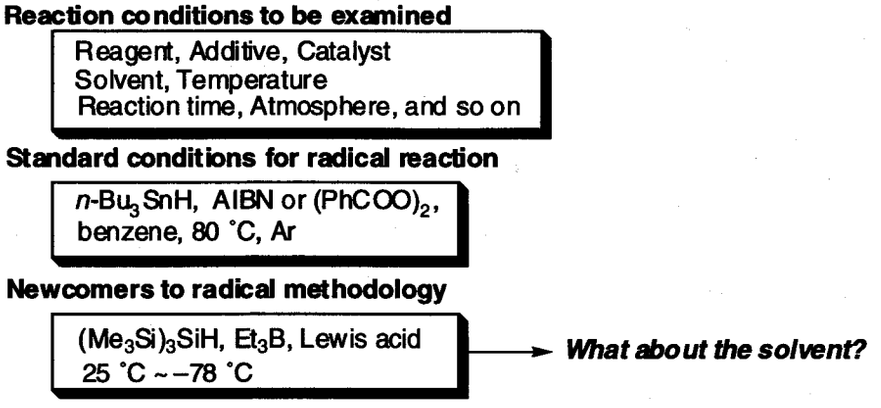
3. Radical Reactions in Aqueous Media

3.1 Introduction

In order to achieve efficient radical reaction, it is important to examine the reaction conditions, including reagents, temperature, and additives (Scheme 35). The development of organomercury and organotin methods has led to dramatic changes in synthetic organic chemistry.[50] After the finding of these radical mediators, radical reaction has become a useful and versatile methodology for carbon-carbon bond formation, and we organic chemists began to consider that radical reactions were controllable. A variety of radical mediators are now available in accordance with the type of the reaction.[51] For instance, tris(trimethylsilyl)silane is preferable to tributyltin hydride for intermolecular reductive radical addition reaction to avoid direct reduction of organic halide.[52]

Reaction temperature, often discussed in conjunction with the initiator to be used, is an important variable in controlling radical reaction. The triethylborane/oxygen initiation system[5] offers lower reaction temperature and milder reaction conditions than the conventional initiation with AIBN or peroxide. Reaction at low temperature results in improvement in yields and selectivities. Systems at lower temperature are also advantageous when a Lewis acid is employed, especially for stereoselective radical reaction.[53] Use of a Lewis acid in free radical reaction was surprising because of the neutral nature of radicals.

Scheme 35



The choice of a solvent, which is crucial for controlling ionic reaction, had been mostly neglected in radical reaction. Benzene is a standard solvent for radical reaction because of the absence of easily transferable hydrogen. The accepted wisdom that most radical reactions show small solvent effects has been widespread.[54] Some organic chemists who were interested in basic study focused on the influence of the solvent on radicals,[55] and many synthetic chemists accepted the standard solvent system.

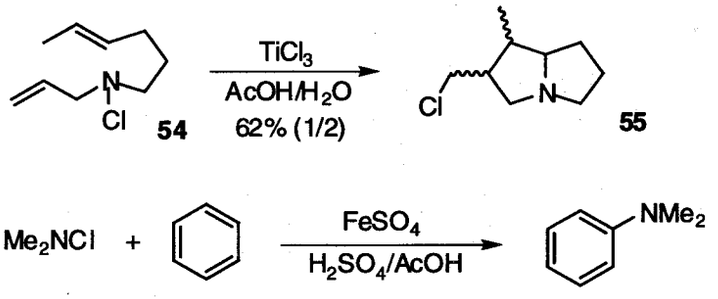
Water has special physical properties, and has therefore provided fascinating solvent effects in conventional ionic reactions such as the S_N1 reaction. In 1982, the solvent effect of water on the Diels-Alder reactions, a concerted reaction, was discovered.[38] Since then, reactions in aqueous media have attracted much attention from the economical, environmental, and scientific points of view.[37]

Free radical is a highly reactive species that can homolytically cleave a carbon-hydrogen bond some cases. However, radical, especially carbon-centered one, hardly reacts with water under the usu

reaction conditions because an oxygen-hydrogen bond has a larger bond energy than an sp^3-carbon–hydrogen bond. Thus, radical reactions in aqueous media would be carried out easily without side reactions of radical species with water. However, synthetic radical reactions in aqueous media had been scatteringly investigated.

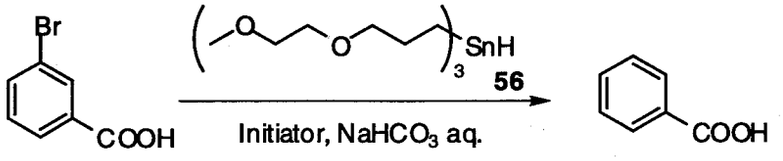
Minisci and Stella reported that nitrogen-centered radical adds to a carbon-carbon multiple bond in acidic media (Scheme 36).[56]

Scheme 36



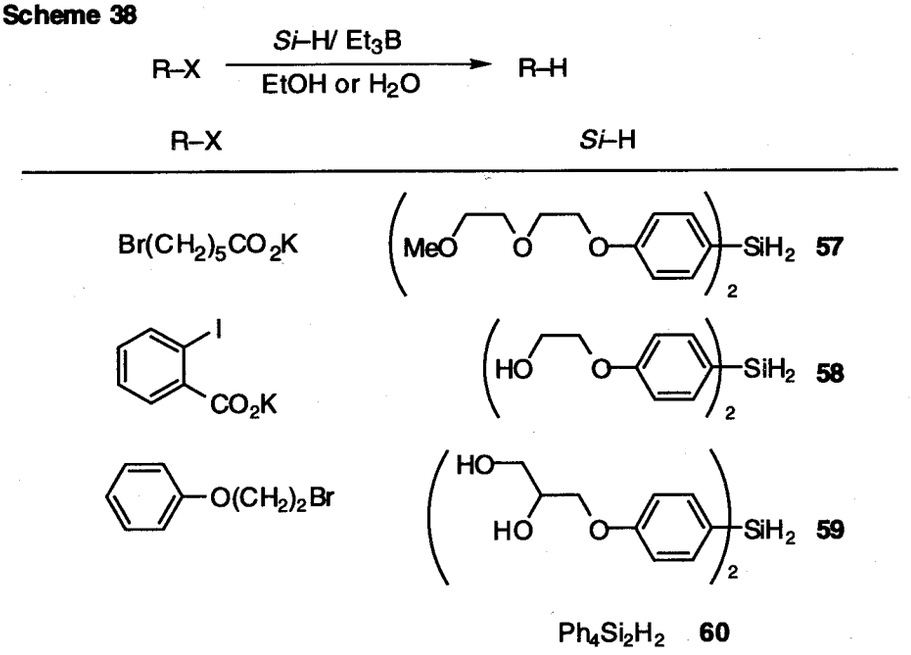
Breslow developed a water-soluble tin hydride reagent **56**, although its use was quite limited (Scheme 37).[57] Reduction of organic halides with tributyltin hydride in water was possible, in which no solvent effect was observed.[58]

Scheme 37



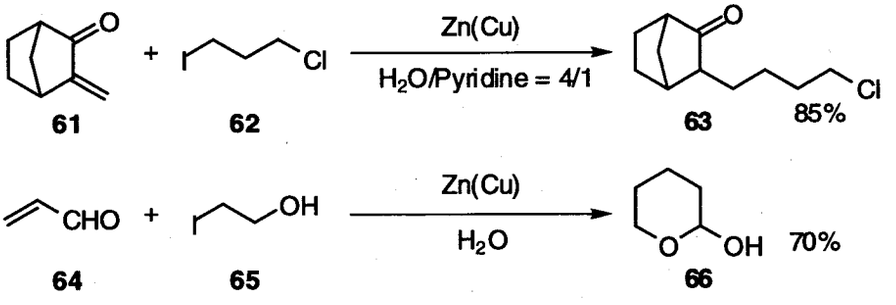
Togo and Yokoyama demonstrated Et_3B-initiated radical reaction with water-soluble organosilanes **57–59** in ethanol or an aqueous medium.[59] Although aryl bromide was hardly reduced, alkyl iodide, bromide, and aryl iodide were converted to the corresponding hydrocarbons in aqueous media. They mentioned that Et_3B was superior to AIBN since AIBN could not initiate the reduction with organosilanes. They also developed 1,1,2,2-tetraphenyldisilane (**60**), which forms stable crystals under aerobic conditions, and radical reduction of alkyl bromide with **60** was examined in ethanol from the ecological and practical points of view (Scheme 38).[60]

Scheme 38



Sonication of alkyl iodide in the presence of zinc copper couple could generate alkyl radical in aqueous media, which led to conjugate addition to α,β-unsaturated carbonyl compound.[61] The reaction could be used for addition of functionalized alkyl groups such as **62** and **65** (Scheme 39).[62]

Scheme 39



The author anticipated interesting solvent effects of water on radical reaction and began to develop radical reactions of synthetic use in aqueous media in 1997. Various concerns to be solved confronted him. Which types of reaction can be carried out, and which should be chosen to attain the stimulating solvent effects on radical reactions? Which initiator can act efficiently in an aqueous medium? Should the reaction system be homogeneous? Are protic media compatible with labile functional groups? Going over these difficulties, the author concluded that the solvent, including water, plays a crucial role also in radical reaction, and that, by changing the

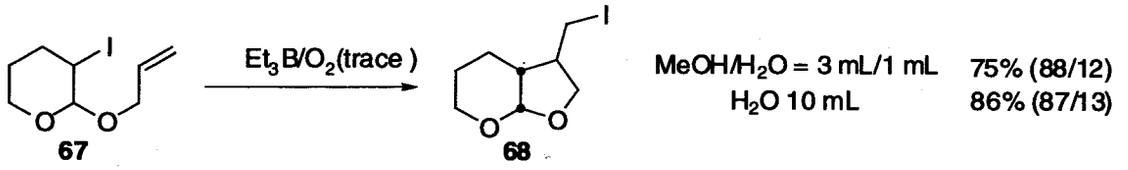
solvent used, the efficiency and the path of radical reaction are controllable. In conducting radical reaction, water is not only an environmentally sound reaction medium but also a preferable solvent utilizing its extreme polarity and strong hydrogen bonding ability. Here the author wishes to summarize the results of his study on radical reaction in aqueous media.

3.2 Triethylborane-Induced Iodine Atom Transfer Radical Cyclization of Iodo Acetals and Allylic Iodoacetates in Aqueous Media (Chapter 1)

At the beginning of this project, it was necessary to choose the initiator to be employed. Triethylborane seemed the most attractive to avoid conceivable solvolysis of substrates and products because triethylborane-induced reactions can be performed at ambient temperature. To explore the nature of water as a solvent, a methanol solution of triethylborane was considered as a suitable initiator for its easy handling as well as for minimizing the influence of an additional solvent. The author was initially anxious about the stability of triethylborane in methanol. Trialkylboranes are said to be stable in a protic medium, except in carboxylic acids, whereas triethylborane is well known for spontaneous ignition on exposure to air. It was doubtful that triethylborane, a very flammable liquid, could be safely diluted with methanol. Fortunately, a methanol solution of triethylborane was able to be safely prepared under argon. The stability of triethylborane in methanol was checked by examination of the ^1H NMR of a CD_3OD solution of triethylborane. The solution worked as well for a few months or longer when stored under argon atmosphere.

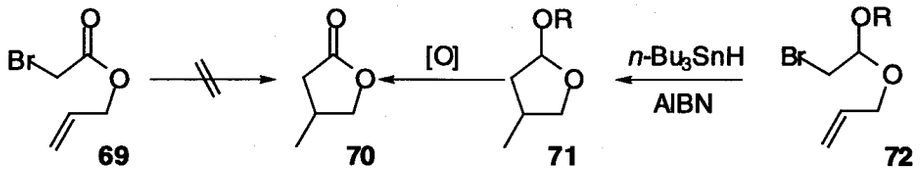
The author set iodine atom transfer radical cyclization[63] of iodo acetals in aqueous methanol as the first trial since the system was homogeneous and tin-free (Scheme 40). Iodo acetal **67** was dissolved in aqueous methanol, and triethylborane in methanol was added to the homogeneous solution to afford the corresponding tetrahydrofuran derivative **68** in good yield. This success prompted him to perform this reaction in water, in which a heterogeneous reaction medium was formed. A similar reaction in water provided **68** in a comparable yield. It was confirmed that radical reaction could be performed in water, irrespective of the heterogeneity of the reaction.

Scheme 40



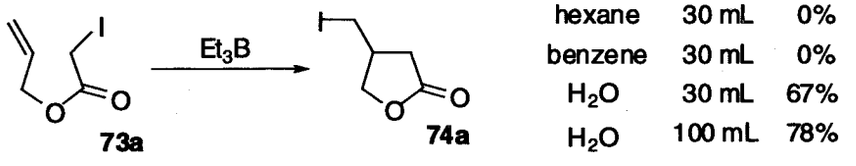
The author's attention moved to atom transfer radical cyclization of allyl iodoacetate. The indirect halo acetal method was developed by Stork and Ueno[64] because direct cyclization of α-halo esters **69** into γ-butyrolactones **70** is an inefficient process. Lactones **70** are usually synthesized by means of this strategy, by oxidation of the products **71** prepared from radical cyclization of bromo acetal **72** (Scheme 41).

Scheme 41

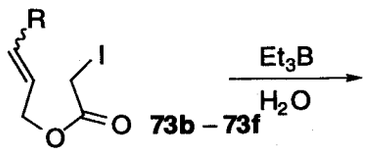


Indeed, treatment of allyl iodoacetate (**73a**) with triethylborane in benzene or hexane at room temperature yielded no lactone **74a** (Scheme 42). The iodide was consumed, and polymeric products were formed. In contrast, in water, **73a** cyclized much more smoothly in the presence of triethylborane at ambient temperature, and yielded lactone **74a** in high yield. The yield of **74a** increased at lower concentration. This powerful solvent effect also operated in a related system (Scheme 43). Crotyl iodoacetate (**73b**) and 2-pentenyl iodoacetate (**73c**) provided the corresponding lactones **74b** and **74c**, respectively, in satisfactory yields. In contrast, iodoacetates **73e** and **73f**, which have longer alkyl substituents such as propyl and decyl groups on the terminal olefinic carbon, afforded the corresponding lactones in very poor yields.

Scheme 42



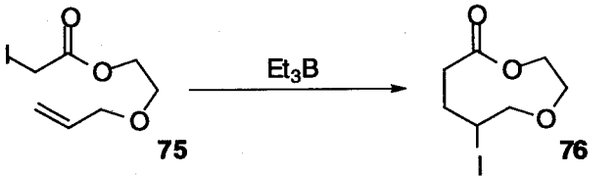
Scheme 43



b: R = Me (77%) **c**: R = Et (72%) **d**: R = CH_2OH (89%) **e**: R = *n*-Pr (18% (70% **73e**)) **f**: R = *n*-$C_{10}H_{21}$ (0% (99% **73f**))

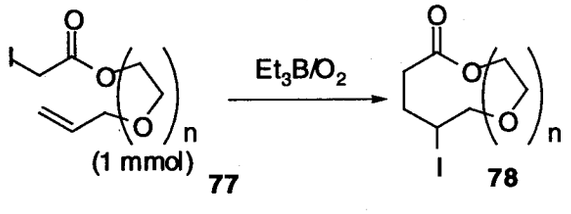
Construction of medium and large rings via a radical process is challenging work.[65] Preparation of medium-ring lactones was next examined (Scheme 44). Treatment of α-iodo ester **75** with triethylborane in water provided nine-membered lactone **76** in 69% yield. Conversely, the atom transfer cyclization reaction of **75** in benzene afforded the corresponding lactone in only 27% yield. Additionally, water as a reaction solvent strikingly promoted the cyclization of a large-membered ring (Scheme 45). Stirring a solution of **77a** in water in the presence of Et_3B at 25 °C provided a 12-membered ring **78a** in 56% yield. In contrast, the reaction in benzene afforded **78a** in only 22% yield, along with the recovered starting material **77a**. It was assumed that a hydrogen bond to oxygen in the carbonyl group would be formed to activate the (alkoxycarbonyl)methyl radical and that hydrophobic interaction may also accelerate the cyclization.

Scheme 44



MeOH	20 mL	0%
hexane	20 mL	10%
benzene	100 mL	23%
H_2O	20 mL	33%
H_2O	100 mL	69%

Scheme 45



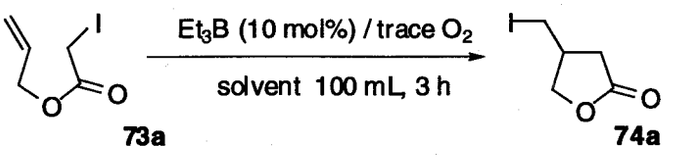
		benzene 20 mL	water 20 mL
77a	n = 2	10 h, 22% (78%) [a]	10 h, 56%
77b	n = 3	3 h, 41% (43%) [a]	3 h, 75%
77c	n = 4	6 h, 14% (83%) [a]	6 h, 70%

a) Starting material was recovered.

To investigate the solvent effect on the radical cyclization of allyl iodoacetate in detail, the cyclization was examined in various solvents (Table 1). Polar solvents such as DMSO, DMF, or

CH_3CN yielded the lactone in better yield than nonpolar solvents, that is, benzene, hexane, and dichloromethane. More interestingly, water was found to be an outstanding solvent among these solvents, even taking the polar nature of water into account.

Table 1. Radical Cyclization of Allyl Iodoacetate in Various Solvents



73a **74a**

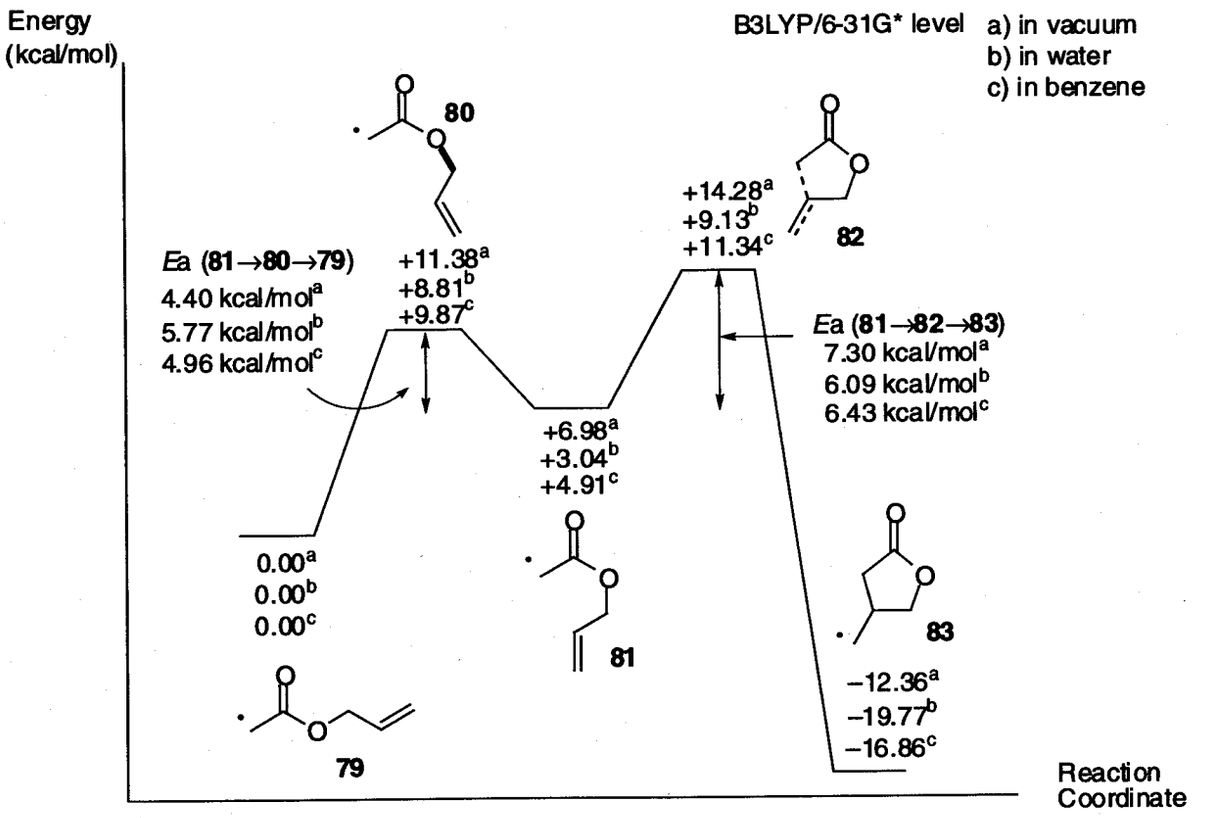
Solvent	Yield/%	Dielectric constant
water	78	78.39
DMSO	37	46.45
DMF	13	36.71
acetonitrile	13	35.94
methanol	6	32.66
THF	<1	7.58
dichloromethane	<1	8.93
benzene	<1	2.27
hexane	<1	1.88

To clarify the origin of the solvent effect, the author carried out ab initio calculations on the cyclization of the (allyloxycarbonyl)methyl radical (Scheme 46). The calculations in vacuum disclosed that the cyclization of allyl iodoacetate is difficult because (1) *E*a(**79**→**80**→**81**) is large for the short-lived **79** to surmount the barrier to rotation smoothly; (2) *E*a(**81**→**82**→**83**) is larger than *E*a(**81**→**80**→**79**); (3) The lifetime of radical species **79** and **81** is too short to allow cyclization, because competitive intermolecular radical addition occurs. The results shown in Table 1 imply that the use of water as a solvent could overcome these difficulties.

The calculations also revealed that the net dipole moment of the radical species increases, in particular, as the rotation of the ester bond proceeds. Hence, it is assumed that polar solvents probably promote the overall cyclization reaction. To confirm this assumption, polarized-continuum-model calculations using the polarizable conductor calculation model based on the self-

consistent reaction field theory (SCRF/CPCM)[66] were performed on the cyclization of the (allyloxycarbonyl)methyl radical to estimate how **79–83** are stabilized in continuum with the dielectric constant as a modeled solvent. The results are as expected; that is, a more polar solvent favors the reaction path leading to the cyclized form **83**. Cyclization from **81** to **83** is almost as fast as the undesirable rotation from **81** to **79** is in water, whereas the former is much slower than the latter in benzene. As depicted in Scheme 46, it becomes clear that the large dielectric constant of water promotes both rotation from **79** to **81** and cyclization from **81** to **83**. However, these calculations could not explain the extraordinary solvent effect of water. The SCRF theory is probably so rudimentary that the calculations could not describe the complex phenomena in this aqueous reaction, arising from the special physical property of water that comes from its strong hydrogen bond.

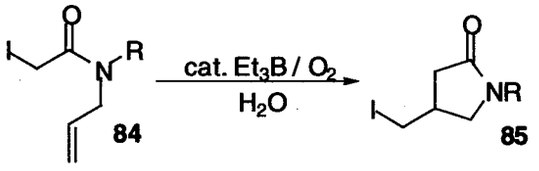
Scheme 46



3.3 Iodine Atom Transfer Radical Cyclization of *N*-Allyl-2-Iodo Amides in Water[67]

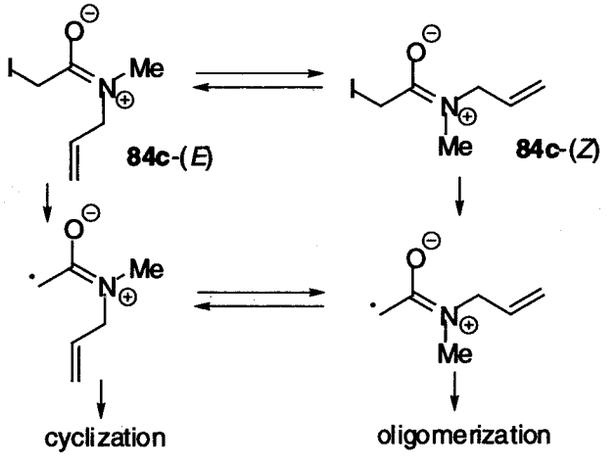
The author next dealt with synthesis of γ-lactam adopting a similar strategy (Scheme 47). *N,N*-Diallyl-2-iodoacetamide (**84a**) underwent atom transfer radical cyclization smoothly to give β-iodomethyl-substituted γ-lactam **85a**. On the other hand, reaction of *N*-methylsulfonyl amide **84b** in water proceeded more slowly compared to the reaction of **84a**. Treatment of *N*-allyl-*N*-methyl amide **84c** with Et_3B gave **85c** in poor yield along with the starting material (72% recovery). Contrary to expectations, no solvent effect of water was observed in these reactions. The low yield of the reaction of **84c** might be ascribed to the preferential existence of the disfavored conformation for cyclization (Scheme 48). In this case, water does not provide a powerful solvent effect. Interestingly, the use of 0.1 M HCl solution in place of water improved the yield of the cyclized product (Scheme 47).

Scheme 47



85a (R = $CH_2CH{=}CH_2$) 1 h, 89%
85b (R = CH_3SO_2) 8 h, 77% (92% in 0.1 M HCl)
85c (R = CH_3) 18 h, 22% (72% of **84c**)

Scheme 48

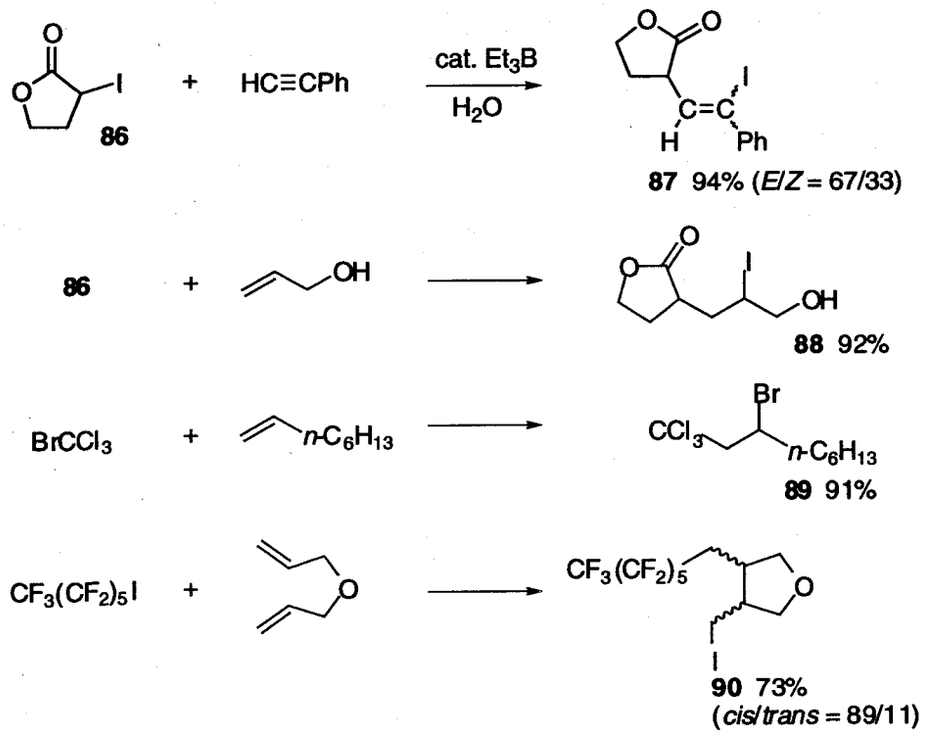


3.4 Atom Transfer Radical Addition of Halogenated Compounds in Water[68]

The next target was intermolecular addition of halogenated compounds to carbon-carbon multiple bonds. Triethylborane effected radical addition of α-iodo lactone **86** to phenylacetylene

in water. Adduct **87** was obtained quantitatively (Scheme 49). It is worth noting that the reactions in water were much more effective compared to the reactions without solvent (**87**, 32%, 3days). Here again, the solvent effect worked. This addition reaction proceeded in various acidic and basic aqueous solutions as aforementioned in the synthesis of γ-lactam.

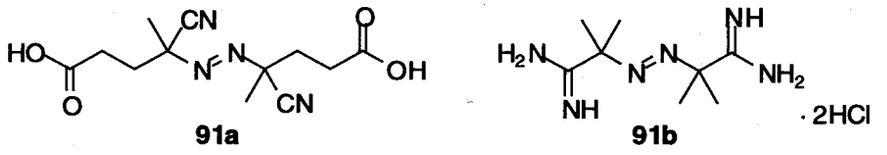
Scheme 49



3.5 Radical Addition of Iodoacetamide to Alkenes with a Water-Soluble Radical Initiator in an Aqueous Medium: Facile Synthesis of γ-Lactones (Chapter 3)

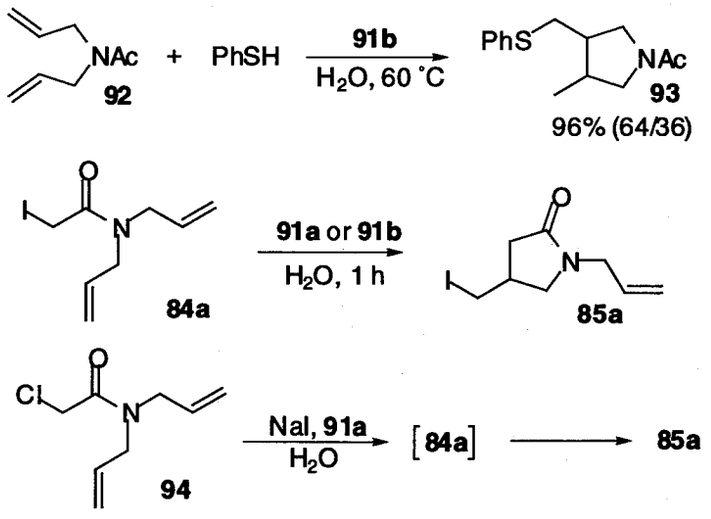
Triethylborane proved to work as a radical initiator in aqueous media. On the other hand, water-soluble radical initiators are commercially available. The soluble initiators are mostly employed for polymerization, and have scarcely been used in organic synthesis. Here the utility of water-soluble azo initiators is described, especially two initiators; 4,4'-azobis(4-cyanopentanoic acid) (ACPA, **91a**) and 2,2'-azobis(isobutyramidine) dihydrochloride (AIBA, **91b**).

Scheme 50



First, radical addition of benzenethiol to carbon-carbon multiple bonds was examined (Scheme 51). All the experiments, including the reaction of **92**, were successful in water, although no significant difference was observed between the reactions in water and those in benzene. These radical initiators were highly effective for the atom transfer radical cyclization of 2-iodo amide **84a** in water. Furthermore, *N,N*-diallyl-2-chloroacetamide (**94**) could be used as a starting material in the presence of sodium iodide, instead of the corresponding iodide **84a**.[67] The reaction proceeded via tandem ionic nucleophilic displacement and radical cyclization. The effectiveness of **91a** and **91b** as initiators in water was confirmed in these experiments.

Scheme 51



The success of intramolecular radical cyclization of 2-iodoalkanamide encouraged to investigate intermolecular radical addition reaction. Consequently, it was found that addition of 2-iodoacetamide (**95**) to alkenol in water afforded γ-substituted γ-lactone **97**, not 4-iodo amide (Scheme 52). The reaction would proceed as follows: Radical **98**, derived from **95**, adds readily to alkenol **96a** to provide **99**. The iodine atom transfer reaction between the radical **99** and **95** affords 4-iodo amide **100** and regenerates **98**. The compound **100** cyclizes to yield γ-lactone **97a** via **101**

under the reaction conditions. Alcohol, having a terminal alkene moiety, was converted into the corresponding lactone in excellent yield (Table 2). 1-Octene did not furnish lactone under the same reaction conditions because of the insolubility of 1-octene in water. The difficulty in using hydrophobic alkene could be overcome when the initiator **91b** was used in aqueous ethanol. It is noteworthy that ethanol itself as a solvent diminished the yield. As illustrated in Scheme 53, a mixture of iodoacetonitrile (**102**) and **96b** was treated with **91a** to afford the anticipated tetrahydrofuran derivative **103**.

Scheme 52

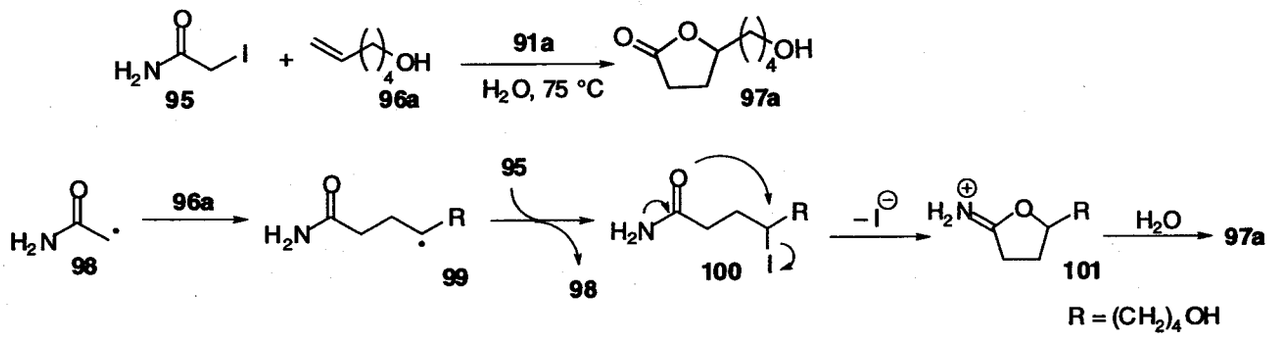
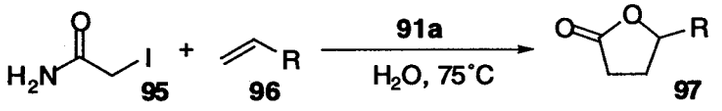


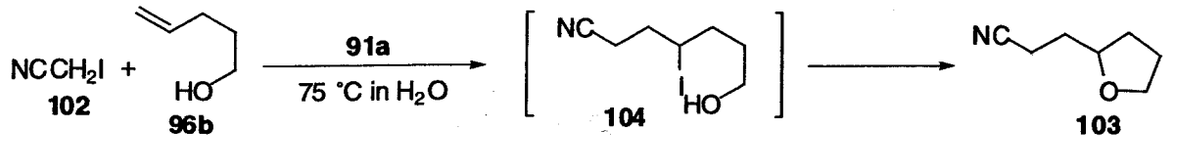
Table 2. γ-Lactone Synthesis by Tandem Radical-Ionic Reaction between 2-Iodoacetamide and Alkene.



R in alkene	Yield /%
96a: $(CH_2)_4OH$	**97a:** 95
96b: $(CH_2)_3OH$	**97b:** 85
96c: CH_2OH	**97c:** 88[a]
96d: $CH_2O(CH_2)_2O$-*i*-Pr	**97d:** 84
96e: *n*-C_6H_{13}	**97e:** 83[b]

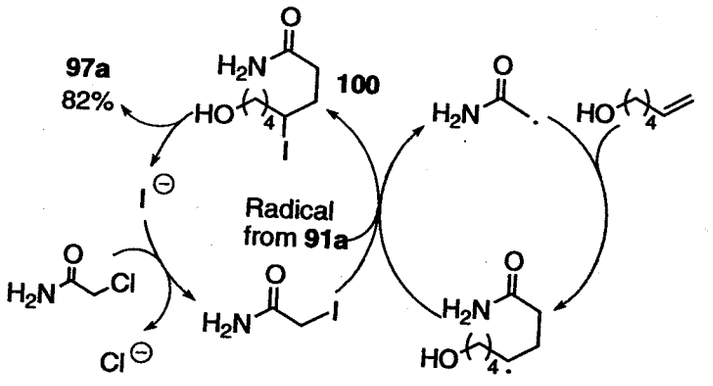
a) Three equiv. of **96c**. b) Reaction was performed in aqueous ethanol. The initiator was **91b**.

Scheme 53



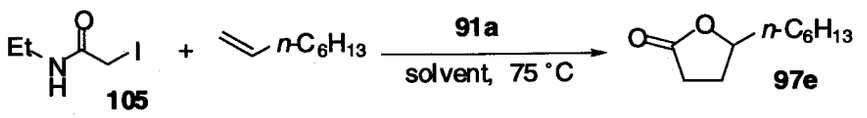
Iodide was liberated in the transformation of **100** into **97**. Thus, it was anticipated that, by adding a catalytic amount of sodium iodide, use of 2-chloroacetamide instead of the iodo amide **95** would provide **97**. It was indeed found that the radical-ionic tandem reaction of 2-chloroacetamide with 5-hexen-1-ol proceeded smoothly in the presence of substoichiometric amount of NaI, as shown in Scheme 54.

Scheme 54



The reaction of *N*-ethyl-2-iodoacetamide (**105**) with 5-hexen-1-ol in water afforded **97a** in 75% yield. On the other hand, surprisingly, the reaction did not proceed at all in refluxing benzene, and **105** was almost completely recovered (Table 3). Benzene, THF, CH_2Cl_2, and acetonitrile were ineffective for the synthesis of the lactone. In each case, **105** was recovered, that is, the radical addition step itself did not take place. Employment of protic solvents, such as ethanol and methanol, led to low conversion to furnish γ-decanolactone (**97e**) in 14% and 26% yields, respectively. Water or aqueous ethanol was found to be the best for this reaction.

Table 3. Reaction in Various Solvents



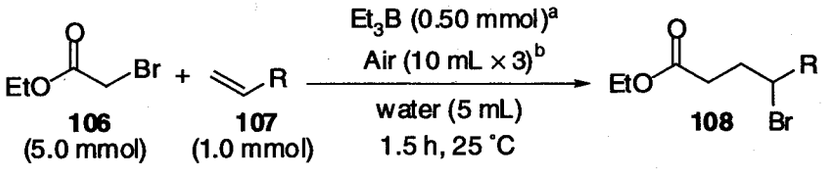
Solvent	Time/h	yield of **97e**/%	Recovered **105**/%
benzene[a]	16	0	97
THF[a]	24	0	89
dichloromethane[a]	24	0	100
acetonitrile	24	0	100
methanol[a]	40	26	68
ethanol	40	14	77
water[b]	16	75	0

a) Reflux. b) 5-Hexen-1-ol was used. The product was **97a**.

3.6 Triethylborane-Induced Bromine Atom Transfer Radical Addition in Aqueous Media: Study of the Solvent Effect on Radical Addition Reaction (Chapter 2)

Iodine atom transfer from α-iodo ester or amide to a radical generated by the addition is facile and very fast, thereby suppressing side reactions. In contrast, bromine atom transfer is not so easy compared to the iodine atom transfer because a Br–C bond is stronger than an I–C bond. The addition of α-bromo esters to alkenes usually requires high reaction temperatures with the aid of explosive peracetic acid.[69] During the course of study on intermolecular radical addition reaction, it was found that bromine atom transfer radical addition of α-bromoacetate to 1-alkene in water could proceed at ambient temperature in the presence of a substoichiometric amount of triethylborane to yield 4-bromoalkanoate **108** (Table 4). A variety of terminal alkenes participate in the addition reaction in water. The reaction mixture was heterogeneous yet clear. Other reactive bromides such as bromomalonate and bromoacetonitrile undergo the radical addition in similar fashion.

Table 4. Triethylborane-Induced Radical Addition of Ethyl Bromoacetate to Alkenes in Water



Entry	107	R	108	Yield/%
1	**107a**	*n*-C_6H_{13}	**108a**	80[c]
2	**107b**	*n*-$C_{20}H_{41}$	**108b**	79[c,d]
3	**107c**	$(CH_2)_4OH$	**108c**	81
4	**107d**	$(CH_2)_3Br$	**108d**	63
5	**107e**	$CH_2CH_2COCH_3$	**108e**	84

a) 1.0 M ethanol solution. b) Air was added every 30 min. c) Additional triethylborane (0.50 mmol) was added 1 h after the reaction started. d) The mixture was cloudy during the reaction.

To reveal the origin of the solvent effect, the bromine atom transfer reaction was examined in various solvents (Table 5). The yields of **108a** were extremely low when hydrocarbons, halogenated solvents, and ethers were employed (entries 1–5). The use of polar aprotic solvents such as acetonitrile, DMF, and HMPA gave rise to remarkable improvement in yield (entries 6–11). In general, the more polar solvent tends to provide **108a** in higher yield in the case of aprotic solvents. The addition proceeded moderately in alcohols (entries 12–16). Interestingly, 2,2,2-trifluoroethanol was highly effective for this addition reaction, whereas **108a** was obtained in only 35% yield when ethanol was used. The high yield would be attributed to the acidity of 2,2,2-trifluoroethanol (vide infra). In water, treatment of a mixture of **106** and **107a** with an ethanol solution of triethylborane provided **108a** in 70% yield under the same reaction conditions. Moreover, the reaction without any solvent led to poor conversion. Thus, the addition reaction in water, which always forms a heterogeneous system, is not the same as a solvent-free reaction in an organic phase, and water clearly plays a critical role as a solvent.

Table 5. Triethylborane-Induced Radical Addition of **106** to **107a** in Various Solvents[a]

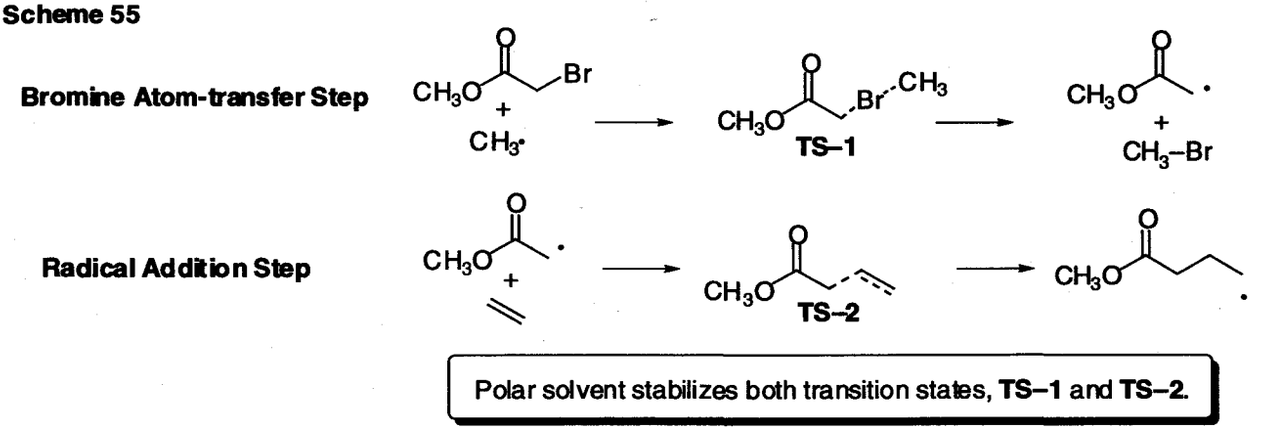
Entry	Solvent	Yield of **108a** /%	Dielectric constant
1	hexane	10	1.88
2	benzene	12	2.27
3	dichloromethane	9	8.93
4	ether	10	4.34
5	THF	4	7.58
6	acetone	15	20.56
7	ethyl acetate	18	6.02
8	DMF	67	36.71
9	acetonitrile	44	35.94
10	HMPA	48	29.30
11	DMSO	72	46.45
12	methanol	36	32.66
13	ethanol	35	24.55
14	isopropyl alcohol	35	19.92
15	*t*-butyl alcohol	48	12.47
16	TFE[b]	73	26.67
17	water	70	79.39
18	no solvent	12	

a) **106** (5.0 mmol), **107a** (1.0 mmol), triethylborane (0.50 mmol) and solvent (5 mL) were employed. Air (5 mL × 2) was added every 30 min. Reaction time was 1 h. b) 2,2,2-Trifluoroethanol.

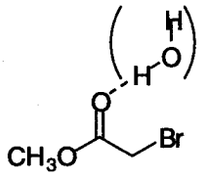
The author felt it quite important to get a reasonable explanation of these observations since the addition reaction is a fundamental reaction. Ab initio calculations were thereby conducted to rationalize the solvent effect on the addition reaction (Scheme 55). The calculations showed that a polar solvent tends to lower the relative energies of the transition states. The polar effect of solvents, which is judged by the dielectric constant, on the transition states in the bromine atom transfer and the radical addition steps proved to be moderately important. Moreover, the coordination of a carbonyl group to proton in a protic solvent, like a Lewis acid, would also increase the efficiency of the chain propagation (Scheme 56). In the bromine atom transfer step, the coordination lowers the LUMO level of methyl bromoacetate and promotes electron transfer from methyl radical to methyl bromoacetate. Furthermore, in the radical addition step, water

effects a lowering of the SOMO level of (methoxycarbonyl)methyl radical and promotes electron transfer from ethylene to the radical.

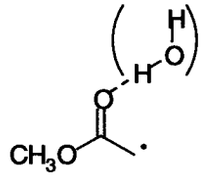
Scheme 55



Scheme 56



	Energy of **TS-1**	LUMO Level
without H_2O	15.43 kcal/mol	3.041 eV
with H_2O	14.73 kcal/mol	2.907 eV
	lower by 0.70 kcal/mol	lower by 0.134 eV



	Energy of **TS-2**	SOMO Level
without H_2O	14.68 kcal/mol	–11.203 eV
with H_2O	14.17 kcal/mol	–11.281 eV
	lower by 0.51 kcal/mol	lower by 0.078 eV

(MP2/6-31G**//B3LYP/6-31G*)

3.7 Reduction of Organic Halides with Tri-2-Furylgermane in Water[14b]

The author has been interested in not only water as a replacement of organic solvents, but also the development of alternatives to toxic tributyltin compounds from the environmental point of view. To this end, tri-2-furylgermane (**109**) was prepared (Scheme 57).[57–59,70] It had been anticipated that tri-2-furylgermane would be soluble in water. However, the solubility was poorer than expected. Most of **109** remained floated on water when **109** (1.0 mmol) was added to water (10 mL). Luckily enough, in spite of the low solubility, reduction of both hydrophobic and hydrophilic organic halides proceeded smoothly in water (Table 6). For example, treatment of 1-bromododecane with tri-2-furylgermane in water provided dodecane in 89% yield under the

triethylborane initiation, although the system was heterogeneous. Trifurylgermane was fairly stable in water and could mediate the radical reduction at an elevated temperature in the presence of V-70 as a radical initiator in water (Method B, Table 6).

Scheme 57

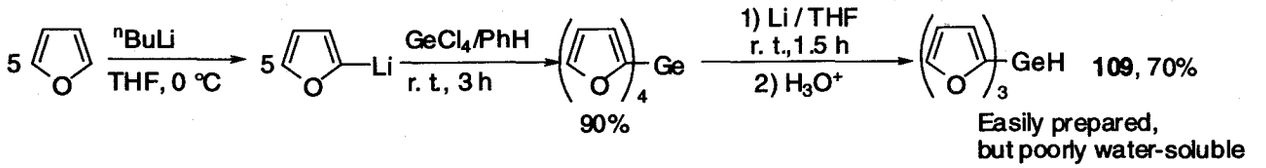


Table 6. Reduction of Organic Halides with Tri-2-Furylgermane in Water

Method A; Et_3B, 25 °C

Entry	R-X	Time/min	Yield/%
1	*n*-$C_{12}H_{25}I$	5	85
2	*n*-$C_{12}H_{25}Br$	25	89
3	*n*-$C_{10}H_{21}CH(Br)CH_3$	15	83
4	1-Bromoadamantane	20	92

Method B; V-70, 80 °C [V-70: 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)]

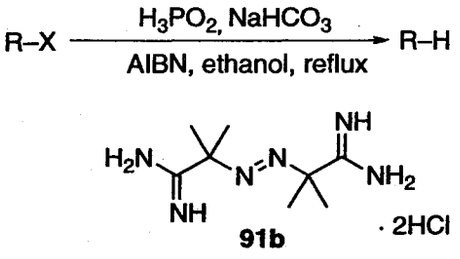
Entry	R-X	Time/h	Yield/%
1	*n*-$C_{12}H_{25}Br$	0.5	83
2	*n*-$C_{10}H_{21}CH(Br)CH_3$	0.33	82
3	$PhCOO(CH_2)_3Br$	1	99
4	$HO(CH_2CH_2O)_3CH_2CH_2I$	1	97
5	*c*-$C_{12}H_{23}OC(=S)SCH_3$	0.5	63

3.8 Radical Reaction by a Combination of Phosphinic Acid and a Base in Aqueous Media: Reduction and Deuteration (Chapter 4)

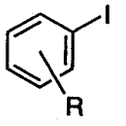
Barton's group developed phosphinic acid (hypophosphorus acid) as a cheap, much less toxic, and easily removable chain carrier in various types of reductions.[71,72] However, they carried out the reactions in benzene or dioxane at reflux. Moreover, they tried to remove water in the reaction mixture to avoid hydrolysis of the substrates, and developed crystalline 1-ethylpiperidine hypophosphite as an anhydrous mediator. The author's interest was directed toward radical reduction with phosphinic acid, and he decided to utilize phosphinic acid in aqueous media.

Reduction with phosphinic acid in water was already reported.[73] However, the substrates examined were limited to only water-soluble compounds. To extend the scope and limitations, the reduction of various organic halides was studied in aqueous ethanol (Scheme 58).[60] A wide range of functional groups was tolerant under the reaction conditions (H_3PO_2/$NaHCO_3$/AIBN/EtOH /reflux). In the case of acetate **110d**, the ester was partly hydrolyzed under the standard conditions, which was overcome by performing the reaction at room temperature with Et_3B as an initiator.

Scheme 58



91b

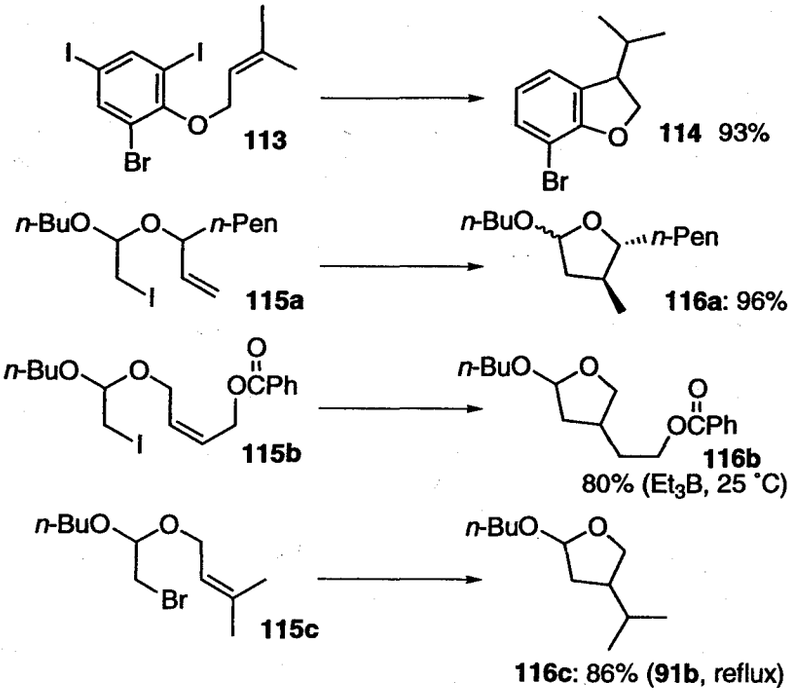


110a: R=*o*-CH_2OH
110b: R=*p*-COO-*n*-C_4H_9
110c: R=*o*-NO_2
110d: R=*o*-CH_2OCOCH_3 (Et_3B, 25 °C)

111: *n*-$C_{12}H_{25}Br$ (**91b**, reflux) **112**: *c*-$C_{12}H_{23}O(C=S)SCH_3$

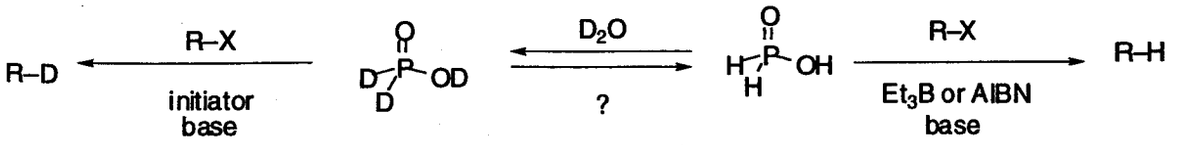
Allylic ether of *o*-iodophenol or 2-haloalkanal allylic acetal underwent radical cyclization under the same conditions to afford the corresponding cyclic product (Scheme 59).

Scheme 59



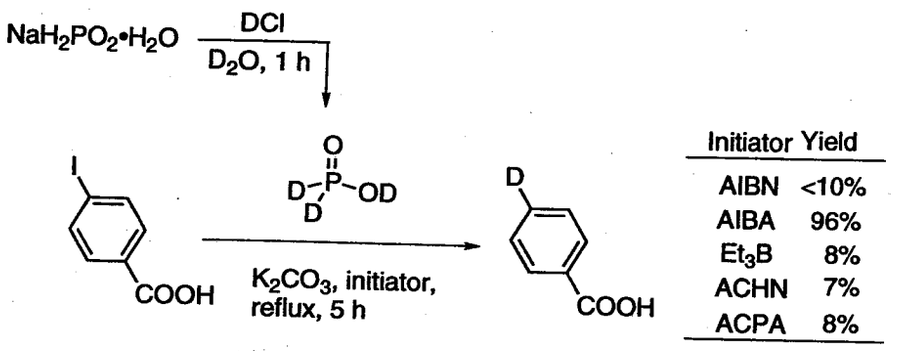
When this project using H_3PO_2 nearing completion, one simple idea occurred to the author. What will happen when the phosphinic acid-mediated reaction is performed in deuterium oxide in place of water? After deuterium exchange of the hydrogens on phosphorus with D_2O, the deuterated phosphinic acid can act as a chain carrier to provide a new method to introduce deuterium into organic compounds via a radical process (Scheme 60).

Scheme 60



After several attempts, it was found that deuterated phosphinic acid was formed from $NaH_2PO_2 \cdot H_2O$ upon treatment with DCl/D_2O (Scheme 61). Deuteration with this D_3PO_2 was achieved under the initiation with AIBA. Other radical initiators including AIBN and Et_3B were ineffective. After several successful experiments, the author found that D_3PO_2 was commercially available. The purchased D_3PO_2 was as effective as the reagent which was prepared from $NaH_2PO_2 \cdot H_2O$ and DCl/D_2O.

Scheme 61

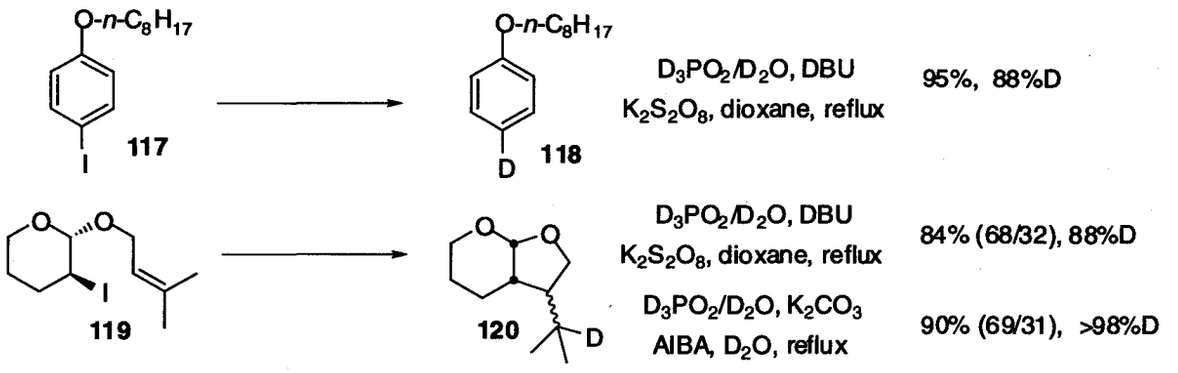


Initiator	Yield
AIBN	<10%
AIBA	96%
Et_3B	8%
ACHN	7%
ACPA	8%

Reduction of various hydrophobic organic halides in organic solvents was also explored (Scheme 62). The $D_3PO_2/DBU/K_2S_2O_8$/dioxane system was the most effective with respect to both the yield of the reduced products and the degree of deuterium incorporation. However, 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 to be abstracted under the usual radical conditions. To obtain higher deuterium incorporation, the reaction of **119** was

performed in D_2O without an organic cosolvent. Although a large amount of D_2O (0.3 mmol/10 mL) was necessary for the cyclization reaction, perfect incorporation of deuterium was achieved. D_3PO_2 is an attractive alternative to *n*-Bu_3SnD for radical deuteration of organic halides. In this case, D_2O proved to be the best solvent for quantitative labeling.

Scheme 62

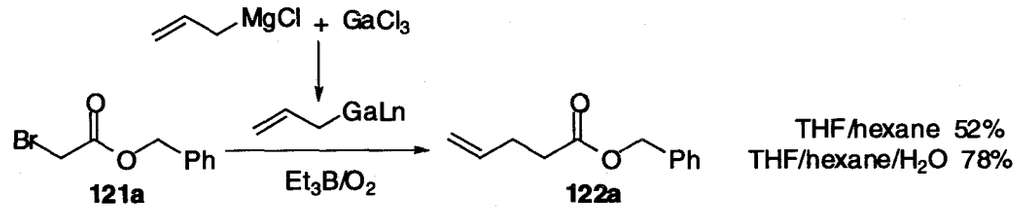


3.9 Triethylborane-induced Radical Allylation of α-Halo Carbonyl Compounds with Allylgallium Reagents in Aqueous Media[75]

Compared with the research for the replacement of tin hydride reagents, the development of other allylating reagents to replace allyltin compounds is still in its infancy. In connection with continuing studies on radical reaction in aqueous media, the author wanted to explore a new reagent for radical allylation in aqueous media. Consequently, an allylindium compound proved to be a good candidate for radical allylation because allylic indiums are stable in the presence of water.[43] The first attempt was indeed auspicious, and radical allylation of benzyl iodoacetate with an allylindium species proceeded smoothly in aqueous THF in the presence of triethylborane. The author soon turned his attention to an allylgallium reagent, whose compatibility with water was not known at that time. Fortunately, allylation of benzyl bromoacetate (**121a**) with the allylgallium reagent proceeded efficiently in aqueous THF to yield 4-pentenoate **122a** (Scheme 63). More interestingly, it was found that the addition of water as a cosolvent improved the yield of the allylated product. The origin of the favorable solvent effect would be owing to the polar nature of water and hydrogen bonding as described in Section 3.6. It is also probable that the structure of the allylgallium species would change and that the addition of water could increase the reactivity of

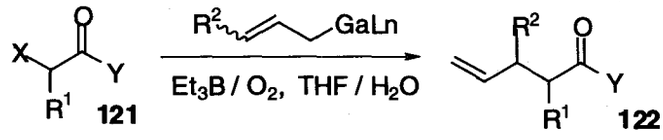
the allylgallium.

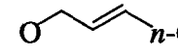
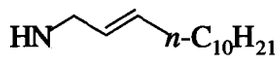
Scheme 63



Representative results of the radical allylation are shown in Table 7. The allylic gallium reagents have so low reactivity toward a carbonyl moiety that allylation of **121g** was accomplished without allylating the carbonyl moiety (entry 7). Reaction with the crotylgallium reagent afforded 3-methyl-4-pentenoate selectively (entries 8–10).

Table 7. Radical Allylation of α-Halo Carbonyl Compounds with Allylic Gallium Species

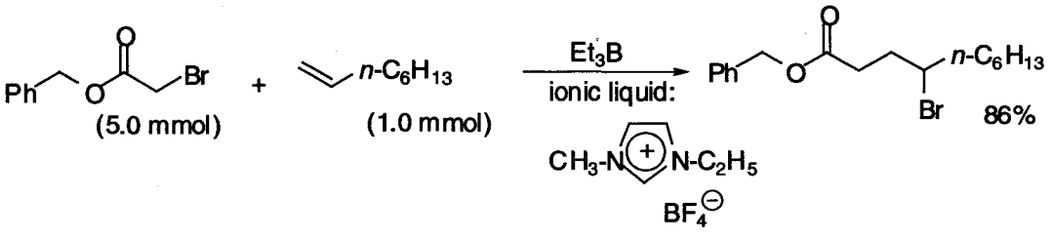


Entry		X	Y	R^1	R^2	Yield/%
1	**121a**	Br	OCH_2Ph	H	H	**122a:** 78
2	**121b**	Br	OCH_2Ph	Me	H	**122b:** 63
3	**121c**	Br	NMe_2	Me	H	**122c:** 64
4	**121d**	I	OCH_2Ph	Me	H	**122d:** 81
5	**121e**	I		H	H	**122e:** 95
6	**121f**	I	$OCH(Ph)CH_2CH{=}CH_2$	H	H	**122f:** 71
7	**121g**	I	$OCH(n\text{-}C_3H_7)CO n\text{-}C_3H_7$	H	H	**122g:** 84
8	**121h**	I		H	Me	**122h':** 85
9	**121i**	I	$O(CH_2)_6Cl$	H	Me	**122i':** 46
10	**121c**	Br	NMe_2	Me	Me	**122c':** 65 (d.r.=2/1)

3.10 Radical Reaction in Modern Solvent (Appendix)

Not only water but also modern solvents are attractive. Fluorous alcohols such as 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol, which have relatively acidic protons, are expected to activate carbonylmethyl radicals and α-halo carbonyl compounds through coordination of the carbonyl group to proton in fluorous alcohol (Chapter 2).[76] Increasing attention has also been paid to ionic liquids. It has been found that bromine atom transfer radical addition of ethyl bromoacetate to alkene proceeds as smoothly at ambient temperature in 1-ethyl-3-methylimidazolium tetrafluoroborate as in water (Scheme 64).

Scheme 64



3.11 Summary

In this thesis, some (mentioned above) of radical reactions in aqueous media are described. In each reaction, the extraordinary solvent effects of water were observed, although an effect of a reaction medium in radical reaction had been regarded to be quite small. We organic chemists have noticed an important variable in optimizing the reaction conditions of a radical reaction or in finding a new radical reaction. The success of a radical reaction examined heavily depends on the choice of a solvent. Among solvents, water can offer remarkable control of the radical reaction. Water as a reaction solvent strongly accelerates radical reactions or dramatically changes reaction paths. Accordingly, what the author is going to maintain here is not only the fact that water is an ecological solvent for radical reaction due to its non-toxicity, inflammability, and economical advantages. The author wishes this thesis to be a guide to using water as a potent reaction medium for radical reaction, furthermore, for other types of reactions where solvent effects of water have not been examined yet. The solvent effect of water leads to high efficiency of radical reactions, thereby offering a new fashion of organic reactions in the future. It is quite difficult to understand the solvent effects on organic reaction, especially radical reaction. Accumulation of

the results of radical reaction in aqueous media and comprehensive consideration of the results will guide chemists to finding environmentally benign processes and novel reactions and to an understanding of the solvent effects of water.

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Instrumentation and Materials

Distillation of the products was performed with Kugelrohr (Büchi), and boiling points are indicated by air-bath temperature without correction. Melting points were obtained on a Yanako MP–50929 melting point apparatus and are uncorrected. ^{1}H 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 are 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. Acetonitrile and acetone were dried with molecular sieves 3A. Dichloromethane, chloroform, DMF, and NMP were dried with molecular sieves 4A. Benzene, hexane, toluene, ether, and dioxane were dried over slices of sodium. Dimethyl carbonate, HMPA, DMSO were distilled from calcium hydride before use. THF was freshly distilled from sodium benzophenone ketyl prior to use. Distilled water was purchased from Wako Pure Chemicals. Et_3B was purchased from Aldrich Chemicals. Initiators ACPA and AIBA were purchased from Fluka Co.

Abbreviations

Ac	acetyl
ACHN	2,2'-azobis(cyclohexanecarbonitrile)
ACPA	4,4'-azobis(4-cyanopentanoic acid)
AIBA	2,2'-azobis(isobutyramidine) dihydrochloride
AIBN	2,2'-azobis(isobutyronitrile)
Bp	boiling point
BPO	benzoyl peroxide
bs	broad singlet
Bu	butyl
Bz	phenylcarbonyl
ca.	circa (about)
calcd	calculated
Cbz	benzyloxycarbonyl
Co.	company
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
Ed.	edition
equiv.	equivalent
Et	ethyl
et al.	et alii (and others)
h	hour(s)
Hex	hexyl
HMPA	hexamethylphosphoric triamide
Hz	hertz (s^{-1})
i	iso
IR	infrared (spectrum)
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar ($mol \cdot dm^{-3}$)
Me	methyl
min	minute(s)
mL	millilitter (1 mL=1 cm^3)
mmol	millimole
Hex	hexyl
HFP	1,1,1,3,3,3-hexafluoro-2-propanol
HOMO	highest occupied molecular orbital
Mp	melting point
mg	milligram
NMP	*N*-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
p.(pp.)	page(s)
Pen	pentyl
Ph	phenyl
Pr	propyl
q	quartet
ref	reference
Rf	relative mobility
r. t.	room temperature (ca. 25 °C)
s	singlet
SCRF	self-consistent reaction field
sept	septet
S. M.	starting material
SOMO	singly occupied molecular orbital
t	triplet
t (*tert*)	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
temp.	temperature
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxyl
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Torr	1 Torr = 133.322 Pa
Ts	*p*-toluenesulfonyl

CHAPTER 1

Powerful Solvent Effect of Water in Radical Reaction. Triethylborane-Induced Atom Transfer Radical Cyclization in Water

Triethylborane-induced atom transfer radical cyclization of iodo acetals and iodoacetates in water is described. Radical cyclization of iodo acetal proceeded smoothly both in aqueous methanol and in water. Atom transfer radical cyclization of allyl iodoacetate (**3a**) is much more efficient in water than in benzene or hexane. For instance, treatment of **3a** with triethylborane in benzene or hexane at room temperature did not give the desired lactone. In contrast, **3a** cyclized much more smoothly in water and gave the corresponding γ-lactone in high yield. The remarkable solvent effect of water was observed in this reaction, although the medium effect is believed to be small in radical reactions. Powerful solvent effects also operate in the preparation of medium- and large-ring lactones. Water as a reaction solvent strikingly promoted the cyclization reaction of large-membered rings. Stirring a solution of 3,6-dioxa-8-nonenyl iodoacetate in water in the presence of triethylborane at 25 °C for 10 h provided a 12-membered ring product, 4-iodo-6,9-dioxa-11-undecanolide, in 84% yield. On the other hand, reaction in benzene afforded the lactone in only 22% yield. *Ab initio* calculations were conducted to reveal the origin of the solvent effect of water in the cyclization of allyl iodoacetate. Calculations with the SCRF/CPCM option indicate that the large dielectric constant of water lowers the barrier not only to rotation from the *Z*-rotamer to the *E*-rotamer that can cyclize but also to cyclization constructing the γ-lactone framework. Moreover, the high cohesive energy density of water also effects acceleration of the cyclization because water forces a decrease in the volume of the reactant.

Introduction

Water is an interesting solvent in organic synthesis because water is cheap, nontoxic, nonflammable, and is expected to show extraordinary solvent effects. It is well-known that water is the solvent of choice for reactions that go through a polar transition state, such as S_N1 reactions, because of the highly polar nature of water that stabilizes a polar substance. Recently, new aspects of the influence of water have been explored, and organic reactions in aqueous media have been rediscovered.[1] Breslow has found that the nonpolar Diels–Alder reaction is strongly accelerated in water.[2] Claisen rearrangement is another example that illustrates the influence of water on pericyclic reactions.[3] It is established that this rate enhancement is due to the large negative value of the activation volume in the Diels–Alder reaction and that water plays a key role in the acceleration by contracting the volume of a substrate. For ionic reactions, Barbier-type allylation of aldehydes mediated by tin is accelerated in water.[4] In the case of zinc, the yields of the allylated products are improved compared to allylation in organic solvents.[5] Reactions by indium in water have also been developed, and an efficient synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) was achieved by applying indium-mediated allylation in water starting with mannose.[6] Lubineau reported that the Mukaiyama aldol reaction was carried out in aqueous solvents without any acid catalyst.[7] The crossed aldol products showed slight syn diastereoselectivity, which was the same as when this reaction was carried out in an organic solvent under high pressure. Lanthanide triflate-catalyzed Mukaiyama aldol reactions in water have also been actively investigated.[8]

On the other hand, radical reactions in water are rare in organic synthesis[9,10] and remain to be studied. In each case reported, no solvent effects were observed. In general, a medium effect in radical reactions is believed to be almost negligible, and little attention has been paid to the solvent that is employed for radical reactions.[11] The author and co-workers have been exploring the usefulness of water as a solvent in radical reactions.[12] Here a triethylborane-induced radical cyclization reaction in water is described. In the course of this study, a remarkable solvent effect was observed, especially in the cyclization of allyl iodoacetate in water. The cyclization reaction in water gave the desired lactone in higher yield. However, in organic solvents, radical oligomerization or polymerization predominantly occurred and the desired lactone was poorly

obtained. The successful radical lactonization proved unique to an aqueous medium. The results of *ab initio* calculations disclosing the origin of this solvent effect are also described.

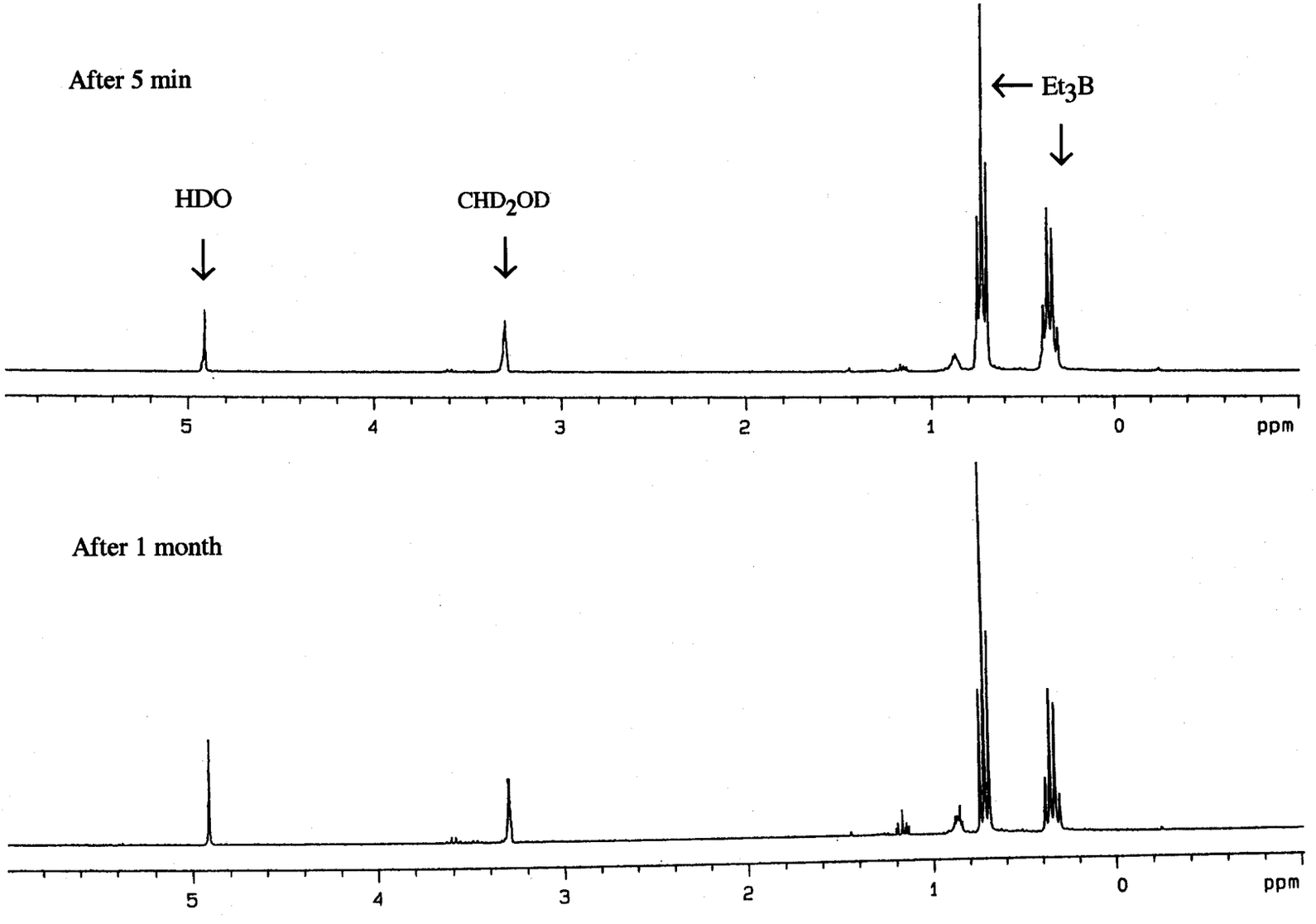
Preparation of a Methanol Solution of Triethylborane

To examine radical cyclization in aqueous media, triethylborane was chosen as a radical initiator,[13] and a methanol solution[14] of triethylborane was prepared to be handled easily. The stability of triethylborane in methanol was checked by the examination of the ^1H NMR of a CD_3OD solution of triethylborane. After standing at ambient temperature for one month, no change was observed in the NMR spectrum (Fig. 1). Indeed, the solution worked as well for a few months or longer when it was stored under argon atmosphere.

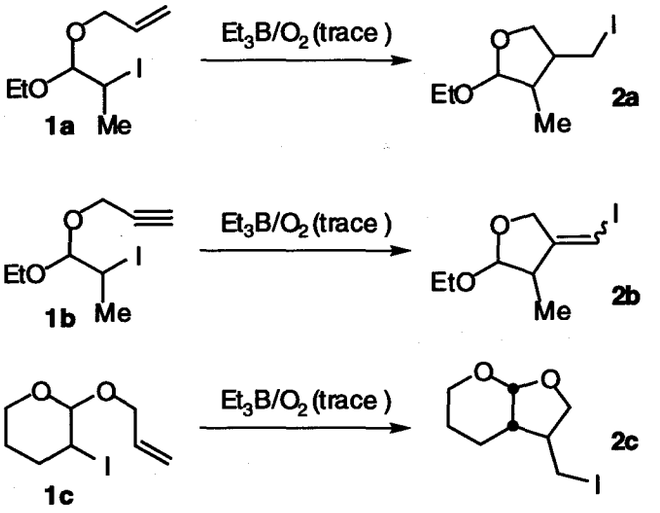
Radical Cyclization of Iodo Acetals in Aqueous Methanol or in Water

First, the author chose iodine atom transfer[15] radical cyclization of iodo acetals in aqueous methanol in order to establish tin-free chemistry[16] (Scheme 1). For example, iodo acetal **1a** (1.0 mmol) was dissolved in aqueous methanol ($MeOH/H_2O$ = 3 /1) and triethylborane in methanol (1.0 M, 0.1 mmol, 0.1 mL) was added to the homogeneous solution under argon atmosphere.[17] After being stirred for 2 h, the reaction mixture was extracted and concentrated, followed by silica gel column purification to afford the corresponding tetrahydrofuran derivative **2a** in 80% yield. This success prompted us to perform this reaction in water, in which a heterogeneous reaction medium was formed. Triethylborane in methanol (1.0 M, 0.1 mmol, 0.1 mL) was added to the suspension of **1a** in water (1.0 mmol in 10 mL), and the mixture was stirred vigorously for 2 h. An extractive workup and purification provided **2a** in 73% yield. Only a small amount of methanol (0.1 mL) was used in this reaction. A slight difference was observed with respect to stereoselectivity as compared to the reaction performed in benzene, in aqueous methanol, and in water.[18]

Fig. 1 ^{1}H NMR Spectra of Triethylborane in Methanol-d_4 (0.25 M)



Scheme 1



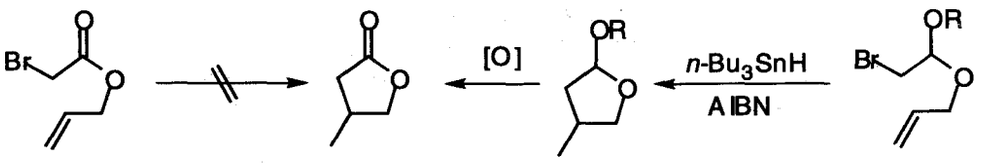
Entry	Substrate	Solvent	Yield
1	**1a**	MeOH/H_2O=3 mL/1 mL	80% (27/29/5/39)
2	**1b**	MeOH/H_2O=3 mL/1 mL	80% (45/29/25/1)[a]
3	**1c**	MeOH/H_2O=3 mL/1 mL	75% (88/12)
4	**1a**	H_2O 10 mL	73% (24/36/7/33)
5	**1b**	H_2O 10 mL	83% (43/34/22/2)[a]
6	**1c**	H_2O 10 mL	86% (87/13)
7	**1a**	benzene 3 mL	71% (30/37/4/29)
8	**1b**	benzene 3 mL	80% (40/39/20/1)[a]
9	**1c**	benzene 3 mL	80% (88/12)

a) Additional triethylborane (0.20 mmol) was added 2 h after the reacton had started.

Radical Cyclization of Allyl Iodoacetate and Its Derivatives

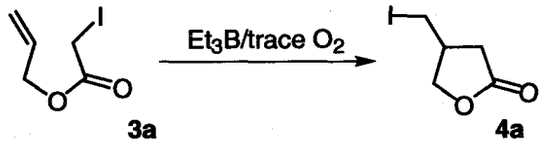
Next, the author focused on atom transfer radical cyclization of allyl iodoacetate. The indirect halo acetal method was developed by Stork[19] and Ueno[20] because direct cyclization of α-halo esters into γ-butyrolactones is an inefficient process.[21] Lactones are usually produced from this strategy by oxidation of the products prepared from radical cyclization of bromo acetal, as shown in Scheme 2.

Scheme 2



Indeed, treatment of allyl iodoacetate **3a** with triethylborane in benzene or hexane at room temperature yielded no lactone **4a** (Scheme 3). The iodide was consumed, and many products of high molecular weight were formed. In contrast, in water, **3a** cyclized much more smoothly and yielded lactone **4a** in high yield. Treatment of allyl iodoacetate **3a** (1.0 mmol) in water (30 mL) with triethylborane (1.0 M methanol solution, 0.1 mL, 0.1 mmol) at 25 °C for 3 h provided **4a** in 67% yield. Furthermore, the yield of **4a** increased to 78% at lower concentration (0.01 M, **3a** (1.0 mmol) / H_2O (100 ml)).

Scheme 3

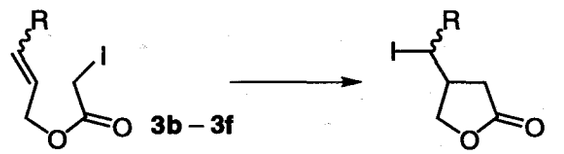


3a **4a**

hexane	30 mL	0%
benzene	30 mL	0%
H_2O	30 mL	67%
H_2O	100 mL	78%

This powerful solvent effect also operates in a related system (Scheme 4). Crotyl iodoacetate **3b** and 2-pentenyl iodoacetate **3c** provided the corresponding lactones **4b** and **4c** in 77% and 72% yield, respectively. 4-Hydroxy-2-butenyl iodoacetate **3d** also gave γ-butyrolactone **4d** in good yield (89%). In contrast, iodoacetate **3e**, which has a longer alkyl substituent (propyl group) on the terminal olefinic carbon, afforded the corresponding lactone **4e** in only 18% yield after stirring for 12 h upon treatment with triethylborane. More than one-half of the iodide **3e** (70%) remained unchanged at the end of the reaction. Moreover, 2-tridecenyl iodoacetate **3f** provided no cyclized γ-lactone **4f**, and **3f** was recovered completely. Similar results were obtained when **5a**, **5b**, and **5c** were employed as substrates (Scheme 5). Whereas **5a** provided the corresponding lactone **6a** in 67% yield, **5c** did not afford any lactone **6c**, and **5c** was recovered unchanged.[22] This favorable solvent effect of water was revealed by using *ab initio* calculation (*vide infra*).

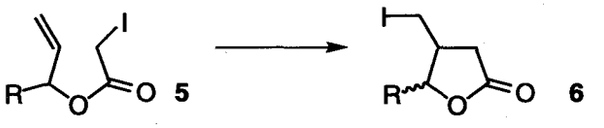
Scheme 4



3b – 3f **4b – 4f**

b: R = Me (77%) **c**: R = Et (72%) **d**: R = CH_2OH (89%) **e**: R = *n*-Pr (18%, (70% **3e**)) **f**: R = *n*-$C_{10}H_{21}$ (0%, (99% **3f**))

Scheme 5

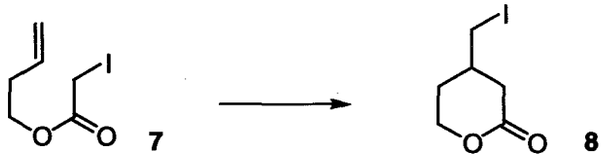


5 **6**

a: R = Me (67%) **b**: R =Et (32%, (51% **5b**)) **c**: R = *n*-Bu (0%, (92% **5c**))

3-Butenyl iodoacetate **7** (1.0 mmol) yielded δ-lactone **8**, which is generated through 6-exo cyclization, in 42% yield upon treatment with triethylborane in water (30 mL). Again, the yield of **8** increased to 70% at lower concentration [0.01 M, **7** (1.0 mmol) / H_2O (100 mL)].

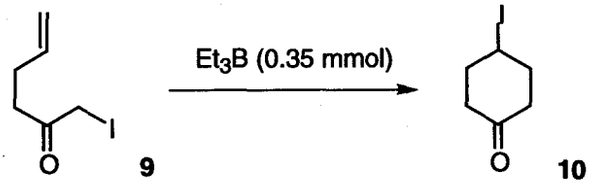
Scheme 6



7 **8**

Water was superior to hexane or benzene in the case of the reaction of α-iodo ketone **9**, 1-iodo-5-hexen-2-one, which underwent 6-endo cyclization to afford 4-iodocyclohexanone (**10**), as previously reported by Curran and Chang.[23]

Scheme 7



9 **10**

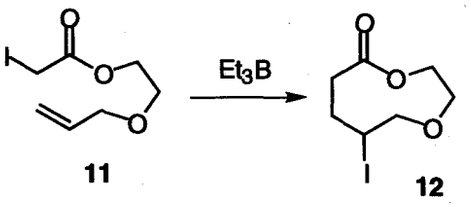
hexane 20 mL 6% (70% **9**)
benzene 20 mL 9% (66% **9**)
water 20 mL 59%

Radical Cyclization to Give Medium and Large Ring Lactone in Water

Construction of medium and large rings via a radical process is challenging work.[24,25]

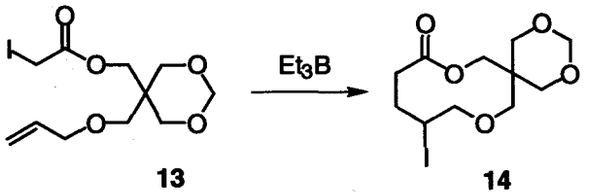
Preparation of medium-ring lactones was then examined(Scheme 8). Treatment of α-iodo ester **11** (1.0 mmol) with triethylborane (0.1 mmol) in water (100 mL) provided nine-membered lactone **12** in 69% yield. Conversely, the atom transfer cyclization reaction of **11** in benzene (100 mL) afforded the corresponding lactone in only 27% yield. Interestingly, using the ratio methanol/water = 7/13 as a solvent furnished the lactone in the highest yield among the varying ratios of water in aqueous methanol. The endo cyclization product was obtained as a single isomer in each solvent without contamination by an exo product. In the case of cyclization of **13**, **14** was obtained in good yield both in benzene and in water.

Scheme 8



11 **12**

MeOH	20 mL	0%	MeOH / H_2O	18/2 mL	12%
hexane	20 mL	10%		10/10 mL	36%
benzene	100 mL	23%		7/13 mL	46%
H_2O	20 mL	33%		5/15 mL	42%
H_2O	100 mL	69%		2/18 mL	26%

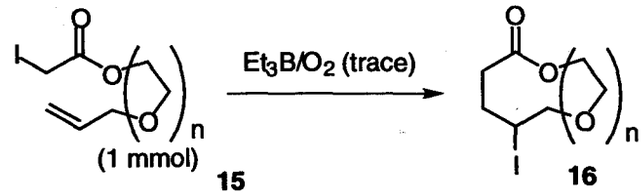


13 **14**

benzene	20 mL	80%
H_2O	20 mL	75%

Scheme 9 shows that water as a reaction solvent strikingly promoted the cyclization of a large-membered ring. Stirring a solution of **15a** (1.0 mmol) in water (30 mL) in the presence of Et_3B (1.0 M MeOH solution, 0.1 mL, 0.1 mmol) at 25 °C for 10 h provided a 12-membered ring **16a** in 56% yield. In contrast, the reaction of **15a** in benzene in the presence of a hexane solution of triethylborane (1.0 M, 0.1 mL, 0.1 mmol) afforded the lactone in only 22% yield, along with the recovered starting material **15a** (78%). Similar results were obtained in the reaction of **15b** (n = 3) and **15c** (n = 4). The exact role of water in promoting these radical reactions is not clear at this stage. It was assumed that a hydrogen bond to oxygen in the carbonyl group could be formed to activate the α-carbonylmethyl radical[26] and that hydrophobic interaction could also accelerate the cyclization.

Scheme 9



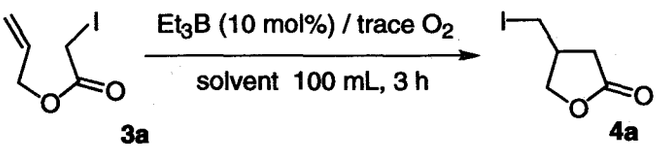
	benzene 20 mL	water 20 mL	water 100 mL
15a n = 2	10 h, 22% (78%)[a]	10 h, 56%	8 h, 84%
15b n = 3	3 h, 41% (43%)[a]	3 h, 75%	10 h, 86%[b]
15c n = 4	6 h, 14% (83%)[a]	6 h, 70%	4 h, 98%

a) Starting material was recovered.
b) Et_3B was added twice (0.05 mmol x 2).

Ab Initio Calculation and Discussion

As described above, radical cyclization of allyl iodoacetate is much easier in water than it is in benzene or hexane. To investigate the solvent effect in detail, the cyclization was examined in various solvents. Table 1 summarizes the results in addition to the dielectric constant[27], $E_T(30)$ polarity parameter[28], and cohesive energy density[29] for various solvents. In each case, the byproduct was an oligomer or polymer of allyl iodoacetate. It is obvious that polar solvents such as DMSO, DMF, or CH_3CN yielded the lactone in better yield than nonpolar solvents, that is, benzene, hexane, and dichloromethane. More interestingly, water was found to be an outstanding solvent among these solvents even taking the polar nature of water into account.

Table 1. Radical Cyclization of Allyl Iodoacetate in Various Solvents



3a **4a**

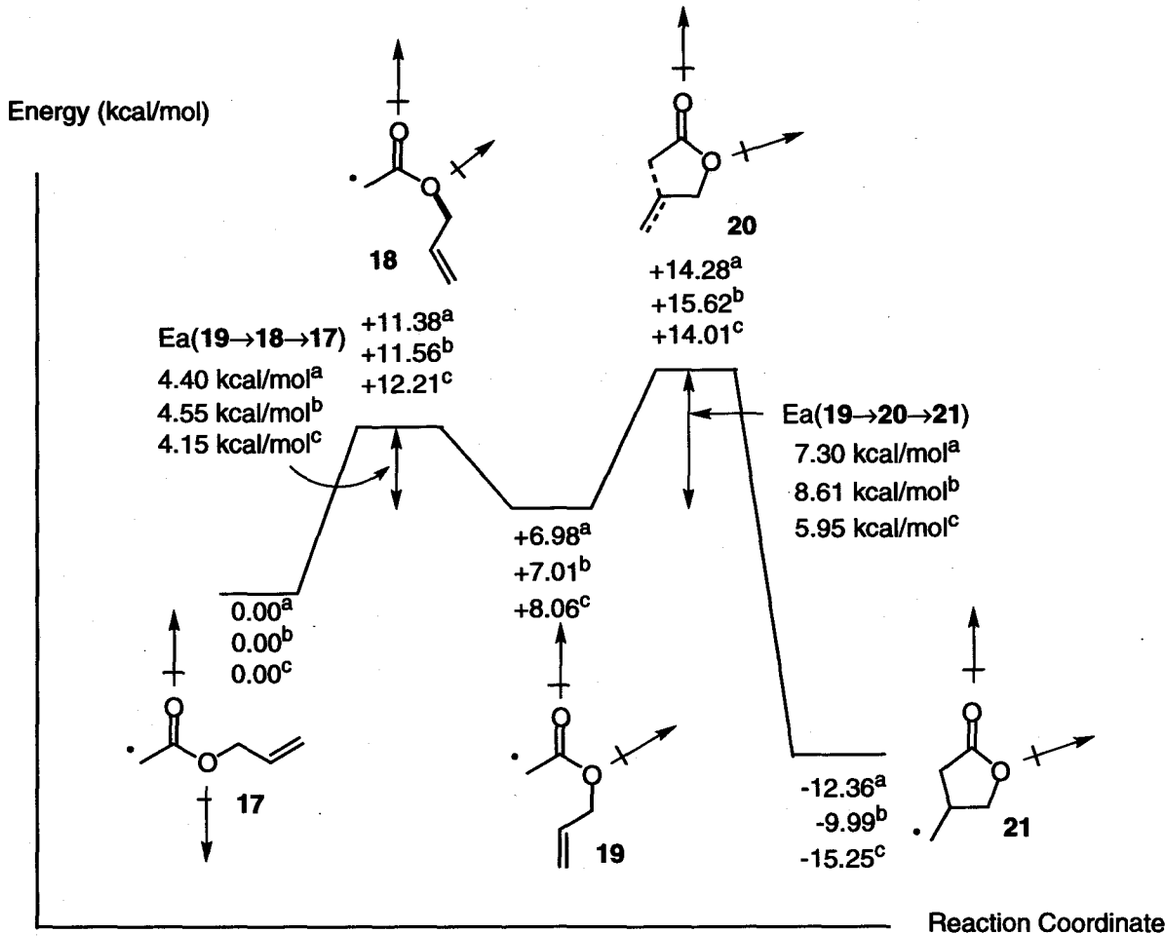
Solvent	Yield/%	Dielectric Constant[a)]	E_T[b)] (kcal/mol)	Cohesive Energy density[c)] (cal/cm^3)
Water	78	78.39	63.1	550.2
DMSO	37	46.45	45.1	168.6
Formamide	24	111.0	55.8	376.4
DMF	13	36.71	43.2	139.2
Acetonitrile	13	35.94	45.6	139.2
Methanol	6	32.66	55.4	208.8
TFE[d)]	18	26.67	59.8	–
Ethanol	3	24.55	51.9	161.3
THF	<1	7.58	37.4	86.9
CH_2Cl_2	<1	8.93	40.7	–
Benzene	<1	2.27	34.3	83.7
Hexane	<1	1.88	31.0	52.4

a) Reproduced from ref. 19. b) Reproduced from ref. 20. c) Reproduced from ref. 21. d) 2,2,2-Trifluoroethanol.

It is established that the rate-determining step is the cyclization step in the iodine atom transfer radical reaction, and iodine transfer is so rapid that one need not consider the solvent effect in the atom transfer step.[30] To clarify the origin of the solvent effect, the author carried out *ab initio* calculations on the cyclization of the (allyloxycarbonyl)methyl radical using the Gaussian 98 program.[31] All structures were optimized with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP)[32] and the 6-31G* basis set. Zero-point energy and thermal energy corrections were made for all of the calculated energies, and the sums of electronic and thermal free energies were obtained. The zero-point energies were not scaled, and the enthalpic corrections were made at 298.150 K. To confirm whether the calculations at the B3LYP level are proper or not, additional calculations were made at the PMP2

level using the 6-31+G** basis set at the optimized UHF/6-31G* geometry. The results of these calculations in a vacuum are shown in Scheme 10. Three calculations show similar results, although some numeric differences are observed. The author hence chooses to discuss the result obtained from the B3LYP calculations with zero-point energy and thermal energy corrections. It is known that the *Z*-rotamer **17** is much more stable than the *E*-rotamer **19** and that most of the ester molecules are present as the *Z*-rotamer.[33] The more stable *Z*-rotamer is topologically prohibited from cyclizing, and conversion into the *E*-rotamer is essential for the cyclization. At the B3LYP/6-31G* level with the zero-point energy and thermal energy corrections, the *Z*-rotamer is more stable than the *E*-rotamer by 7.01 kcal/mol. The activation barrier to rotation from **17** to **19** (*Ea*(**17**→**18**→**19**)[34], 11.56 kcal/mol) is higher than that to 5-exo cyclization from **19** to **21** (*Ea*(**19**→**20**→**21**), 8.61 kcal/mol). Moreover, the activation barrier to rotation from **19** to **17** (*Ea*(**19**→**18**→**17**)) is calculated to be 4.55 kcal/mol, which is much smaller than *Ea*(**19**→**20**→**21**). Therefore, even when **19** manages to be formed through the high activation barrier, the reverse path, **19**→**18**→**17**, proceeds predominantly and the cyclization fails, and intermolecular addition providing oligomers takes place. These results show that the cyclization of allyl iodoacetate is difficult because (1) *Ea*(**17**→**18**→**19**) is large for the short-lived **17** to surmount the barrier to rotation smoothly; (2) *Ea*(**19**→**20**→**21**) is larger than *Ea*(**19**→**18**→**17**); (3) The lifetime of radical species **17** and **19** is too short to allow cyclization, because competitive intermolecular radical addition occurs. The results shown in Table 1 imply that the use of water as a solvent could overcome these difficulties.

Scheme 10. Calculated energy profile for the transformation of *Z*-(allyloxycarbonyl)methyl radical into its cyclized form in vacuum. An arrow with a crossed end symbolizes a dipole moment that makes a large contribution to the net dipole moment of a molecule.



	17	18	19	20	21
Total Energy (au)	–345.11641[a]	–345.09828[a]	–345.10529[a]	–345.09365[a]	–345.13611[a]
	–345.03972[b]	–345.02129[b]	–345.02854[b]	–345.01483[b]	–345.05563[b]
	–344.12488[c]	–344.10543[c]	–344.11204[c]	–344.10257[c]	–344.14919[c]
Relative Energy	0.00[a]	11.38[a]	6.98[a]	14.28[a]	–12.36[a]
(kcal/mol)	0.00[b]	11.56[b]	7.01[b]	15.62[b]	–9.99[b]
	0.00[c]	12.21[c]	8.06[c]	14.01[c]	–15.25[c]
Dipole Moment	1.6433[a]	3.6482[a]	4.4132[a]	4.5977[a]	4.2826[a]
(Debye)	1.8288[c]	3.9707[c]	4.9190[c]	5.2192[c]	5.1930[c]

a) B3LYP/6-31G* without zero-point energy and thermal energy corrections. b) B3LYP/6-31G* with zero-point energy and thermal energy corrections. c) PMP2/6-31+G**//UHF/6-31G* without zero-point energy and thermal energy corrections.

The dipole moment is an important factor in considering the solvent effect because a molecule with a larger dipole moment is more stabilized in a polar solvent. Scheme 10 shows that the net dipole moment of the radical species increases, in particular, as the rotation of the ester bond proceeds. Therefore, it is assumed that polar solvents probably promote the overall cyclization reaction.[35]

To confirm this assumption, polarized-continuum-model calculations using the polarizable conductor calculation model based on the self-consistent reaction field theory (SCRF/CPCM)[36] were performed at the B3LYP/6-31G* and PMP2/6-31+G**//UHF/6-31G* levels on the cyclization of the (allyloxycarbonyl)methyl radical to estimate how **17**-**21** are stabilized in continuum with the dielectric constant as a modeled solvent. The results, performed in water, DMSO, methanol, dichloromethane, and benzene are summarized in Table 2. The results are as expected; that is, a more polar solvent favors the reaction path leading to the cyclized form **21**. The results in benzene and in water at the B3LYP/6-31G* level were taken into account, and one gets an easy explanation for the calculated solvent effect on the radical cyclization of (allyloxycarbonyl)methyl radical. The barriers to rotation from the *Z*-rotamer to the *E*-rotamer, *E*a(**17**→**18**→**19**), decrease to 9.87 and 8.81 kcal/mol in benzene and in water, respectively. This means that water stabilizes **18** and **19** more efficiently than it does **17** and that water promotes the rotation from **17** to **19**. Furthermore, in water, *E*a(**19**→**18**→**17**) and *E*a(**19**→**20**→**21**) are calculated to be 5.77 and 6.09 kcal/mol, respectively. The difference between *E*a(**19**→**18**→**17**) and *E*a(**19**→**20**→**21**) in water is much smaller (0.32 kcal/mol) than in a gas phase. On the other hand, calculation at the B3LYP/6-31G* level reveals that *E*a(**19**→**20**→**21**) is larger than *E*a(**19**→**18**→**17**) by 1.47 kcal/mol in benzene. Therefore, cyclization from **19** to **21** is almost as fast as the undesirable rotation from **19** to **17** is in water, whereas the former is slower than the latter in benzene. The PMP2/6-31+G**//UHF/6-31G* calculations with the SCRF/CPCM option also lead to the same explanation. *E*a(**17**→**18**→**19**) in water is smaller than that in benzene by 1.5 kcal/mol, which supports the same suggestion that interconversion from **17** to **19** is easier in water than it is in benzene, as calculated at the B3LYP/6-31G* level. Additionally, the PMP2/6-31+G**//UHF/6-31G* calculations indicate that *E*a(**19**→**20**→**21**) is smaller than *E*a(**19**→**18**→**17**) by 0.23 kcal/mol and that cyclization from **19** to **21** is preferable to rotation from **19** to **17** in water. Thus, it becomes clear that the large

dielectric constant of water promotes both rotation from **17** to **19** and cyclization from **19** to **21**.

Table 2. Calculated Relative Energy (kcal/mol) for the Transformation of *Z*-(Allyloxycarbonyl)-methyl Radical into Its Cyclized Form in Various Solvents Using the SCRF/CPCM Option.

Solvent	**17**	**18**	**19**	**20**	**21**	E_a (**19**→**18**→**17**)	E_a (**19**→**20**→**21**)	ΔE_a[c]
Water	0.00[a]	8.81[a]	3.04[a]	9.13[a]	–19.77[a]	5.77[a]	6.09[a]	0.34[a]
	0.00[b]	9.82[b]	7.35[b]	9.59[b]	–20.29[b]	2.47[b]	2.24[b]	–0.23[b]
DMSO	0.00[a]	9.17[a]	3.86[a]	9.87[a]	–18.71[a]	5.31[a]	6.01[a]	0.70[a]
	0.00[b]	10.54[b]	5.36[b]	10.37[b]	–20.13[b]	5.18[b]	5.01[b]	–0.17[b]
Methanol	0.00[a]	9.19[a]	3.48[a]	9.83[a]	–18.75[a]	5.71[a]	6.35[a]	0.64[a]
	0.00[b]	9.87[b]	4.57[b]	9.99[b]	–20.56[b]	5.30[b]	5.42[b]	0.12[b]
CH_2Cl_2	0.00[a]	9.54[a]	4.36[a]	10.77[a]	–17.89[a]	5.18[a]	6.41[a]	1.23[a]
	0.00[b]	10.72[b]	5.69[b]	10.87[b]	–19.78[b]	5.03[b]	5.18[b]	0.15[b]
Benzene	0.00[a]	9.87[a]	4.91[a]	11.34[a]	–16.86[a]	4.96[a]	6.43[a]	1.47[a]
	0.00[b]	11.33[b]	6.56[b]	11.81[b]	–18.22[b]	4.77[b]	5.25[b]	0.48[b]

a) B3LYP/6-31G* b) PMP2/6-31+G**//UHF/6-31G* c) ΔEa = Ea(**19**→**20**→**21**)–Ea(**19**→**18**→**17**)

Conducting the CPCM method reveals that a larger dielectric constant is favorable in the cyclization of the (allyloxycarbonyl)methyl radical. However, it is difficult to explain the results of this powerful solvent effect of water that is shown in Table 1 by only the effect of a large dielectric constant. This effect seems too small to account for the dramatic differences between water and other solvents. In the CPCM method, each solvent is modeled as a homogeneous and isotropic continuous medium with a dielectric constant. Hydrogen bonds, which give water some extraordinary characteristics, are not taken into account. To discuss the reaction in water, it is necessary to pay attention to its cohesive energy density. Water, which is known for the highest cohesive energy density (550.2 cal/cm^3) among the solvents, due to its hydrogen-bond network, requires the highest energy necessary to form a cavity for a reactant in water. Therefore, a reaction in which the volume of a reactant decreases is strongly accelerated in water in order to

occupy the smallest possible volume of a cavity. Rate enhancement in the Diels–Alder reaction in water is suggested to be due to this effect.[1,2] The author assumed that this acceleration effect would work in the case of the cyclization of the (allyloxycarbonyl)methyl radical and focused on the volume of each radical **17-21** that appeared in each output file of the SCRF/CPCM calculation (Table 3). Whereas the rotation step appears to be unrelated to acceleration, ring closure would be strongly enhanced, due to decreasing the volume of the radical. Compound **20** is smaller than **19**; therefore, transition state **20** is more stabilized than **19**, and the activation barrier to cyclization becomes smaller in water than it is in a vacuum. Thus, the cyclization step is accelerated by high cohesive energy, in addition to the electrostatic effect.[37]

Table 3. Calculated Volumes ($Å^3$) of **17-21** in Water

V(**17**)	*V*(**18**)	*V*(**19**)	*V*(**20**)	*V*(**21**)
156.67019[a]	156.54624[a]	155.32790[a]	148.28529[a]	131.65214[a]
155.95854[b]	155.88738[b]	154.61012[b]	147.73254[b]	130.69289[b]

a) B3LYP/6-31G* : $\Delta V^{\neq}$ = *V*(**20**)–*V*(**19**) = –7.04 $Å^3$ / a molecule = –4.24 cm^3/mol b) PMP2/6-31+G**//UHF/6-31G* : $\Delta V^{\neq}$ = *V*(**20**) –*V*(**19**) = –6.88 $Å^3$ / a molecule = –4.14 cm^3/mol

Curran and Tamine[21h] reported successful iodine atom transfer radical cyclization of allyl iodoacetate in the presence of hexabutylditin under irradiation with a sunlamp in benzene at reflux, although the same reaction failed at room temperature. They attributed the success to the higher temperature that induces rapid rotation of the ester bond. Scheme 10 indicates that their speculation is correct. At higher temperature, (allyloxycarbonyl)methyl radical **17** possesses sufficient energy to surmount the barrier to rotation. *E*-rotamer **19**, some of which have sufficient energy to pass the second barrier to cyclization, can cyclize. The intramolecular cyclization to yield the lactone would predominate the intermolecular radical addition to afford oligomeric products. On the other hand, in the present case, a similar reaction was performed in water, even

at room temperature, to furnish the lactone in high yield. The solvent effect of water is rationalized from the results of the calculation and is summarized as follows. The large dielectric constant of water reduces the barrier to rotation to make rotation easier than in benzene. Once **17** isomerizes to **19**, the cyclization becomes easier not only because water has a large dielectric constant but also because water strongly forces a decrease in the volume of the reactant.

In conclusion, organic chemists can control the reactivity of a carbanion by changing its counterion, solvent, and reaction temperature. In contrast, shifting a reaction path in a radical reaction is more difficult because *free* radicals are active species.[26] The medium effect had been regarded as being negligible. The present study has demonstrated that the solvent is an important variable in free radical chemistry. Water offers control of radical reactions.

Experimental Section

Preparation of the Starting Materials

Iodo acetals were prepared by treatment of an equimolar mixture of the corresponding vinyl ether and allyl or propargyl alcohol with an equal amount of *N*-iodosuccimide in dichloromethane at 0 °C for 1 h. Iodoacetates were synthesized as follows. Alcohol (10 mmol) and pyridine (11 mmol) were dissolved in THF, and chloroacetyl chloride (11 mmol) was added dropwise to the mixture at 0 °C. The resulting suspension was stirred for 1 h at 25 °C. The reaction was quenched with water, and the product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was dissolved in 20 mL of acetone and treated with sodium iodide (20 mmol) at ambient temperature. A slightly exothermic reaction started. After 1 h, extractive workup followed by silica gel column purification provided the corresponding iodoactates in 80–90% yields.

A Typical Procedure for Cyclization of 2-Iodopropanal Allyl Ethyl Acetal in Water. Iodo acetal **1a** (270 mg, 1.0 mmol) was placed in a 50 mL flask and distilled water (10 mL) was added. The mixture was flushed with argon in a toy balloon and stirred to suspend the starting material. A solution of triethylborane in methanol (1.0 M, 0.10 mL, 0.10 mmol) was then added dropwise. After stirring for 2 h at room temperature, the reaction mixture was extracted with hexane (20 ml × 3) and the organic layer was concentrated. Silica gel column purification (hexane:ethyl acetate = 20:1) of the crude product provided **2a** (197 mg, 0.73 mmol) in 73% yield.

A Typical Procedure for Cyclization of Allyl Iodoacetate in Water. Allyl iodoacetate **3a** (224 mg, 1.0 mmol) was placed in a 50 mL flask and distilled water (30 mL) was added. The mixture was flushed with argon and stirred vigorously. A solution of triethylborane in methanol (1.0 M, 0.10 mL, 0.10 mmol) was then added. After being stirred for 3 h at ambient temperature, the reaction mixture was extracted with ethyl acetate (20 ml × 3) and the organic layer was concentrated. Silica gel column purification (hexane:ethyl acetate = 3:1) of the crude product provided β-(iodomethyl)-γ-butyrolactone **4a** (150 mg, 0.67 mmol) in 67% yield, which showed the identical ^{1}H spectrum as reported in the literature.[21h]

Radical Cyclization of 1-Iodo-5-hexen-2-one in Water. Iodo ketone **9** (224 mg, 1.0 mmol) was placed in a 50 mL flask and distilled water (20 mL) was added. The mixture was flushed with argon in a toy balloon and stirred to suspend the starting material. A solution of triethylborane in methanol (1.0 M, 0.05 mL, 0.05 mmol) was then added. A solution of triethylborane was added every 5 h until **9** was completely consumed. The reaction mixture was extracted with ethyl acetate (20 ml × 3) and the organic layer was concentrated. Silica gel column purification provided **10** (132 mg, 0.59 mmol) in 59% yield.

A Typical Cyclization Procedure for Large Ring Lactones in Water. To 3,6-dioxa-8-nonenyl iodoacetate **15a** (314 mg, 1.0 mmol) in a 50 mL flask was added distilled water (20 mL) and the resulting mixture was set under argon atmosphere with a toy balloon. With stirring to suspend the iodoacetate, triethylborane (1.0 M methanol solution, 0.10 mL, 0.10 mmol) was added dropwise to the resulting suspension. The suspension was stirred for 10 h at room temperature. Extraction with ethyl acetate (20 ml × 3) followed by silica gel column purification afforded endo-cyclized product **16a** (176 mg) in 56% yield.

A Typical Procedure for Cyclization for Large Ring Lactones in Benzene. A solution of **15a** in benzene (20 mL) was flushed with argon in a toy balloon. To the solution was added triethylborane (1.0 M hexane solution, 0.10 mL, 0.10 mmol) and the resulting mixture was stirred for 10 h. Then, benzene and triethylborane were removed under reduced pressure to stop the reaction. The yields of the product **16a** (22%) and the recovered iodoacetate **15a** (78%) were determined by ^{1}H NMR measurement with dibenzyl ether (59 mg, 0.30 mmol) as an internal standard.

2-Iodopropanal Allyl Ethyl Acetal (1a, mixture of diastereomers, 78/22) IR (neat) 2972, 2924, 2868, 1652, 1450, 1376, 1342, 1048, 926 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.88 (d, J = 7.2 Hz, 3H), 3.54–3.78 (m, 2H), 4.03–4.25 (m, 3H), 4.32 (d, J = 5.7 Hz, 0.78H), 4.46 (d, J = 5.4 Hz, 0.22H), 5.17–5.24 (m, 1H), 5.28–5.37 (m, 1H), 5.87–6.01 (m, 1H); ^{13}C NMR

($CDCl_3$) For major isomer: δ 14.93, 22.24, 26.57, 63.13, 68.21, 104.66, 117.23, 134.06. For minor isomer: δ 14.93, 22.30, 26.54, 63.07, 67.96, 104.66, 117.14, 134.06. Found: C, 35.56; H, 5.59%. Calcd for $C_8H_{15}IO_2$: C, 35.57; H, 5.60%.

2-Ethoxy-4-iodomethyl-3-methyltetrahydrofuran (2a, mixture of diastereomers, 24/36/7/33): IR (neat) 2966, 2928, 2902, 2872, 1455, 1372, 1188, 1100, 1068, 996, 931 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 7.5 Hz, 0.72H), 1.00 (d, *J* = 7.5 Hz, 1.08H), 1.03 (d, *J* = 7.2 Hz, 0.21H), 1.09 (d, *J* = 7.2 Hz, 0.99H), 1.14–1.22 (m, 3H), 1.89–2.00 (m, 0.33H), 2.16–2.34 (m, 1H), 2.63–2.77 (m, 0.36H), 2.94–3.78 (m, 4.95H), 3.83 (dd, *J* = 9.0 Hz, 4.2 Hz, 0.36H), 4.05–4.16 (m, 1H), 4.81 (d, *J* = 2.7 Hz, 0.33H), 4.83 (d, *J* = 0.6 Hz, 0.24H), 4.99 (d, *J* = 3.9 Hz, 0.07H), 5.01 (d, *J* = 4.5 Hz, 0.36H); ^{13}C NMR ($CDCl_3$) δ 2.70, 7.64, 8.31, 8.80, 10.52, 11.36, 14.97, 15.00, 15.06, 15.10, 17.20, 41.99, 42.80, 43.38, 43.66, 44.90, 45.34, 47.13, 48.87, 62.57, 62.62, 62.74, 62.86, 71.32, 72.74, 73.15, 73.54, 104.81, 105.78, 109.74, 110.27. Found: C, 35.58; H, 5.67%. Calcd for $C_8H_{15}IO_2$: C, 35.57; H, 5.60%.

2-Iodopropanal propargyl Ethyl Acetal (1b, mixture of diastereomers, 8/2): IR (neat) 3284, 2972, 2926, 2138, 1447, 1377, 1344, 1262, 1200-860 (broad), 631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.87 (d, *J* = 6.9 Hz, 2.4H), 1.89 (d, *J* = 6.6 Hz, 0.6H), 2.45–2.48 (m, 1H), 3.61–3.82 (m, 2H), 4.12–4.22 (m, 1H), 4.30 (d, *J* = 2.4 Hz, 2H), 4.54-4.58 (m, 1H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 14.93, 21.88, 26.09, 54.34, 64.06, 74.77, 79.03, 103.70. For minor isomer: δ 14.93, 22.46, 26.04, 53.88, 63.71, 74.73, 79.03, 103.70. Found: C, 36.08; H, 4.97%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

2-Ethoxy-4-iodomethene-3-methyltetrahydrofuran (2b, mixture of diastereomers, 42/34/22/2): IR (neat) 2970, 2926, 2870, 1644, 1453, 1377, 1344, 1261, 1246, 1138, 1086, 1039, 1014, 993, 936, 880, 770, 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09–1.23 (m, 6H), 2.67–2.84 (m, 1H), 3.41–3.53 (m, 1H), 3.66–3.80 (m, 1H), 4.24–4.45 (m, 2H), 4.93 (s, 0.22H), 4.99 (d, *J* = 1.2 Hz, 0.42H), 5.13 (d, *J* = 5.1 Hz, 0.02H), 5.23 (d, *J* = 4.8 Hz, 0.34H), 5.84 (q, *J* = 2.7 Hz, 0.34H), 5.95–6.20 (m, 0.66H); ^{13}C NMR ($CDCl_3$) For major 3 isomers δ 10.42, 14.73, 14.85, 14.90 (2C), 17.88, 45.10, 47.18,

48.90, 62.39, 62.67, 62.73, 66.25, 66.76, 67.51, 69.13, 73.34, 43.78, 105.71, 108.45, 110.14, 154.18, 154.39, 155.00. Found: C, 35.82; H, 4.76%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%

2-Alylloxy-3-iodotetrahydropyran (1c): IR (neat) 3074, 3008, 2926, 2848, 2726, 1648, 1463, 1452, 1435, 1390, 1353, 1338, 1303, 1281, 1203, 1175-900 (broad), 867, 848, 810, 696, 585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52-1.65 (m, 1H), 1.72–1.84 (m, 1H), 1.97–2.09 (m, 1H), 2.34–2.44 (m, 1H), 3.59 (ddd, *J* = 3.9 Hz, 7.8 Hz, 11.1 Hz, 1H), 3.95–4.15 (m, 3H), 4.27 (ddt, *J* = 5.4 Hz, 12.9 Hz, 5.4 Hz, 1H), 4.69 (d, *J* = 5.4 Hz, 1H), 5.22 (dq, *J* = 10.2 Hz, 1.5 Hz, 1H), 5.34 (dq, *J* = 17.1 Hz, 1.5 Hz, 1H), 5.88–6.01 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.35, 29.07, 32.54, 63.39, 68.85, 101.50, 117.50, 133.93. Found: C, 36.10; H, 4.89%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

7-Iodomethyl-2,9-dioxabicyclo[4.3.0]nonane (2c, mixture of diastereomers, 87/13): IR (neat) 2852, 1722, 1403, 1276, 1184, 1097, 1016, 983, 946, 896, 867, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.87 (m, 4.13H), 2.06–2.15 (m, 0.87H), 2.52–2.64 (m, 0.13H), 2.77–2.91 (m, 0.87H), 3.08–3.18 (m, 1.87H), 3.31–3.48 (m, 0.26H), 3.60–3.82 (m, 2.74H), 3.84–3.94 (m, 0.13H), 4.04 (dt, *J* = 4.8 Hz, 8.1 Hz, 0.87H), 4.31 (dt, *J* = 2.1 Hz, 8.4 Hz, 0.13H), 5.11 (d, *J* = 3.0 Hz, 0.13H), 5.29 (d, *J* = 3.9 Hz, 0.87H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 2.07, 18.38, 22.44, 38.07, 44.02, 61.00, 69.95, 101.50. For minor isomer: δ 7.57, 20.29, 22.00, 40.26, 44.49, 64.04, 74.35, 102.29. Found: C, 35.72; H, 4.65%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%

(*E*)-2-Butenyl Iodoacetate (3b): IR (neat) 2938, 1730, 1264, 1090, 966 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (ddt, *J* = 6.6 Hz, 1.5 Hz, 1.2 Hz, 3H), 3.70 (s, 2H), 4.57 (ddq, *J* = 6.6 Hz, 1.2 Hz, 1.2 Hz, 2H), 5.60 (dtq, *J* = 15.6 Hz, 6.6 Hz, 1.5 Hz, 1H), 5.85 (dtq, *J* = 15.6 Hz, 1.2 Hz, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.41, 17.58, 66.52, 124.15, 132.20, 168.47. Found: C, 30.29; H, 3.73%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

(*Z*)-2-Pentenyl Iodoacetate (3c): IR (neat) 2960, 1736, 1249, 1089, 967 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.5 Hz, 3H), 2.13 (dq, *J* = 7.5 Hz, 7.5 Hz, 2H), 3.70 (s, 2H), 4.69 (d, *J* = 6.9 Hz, 2H), 5.51 (dt, *J* = 10.8 Hz, 6.9 Hz, 1H), 5.70 (dt, *J* = 10.8 Hz, 7.5 Hz, 1H); ^{13}C NMR

($CDCl_3$) δ –5.49, 13.91, 20.76, 61.69, 121.70, 137.96, 168.76. Found: C, 33.38; H, 4.29%. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36%.

(*Z*)-4-Hydroxy-2-butenyl Iodoacetate (3d): IR (neat) 3304, 1721, 1258, 1092, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–2.13 (broad, 1H), 3.70 (s, 1H), 4.28 (d, *J* = 6.6 Hz, 2H), 4.76 (d, *J* = 6.9 Hz, 2H), 5.65 (dt, *J* = 11.1 Hz, 6.9 Hz, 1H), 5.91 (dt, *J* = 11.1 Hz, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.57, 57.89, 61.42, 123.99, 134.02, 168.85. Found: C, 28.03; H, 3.45%. Calcd for $C_6H_9IO_3$: C, 28.15; H, 3.54%.

(*E*)-2-Hexenyl Iodoacetate (3e): IR (neat) 2954, 1727, 1252, 1089, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.42 (tq, *J* = 7.2 Hz, 7.2 Hz, 2H), 2.05 (dt, *J* = 7.2 Hz, 7.2 Hz, 2H), 3.70 (s, 2H), 4.59 (d, *J* = 6.6 Hz, 2H), 5.57 (dt, *J* = 15.3 Hz, 6.6 Hz, 1H), 5.83 (dt, *J* = 15.3 Hz, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.39, 13.41, 21.74, 34.07, 66.63, 122.99, 137.24, 168.51. Found: C, 36.03; H, 4.81%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

(*E*)-2-Tridecenyl Iodoacetate (3f): IR (neat) 2920, 1737, 1264, 1089, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20–1.46 (m, 16H), 2.06 (dt, *J* = 6.6 Hz, 7.2 Hz, 2H), 3.70 (s, 2H), 4.59 (d, *J* = 6.6 Hz, 2H), 5.56 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H), 5.83 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.43, 13.94, 22.50, 28.63, 28.96, 29.16, 29.29, 29.42, 29.44, 31.74, 32.09, 66.70, 122.79, 137.61, 168.55. Found: C, 49.46; H, 7.65%. Calcd for $C_{15}H_{27}IO_2$: C, 49.19; H, 7.43%.

β-(1-Iodoethyl)-γ-butyrolactone (4b, faster moving band): R_f = 0.30 (hexane:ethyl acetate = 3:1) IR (neat) 2958, 2910, 1775, 1177, 1037, 1008 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (d, *J* = 6.9 Hz, 3H), 2.25–2.37 (m, 1H), 2.65–2.78 (m, 2H), 4.01 (dd, *J* = 9.3 Hz, 5.4 Hz, 1H), 4.13 (dq, *J* = 6.9 Hz, 6.9 Hz, 1H), 4.47 (dd, *J* = 9.3 Hz, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.53, 27.98, 34.30, 44.48, 73.73, 175.82. Found: C, 30.14; H, 3.81%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

β-(1-Iodoethyl)-γ-butyrolactone (4b, slower moving band): R_f = 0.26 (hexane:ethyl acetate =

3:1) IR (neat) 2964, 2910, 1766, 1179, 1054, 993 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (d, *J* = 6.9 Hz, 3H), 2.40–2.54 (m, 1H), 2.57–2.75 (m, 2H), 4.06 (dd, *J* = 9.3 Hz, 7.2 Hz, 1H), 4.22 (dq, *J* = 5.7 Hz, 6.9 Hz, 1H), 4.45 (dd, *J* = 9.3 Hz, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.97, 28.39, 34.69, 44.29, 71.66, 175.47. Found: C, 29.79; H, 3.73%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

β-(1-Iodopropyl)-γ-butyrolactone (4c, faster moving band): R_f = 0.38 (hexane:ethyl acetate = 3:1) IR (neat) 2964, 1778, 1174, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (dt, *J* = 1.8 Hz, 6.9 Hz, 3H), 1.65–1.76 (m, 2H), 2.28 (ddd, *J* = 17.4 Hz, 9.9 Hz, 1.8 Hz, 1H), 2.62 (ddd, *J* = 17.4 Hz, 8.7 Hz, 1.8 Hz, 1H), 2.67–2.83 (m, 1H), 3.90–3.94 (m, 2H), 4.43 (ddd, *J* = 9.6 Hz, 7.2 Hz, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.86, 31.41, 34.73, 40.46, 42.75, 74.09, 175.86. Found: C, 33.10; H, 4.31%. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36%.

β-(1-Iodopropyl)-γ-butyrolactone (4c, slower moving band): R_f = 0.33 (hexane:ethyl acetate = 3:1) IR (neat) 2964, 1779, 1179, 1013 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.65–1.87 (m, 2H), 2.52 (dd, *J* = 14.7 Hz, 8.1 Hz, 1H), 2.60–2.74 (m, 2H), 4.04–4.12 (m, 2H), 4.45 (dd, *J* = 9.3 Hz, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.31, 31.36, 34.93, 41.19, 42.60, 71.97, 175.41. Found: C, 32.94; H, 4.27%. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36%.

β-(2-Hydroxy-1-iodoethyl)-γ-butyrolactone (4d, 1/1 mixture of diastereomers): IR (neat) 3380, 2906, 1760, 1177, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26–2.40 (broad, 1H), 2.41 (dd, *J* = 17.4 Hz, 9.9 Hz, 0.5H), 2.53 (dd, *J* = 17.4 Hz, 9.3 Hz, 0.5H), 2.68 (dd, *J* = 17.4 Hz, 8.1 Hz, 0.5H), 2.73 (dd, *J* = 17.4 Hz, 9.3 Hz, 0.5H), 2.80–2.97 (m, 1H), 3.70–3.94 (m, 2H), 4.03–4.16 (m, 1H), 4.19–4.28 (m, 1H), 4.47–4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 34.86, 35.00, 38.00, 38.38, 39.20, 39.34, 66.82 (2C), 72.33, 74.00, 176.23, 176.73. Found: C, 28.09; H, 3.44%. Calcd for $C_6H_9IO_3$: C, 28.15; H, 3.54%.

β-(1-Iodobutyl)-γ-butyrolactone (4e, faster moving band): R_f = 0.39 (hexane:ethyl acetate = 3:1) IR (neat) 2956, 2928, 1778, 1178, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.37–1.51 (m, 1H), 1.54–1.85 (m, 3H), 2.36 (dd, *J* = 17.1 Hz, 9.3 Hz, 1H), 2.69 (dd, *J* = 17.1 Hz,

8.7 Hz, 1H), 2.74–2.86 (m, 1H), 3.99–4.10 (m, 2H), 4.49 (dd, J = 9.0 Hz, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.89, 22.49, 34.85, 38.39, 40.05, 42.95, 73.95, 175.88. Found: C, 35.90; H, 4.80%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

β-(1-Iodobutyl)-γ-butyrolactone (4e, slower moving band): R_f = 0.34 (hexane:ethyl acetate = 3:1) IR (neat) 2956, 2926, 1776, 1177, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.35–1.70 (m, 3H), 1.76–1.89 (m, 1H), 2.50 (dd, J = 20.1 Hz, 11.7 Hz, 1H), 2.59–2.71 (m, 2H), 4.07–4.17 (m, 2H), 4.45 (dd, J = 9.0 Hz, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.92, 22.82, 34.83, 38.89, 39.98, 42.77, 72.12, 175.47. Found: C, 36.12; H, 4.91%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

1-Methyl-2-propenyl Iodoacetate (5a): IR (neat) 2978, 1726, 1414, 1260, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6.3 Hz, 3H), 3.69 (s, 2H), 5.20 (ddd, J = 10.5 Hz, 1.2 Hz, 1.2 Hz,1H), 5.31 (ddd, J = 17.1 Hz, 1.2 Hz, 1.2 Hz, 1H), 5.37 (dddq, J = 1.2 Hz, 1.2 Hz, 6.0 Hz, 6.3 Hz, 1H), 5.86 (ddd, J = 17.1 Hz, 10.5 Hz, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –4.95, 19.30, 72.57, 116.44, 136.71, 167.95. Found: C, 30.23; H, 3.72%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

1-Ethyl-2-propenyl Iodoacetate (5b): IR (neat) 2966, 1727, 1266, 1089, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.69 (dq, J = 6.6 Hz, 7.5 Hz, 2H), 3.71 (s, 2H), 5.18 (dddt, J = 1.2 Hz, 1.2 Hz, 6.6 Hz, 6.6 Hz, 1H), 5.23 (ddd, J = 10.5 Hz, 1.2 Hz, 1.2 Hz, 1H), 5.31 (ddd, J = 17.1 Hz, 1.2 Hz, 1.2 Hz, 1H), 5.79 (ddd, J = 17.1 Hz, 10.5 Hz, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.17, 9.19, 26.91, 77.76, 117.53, 135.47, 168.27. Found: C, 33.17; H, 4.30%. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36%.

1-Vinylpentyl Iodoacetate (5c): IR (neat) 2952, 1728, 1262, 1086, 976 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.27–1.39 (m, 4H), 1.59–1.70 (m, 2H), 3.70 (s, 2H), 5.21 (dd, J = 10.5 Hz, 1.2 Hz, 1H), 5.22 (dt, J = 6.3 Hz, 6.3 Hz, 1H), 5.30 (dd, J = 17.1 Hz, 1.2 Hz, 1H), 5.79 (ddd, J = 17.1 Hz, 10.5 Hz, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.12, 13.77, 22.12, 26.88, 33.50, 76.47, 117.26, 135.76, 168.14. Found: C, 38.54; H, 5.31%. Calcd for $C_9H_{15}IO_2$: C, 38.32; H,

5.36%.

β-(Iodomethyl)-γ-valerolactone (6a, mixture of diastereomers, *trans/cis* = 84/16): IR (neat) 2972, 1776, 1170, 1044, 940 cm^{-1}; ^1H NMR ($CDCl_3$) for *trans* isomer δ 1.45 (d, J = 6.3 Hz, 3H), 2.30–2.51 (m, 2H), 2.75 (dd, J = 17.4 Hz, 8.4 Hz, 1H), 3.21 (dd, J = 10.5 Hz, 6.6 Hz, 1H), 3.30 (dd, J = 10.5 Hz, 5.7 Hz, 1H), 4.35 (dq, J = 6.3 Hz, 6.3 Hz, 1H), for *cis* isomer δ 1.35 (d, J = 6.6 Hz, 3H), 2.27–2.50 (m, 2H), 2.56–2.70 (m, 1H), 2.99 (dd, J = 14.1 Hz, 6.9 Hz, 1H), 3.12–3.23 (m, 1H), 4.72 (dq, J = 6.6 Hz, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) for *trans* isomer δ 6.05, 19.71, 36.11, 44.22, 81.17, 174.65, for *cis* isomer δ 1.88, 14.43, 35.24, 41.63, 78.25, 174.90. Found: C, 29.96; H, 3.62%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

β-(1-Iodoethyl)-γ-caprolactone (6b, mixture of diastereomers, *trans/cis* = 88/12): IR (neat) 2965, 1775, 1182, 974 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H), 1.61-1.85 (m, 2H), 2.35-2.50 (m, 2H), 2.74 (dd, J = 19.8 Hz, 10.8 Hz, 1H), 3.20 (dd, J = 10.5 Hz, 6.3 Hz, 1H), 3.30 (dd, J = 10.5 Hz, 5.4 Hz, 1H), 4.18 (dt, J = 7.5 Hz, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.95, 9.51, 27.49, 36.21, 42.00, 86.29, 174.93. Found: C, 33.28; H, 4.30%. Calcd for $C_6H_9IO_2$: C, 33.09; H, 4.36%.

3-Butenyl Iodoacetate (7): IR (neat) 2974, 1736, 1415, 1251, 1090, 988, 919 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (dddt, J = 1.5 Hz, 1.5 Hz, 6.9 Hz, 6.9 Hz, 2H), 3.70 (s, 2H), 4.20 (t, J = 6.9 Hz, 2H), 5.11 (ddt, J = 10.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.14 (ddt, J = 17.1 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.80 (ddt, J = 17.1 Hz, 10.2 Hz, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.66, 32.58, 64.92, 117.64, 133.48, 168.86. Found: C, 29.97; H, 3.80%. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

β-(Iodomethyl)-δ-valerolactone (8): IR (neat) 2952, 1728, 1401, 1256, 1174, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–1.74 (m, 1H), 2.03–2.21 (m, 2H), 2.30 (dd, J = 10.5 Hz, 17.1 Hz, 1H), 2.78 (dd, J = 16.8 Hz, 5.4 Hz, 1H), 3.18 (dd, J = 9.9 Hz, 5.7 Hz,1H), 3.23 (dd, J = 9.9 Hz, 5.7 Hz, 1H), 4.29 (ddd, J = 11.7 Hz, 10.5 Hz, 3.9 Hz, 1H), 4.44 (ddd, J = 11.7 Hz, 5.1 Hz, 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.42, 29.34, 33.19, 36.59, 67.77, 170.34. Found: C, 29.93; H, 3.80%. Calcd

for $C_6H_9IO_2$: C, 30.02; H, 3.78%.

3-Oxa-5-hexenyl Iodoacetate (11): Bp 150 °C / 0.5 torr; IR (neat) 2862, 1734, 1419, 1261, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (t, *J* = 4.8 Hz, 2H), 3.74 (s, 2H), 4.05 (ddd, *J* = 5.7 Hz, 1.5 Hz, 1.5 Hz, 2H), 4.31 (t, *J* = 4.8 Hz, 2H), 5.22 (ddt, *J* = 10.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.31 (ddt, *J* = 17.1 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.92 (ddt, *J* = 17.1 Hz, 10.2 Hz, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.74, 65.17, 67.42, 72.14, 117.61, 134.35, 168.96. Found: C, 31.24; H, 4.20%. Calcd for $C_7H_{11}IO_3$: C, 31.13; H, 4.11%.

4-Iodo-6-oxa-8-octanolide (12): IR (neat) 2954, 1740, 1452, 1248, 1172, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35–2.57 (m, 3H), 2.69–2.77 (m, 1H), 3.46 (ddd, *J* = 11.7 Hz, 9.9 Hz, 4.2 Hz, 1H), 3.79–3.92 (m, 3H), 4.00 (ddd, *J* = 11.7 Hz, 3.6 Hz, 3.6 Hz, 1H), 4.37–4.45 (m, 1H), 4.80 (ddd, *J* = 11.7 Hz, 9.9 Hz, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.93, 36.37, 37.73, 63.11, 70.42, 80.97, 174.56; MS (Peak Match; Calcd: 270, Meas: EI) 270, 143, 99, 55. Found: C, 31.11; H, 4.13%. Calcd for $C_7H_{11}IO_3$: C, 31.13; H, 4.11%.

2-(2,4-Dioxamethylene)-4-oxa-6-heptenyl Iodoacetate (13): IR (neat) 2862, 1734, 1419, 1261, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (t, *J* = 4.8 Hz, 2H), 3.74 (s, 2H), 4.05 (ddd, *J* = 5.7 Hz, 1.5 Hz, 1.5 Hz, 2H), 4.31 (t, *J* = 4.8 Hz, 2H), 5.22 (ddt, *J* = 10.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.31 (ddt, *J* = 17.1 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.92 (ddt, *J* = 17.1 Hz, 10.2 Hz, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.74, 65.17, 67.42, 72.14, 117.61, 134.35, 168.96. Found: C, 31.24; H, 4.20%. Calcd for $C_7H_{11}IO_3$: C, 31.13; H, 4.11%.

2,4,8,14-Tetraoxa-9-oxo-12-iodospiro[5.9]pentadecane (14): Mp 98-100 °C; IR (nujol) 1727, 1273, 1257, 1210, 1169, 1127, 1089, 1064, 1033, 971, 928 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27–2.53 (m, 4H), 3.34–3.51 (m, 3H), 3.57–3.85 (m, 5H), 4.20–4.29 (m, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.87 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.87, 34.66, 35.71, 38.60, 65.12, 69.56, 69.58, 71.44, 76.20, 94.45, 174.30. Found: C, 36.93; H, 4.69%. Calcd for $C_{11}H_{17}IO_5$: C, 37.10; H, 4.81%.

3,6-Dioxa-8-nonenyl Iodoacetate (15a): Bp 210 °C/0.5 torr; IR (neat) 2862, 1731, 1420, 1261, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59–3.64 (m, 2H), 3.66–3.70 (m, 2H), 3.73 (s, 2H), 3.73 (t, *J* = 4.8 Hz, 2H), 4.04 (ddd, *J* = 5.7 Hz, 1.5 Hz, 1.5 Hz, 2H), 4.31 (t, *J* = 4.8 Hz, 2H), 5.20 (ddt, *J* = 10.2 Hz, 1.8 Hz, 1.8 Hz, 1H), 5.29 (ddt, *J* = 17.4 Hz, 1.8 Hz, 1.8 Hz, 1H), 5.93 (ddt, *J* = 17.4 Hz, 10.2 Hz, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.68, 65.15, 68.76, 69.35, 70.67, 72.27, 117.32, 134.73, 165.64. Found: C, 34.15; H, 4.65%. Calcd for $C_9H_{15}IO_4$: C, 34.41; H, 4.81%.

3,6,9-Trioxa-11-dodecenyl Iodoacetate (15b): IR (neat) 2862, 1736, 1266, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59–3.74 (m, 12H), 4.03 (ddd, *J* = 5.4 Hz, 1.5 Hz, 1.5 Hz, 2H), 4.30 (t, *J* = 4.8 Hz, 2H), 5.19 (ddt, *J* = 10.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.28 (ddt, *J* = 17.1 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.92 (ddt, *J* = 17.1 Hz, 10.2 Hz, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.72, 65.03, 68.60, 69.28, 70.49, 70.54 (2C), 72.09, 117.08, 134.72, 168.82. Found: C, 37.19; H, 5.50%. Calcd for $C_{11}H_{19}IO_5$: C, 36.89; H, 5.35%.

3,6,9,12-Tetraoxa-14-pentadecenyl Iodoacetate (15c): IR (neat) 2866, 1736, 1266, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59–3.74 (m, 16H), 4.03 (ddd, *J* = 5.7 Hz, 1.5 Hz, 1.5 Hz, 2H), 4.30 (t, *J* = 4.8 Hz, 2H), 5.19 (ddt, *J* = 10.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.28 (ddt, *J* = 17.1 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.92 (ddt, *J* = 17.1 Hz, 10.2 Hz, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.74, 64.99, 68.55, 69.25, 70.41, 70.46 (3C), 70.48, 72.05, 117.02, 134.70, 168.80. Found: C, 38.70; H, 5.85%. Calcd for $C_{13}H_{23}IO_6$: C, 38.82; H, 5.76%.

4-Iodo-6,9-dioxa-11-undecanolide (16a): IR (neat) 2864, 1735, 1439, 1248, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02–2.14 (m, 1H), 2.44–2.66 (m, 3H), 3.42–3.80 (m, 8H), 3.95–4.02 (m, 1H), 4.21–4.31 (m, 1H), 4.71–4.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.85, 33.49, 34.23, 62.17, 68.82, 70.38, 70.91, 76.89, 172.66; MS (Peak Match; Calcd: 314, Meas: EI) 314, 187, 143, 99, 55. Found: C, 34.16; H, 4.65%. Calcd for $C_9H_{15}IO_4$: C, 34.41; H, 4.81%.

4-Iodo-6,9,12-trioxa-14-tetradecanolide (16b): IR (neat) 2858, 1732, 1352, 1086 cm^{-1}; ^1H

NMR ($CDCl_3$) δ 2.03–2.17 (m, 1H), 2.42–2.68 (m, 3H), 3.58–3.78 (m, 11H), 3.88 (dd, J = 10.8 Hz, 5.7 Hz, 1H), 4.22–4.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 32.12, 32.53, 34.32, 63.02, 68.69, 70.30 (2C), 70.43, 70.98, 76.91, 172.61; MS (Peak Match; Calcd: 358, Meas: EI) 358, 231, 187, 143, 99, 55. Found: C, 37.08; H, 5.28%. Calcd for $C_{11}H_{19}IO_5$: C, 36.89; H, 5.35%.

4-Iodo-6,9,12,15-tetraoxa-17-heptadecanolide (16c): IR (neat) 2858, 1737, 1352, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04–2.20 (m, 1H), 2.31–2.55 (m, 2H), 2.60–2.71 (m, 1H), 3.60–3.75 (m, 15H), 3.85 (dd, J = 10.5 Hz, 4.5 Hz, 1H), 4.20–4.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.83, 32.18, 34.32, 63.36, 68.77, 70.10, 70.38, 70.41, 70.65, 70.85 (3C), 76.31, 172.62; MS (Peak Match; Calcd: 402, Meas: EI) 402, 275, 231, 187, 143, 99, 55. Found: C, 39.11; H, 5.80%. Calcd for $C_{13}H_{23}IO_6$: C, 38.82; H, 5.76%.

Table S1. The Coordinates of Atoms in **17** optimized at the B3LYP/6-31G* level

Total Energy (au): –345.11641 (B3LYP/6-31G*)

atom	x	y	z
C	–2.546048	–0.076128	–0.587044
C	–1.272386	0.188325	0.048523
O	–0.501987	–0.935586	0.112258
C	0.821960	–0.766560	0.676550
C	1.817608	–0.400712	–0.386242
C	2.526374	0.727605	–0.380232
H	–2.792150	–1.061380	–0.964312
H	–3.252609	0.738806	–0.679070
O	–0.932137	1.278297	0.485586
H	1.050057	–1.743126	1.114905
H	0.786986	–0.009738	1.463144
H	1.940759	–1.125126	–1.190919
H	3.251009	0.951581	–1.158588
H	2.403890	1.472116	0.402755

Table S2. The Coordinates of Atoms in **18** optimized at the B3LYP/6-31G* level

Total Energy (au): –345.09828 (B3LYP/6-31G*)

atom	x	y	z
C	–1.060852	1.473828	–0.333590
C	–1.376248	0.100942	–0.035945
O	–0.531897	–0.860927	–0.563377
C	0.730615	–1.068815	0.102866
C	1.802398	–0.111723	–0.338300
C	2.544258	0.619556	0.494199
H	–0.193701	1.747560	–0.920924
H	–1.723414	2.245368	0.041252
O	–2.371174	–0.231714	0.591782
H	1.006372	–2.094032	–0.167191
H	0.591999	–1.034559	1.191082
H	1.970995	–0.062539	–1.414193
H	3.337711	1.269738	0.135776
H	2.393585	0.586869	1.571577

Table S3. The Coordinates of Atoms in **19** optimized at the B3LYP/6-31G* level

Total energy (au): –345.10529 (B3LYP/6-31G*)

atom	x	y	z
C	–0.961530	1.423026	0.281692
C	–1.413457	0.083576	–0.034359
O	–0.558193	–0.978874	0.062336
C	0.772703	–0.829481	0.585889
C	1.743838	–0.310078	–0.436868
C	2.678186	0.608426	–0.189573
H	0.074473	1.695658	0.433628
H	–1.716908	2.198664	0.272073
O	–2.557518	–0.135600	–0.404285
H	1.045709	–1.848749	0.880740
H	0.770903	–0.211121	1.492241
H	1.664746	–0.767480	–1.422451
H	3.388878	0.919771	–0.949768
H	2.779442	1.076229	0.788444

Table S4. The Coordinates of Atoms in **20** optimized at the B3LYP/6-31G* level

Total Energy (au): –345.09365 (B3LYP/6-31G*)

atom	x	y	z
C	0.350203	–1.219817	0.427803
C	1.297470	–0.161128	0.045519
O	0.773711	1.102248	0.064483
C	–0.653795	1.160042	0.200460
C	–1.331903	–0.009163	–0.479329
C	–2.536611	–0.498489	–0.074846
H	–0.083596	–1.194402	1.422819
H	0.508475	–2.202613	–0.003512
O	2.446258	–0.339190	–0.294764
H	–0.944291	2.106411	–0.268029
H	–0.933216	1.207137	1.261737
H	–1.009055	–0.197281	–1.502768
H	–3.094732	–1.202900	–0.683138
H	–2.955508	–0.249484	0.897488

Table S5. The Coordinates of Atoms in **21** optimized at the B3LYP/6-31G* level

Total Energy (au): –345.13611(B3LYP/6-31G*)

atom	x	y	z
C	0.008515	–1.070302	0.086289
C	1.254980	–0.193169	0.021807
O	0.873082	1.119308	–0.002579
C	–0.558240	1.233095	0.085616
C	–1.126534	–0.130076	–0.385719
C	–2.484988	–0.436937	0.131447
H	–0.142305	–1.381320	1.128793
H	0.134524	–1.972318	–0.515681
O	2.408628	–0.529652	–0.001025
H	–0.868826	2.072641	–0.539697
H	–0.834341	1.441679	1.127191
H	–1.135135	–0.131180	–1.482535
H	–3.296974	–0.720731	–0.527691
H	–2.673022	–0.441683	1.201812

Table S6. The Coordinates of Atoms in **17** optimized at the UHF/6-31G* level

Total Energy (au): –344.12488 (PMP2/6-31+G**//UHF/6-31G*)

atom	x	y	z
C	–2.550090	–0.080274	–0.574371
C	–1.263820	0.187347	0.051825
O	–0.499004	–0.901042	0.124984
C	0.812807	–0.762736	0.662579
C	1.797828	–0.381629	–0.403408
C	2.551583	0.697692	–0.357182
H	–2.795996	–1.060959	–0.929413
H	–3.244736	0.729665	–0.669841
O	–0.940388	1.262480	0.463600
H	1.043553	–1.740922	1.062347
H	0.805464	–0.043658	1.466639
H	1.872157	–1.062530	–1.235818
H	3.261583	0.922703	–1.132817
H	2.483263	1.401795	0.453582

Table S7. The Coordinates of Atoms in **18** optimized at the UHF/6-31G* level

Total Energy (au): –344.10543 (PMP2/6-31+G**//UHF/6-31G*)

atom	x	y	z
C	–1.115097	1.488023	–0.213392
C	–1.404738	0.085535	–0.056428
O	–0.490803	–0.796920	–0.524649
C	0.706957	–0.983458	0.215412
C	1.844415	–0.176307	–0.341382
C	2.635892	0.591758	0.380679
H	–0.215025	1.827022	–0.684654
H	–1.836204	2.195730	0.144684
O	–2.432722	–0.304834	0.431260
H	0.926892	–2.039597	0.132899
H	0.543553	–0.759320	1.263519
H	2.006754	–0.281425	–1.401763
H	3.462582	1.121126	–0.057939
H	2.495069	0.717196	1.441030

Table S8. The Coordinates of Atoms in **19** optimized at the UHF/6-31G* level

Total energy (au): –344.11204 (PMP2/6-31+G**//UHF/6-31G*)

atom	x	y	z
C	–1.002304	1.425533	0.276950
C	–1.405251	0.067011	–0.039499
O	–0.540847	–0.950662	0.075193
C	0.766043	–0.809108	0.591880
C	1.737144	–0.298598	–0.435469
C	2.675577	0.595274	–0.194614
H	0.000122	1.717055	0.508651
H	–1.766932	2.172371	0.206219
O	–2.519624	–0.170373	–0.411317
H	1.040494	–1.813168	0.886397
H	0.769051	–0.193733	1.483959
H	1.648137	–0.747488	–1.410996
H	3.376920	0.894119	–0.952347
H	2.788725	1.058444	0.771624

Table S9. The Coordinates of Atoms in **20** optimized at the UHF/6-31G* level

Total Energy (au): –344.10257 (PMP2/6-31+G**//UHF/6-31G*)

atom	x	y	z
C	0.322315	–1.226852	0.360131
C	1.296965	–0.155408	0.036375
O	0.773863	1.073072	0.047752
C	–0.630278	1.161022	0.186139
C	–1.316572	–0.012479	–0.468853
C	–2.544936	–0.471989	–0.032936
H	–0.021278	–1.275912	1.378741
H	0.471383	–2.169382	–0.132885
O	2.436181	–0.331432	–0.235808
H	–0.909193	2.093166	–0.286132
H	–0.892842	1.221364	1.236748
H	–1.050451	–0.181616	–1.499598
H	–3.119312	–1.163434	–0.620526
H	–2.923624	–0.223068	0.942966

Table S10. The Coordinates of Atoms in **21** optimized at the UHF/6-31G* level

Total Energy (au): –344.14919 (PMP2/6-31+G**//UHF/6-31G*)

atom	x	y	z
C	0.008767	–1.064639	0.082843
C	1.244331	–0.188818	0.024302
O	0.868178	1.092554	–0.006579
C	–0.540298	1.229221	0.074251
C	–1.110258	–0.120641	–0.385653
C	–2.480573	0.373708	1.114463
H	0.139060	–1.953504	–0.517816
O	2.374723	–0.527487	0.010182
H	–0.833086	2.059185	–0.550561
H	–0.812608	1.448717	1.100904
H	–1.127835	–0.128217	–1.471260
H	–3.218226	–0.889748	–0.482322
H	–2.685245	–0.329679	1.188897

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37. Quantitative discussion seems difficult regarding the relationship between the activation volume and rate enhancement. In the case of the Diels–Alder reaction, the value of the decrease in the volume of activation ($\Delta V^{\neq}$) in forming the transition state is between –20 and –45 cm^3/mol. The value of $\Delta V^{\neq}$ typically is –10 cm^3/mol for Cope and Claisen rearrangement. In the present cyclization step, $\Delta V^{\neq}$ is calculated as –4.24 cm^3/mol and –4.14 cm^3/mol at the B3LYP/6-31G* and PMP2/6-31+G**//UHF/6-31G* levels of theory, respectively. For the value of $\Delta V^{\neq}$, see: van Eldik, R.; Asano, T.; Le Nobel, W. J. *Chem. Rev.* **1989**, *89*, 549–688.

CHAPTER 2

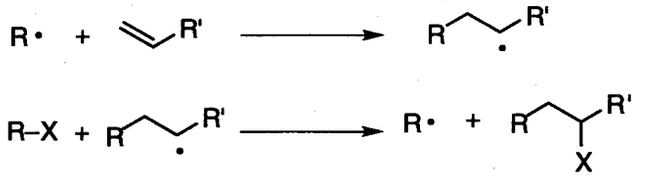
Triethylborane-Induced Bromine Atom Transfer Radical Addition in Aqueous Media: Study of the Solvent Effect on Radical Addition Reaction

A mixture of ethyl bromoacetate and 1-octene was treated with triethylborane in water at ambient temperature to provide ethyl 4-bromodecanoate in good yield. The bromine atom transfer radical addition in benzene was not satisfactory. The addition proceeded smoothly in polar solvents such as DMF and DMSO and protic solvents such as 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-2-propanol, and aqueous media. Ab initio calculations were conducted to reveal the origin of the solvent effect of water in the addition reaction. The polar effect of solvents, which is judged by dielectric constant, on the transition states in the bromine atom transfer and the radical addition steps is moderately important. Calculations show that a polar solvent tends to lower the relative energies of the transition states. The coordination of a carbonyl group to proton in a protic solvent, like a Lewis acid, would also increase the efficiency of the propagation.

Introduction

Halogen atom transfer addition has been extensively studied and widely used in organic synthesis.[1] The addition of a C-X bond across a double bond was pioneered by Kharasch[2] (Scheme 1) and provides new C-C and C-X bonds in a single operation. The choice of the halogen that transfers in the reaction is crucial for the success of atom transfer addition. In the case of α-iodo esters employed as the halide, the reaction proceeded smoothly to give the corresponding adducts under mild conditions.[3] Fast iodine atom transfer from an α-iodo ester to a radical generated by the addition suppresses side reactions and sustains the radical chain. However, the addition of α-bromo esters usually requires high reaction temperatures.[4] The addition of ethyl bromoacetate to 1-octene was performed at 90 °C without solvent in the presence of highly explosive peracetic acid.[2a] Very recently, it was reported that bromine atom transfer radical addition of *N*-bromoacetyl-2-oxazolidinone proceeded smoothly in the presence of a Lewis acid at 25 °C.[5] The addition resulted in poor conversion without Lewis acids such as $Yb(OTf)_3$ and $Sc(OTf)_3$. The use of Lewis acids in radical reactions often enhances a reaction rate and controls stereoselectivity.[6,7]

Scheme 1



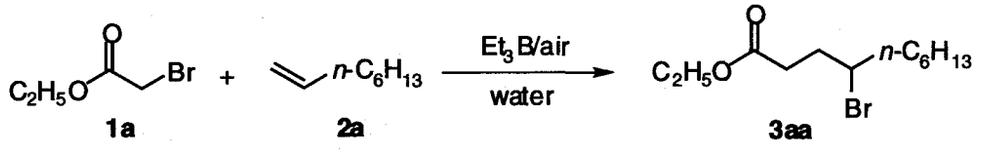
During the last two decades, organic reactions in aqueous media have been attracting increasing attention.[8] On the other hand, radical reactions in water are immature and have not been studied extensively.[9] The author has been investigating radical reactions in aqueous media and disclosed the remarkable solvent effects of water.[10] Here, the bromine atom transfer radical addition of α-bromoacetate with 1-alkene in water is discussed. The reaction in water could be performed at ambient temperature in the presence of triethylborane[11] to yield 4-bromoalkanoate, which will be converted into γ-lactone[2a,12] or γ-lactam.[13] The author has also investigated the solvent effect in detail by performing the reaction in various solvents and found that a polar solvent

as well as a protic solvent gave better yield. Furthermore, ab initio calculations have revealed the origin of the solvent effect on bromine atom transfer addition.

Radical Addition of α-Bromo Carbonyl Compounds to Alkenes.

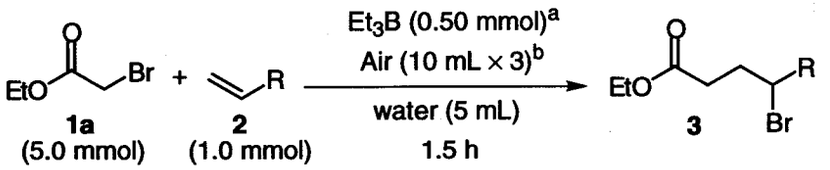
Triethylborane (1.0 M ethanol solution[14], 0.50 mL, 0.50 mmol) was added to a suspension of ethyl bromoacetate (**1a**, 5.0 mmol) and 1-octene (**2a**, 1.0 mmol) in water (5 mL) under argon. Air (10 mL) was then introduced to the reaction flask by a syringe with vigorous stirring. Air was injected every 30 min. The reaction mixture was heterogeneous yet clear. After 1.5 h of reaction, extractive workup followed by silica gel column purification provided ethyl 4-bromodecanoate (**3aa**) in 74% yield (Scheme 2). In contrast to the reaction in water, the reaction proceeded sluggishly in benzene and dichloromethane (12% and 9%, respectively) under the similar reaction conditions. When the reaction mixture in water was kept strictly under argon until concentration, poor conversion was seen (<7%). An excess of **1a** was crucial to obtain **3aa** in satisfactory yield.[15] The reaction of stoichiometric **1a** with **2a** gave **3aa** in only 10% yield with stirring for 1.5 h. Employing 5 equimolar amounts of **2a** also resulted in a miserable yield (19% based on **1a**). However, **3aa** was satisfactorily obtained in 71% yield upon treatment of a mixture of **2a** and 1.3 molar amounts of **1a** with triethylborane (0.50 mmol × 2) for 3 h. These observations suggest that the rate-determining step in the chain propagation would be the bromine atom transfer step.

Scheme 2



The results of the addition of **1a** (5 eq.) to various olefins in water are summarized in Table 1. A wide range of functionalities in **2d–2j** could survive under the reaction conditions. Interestingly, waxy 1-docosene (**2c**) also reacted with **1a** in an aqueous medium, although the mixture was cloudy during the reaction. Allyl alcohol (**2e**) was not a good substrate. Internal double bonds **2k** and **2l** were less reactive (entries 11 and 12). 1,1-Disubstituted alkene could be employed to yield the corresponding tertiary bromide **3am**.

Table 1. Triethylborane-Induced Radical Addition of Ethyl Bromoacetate to Alkenes in Water



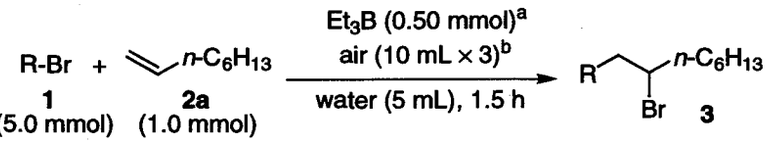
Entry	2	R	3	Yield/%
1	**2a**	*n*-C_6H_{13}	**3aa**	80[c]
2	**2b**	*n*-$C_{10}H_{21}$	**3ab**	65[c]
3	**2c**	*n*-$C_{20}H_{41}$	**3ac**	79[c]
4	**2d**	$(CH_2)_4OH$	**3ad**	81
5	**2e**	CH_2OH	**3ae**	26
6	**2f**	$CH_2CH_2COCH_3$	**3af**	84
7	**2g**	$(CH_2)_3Br$	**3ag**	63
8	**2h**	$(CH_2)_8COOCH_3$	**3ah**	79
9	**2i**	$(CH_2)_4OTHP$	**3ai**	69
10	**2j**	$(CH_2)_3NPH$[d]	**3aj**	82
11	**2k**	cyclohexene	**3ak**	22(54/46)[c,e]
12	**2l**	*trans*-4-octene	**3al**	10(1/1)[c,e]
13	**2m**	2-methyl-1-dodecene	**3am**	77[c]

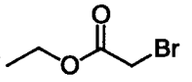
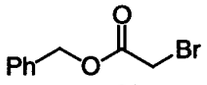
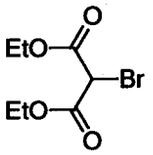
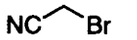
a) 1.0 M Ethanol solution. b) Air was added every 30 min. c) Additional triethylborane (0.50 mmol) was added 1 h after the reaction started. d) NPH = phthalimidyl group. e) Diastereomer ratios are in parentheses.

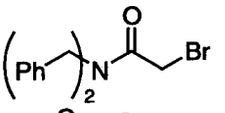
Not only ethyl bromoacetate but also other reactive bromides underwent radical addition (Table 2). Bromomalonate **1c** was so reactive[4] that the addition requires only 1.5 equimolar amounts of **1c**. Similar to bromoacetate, bromoacetonitrile (**1d**) reacted easily with **2a**. However, bromo amide **1e** and *N*-bromoacetyl-2-oxazolidinone (**1f**) were recovered after subjection to radical addition reaction, probably due to the relatively stronger carbon–bromine bond of bromo amides. Unfortunately, the reaction of secondary bromo ester **1g** and **1h** gave a poor conversion in this system. The addition of **1b** with allyltrimethylsilane yielded a mixture of the adduct **3bn** and benzyl 4-pentenoate (**4**). The crude mixture (**3bn/4** = 94/6) was treated with tetrabutylammonium

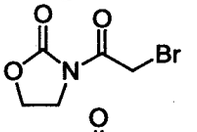
fluoride in THF at 25 °C to furnish **4** in 68% overall yield (Scheme 3).

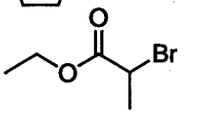
Table 2. Et_3B-Induced Radical Addition of α-Bromo Carbonyl Compounds to 1-Octene in Water

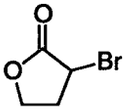


Entry	1	R-Br	3	Yield/%
1	**1a**		**3aa**	80[c]
2	**1b**[d]		**3ba**	99[e]
3	**1c**[f]		**3ca**	81[c]
4	**1d**		**3da**	78

1e  No reaction

1f 

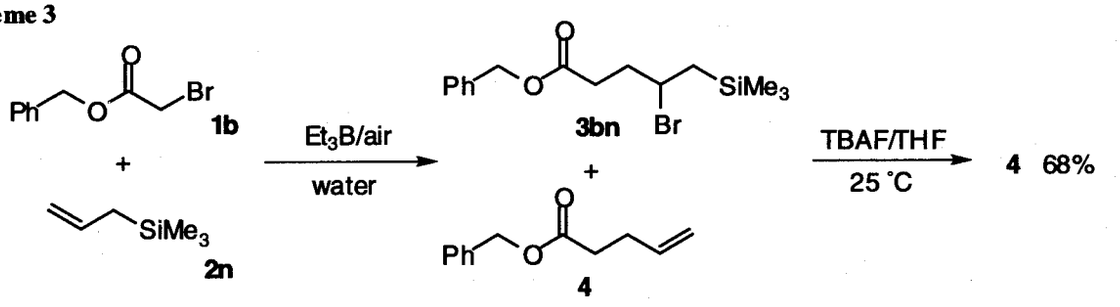
1g 

1h 

<10% yield

a) 1.0 M ethanol solution. b) Air was added every 30 min. c) Additional triethylborane (0.50 mmol) was added 1 h after the reaction started. d) 2.5 mmol of **1b** and 0.50 mmol of **2a** were used. e) Compound**1b** was recovered (1.82 mmol). f) A 1.5 mmol sample of **1c** was used.

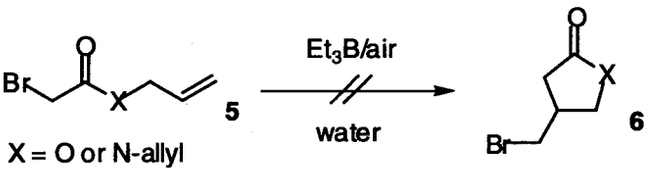
Scheme 3



Radical cyclization of *N,N*-diallyl-2-bromoacetamide or allyl bromoacetate resulted in recovery of the starting materials (Scheme 4). As described above, an excess of bromide is necessary to accomplish the bromine atom transfer reaction. These intramolecular versions

invariably consist of the reaction of an α-bromo amide or ester with 2 or 1 equiv of alkene, respectively. Therefore, bromine atom transfer would not be sufficiently efficient to maintain the radical chain in these cyclizations.

Scheme 4



Radical Addition of Ethyl Bromoacetate to 1-Octene in Various Solvents.

The author observed a significant solvent effect in the intermolecular bromine atom transfer addition; that is, radical addition of **1a** to **2a** was much easier in water than it was in benzene or dichloromethane. To investigate the solvent effect in detail, a series of solvents were surveyed in the reaction of **1a** with **2a** under the otherwise same reaction conditions. Triethylborane (0.50 mmol) was added to a mixture of **1a** (5.0 mmol) and **2a** (1.0 mmol) in a solvent (5 mL) with vigorous stirring, and 5 mL of air was added by a syringe. After 30 min, air (5 mL) was again introduced, and the whole mixture was vigorously stirred for an additional 30 min. Evaporation of the solvent or extractive workup with hexane yielded a crude oil. The yield of **3aa** was determined by fine NMR experiments with dibenzyl ether as an internal standard. Three different procedures for introducing triethylborane were set up. For reactions in nonpolar solvents such as benzene or dichloromethane, a hexane solution of triethylborane was used as an initiator (Method A). An ethanol solution of triethylborane was added in the case where ethanol, aqueous ethanol, aqueous THF, or water was employed as a solvent (Method B). Neat triethylborane was directly added dropwise when reactions were conducted in other solvents (Method C).

The results are listed in Table 3 with the dielectric constant[16] for the solvents examined. The starting materials were almost unchanged when hydrocarbons or halogenated solvents were employed (entries 1–6). The adduct **3aa** was obtained in more than 20% yield in DME and dioxane, although the reaction proceeded sluggishly in ether and THF (entries 7–10). The use of *N*-methylformamide, *N*-methylacetamide, and DMF gave rise to remarkable improvement in yield

among polar solvents having a carbonyl moiety (entries 11–19). *N*-Methylformamide, which has a much larger dielectric constant than water, gave the best result (83% yield) among the solvent systems examined. However, formamide itself resulted in the marginal yield of **3aa**. The reason for the difference is not clear. The reactions in cyclic propylene carbonate and NMP afforded **3aa** in moderate yields. Acetonitrile and HMPA also performed fairly well (entries 20 and 21). DMSO gave a satisfactory result (entry 22, 72% yield). In general, the more polar solvent tends to provide **3aa** in a higher yield.

The addition proceeded moderately in alcohols to afford **3aa** (entries 23–29). It is worth noting that 2,2,2-trifluoroethanol[17] was highly effective for this addition reaction, whereas **3aa** was obtained in only 35% yield when ethanol was used. Thus, the highest yield would be attributed to the acidity of 2,2,2-trifluoroethanol (p*K*a = 12.8). Moreover, 1,1,1,3,3,3-hexafluoro-2-propanol (p*K*a = 9.3) was also superior to 2-propanol.

In water, treatment of a mixture of **1a** and **2a** with an ethanol solution of triethylborane provided **3aa** in 70% yield under the same reaction conditions. Utilization of neat triethylborane, instead of an ethanol solution, resulted in a lower yield (50%). It is therefore likely that a small amount of ethanol may increase the solubility of the reactants in water. Moreover, the reaction without any solvent led to a poor conversion. Thus, the addition in water, which always forms a heterogeneous system, is not a mere solvent-free reaction in the organic phase, and water clearly plays a critical role as a solvent. Lipophilic galvinoxyl and TEMPO (10 mol%) inhibited the reactions. In addition, the reaction in the presence of 4-carboxyTEMPO in 0.10 M NaOH furnished **3aa** in a very poor yield. In this reaction, 4-carboxyTEMPO was mostly converted to the corresponding anion and would trap the radicals in the aqueous phase. These results suggest that the free radicals that are involved in this reaction would easily migrate from the aqueous phase to the organic phase and vice versa. The reaction might involve an interfacial process.

Mixed solvent systems, ethanol/water and THF/water, improved the yield in comparison to ethanol and THF themselves. Notably, the yields were dependent on an ethanol/water ratio. The 3.5/1.5 ethanol/water ratio gave the highest yield. Interestingly, the reaction in perfluorohexane or perfluoro-2-butyltetrahydrofuran (FC-75) furnished **3aa** in a moderate yield.[18] Although the reaction systems are heterogeneous, a higher yield was achieved in a fluorinated solvent than in

hexane or THF. The reason for the effectiveness of fluorous solvents is not clear, because two possibilities, namely, the acceleration by fluorophobic interaction[19] or the high solubility of oxygen in a perfluorinated solvent to improve the efficiency of an initiator,[18,20] could not be distinguished.

Table 3. Triethylborane-Induced Radical Addition of **1a** to **2a** in Various Solvents[a]

Entry	Solvent	Method[b]	Yield of **3aa** /%[c]	Dielectric Constant[d]
1	hexane	A	10	1.88
2	benzene	A	12	2.27
3	toluene	A	6	2.38
4	chlorobenzene	A	5	5.62
5	dichloromethane	A	9	8.93
6	chloroform	C	3	4.81
7	ether	C	10	4.34
8	THF	C	4	7.58
9	DME	C	23	7.20
10	dioxane	C	24	2.21
11	acetone	C	15	20.56
12	ethyl acetate	C	18	6.02
13	dimethyl carbonate	C	30	–
14	propylene carbonate	C	39	64.92
15	formamide	C	16	111.0
16	*N*-methylformamide	C	83	182.4
17	*N*-methylacetamide	C	65	191.3
18	DMF	C	67	36.71
19	NMP	C	42	33.2
20	acetonitrile	C	44	35.94
21	HMPA	C	48	29.30
22	DMSO	C	72	46.45
23	methanol	C	36	32.66
24	ethanol	B	35	24.55
25	isopropyl alcohol	C	35	19.92
26	*t*-butyl alcohol	C	48	12.47
27	ethylene glycol	C	16	37.7
28	TFE[e]	C	73	26.67
29	HFP[f]	C	64	–
30	water	B	70	79.39
31	water	C	50	

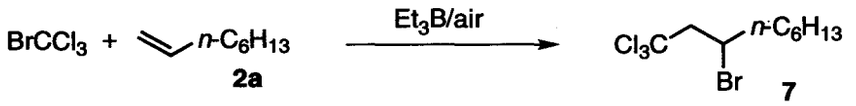
32	no solvent	C	12	
33	0.10 M HCl	B	63	
34	0.10 M NaOH	B	50	
35	water[g]	B	8	
36	water[h]	B	2	
37	0.10 M NaOH[i]	B	14	
38	ethanol/water = 4.5/0.5	B	57	
39	ethanol/water = 4.0/1.0	B	77	
40	ethanol/water = 3.5/1.5	B	81	
41	ethanol/water = 3.0/2.0	B	49	
42	ethanol/water = 2.5/2.5	B	47	
43	ethanol/water = 2.0/3.0	B	48	
44	ethanol/water = 1.5/3.5	B	50	
45	ethanol/water = 1.0/4.0	B	43	
46	ethanol/water = 0.5/4.5	B	53	
47	THF/water = 4.0/1.0	B	61	
48	THF/water = 2.5/2.5	B	43	
49	THF/water = 1.0/4.0	B	46	
50	C_6F_{14}	C	33	–
51	FC-75[j]	C	43	–

a) Compounds **1a** (5.0 mmol) and **2a** (1.0 mmol), triethylborane (0.50 mmol) and solvent (5 mL) were employed. Air (5 mL × 2) was added every 30 min. Reaction time was 1 h. b) Method A: a hexane solution of triethylborane (1.0 M) was added. Method B: an ethanol solution of triethylborane (1.0 M) was used. Method C: neat triethylborane was added. c) Yields were determined by ^{1}H NMR measurement with dibenzyl ether as an internal standard. d) Reproduced from ref. 16. e) 2,2,2-Trifluoroethanol. f) 1,1,1,3,3,3-Hexafluoro-2-propanol. g) Galvinoxyl (10 mol%) was used. h) TEMPO (10 mol%) was used. i) 4-CarboxyTEMPO (10 mol%) was employed. j) Perfluoro-2-butyltetrahydrofuran.

Radical addition of bromotrichloromethane to 1-octene was also examined to attain more information about the solvent effect of bromine atom transfer radical addition. The reaction employed a smaller amount of triethylborane because bromotrichloromethane adds to alkenes very easily. The results are listed in Table 4. The yields of **7** depend on the solvent polarity. This tendency is similar to the result in Table 3. However, two considerable differences were observed. One is the lower yield in the reaction in 2,2,2-trifluoroethanol (60%). The reaction in ethanol yielded the adduct **7** in 80% yield. These results indicate that 2,2,2-trifluoroethanol would

promote the radical addition of ethyl bromoacetate through hydrogen bonding between the oxygen of the carbonyl group and the hydrogen of the fluorous alcohol, while bromotrichloromethane cannot form such a hydrogen bond that lowers the activation energy of the radical reaction (*vide infra*). The other difference is the quantitative formation of **7** in the reaction without solvent and in water. Under the highly concentrated conditions, the addition of bromotrichloromethane proceeded efficiently enough to be completed. The author supposes that the reaction in water would proceed in the organic phase consisting of bromotrichloromethane and 1-octene. Interestingly, comparing entry 9 with entry 11 reveals that the reaction in water was more efficient than the reaction with no solvent.

Table 4. Et_3B-Induced Radical Addition of bromotrichloromethane to **2a** in Various Solvents[a]



Entry	Solvent	Method[b]	Yield of **7** /%[c]	Dielectric Constant[d]
1	hexane	A	45	1.88
2	THF	A	32	7.58
3	ethyl acetate	A	67	6.02
4	acetonitrile	C	84	35.94
5	DMSO	C	77	46.45
6	ethanol	B	80	24.55
7	TFE[e]	C	60	26.67
8	water	B	99[f]	79.39
9	water	B	39[g]	79.39
10	no solvent	A	100[f]	
11	no solvent	A	28[g]	

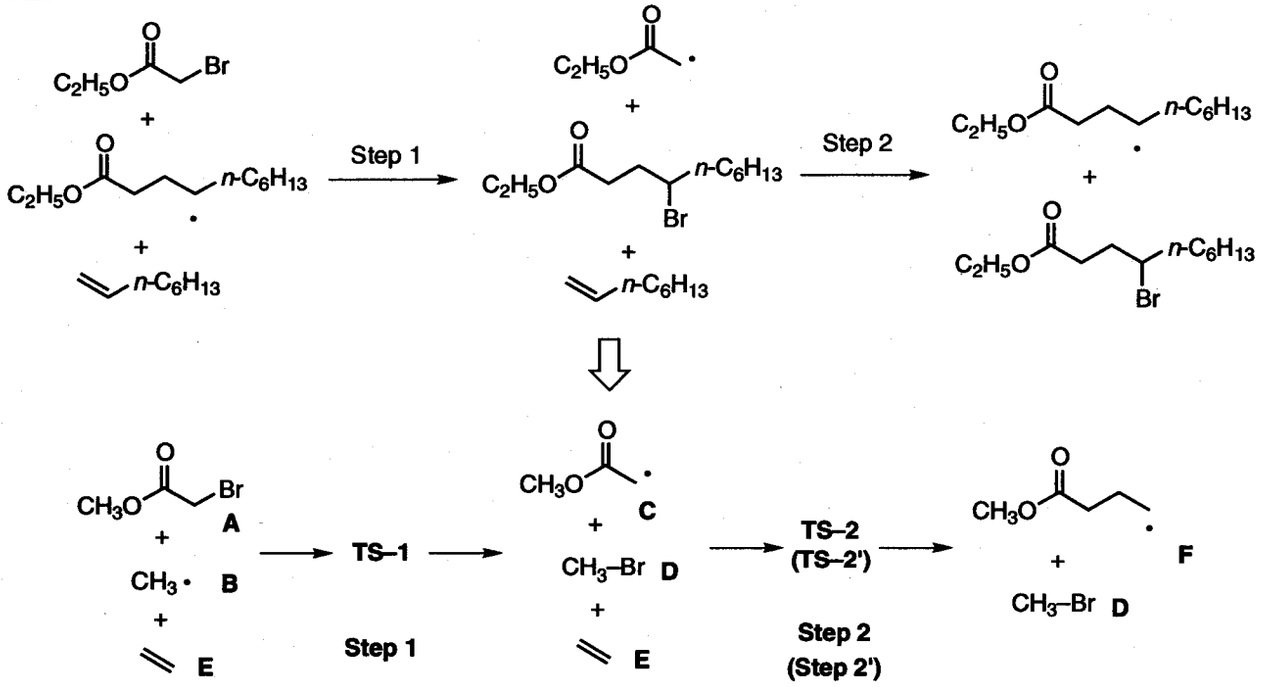
a) Bromotrichloromethane (3.3 mmol), **2a** (3.0 mmol), triethylborane (0.20 mmol), and solvent (5 mL) were employed unless otherwise noted. Air (2 mL × 2) was added every 30 min. Reaction time was 2 h. b) Method A: a hexane solution of triethylborane (1.0 M) was added. Method B: an ethanol solution of triethylborane (1.0 M) was used. Method C: neat triethylborane was added. c) Yields were determined by ^1H NMR measurement with dibenzyl ether as an internal standard. d) Reproduced from ref. 16. e) 2,2,2-Trifluoroethanol. f) Triethylborane (0.10 mmol) was used. g) Triethylborane (0.03 mmol) was used.

Ab Initio Calculations and Discussion.

To explain these results, the author carried out ab initio calculations on the chain-propagation steps consisting of bromine atom transfer and radical addition, using the Gaussian 98 program.[21] All the structures were optimized with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP)[22] using the 6-31G* basis set. Single point calculations of the total energies were performed at second order Møller-Presset perturbation theory[23] with the 6-31G** basis set at the B3LYP/6-31G* optimized geometries. Zero point energy and thermal energy corrections were made at the B3LYP/6-31G* level of theory, and the correction was added to the energy obtained at the PMP2/6-31G**//B3LYP/6-31G* level of theory. The enthalpic corrections were made at 298.150 K. The transition states were obtained with hand-guesses. These transition states gave single imaginary frequencies, and IRC calculations supported the transition structures. Orbital alteration around the frontier orbitals did not affect the result of calculations. A solvent effect that comes from its permittivity was estimated by polarized-continuum-model calculations using the polarizable conductor calculation model based on the self-consistent reaction field theory (SCRF/CPCM)[24,25] at the B3LYP/6-31G* level. The total energy value in a solution was obtained as the sum of the energy at the PMP2/6-31G**//B3LYP/6-31G* level, the solvation energy obtained at the B3LYP/6-31G* level, and the thermodynamic corrections calculated at the B3LYP/6-31G* level. No structures were reoptimized with the continuum solvent model, and the solvent-phase energies were estimated via single point calculations of the gas-phase structure.

To make ab initio MO calculations feasible, the author set up simplified reaction models as shown in Scheme 5. The transition structures of bromine atom transfer (**TS-1** in Step 1) and those of radical addition, which consists of two possible modes with regard to the orientation of the approaching radical to ethylene (**TS-2** and **TS-2'** in Step 2 and Step 2', respectively),[26] are shown in Figures 1 and 2.

Scheme 5.



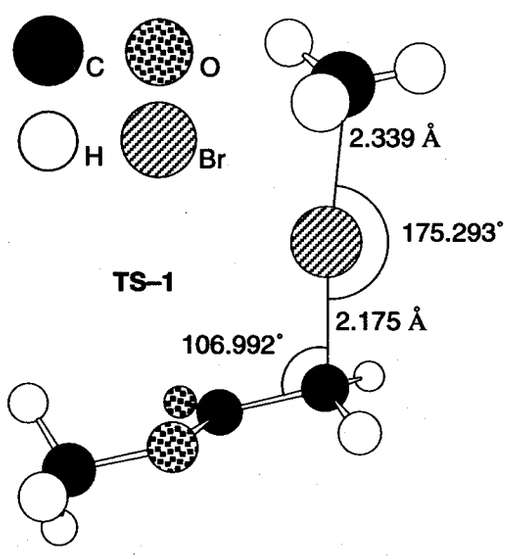


Figure 1. Transition Structure of the Bromine Atom-Transfer Step (Step 1)

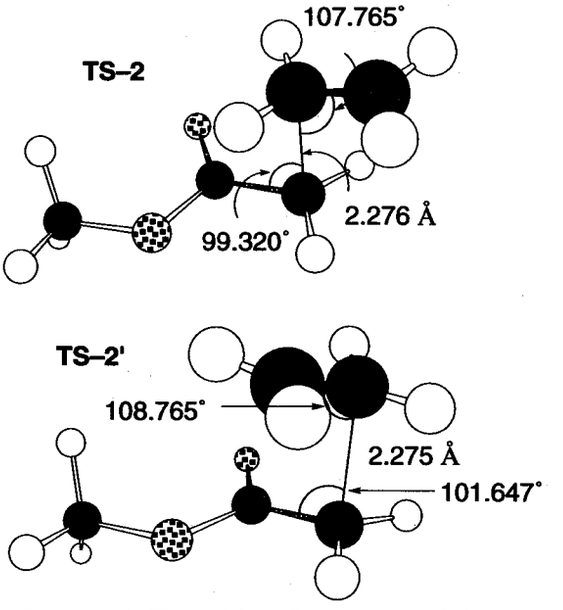


Figure 2. Transition Structures of the Radical Addition Step (Step 2 and Step 2')

The energy of each structure in a vacuum, cyclohexane, acetone, methanol, DMSO, and water is given in Table 5. At the PMP2/6-31G**//B3LYP/6-31G* level of theory, the energy difference between reactants **A** + **B** and the transition state **TS-1** in the bromine atom transfer step under vacuum is 16.26 kcal/mol. On the other hand, the computed activation energies for Step 2 and Step 2' are 14.57 and 14.47 kcal/mol, respectively. The former, the bromine atom transfer step, is suggested to be rate-determining, which is consistent with the experiment. The effect of solvation on the activation energy was then considered. As a whole, the CPCM method could account for the results in Table 3. The energy barriers to bromine atom transfer are calculated to be 15.96, 15.60, 15.71, 15.49, and 15.43 kcal/mol in cyclohexane, benzene, acetone, DMSO, and water, respectively. Polar solvents tend to lower the barrier. This tendency is also observed in the addition step via **TS-2** or **TS-2'**. The calculations in benzene show exceptionally lower energies of the three transition states than those anticipated, judging from its permittivity. The reason for the unexpected results of calculations in benzene is not clear. The energy differences shown in Table 5 are not very sufficient to explain the solvent effect. The difference, for example, between the relative energy of **TS-1** in cyclohexane and that in water is calculated to be 0.53 kcal/mol. The energy difference ($\Delta G^{\neq}_{water}$–$\Delta G^{\neq}_{cyclohexane}$) corresponds to $k_{water}/k_{cyclohexane} = 2.44$, according to the equation $k = (k_B T/h)\exp(-\Delta G^{\neq}/RT)$, where k, k_B, h, R, T, and $\Delta G^{\neq}$ are the rate constant, Boltzmann constant, Planck constant, gas constant, temperature (298.15 K here), and activation energy, respectively. However, qualitative discussion would be acceptable.

Table 5. Calculated Energies for the Simplified Model in Scheme 5

	A+B+E	TS-1+E = $\Delta G^{\neq}$ for Step 1	C+D+E	TS-2+D[a] TS-2'+D[b]	$\Delta G^{\neq}$ for Step 2[a] $\Delta G^{\neq}$ for Step 2'[b]	F+D[a] F'+D[b]
Absolute Energy (au)	–2854.948663	–2854.922758	–2854.957493	–2854.934276[a]		–2854.976258[a]
				–2854.934426[b]		–2854.977179[b]
Relative Energy (kcal/mol)						
in Vacuum	0.00	16.26	–5.54	9.03[a]	14.57[a]	–17.32[a]
				8.93[b]	14.47[b]	–17.89[b]
in Cyclohexane	0.00 (–1.15)	15.96 (–1.45)	–6.75 (–2.36)	8.29 (–1.89)[a]	15.04[a]	–19.57 (–3.40)
				8.31 (–1.77)[b]	15.06[b]	–20.17 (–3.43)[b]
in Benzene	0.00 (1.81)	15.60 (1.15)	–6.81 (0.54)	7.88 (0.66)[a]	14.69[a]	–19.66 (–0.53)[a]
				7.86 (0.74)[b]	14.67[b]	–20.25 (0.55)[b]
in Acetone	0.00 (–0.84)	15.71 (–1.39)	–6.87 (–2.17)	8.02 (–1.85)[a]	14.89[a]	–19.64 (–3.16)[a]
				7.94 (–1.83)[b]	14.81[b]	–20.18 (–3.13)[b]
in DMSO	0.00 (1.12)	15.49 (0.35)	–7.14 (–0.48)	7.69 (–0.22)[a]	14.83[a]	–20.47 (–2.03)[a]
				7.64 (–0.17)[b]	14.78[b]	–21.05 (–2.04)[b]
in Water	0.00 (–0.03)	15.43 (–0.86)	–6.95 (–1.44)	7.84 (–1.22)[a]	14.79[a]	–20.61 (–3.32)[a]
				7.73 (–1.23)[b]	14.68[b]	–21.22 (–3.36)[b]

The absolute energies are values in vacuum. Solvation energies are in parentheses. a) Data for Step 2. b) Data for Step 2'.

There remains another problem: the remarkable solvent effect of protic solvents, especially fluorinated alcohols. Protic solvents usually have large values of a dielectric constant due to their hydrogen bonds. However, it is difficult to explain the extraordinary reactivity in fluorinated alcohols. Fluorous alcohols are highly acidic. Accordingly, a carbonyl group in reactants would coordinate to proton in a fluorous solvent more strongly than in usual alcohols. The author then considered the importance of the coordination of a carbonyl oxygen to hydrogen in a solvent molecule in the present radical reaction. In fact, Lewis acid-promoted radical reactions were reported,[6,7] and it is therefore of significance to conduct calculations including coordination.

For the case where one explicit water molecule is arranged to be coordinated by a carbonyl group, the structures were optimized again in a similar way.[27] The results were summarized in Figures 3 and 4, and Table 6. Comparison of the activation energies for Step 1 (16.26 kcal/mol), Step 2 (14.57 kcal/mol), and Step 2' (14.47 kcal/mol) with those for Step 1(W) (15.59 kcal/mol), Step 2(W) (13.88 kcal/mol), and Step 2'(W) (13.51 kcal/mol), respectively, showed that the coordination lowered the activation energy in each case.

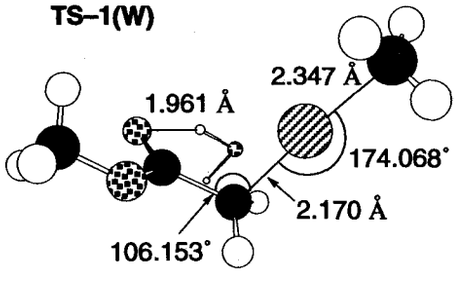


Figure 3. Transition Structure of Step 1 with Explicit Water

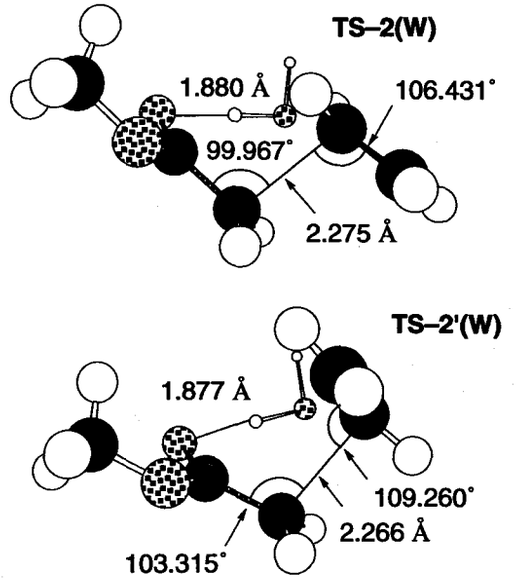


Figure 4. Transition Structures of Step 2 and 2' with Explicit Water

Table 6. Calculated Energies with Explicit Water

	A(W)+B+E	TS-1(W)+E $=\Delta G^{\neq}$ for Step1(W)	C(W)+D+E	TS-2(W)+D[a] TS-2(W)'+D[b]	$\Delta G^{\neq}$ for Step2(W)[a] $\Delta G^{\neq}$ for Step2'(W)[b]	F(W)+D[a] F'(W)+D[b]
Absolute Energy (au)	–3031.160997	–3031.136158	–3031.170732	–3031.148611[a] –3031.149201[b]		–3031.190085[a] –3031.189851[b]
Relative Energy (kcal/mol)						
in Vacuum	0.00	15.59	–6.11	7.77[a] 7.40[b]	13.88[a] 13.51[b]	–18.26[a] –18.11[b]
in Water	0.00 (–0.67)	14.73 (–1.53)	–7.80 (–2.36)	6.78 (–1.66)[a] 6.37 (–1.70)[b]	14.58[a] 14.17[b]	–21.76 (–4.17)[a] –21.47 (–4.03)[b]

The absolute energies are values in vacuum. Solvation energies are in parentheses. a) Data for Step 2. b) Data for Step 2'.

The HOMO, HOMO–1, and LUMO of **A** and the SOMO of a (methoxycarbonyl)methyl radical **C** are shown in Figure 5. The water-coordinated form also has similar orbitals. The energies of these orbitals are listed in Table 7. The HOMO and the HOMO–1 of **A** exist as the lone pairs of bromine, and these are almost orthogonal to the SOMO of an approaching methyl radical. Thus, the HOMO of **A** and the SOMO of **B** do not overlap with each other. On the other hand, the LUMO of **A**, the σ* orbital of the C–Br bond, can interact closely with the SOMO of **B**. The lower the energy of LUMO becomes, the faster the atom transfer proceeds. This is indeed the case, and the LUMO of **A(W)** is calculated to be lower than that of **A** by 0.134 eV. Additionally, the author focused on the electron populations of **A** and **TS-1** (Table 8). The Mulliken charges on the (methoxycarbonyl)methyl moiety of **A** and of **TS-1** are +0.0996 and +0.0087, respectively. Thus, the electron population of the (methoxycarbonyl)methyl moiety becomes larger as the reaction proceeds to the transition state. Furthermore, the length of the hydrogen bond of **TS-1(W)** optimized at the B3LYP/6-31G* level is shorter than that of **A(W)** by 0.024 Å. Some of the increasing electron population is probably delocalized around the water molecule, and **TS-1** would be stabilized. To clarify the assumption, the stabilization energies generated by the coordination to a water molecule were estimated at **A(W)** and **TS-1(W)** (Table 9) as follows. The author first obtained the sum of the energy given *E*[**A(W)***] by the single point calculations at the PMP2/6-31G** level on the structure obtained by lifting water from **A(W)** and the energy of water extracted from **A(W)**. Next, the author prescribed the difference between the total energy *E*[**A(W)***] and the energy of **A(W)** *E*[**A(W)**] as the stabilization energy provided by the coordination (ΔE_{coord}) at **A(W)**. Similar calculations were done on **TS-1(W)**. The coordination of the transition states to water affords the stabilization energies at **TS-1(W)** as 8.58 kcal/mol. In contrast, ΔE_{coord} at **A(W)** is calculated to be 8.23 kcal/mol. Thus, water binds more firmly at **TS-1(W)** than at **A(W)**, and the coordination would promote electron transfer to methyl bromoacetate.

Next, the SOMO of **C** is discussed to examine the addition step. It is known that radicals with electron-withdrawing substituents at the radical center have low-level SOMOs, and the interaction between the SOMO of the radical and the HOMO of olefin therefore dominates, with an electron in the HOMO being transferred to the SOMO.[28] In fact, the Mulliken charges of the (methoxycarbonyl)methyl moieties of **TS-2** and **TS-2'** are calculated to be –0.0761 and –0.0777,

respectively (Table 8), which indicates the electron transfer from **E** to **C** during the uphill stage toward the transition states. Lowering the level of the SOMO of **C** would thereby give rise to easier electron transfer to the SOMO and promotes Steps 2 and 2'. Actually, the SOMO energy is found to be lower by 0.0781 eV as a result of the coordination to water as shown in Table 7. Furthermore, as illustrated in Figures 4 and 6, the length of the hydrogen bond between water and the carbonyl group becomes shorter as the reaction progresses, which seems to help the electron transfer. The author calculated the stabilization energy ΔE_{coord} as performed in the bromine atom transfer step, applying corrections due to the basis set superposition error.[29] The coordinations of the transition states to water afford values of 15.36 and 15.51 kcal/mol for the stabilization energies at **TS-2(W)** and **TS-2'(W)**, respectively. In contrast, ΔE_{coord} at **C(W)** is calculated to be 12.64 kcal/mol. Thus, the hydrogen bond is stronger at **TS-2(W)** and **TS-2'(W)** than at **C(W)**. This fact indicates that the negative charge on the (methoxycarbonyl)methyl moiety that comes from the electron transfer from the olefin would be stabilized by the hydrogen bond. The water molecule stabilizes the transition states of the addition step by having a stronger hydrogen bond than it does the initial state. Consequently, water enhances electron transfer from ethylene to the radical.

The coordination to water has proved to lower the activation barriers in both steps. Furthermore, the author applied the CPCM option to the structures with water coordination. The relative energy of the transition structure of the bromine atom transfer in water is calculated to be 14.73 kcal/mol (Table 6), lower than that in cyclohexane without explicit water (15.96 kcal/mol, Table 5) by 1.23 kcal/mol. The energy difference means that the reaction in water with coordination proceeds 7.9 times faster than that in cyclohexane without coordination. In the addition step, the computed activation energies for Step 2(W) and Step 2'(W) in water are 14.58 and 14.17 kcal/mol, respectively. Compared with the result in cyclohexane shown in Table 5, the activation energies decrease by 0.46 kcal/mol in Step 2(W) and 0.89 kcal/mol in Step 2'(W). Hence, not only a polar effect but also the coordination of a carbonyl group to a protic solvent plays an significant role in the enhancement of intermolecular bromine atom transfer addition reactions.

The result of the calculations on the explicit water model would be regarded as the model of a Lewis acid-promoted radical reaction. The coordination of a Lewis acid would accelerate

propagation in a similar fashion. Consequently, a catalytic amount of Lewis acid[7a–7g] as well as a stoichiometric Lewis acid could control radical reactions.

Table 7. Energies of the HOMO and the LUMO of **A** and the SOMO of **C**

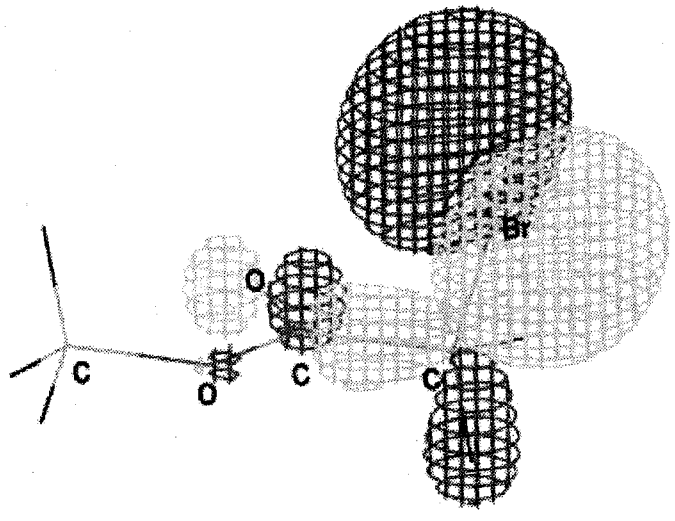
	HOMO	HOMO–1	LUMO
A (au)	–0.40919	–0.40953	0.11173
A(W) (au)	–0.40629	–0.40858	0.10680
ΔE**[A(W)–A] (eV)**	0.0790	0.0260	–0.134

	SOMO
C (au)	–0.41157
C(W) (au)	–0.41444
ΔE**[C(W)–C] (eV)**	–0.0781

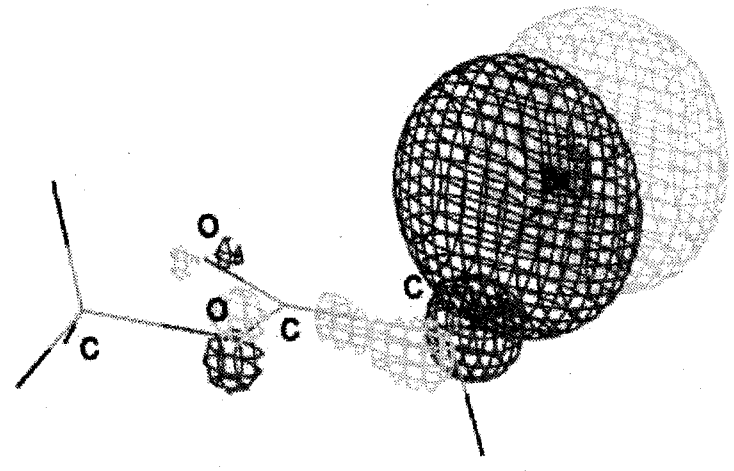
Table 8. Mulliken Charges on the (Methoxycarbonyl)methyl Moiety

	Charge
A	+0.0996
TS-1	+0.0087
C	0
TS-2	–0.0761
TS-2'	–0.0777

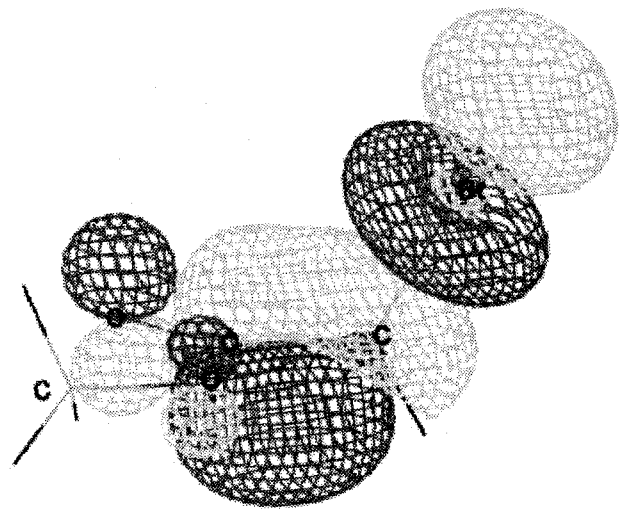
Figure 5. Molecular Orbitals of **A** and **C**



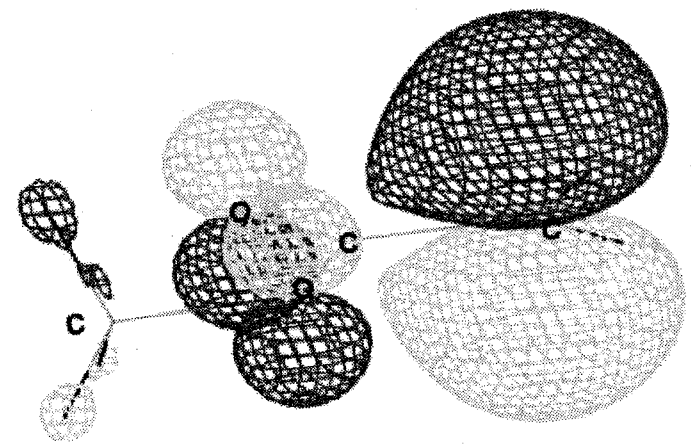
a) HOMO of **A**



b) HOMO–1 of **A**



c) LUMO of **A**



d) SOMO of **C**

Table 9. Stabilization Energies Generated by the Coordination

	Energy /au[a]
Methyl bromoacetate of **A(W)**	–2837.023988
Water of **A(W)**	–76.219529
The sum of the above two energies E[**A(W)***]	–2913.243518
E[**A(W)**]	–2913.256630
ΔE_{coord}[**A(W)**] = E[**A(W)**] – E[**A(W)***]	–0.01311 = –8.23 kcal/mol
TS-1(W) without water	–2876.708310
Water of **TS-1(W)**	–76.219504
The sum of the above two energies E[**TS-1(W)***]	–2952.927814
E[**TS-1(W)**]	–2952.941483
ΔE_{coord}[**TS-1(W)**] = E[**TS-1(W)**] – E[**TS-1(W)***]	–0.01367 = –8.58 kcal/mol
(Methoxycarbonyl)methyl moiety of **C(W)**	–266.953391[b]
Water of **C(W)**	–76.220755[b]
The sum of the above two energies E[**C(W)***]	–343.174146[b]
E[**C(W)**]	–343.194289
ΔE_{coord}[**C(W)**] = E[**C(W)**] – E[**C(W)***]	–0.02014 = –12.64 kcal/mol[b]
TS-2(W) without water	–345.263045[b]
Water of **TS-2(W)**	–76.221187[b]
The sum of the above two energies E[**TS-2(W)***]	–421.484232[b]
E[**TS-2(W)**]	–421.508705
ΔE_{coord} [**TS-2(W)**] = E[**TS-2(W)**] – E[**TS-2(W)***]	–0.024473 = –15.36 kcal/mol[b]
(Methoxycarbonyl)methyl moiety of **TS-2'(W)**	–345.263324[b]
Water of **TS-2'(W)**	–76.221127[b]
The sum of the above two energies E[**TS-2'(W)***]	–421.484451[b]
E[**TS-2'(W)**]	–421.509167
ΔE_{coord} [**TS-2'(W)**] = E[**TS-2'(W)**] – E[**TS-2'(W)***]	–0.024716 = –15.51 kcal/mol[b]

a) None of the energies include thermal energy corrections. b) Basis set superposition errors are considered.

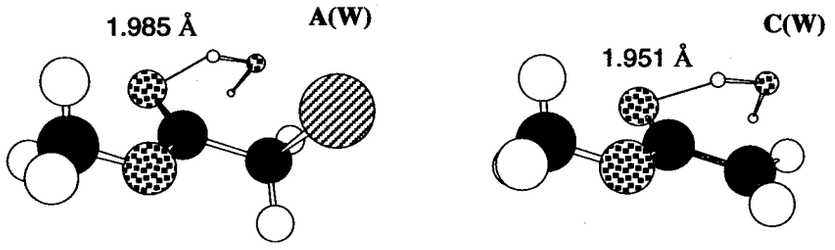


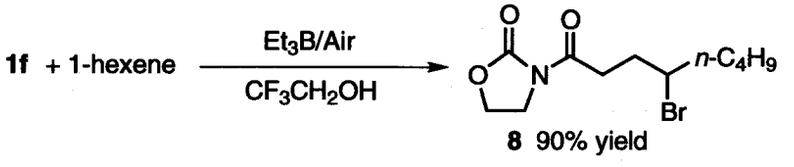
Figure 6. Optimized Structures of **A(W)** and **C(W)**

Miscellaneous Experimental Results

Other successful results in a protic solvent are summarized in Table 10. Similar to the reaction in water, comparable results were given in aqueous ethanol and in 2,2,2-trifluoroethanol. The addition of **1a** to allyl alcohol (**2e**) is more effective in 2,2,2-trifluoroethanol (Entry 6, Table 10) than in water (Entry 5, Table 1) or in aqueous ethanol (Entry 5, Table 10). Carbonyl groups in **2f** and **2h** also survived under these conditions. The yield of the adducts is dependent on the amount of the solvent employed (entries 13–17). The reactions in 3 mL and 1 mL of 2,2,2-trifluoroethanol provided **3aa** in 80 and 50% yields, respectively. The highest yield was achieved using 3 mL of water (entry 16).

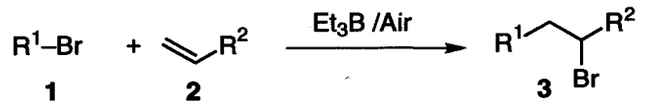
Interestingly, bromo oxazolidinone **1f** underwent radical addition in 2,2,2-trifluoroethanol without a Lewis acid.[7] A mixture of 1-hexene (3 mmol) and **1f** (1 mmol) was treated with neat triethylborane (0.5 mmol) for 1.5 h. Evaporation of the solvent followed by silica gel column purification provided **8**[5] in 90% yield (Scheme 6). In contrast, the reaction of **1f** in water resulted in a poor yield in the presence or absence of 10 mol% $Yb(OTf)_3$. Coordination of **1f** to the solvent enhanced the reaction.

Scheme 6.



8 90% yield

Table 10. Results of Radical Addition in a Protic Solvent.



Entry	1	2	Solvent[a]	Yield /%
1	**1a**	**2a**	A	64
2	**1a**	**2a**	B	73
3	**1a**	**2d**	A	91
4	**1a**	**2d**	B	64
5	**1a**	**2e**	A	18
6	**1a**	**2e**	B	41
7	**1a**	**2f**	A	51
8	**1a**	**2f**	B	53
9	**1a**	**2g**	A	65
10	**1a**	**2g**	B	72
11	**1a**	**2h**	A	72
12	**1a**	**2h**	B	70
13	**1a**	**2a**	B[b]	80
14	**1a**	**2a**	B[c]	50
15	**1a**	**2a**	C[d,e]	81
16	**1a**	**2a**	C[b,d]	94
17	**1a**	**2a**	C[c,d]	76
18	**1d**	**2a**	B	79

a) Otherwise, conditions are the same as those in Table 1. Solvent A: a mixed solvent of ethanol and water (3.5/1.5). Solvent B: 2,2,2-trifluoroethanol. Solvent C: water. b) A 3 mL volume of solvent. c) A 1 mL volume of solvent. d) Triethylborane was added twice. e) A 10 mL volume of solvent.

In conclusion, the author has disclosed that the intermolecular bromine atom transfer addition reaction of α-bromo ester to an alkene, which resulted in poor conversion in nonpolar solvents at ambient temperature, proceeded efficiently in water. The addition reaction was examined in various solvents at ambient temperature, and more polar solvents as well as protic solvents, especially perfluorinated alcohols, improved the efficiency of the reaction. The origin of the solvent effect was revealed by ab initio calculations. The polar nature of both the reactants and

transition states in the bromine atom transfer and in the radical addition would promote the reaction. Furthermore, the coordinations of the carbonyl groups to protons in a protic solvent would also increase the efficiency of the propagation. The choice of solvent is worth consideration in radical reactions.

Experimental Section

Typical Procedure for Bromine Atom Transfer Addition of an α-Bromo Carbonyl Compound to an Alkene. The reaction of ethyl bromoacetate (**1a**) with 1-octene (**2a**) is representative. Compounds **1a** (0.55 mL, 5.0 mmol), **2a** (0.16 mL, 1.0 mmol) and distilled water (5.0 mL) were placed in a 20-mL reaction flask under an argon atmosphere. Triethylborane (1.0 M ethanol solution, 0.50 mL, 0.50 mmol) was then added at 25 °C with vigorous stirring. Air (10 mL) was immediately introduced into the reaction flask (not by bubbling). **CAUTION:** *Triethylborane may ignite spontaneously when exposed to air.* The reaction mixture was treated with additional air (10 mL × 2) every 30 min. The reaction was quenched with 10 mL of hexane, and an organic layer was dried over anhydrous sodium sulfate and was concentrated in vacuo. Silica gel column chromatography of the crude oil (hexane/ethyl acetate = 20/1) provided ethyl 4-bromodecanoate (**3aa**, 207 mg) in 74% yield.

Alternatively, the following procedure is useful. In a 20-mL reaction flask filled with argon, a mixture of **1a** (0.14 mL, 1.3 mmol) and **2a** (0.16 mL, 1.0 mmol) was treated with neat triethylborane (0.07 mL, 0.5 mmol) in water (5.0 mL). Air (10 mL) was introduced into the reaction flask with stirring. After 30 min, air was added again. The mixture was stirred for an additional 30 min. Neat triethylborane was added again, and the mixture was then exposed to air with stirring for 2 h. Usual workup and silica gel column purification afforded 198 mg of **3aa** (71%).

The addition of **1b** to allyltrimethylsilane shown in Scheme 3 provided a mixture of **3bn** and **4** (94/6). The crude product was dissolved in 3 mL of THF and was treated with tetrabutylammonium fluoride (1.0 M THF solution, 2.0 mL, 2.0 mmol) at 25 °C. The temperature of the mixture raised somewhat. After the mixture was stirred for 30 min, the reaction was quenched with water, and the products were extracted twice with hexane. Concentration of the organic layer followed by silica gel column purification furnished 0.68 mmol of **4**.

Procedure for Bromine Atom Transfer Addition in Various Solvents (Table 3). Method A. The reaction in hexane is representative. A 20-mL reaction flask was filled with argon, and hexane (5 mL) was added to the reaction flask. Compounds **1a** (5.0 mmol) and **2a** (1.0 mmol)

were then added. A 1.0 M hexane solution of triethylborane (0.50 mL, 0.50 mmol) was introduced by a syringe, and air (5 mL) was added. After 30 min, 5 mL of air was injected again. The reaction mixture was stirred for 1 h overall. After evaporation of hexane, dibenzyl ether (0.3 mmol) was added to the residual oil as an internal standard. ^{1}H NMR experiment indicated 10% yield of **3aa**. **Method B.** Compounds **1a** and **2a** were placed in a 20-mL flask, and ethanol (3.5 mL) and water (1.5 mL) were added under argon. A solution of triethylborane in ethanol (1.0 M, 0.50 mL, 0.50 mmol) and air were sequentially added with vigorous stirring. The reaction mixture was homogeneous. After the mixture was treated with additional air as described in Method A, extractive workup (hexane/brine) followed by ^{1}H NMR measurement yielded **3aa** in 81% yield. **Method C.** Neat triethylborane (0.07 mL, 0.5 mmol) was added to a solution of **1a** and **2a** in 2,2,2-trifluoroethanol under argon. Air was then introduced twice as described above. Concentration in vacuo provided **3aa** in 73% yield.

Characterization Data

5-Hexenyl Tetrahydro-2-pyranyl Ether (2i): IR (neat) 2924, 1643, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41–1.90 (m, 10H), 2.09 (dt, *J* = 6.6, 6.6 Hz, 2H), 3.39 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.46–3.54 (m, 1H), 3.75 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.83–3.91 (m, 1H), 4.59 (dd, *J* = 4.2, 2.7 Hz, 1H), 4.92–5.05 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.46, 25.34, 25.42, 29.06, 30.60, 33.43, 62.15, 67.30, 98.75, 114.46, 138.80. Found: C, 71.85; H, 10.97%. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94%.

Ethyl 4-Bromodecanoate (3aa): IR (neat) 2930, 2858, 1738, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.23–1.57 (m, 11H), 1.74–1.91 (m, 2H), 1.97–2.11 (m, 1H), 2.13–2.26 (m, 1H), 2.44–2.65 (m, 2H), 4.01–4.11 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.88, 14.05, 22.41, 27.34, 28.51, 31.51, 32.25, 33.87, 39.14, 57.18, 60.41, 172.98. Found: C, 51.86; H, 8.58%. Calcd for $C_{12}H_{23}BrO_2$: C, 51.62; H, 8.30%.

Ethyl 4-Bromotetradecanoate (3ab): IR (neat) 2926, 2855, 1738, 1464, 1184 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.16–1.62 (m, 19H), 1.74–1.93 (m, 2H), 1.97–2.11 (m, 1H),

2.14–2.26 (m, 1H), 2.44–2.65 (m, 2H), 4.01–4.11 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.98, 14.09, 22.57, 27.43, 28.89, 29.21, 29.35, 29.45, 29.48, 31.80, 32.30, 33.90, 39.18, 57.26, 60.46, 173.05. Found: C, 57.20; H, 9.58%. Calcd for $C_{16}H_{31}BrO_2$: C, 57.31; H, 9.32%.

Ethyl 4-Bromotetracosanoate (3ac): IR (neat) 2916, 2851, 1738, 1468, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H), 1.10–1.36 (m, 37H), 1.36–1.60 (m, 2H), 1.75–1.90 (m, 2H), 1.99–2.11 (m, 1H), 2.12–2.25 (m, 1H), 2.44–2.65 (m, 2H), 4.00–4.10 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.93, 14.03, 22.55, 27.40, 28.87, 29.25, 29.34, 29.44, 29.51, 29.55, 29.59 (8C), 31.47, 31.81, 32.20, 33.86, 39.17, 56.99, 60.32, 172.85. Found: C, 65.93; H, 11.10%. Calcd for $C_{26}H_{51}BrO_2$: C, 65.66; H, 10.81%.

Ethyl 4-Bromo-8-hydroxyoctanoate (3ad): IR (neat) 3322, 2936, 1724, 1377, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.46–1.70 (m, 4H), 1.70–1.82 (m, 1H), 1.82–1.92 (m, 2H), 1.98–2.12 (m, 1H), 2.14–2.26 (m, 1H), 2.45–2.65 (m, 2H), 3.66 (t, J = 4.8 Hz, 2H), 4.02–4.10 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.89, 23.59, 31.66, 32.07, 33.66, 38.69, 56.75, 60.37, 62.11, 172.95. Found: C, 44.88; H, 6.87%. Calcd for $C_{10}H_{19}BrO_3$: C, 44.96; H, 7.17%.

Ethyl 4-Bromo-5-hydroxypentanoate (3ae): IR (neat) 3250, 2902, 1723, 1480–1000 (broad) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 2.06–2.30 (m, 3H), 2.45–2.68 (m, 2H), 3.74–3.86 (m, 2H), 4.12–4.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.94, 29.42, 31.60, 57.11, 60.62, 66.63, 173.08. Found: C, 37.64; H, 5.83%. Calcd for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82%.

Ethyl 4-Bromo-7-oxooctanoate (3af): IR (neat) 2978, 1729, 1365, 1252, 1185, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 6.9 Hz, 3H), 1.92–2.32 (m, 7H), 2.38–2.81 (m, 4H), 4.03–4.18 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.90, 29.81, 32.02, 32.42, 33.95, 41.11, 56.08, 60.31, 172.56, 207.30. Found: C, 45.53; H, 6.75%. Calcd for $C_{10}H_{17}BrO_3$: C, 45.30; H, 6.46%.

Ethyl 4,7-Dibromoheptanoate (3ag): IR (neat) 2960, 1729, 1442, 1375, 1258, 1176, 1033

cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.90–2.27 (m, 6H), 2.46–2.66 (m, 2H), 3.45 (t, J = 6.0 Hz, 2H), 4.02–4.11 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.01, 30.36, 32.08, 32.59, 33.90, 37.31, 55.39, 60.44, 172.68. Found: C, 34.46; H, 5.03 %. Calcd for $C_9H_{16}Br_2O_2$: C, 34.21; H, 5.10%.

Ethyl 4-Bromo-12-(methoxycarbonyl)tridecanoate (3ah): IR (neat) 2926, 1738, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 6.9 Hz, 3H), 1.26–1.34 (m, 8H), 1.38–1.69 (m, 4H), 1.77–1.88 (m, 2H), 1.97–2.10 (m, 1H), 2.13–2.25 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 2.44–2.65 (m, 2H), 3.67 (s, 3H), 4.01–4.10 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.91, 24.60, 27.19, 28.59, 28.78, 28.84, 28.93, 32.06, 33.72, 33.75, 38.94, 51.15, 56.96, 60.23, 172.75, 174.14. Found: C, 52.56; H, 8.14%. Calcd for $C_{16}H_{29}BrO_4$: C, 52.61; H, 8.00%.

Ethyl 4-Bromo-8-(tetrahydro-2-pyranyloxy)octanoate (3ai, 50/50 mixture of diastereomers**):** IR (neat) 2932, 2864, 1737, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.44–1.92 (m, 12H), 1.97–2.10 (m, 1H), 2.13–2.25 (m, 1H), 2.44–2.64 (m, 2H), 3.35–3.43 (m, 1H), 3.46–3.54 (m, 1H), 3.71–3.79 (m, 1H), 3.82–3.90 (m, 1H), 4.01–4.17 (m, 3H), 4.58 (dd, J = 4.2, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.97 (2C), 19.40, 19.41, 24.14, 24.16, 25.24 (2C), 28.82, 28.85, 30.51 (2C), 32.12 (2C), 33.75 (2C), 38.81, 38.82, 56.81 (2C), 60.32 (2C), 61.15 (2C), 67.00, 67.04, 98.72, 98.77, 172.83 (2C). Found: C, 51.24; H, 7.50%. Calcd for $C_{15}H_{27}BrO_4$: C, 51.29; H, 7.75%.

Ethyl 4-Bromo-7-Phthalimidylheptanoate (3aj): IR (neat) 2937, 1771, 1713, 1398, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.79–2.31 (m, 6H), 2.44–2.64 (m, 2H), 3.73 (t, J = 6.6 Hz, 2H), 4.05–4.17 (m, 3H), 7.73 (dd, J = 4.8, 3.0 Hz, 2H), 7.86 (dd, J = 4.8, 3.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.82, 26.44, 31.90, 33.64, 35.86, 36.71, 55.73, 60.19, 123.00, 131.79, 133.80, 168.14, 172.52. Found: C, 53.30; H, 5.28%. Calcd for $C_{17}H_{20}BrNO_4$: C, 53.42; H, 5.27%.

Ethyl (2-Bromocyclohexyl)acetate (3ak, 54/46 mixture of diastereomers**):** IR (neat) 2936, 2860, 1732, 1285, 1161, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06–1.43 (m, 5H), 1.46–1.60 (m, 2H),

1.71–2.01 (m, 3.54H), 2.07–2.49 (m, 3H), 2.91 (dd, J = 15.0, 3.0 Hz, 0.46H), 3.88 (dt, J = 4.2, 10.8 Hz, 0.46H), 4.14 (q, J = 7.2 Hz, 2H), 4.64 (q, $J \approx 3$ Hz, 0.54H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 14.08, 25.01, 27.01, 34.78, 38.93, 40.14, 40.34, 60.31, 60.85, 172.52, for minor isomer, δ 14.09, 20.49, 25.11, 27.29, 32.32, 38.51, 43.20, 58.56, 60.26, 172.56. Found: C, 48.21; H, 6.96%. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88%.

Ethyl 4-Bromo-3-propylheptanoate (3al, 1/1 mixture of diastereomers)**:** IR (neat) 2934, 2874, 1738, 1464, 1373, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–0.98 (m, 6H), 1.20–1.54 (m, 9H), 1.54–2.04 (m, 3H), 2.04–2.16 (m, 1H), 2.25 (dd, J = 15.9, 8.4 Hz, 0.5H), 2.36 (dd, J = 16.2, 6.0 Hz, 0.5H), 4.15 (q, J = 7.2 Hz, 2H), 4.17–4.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.28 (2C), 13.89, 14.08 (2C), 14.11, 19.79, 20.23, 21.21, 21.29, 32.38, 35.55, 36.15, 37.23, 38.22, 39.03, 40.60, 40.81, 60.40, 60.45, 61.99, 62.83, 173.14, 173.21. Found: C, 51.85; H, 8.06%. Calcd for $C_{12}H_{23}BrO_2$: C, 51.62; H, 8.30%.

Ethyl 4-Bromo-4-methyltetradecanoate (3am): IR (neat) 2926, 2855, 1738, 1464, 1379, 1304, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.22–1.34 (m, 17H), 1.40–1.52 (m, 2H), 1.70 (s, 3H), 1.74–1.92 (m, 2H), 2.01–2.24 (m, 2H), 2.56 (t, J = 7.8 Hz, 2H), 4.15 (t, J = 7.2 Hz, 2H); ^{13}C NMR (CDCl3) δ 13.90, 14.00, 22.49, 25.49, 29.15, 29.31, 29.42 (2C), 29.47, 30.98, 31.11, 31.73, 39.69, 45.51, 60.37, 71.60, 173.13. Found: C, 58.71; H, 9.77%. Calcd for $C_{17}H_{33}BrO_2$: C, 58.45; H, 9.52%.

Benzyl 4-Bromodecanoate (3ba): IR (neat) 2930, 2858, 1738, 1456, 1163, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3H), 1.20–1.58 (m, 8H), 1.72–1.92 (m, 2H), 1.99–2.12 (m, 1H), 2.15–2.27 (m, 1H), 2.51–2.72 (m, 2H), 3.99–4.09 (m, 1H), 5.13 (s, 2H), 7.30–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.90, 22.42, 27.36, 28.51, 31.51, 32.26, 33.84, 39.14, 57.10, 66.32, 128.28, 128.33, 128.63, 135.91, 172.82. Found: C, 60.03; H, 7.45%. Calcd for $C_{17}H_{25}BrO_2$: C, 59.83; H, 7.38%.

Diethyl 2-(2-Bromooctyl)malonate (3ca): IR (neat) 2932, 1732, 1466, 1369, 1153, 1030 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.3 Hz, 3H), 1.16–1.36 (m, 12H), 1.38–1.65 (m, 2H), 1.78–1.90 (m, 2H), 2.25 (ddd, J = 15.0, 10.5, 4.2 Hz, 1H), 2.47 (ddd, J = 15.0, 10.2, 3.3 Hz, 1H), 3.79 (dd, J = 10.2, 4.2 Hz, 1H), 3.95–4.05 (m, 1H), 4.16–4.29 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.85 (2C), 13.88, 22.37, 27.21, 28.43, 31.45, 37.74, 39.30, 50.48, 54.92, 61.49, 61.57, 168.90, 169.10. Found: C, 51.51; H, 7.86%. Calcd for $C_{15}H_{27}BrO_4$: C, 51.29; H, 7.75%.

4-Bromodecanenitrile (3da): IR (neat) 2920, 2244, 1466, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.20–1.62 (m, 8H), 1.75–1.95 (m, 2H), 2.00–2.25 (m, 2H), 2.61 (t, J = 7.2 Hz, 2H), 4.02–4.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.68, 15.68, 22.17, 27.05, 28.21, 31.24, 34.20, 38.55, 54.91, 118.63. Found: C, 51.93; H, 7.63%. Calcd for $C_{10}H_{18}BrN$: C, 51.74; H, 7.81%.

Table A. The Coordinates of Atoms in **A** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –2837.024128 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –2836.976064 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	–0.497866	–0.806223	–0.668092
C	–0.497866	–0.806223	0.846381
O	0.754542	–0.806223	1.333758
C	0.856501	–0.783583	2.768648
O	–1.501631	–0.825920	1.522676
H	0.171759	–1.565727	–1.070182
H	–1.513519	–0.928349	–1.034430
H	0.381325	–1.668665	3.199708
H	1.924903	–0.775971	2.983680
H	0.375653	0.112202	3.169806
Br	0.156343	0.921710	–1.365190

Table B. The Coordinates of Atoms in **B** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –39.694503 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –39.684515 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	–0.000001	0.000005	0.000004
H	–0.000001	0.000005	1.083261
H	0.938126	0.000005	–0.541636
H	–0.938122	–0.000044	–0.541646

Table TS-1. The Coordinates of Atoms in **TS-1** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –2876.708500 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –2876.634674 (PMP2/6-31G**//B3LYP/6-31G*)

Imaginary frequency: –332.9355 cm^{-1}

atom	x	y	z
C	–0.372664	–1.327402	–0.446462
C	–0.372664	–1.327402	1.041252
O	0.887909	–1.327402	1.530807
C	0.984958	–1.282983	2.962215
O	–1.370176	–1.321550	1.733956
H	0.468158	–1.833447	–0.911266
H	–1.343701	–1.559232	–0.870421
H	0.495054	–2.152227	3.409591
H	2.052670	–1.288245	3.183270
H	0.516578	–0.374037	3.349827
Br	–0.061828	0.729757	–1.082164
C	0.256978	2.879521	–1.946911
H	–0.109534	2.758681	–2.960459
H	–0.366387	3.457535	–1.273161
H	1.329611	2.990693	–1.830310

Table C. The Coordinates of Atoms in **C** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –266.960848 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –266.913368 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	–0.363489	0.000000	–1.844593
C	–0.363489	0.000000	–0.397271
O	0.899257	0.000000	0.110039
C	0.975304	–0.000001	1.541421
O	–1.368663	0.000001	0.299778
H	0.562534	0.000008	–2.406804
H	–1.316574	–0.000006	–2.357677
H	0.489810	–0.888869	1.954873
H	2.039706	0.000008	1.778869
H	0.489798	0.888860	1.954875

Table D. The Coordinates of Atoms in **D** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –2609.768591 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –2609.756041 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.684457	–1.297481	0.468265
H	0.684457	–1.297481	1.556772
H	1.699489	–1.297481	0.075007
H	0.110681	–2.134878	0.075337
Br	–0.188611	0.357564	–0.129049

Table E. The Coordinates of Atoms in **E** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –78.317127 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –78.288084 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.000000	0.000003	–0.665448
C	0.000000	0.000003	0.665448
H	0.923557	0.000003	–1.239620
H	–0.923557	–0.000081	–1.239620
H	0.923557	0.000066	1.239620
H	–0.923557	–0.000026	1.239620

Table TS-2. The Coordinates of Atoms in **TS-2** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –345.273652 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –345.178235 (PMP2/6-31G**//B3LYP/6-31G*)

Imaginary frequency: –412.2991 cm^{-1}

atom	x	y	z
C	–0.283492	–0.692539	–1.010706
C	–0.283492	–0.692539	0.444697
O	0.986149	–0.692539	0.947321
C	1.069881	–0.654639	2.377130
O	–1.277417	–0.643546	1.153119
H	0.621001	–0.970909	–1.537724
H	–1.233288	–0.886696	–1.492067
H	0.588447	–1.532517	2.817905
H	2.135739	–0.648424	2.609686
H	0.586116	0.243673	2.771964
C	–0.191708	1.552067	–1.379162
C	–0.233099	1.754390	–2.726412
H	0.753034	1.595170	–0.844509
H	–1.084779	1.677818	–0.773612
H	0.670951	1.763174	–3.329259
H	–1.175604	1.846933	–3.259176

Table TS-2'. The Coordinates of Atoms in **TS-2'** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –345.273657 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –345.178385 (PMP2/6-31G**//B3LYP/6-31G*)

Imaginary frequency: –415.1296 cm^{-1}

atom	x	y	z
C	–0.387201	–0.742857	–1.226827
C	–0.387201	–0.742857	0.228258
O	0.878556	–0.742857	0.733589
C	0.958151	–0.703101	2.163288
O	–1.384274	–0.699520	0.933363
H	0.530095	–0.972399	–1.755150
H	–1.328215	–0.986483	–1.705806
H	0.472601	–1.578614	2.604287
H	2.023350	–0.699636	2.399026
H	0.476067	0.197164	2.555916
C	–0.538295	1.480265	–1.686025
C	0.642447	2.077159	–1.357645
H	–0.762122	1.245698	–2.723368
H	–1.392934	1.538793	–1.018080
H	1.462744	2.145098	–2.066965
H	0.836744	2.437761	–0.351746

Table F. The Coordinates of Atoms in **F** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –345.317618 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –345.220217 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	–0.402480	–0.410890	–0.956534
C	–0.402480	–0.410890	0.557948
O	0.863029	–0.410890	1.043210
C	0.972395	–0.371039	2.474925
O	–1.386480	–0.383913	1.264884
H	0.262526	–1.202553	–1.318499
H	–1.420416	–0.629438	–1.287584
H	0.490557	–1.244911	2.921738
H	2.041946	–0.372807	2.687805
H	0.502692	0.532751	2.872555
C	0.071771	0.959552	–1.534141
C	0.055793	0.990071	–3.024211
H	1.082641	1.152185	–1.154993
H	–0.582104	1.743388	–1.130007
H	0.888496	0.592273	–3.596612
H	–0.848742	1.246687	–3.567072

Table F'. The Coordinates of Atoms in **F'** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –345.319140 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –345.221138 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.516971
O	1.263613	0.000000	1.999904
C	1.375334	–0.044613	3.431740
O	–0.984154	–0.023695	2.224722
H	0.764627	0.700854	–0.352223
H	0.326568	–0.998494	–0.324881
H	0.907072	–0.950164	3.827032
H	2.445308	–0.043141	3.642274
H	0.893988	0.827587	3.882203
C	–1.388227	0.328902	–0.597167
C	–1.833299	1.732237	–0.348033
H	–1.342439	0.130027	–1.675033
H	–2.109790	–0.375242	–0.164166
H	–1.640962	2.518180	–1.071990
H	–2.235165	2.014673	0.618783

Table A(W). The Coordinates of Atoms in **A(W)** Optimized at the B3LYP/6-31G* Level
Total energy
Without thermal energy corrections (au): –2913.256630 (PMP2/6-31G**//B3LYP/6-31G*)
Including thermal energy corrections (au): –2913.188398 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.419104	–0.458037	–0.713011
C	0.391040	–0.650823	0.786164
O	1.349499	0.051032	1.400162
C	1.374245	–0.042135	2.837426
O	–0.399885	–1.370267	1.370486
H	1.434339	–0.514689	–1.103374
H	–0.256521	–1.168938	–1.186426
H	1.535778	–1.076880	3.149692
H	2.203059	0.590822	3.153016
H	0.431295	0.318022	3.255830
Br	–0.237371	1.351192	–1.156998
O	–1.834291	–2.747451	–0.731325
H	–1.596657	–2.355843	0.130632
H	–1.472201	–3.644784	–0.682489

Table TS-1(W). The Coordinates of Atoms in **TS-1(W)** Optimized at the B3LYP/6-31G* Level
Total energy
Without thermal energy corrections (au): –2952.941483 (PMP2/6-31G**//B3LYP/6-31G*)
Including thermal energy corrections (au): –2952.848074 (PMP2/6-31G**//B3LYP/6-31G*)
Imaginary frequency: –326.1653 cm^{-1}

atom	x	y	z
C	0.563645	–1.019158	–0.387304
C	0.224878	–1.079597	1.056364
O	1.226675	–0.630535	1.833037
C	0.957838	–0.610256	3.244712
O	–0.840075	–1.478889	1.506819
H	1.619247	–1.128581	–0.615996
H	–0.126232	–1.590781	–1.001895
H	0.746701	–1.618684	3.610417
H	1.862707	–0.215469	3.706861
H	0.101645	0.034155	3.460564
Br	0.181172	1.022833	–1.013023
C	–0.256457	3.144698	–1.915515
H	–1.314783	3.055600	–2.134367
H	0.015917	3.772850	–1.074115
H	0.416475	3.152806	–2.765885
O	–2.203861	–2.651248	–0.748834
H	–1.990344	–2.201584	0.091990
H	–2.073679	–3.588192	–0.539503

Table C(W). The Coordinates of Atoms in **C(W)** Optimized at the B3LYP/6-31G* Level
Total energy
Without thermal energy corrections (au): –343.194289 (PMP2/6-31G**//B3LYP/6-31G*)
Including thermal energy corrections (au): –343.126606 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.296594	0.365660	–1.514616
C	0.266117	0.260155	–0.073969
O	1.168729	1.065948	0.531220
C	1.182646	1.009742	1.965486
O	–0.490246	–0.478484	0.558368
H	0.989664	1.039955	–2.002787
H	–0.399078	–0.245995	–2.078484
H	1.423658	–0.000131	2.309089
H	1.953231	1.715146	2.277241
H	0.209133	1.298374	2.371383
O	–2.079183	–1.779682	–1.467170
H	–1.723737	–1.403873	–0.637601
H	–1.719421	–2.679069	–1.479574

Table TS-2(W). The Coordinates of Atoms in **TS-2(W)** Optimized at the B3LYP/6-31G* Level
Total energy
Without thermal energy corrections (au): –421.508705 (PMP2/6-31G**//B3LYP/6-31G*)
Including thermal energy corrections (au): –421.392570 (PMP2/6-31G**//B3LYP/6-31G*)
Imaginary frequency: –388.4195 cm^{-1}

atom	x	y	z
C	0.292876	–0.734641	–0.968079
C	0.292876	–0.734641	0.481021
O	1.547355	–0.734641	0.998808
C	1.624933	–0.696603	2.430346
O	–0.706735	–0.689462	1.199583
H	1.222452	–0.936720	–1.484795
H	–0.635731	–0.994431	–1.458707
H	1.136772	–1.571875	2.868056
H	2.690031	–0.696723	2.664928
H	1.146071	0.205639	2.821508
O	–2.891937	0.253180	–0.340863
H	–2.261012	–0.175579	0.274467
H	–3.371025	0.881826	0.218959
C	0.074603	1.495171	–1.361891
C	0.332936	1.679749	–2.688623
H	0.833919	1.746730	–0.625345
H	–0.948835	1.403297	–1.004769
H	1.332437	1.901401	–3.053816
H	–0.443876	1.549586	–3.437344

Table TS-2'(W). The Coordinates of Atoms in **TS-2'(W)** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –421.509168 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –421.393160 (PMP2/6-31G**//B3LYP/6-31G*)

Imaginary frequency: –396.8298 cm^{-1}

atom	x	y	z
C	0.219462	–0.780493	–1.169162
C	0.219462	–0.780493	0.280550
O	1.471435	–0.780493	0.797553
C	1.549305	–0.733394	2.228678
O	–0.780680	–0.738661	0.998032
H	1.151057	–0.979005	–1.684389
H	–0.709817	–1.044817	–1.658493
H	1.058482	–1.604097	2.672384
H	2.614392	–0.734874	2.463297
H	1.073182	0.172962	2.613467
C	–0.047505	1.408451	–1.690974
C	0.920908	2.141065	–1.067965
H	0.060365	1.160064	–2.744235
H	–1.056550	1.335834	–1.291195
H	1.887196	2.325457	–1.529760
H	0.787890	2.512128	–0.055098
O	–2.967817	0.124886	–0.580902
H	–2.334389	–0.265995	0.056918
H	–3.485136	0.745693	–0.047118

Table F(W). The Coordinates of Atoms in **F(W)** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –421.550737 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –421.434044 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.485673	–0.356860	–0.963866
C	0.485673	–0.356860	0.547377
O	1.728763	–0.356860	1.059993
C	1.813896	–0.337722	2.496946
O	–0.511725	–0.333363	1.251059
H	1.509240	–0.461877	–1.331383
H	–0.093165	–1.225283	–1.297752
H	1.313256	–1.211603	2.921190
H	2.879730	–0.355518	2.724662
H	1.349074	0.567905	2.894987
O	–3.055156	–0.212140	–0.110934
H	–2.255779	–0.350661	0.433782
H	–3.511451	0.514689	0.338153
C	–0.181165	0.936087	–1.532189
C	–0.165754	0.971086	–3.021745
H	0.348218	1.807530	–1.124635
H	–1.211915	0.956186	–1.160127
H	0.664003	1.410744	–3.566775
H	–0.916193	0.432382	–3.592188

Table F'(W). The Coordinates of Atoms in **F'(W)** Optimized at the B3LYP/6-31G* Level

Total energy

Without thermal energy corrections (au): –421.551578 (PMP2/6-31G**//B3LYP/6-31G*)

Including thermal energy corrections (au): –421.433810 (PMP2/6-31G**//B3LYP/6-31G*)

atom	x	y	z
C	0.467902	–0.494305	–1.216868
C	0.467902	–0.494305	0.297322
O	1.711519	–0.494305	0.806940
C	1.799729	–0.503601	2.243842
O	–0.528020	–0.500397	1.001531
H	1.500326	–0.471230	–1.577529
H	0.019166	–1.441739	–1.540414
H	1.308972	–1.390936	2.651409
H	2.866216	–0.514846	2.468948
H	1.326636	0.389234	2.660311
C	–0.350584	0.681275	–1.793430
C	0.229887	2.017887	–1.473521
H	–0.400402	0.535490	–2.888169
H	–1.384793	0.604635	–1.437114
H	1.306569	2.166198	–1.452397
H	–0.398433	2.901914	–1.435591
O	–3.189034	–0.268292	–0.111995
H	–2.339619	–0.479358	0.322253
H	–3.449374	0.562905	0.312409

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CHAPTER 3

Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenes with a Water-Soluble Radical Initiator in Aqueous Media. Facile Synthesis of γ-Lactones

Radical reactions in water or aqueous ethanol using a water-soluble radical initiator are described. Heating a mixture of 2-iodoacetamide and 5-hexen-1-ol in water at 75 °C in the presence of a water-soluble radical initiator, 4,4'-azobis(4-cyanopentanoic acid), afforded 5-(4-hydroxybutyl)dihydrofuran-2(3*H*)-one in 95% yield. The use of 2-iodoacetic acid in place of 2-iodoacetamide also gave the same γ-lactone in 93% yield. The reaction of 2-iodoacetamide with 1-octene in aqueous ethanol was initiated by 2,2'-azobis(isobutyramidine) dihydrochloride to provide γ-decanolactone. Employing water as a solvent is crucial to obtain lactone in satisfactory yield.

Introduction

Recently, processes using a less toxic solvent or no solvent have been required in the design of new synthetic methods from the ecological point of view. Water might be the best among many kinds of solvents. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents.[1] For example, pericyclic reactions, such as the Diels-Alder reaction[2], were carried out in water, and rate enhancement was observed. Indium-mediated allylation of aldehyde is also a well-known reaction in water.[3] However, methods for carbon-carbon bond formation based on a radical process in aqueous media have been limited.[4] The author has studied radical reactions in aqueous media,[5] and more recently have focused on the reaction with water-soluble radical initiators. Here the author chose the following two commercially available initiators,[6] 4,4'-azobis(4-cyanopentanoic acid) (**1a**, ACPA, $t_{1/2}$ = 10 h, 69 °C in H_2O) and 2,2'-azobis(isobutyramidine) dihydrochloride (**1b**, AIBA, $t_{1/2}$ = 10 h, 56 °C in H_2O). Here it will be described that (1) the addition of PhSH to alkene or alkyne proceeds smoothly to give the corresponding adducts, (2) atom transfer cyclization of *N,N*-diallyl-2-iodoacetamide affords γ-lactams in excellent yields, and (3) the addition of 2-iodoacetamide to alkene followed by ionic cyclization gives γ-lactone in good yield. Particularly, the last reaction provides a much less toxic and safer synthesis of γ-lactone. Kharasch's addition of α-bromoacetate to alkene employed highly explosive peracetic acid.[7] Radical addition of tributylstannyl iodoacetate to alkene also provided γ-lactone.[8,9] In this case, the stannyl ester should be prepared in advance, and the toxic residual tin compounds might be troublesome to handle.

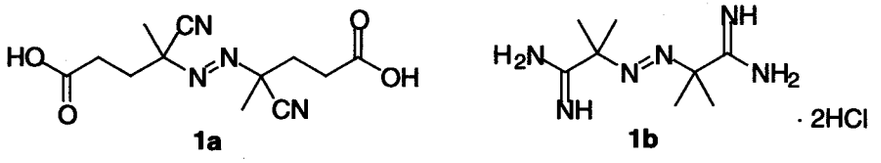
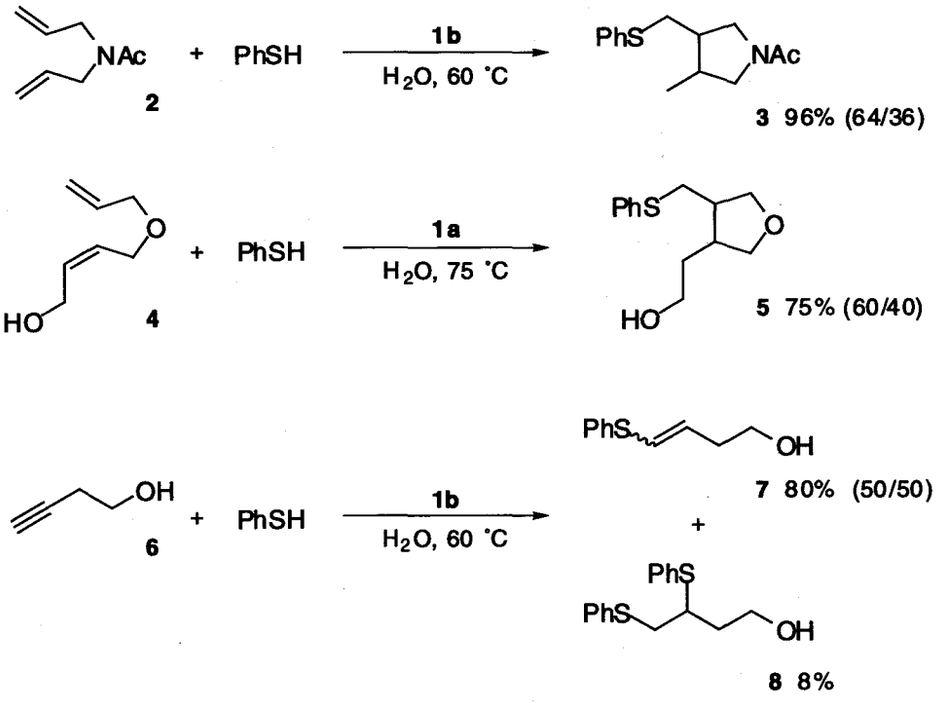


Figure 1. Water-soluble radical initiators

Radical Addition of Benzenethiol to Carbon-Carbon Multiple Bonds and Radical Cyclization of *N*-Allyl-2-iodoalkanamide in Water

Radical addition of benzenethiol to alkenes or alkynes was first examined (Scheme 1).[10] Heating a mixture of *N,N*-diallylacetamide (**2**, 1.0 mmol), benzenethiol (1.5 mmol), and **1b** (0.30 mmol) in water (10 mL) at 60 °C for 2 h provided *N*-acetylpyrrolidine derivative **3** in 96% yield. In similar fashion, treatment of diallylic ether **4** with benzenethiol in the presence of **1a** at 75 °C gave tetrahydrofuran derivative **5** in 75% yield. The reaction of 3-butyn-1-ol (**6**) with PhSH at 60 °C in the presence of **1b** afforded 4-(phenylthio)-3-buten-1-ol (**7**) in 80% yield, in addition to 3,4-bis(phenylthio)-1-butanol (**8**, 8%).

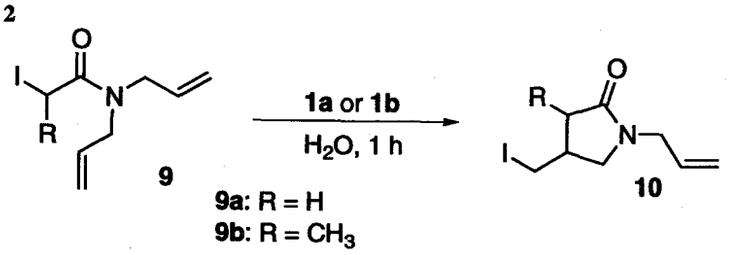
Scheme 1



These radical initiators were highly effective for the atom transfer radical cyclization of 2-iodoamide **9** in water (Scheme 2).[11] Stirring a mixture of *N,N*-diallyl-2-iodoacetamide **9a** (1.0 mmol) and **1a** or **1b** (0.30 mmol) at 75 °C or 60 °C in water (30 mL) for 1 h provided γ-lactam **10a** in 80 % or 99% yield, respectively. 2-Iodopropanamide **9b** also underwent cyclization in the presence of **1a** or **1b** t

afford the corresponding lactam **10b** in 95% or 85% yield, respectively.[12] The effectiveness of **1a** and **1b** as an initiator in water was confirmed by these experiments.

Scheme 2

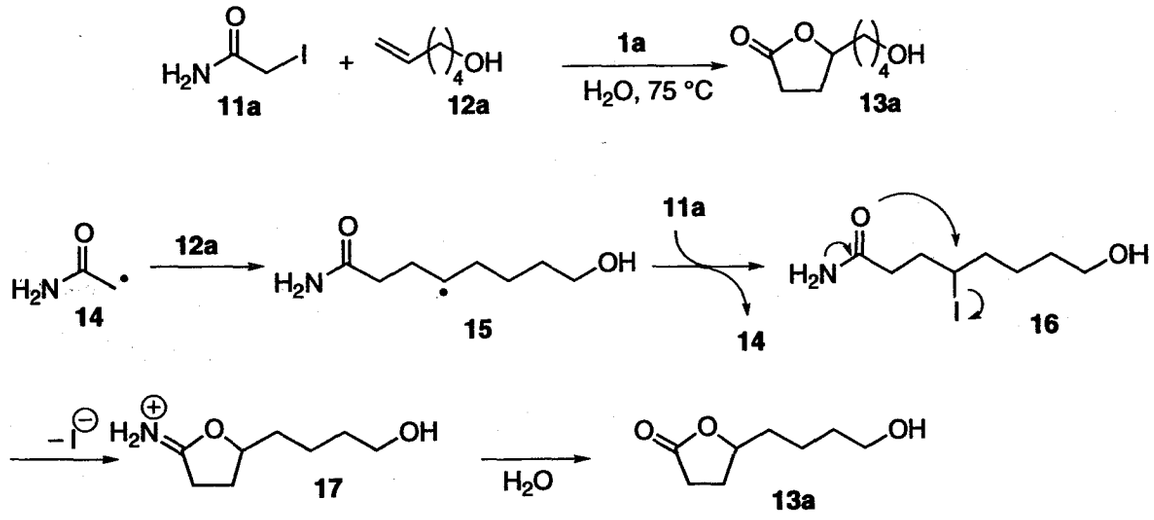


9a: R = H
9b: R = CH_3

Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenes in Aqueous Media to Yield γ-Lactones

The success of intramolecular radical cyclization of 2-iodoalkanamide encouraged us to investigate an intermolecular radical addition reaction. The author thus turned his attention to the reaction of 2-iodoacetamide with alkenol. The addition of 2-iodoacetamide to alkenol in water afforded γ-substituted γ-lactone in high yields. For instance, the reaction of 2-iodoacetamide (**11a**) with 5-hexen-1-ol (**12a**) in the presence of **1a** at 75 °C for 16 h provided 5-(4-hydroxybutyl)dihydrofuran-2(3*H*)-one (**13a**) in an isolated yield of 95% (Scheme 3). The reaction would proceed as follows. Radical **14** derived from **11a** adds readily to the alkenyl terminal carbon of alkenol **12a** to provide **15**. The iodine atom transfer reaction between the radical **15** and **11a** affords 8-hydroxy-4-iodooctanamide (**16**) and regenerates **14**. The compound **16** cyclizes to γ-lactone **13a** via **17** under the reaction conditions[13] due to the well-known ionic lactonization[14,15] of 4-iodoalkanamide. Typical examples are shown in Table 1.[16,17] Alcohol, having a terminal alkene moiety, as well as 4-pentenoic acid (**12f**) was converted into the corresponding lactone in excellent yield. However, the addition to alkenol containing an internal double bond such as 2-buten-1-ol did not take place. 1-Octene did not give lactone under the same reaction conditions because of the insolubility of 1-octene in water, whereas hydrophilic allyl ether **12e** gave **13e**.

Scheme 3



Not only 2-iodoacetamide but 2-iodoacetic acid (**11b**) provided γ-lactones in the reaction with alkenol in water at 75 °C in the presence of **1a**. Some representative results are also summarized in Table 1. Interestingly, **11b** was added to 4-penten-1-ol (**12b**) to give tetrahydrofuran derivative **19** in 40% yield in addition to the expected γ-lactone **13b** (53%) (Scheme 4). The former compound **19** was obtained by an intramolecular etherification of the iodine transfer product **18**.

Scheme 4

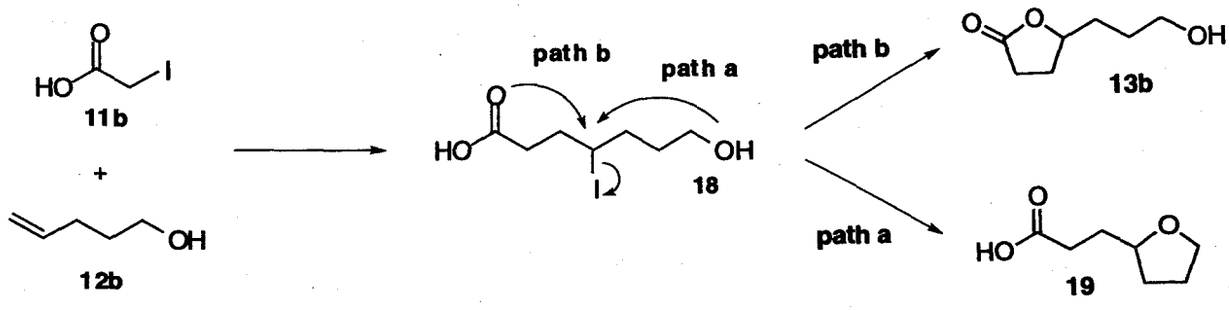
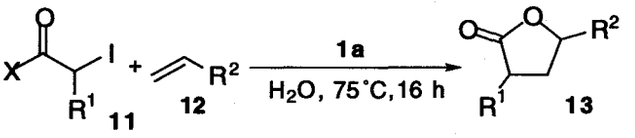
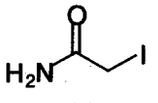
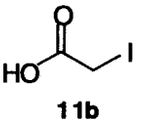
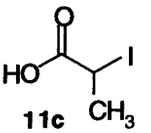


Table 1. γ-Lactone Synthesis by Tandem Radical-Ionic Reaction between 2-Iodoacetamide or 2-Iodoacetic Acid and Alkenol[a]

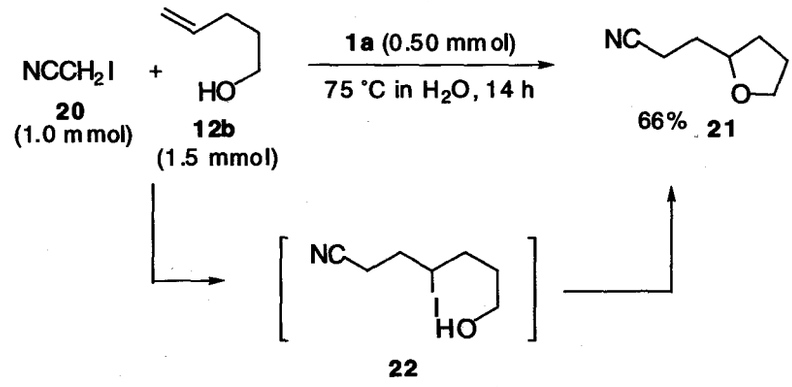


2-Iodocarbonyl Compound	R^2 in alkenol	Product /%
 11a	**12a**: $(CH_2)_4OH$	**13a**: 95
	12b: $(CH_2)_3OH$	**13b**: 85
	12c: $(CH_2)_2OH$	**13c**: 91[b]
	12d: CH_2OH	**13d**: 88[b]
	12e: $CH_2O(CH_2)_2O$*i*-Pr	**13e**: 84
	12f:$(CH_2)_2COOH$	**13f**: 94[c]
	12g: $CH(CH_3)OH$	**13g**: 84 (54/46)
 11b	**12a**: $(CH_2)_4OH$	**13a**: 93
	12c: $(CH_2)_2OH$	**13c**: 95
	12d: CH_2OH	**13d**: 76
	12f: $(CH_2)_2COOH$	**13f**: 100[c]
 11c	**12a**: $(CH_2)_4OH$	**13h**: 86 (55/45)

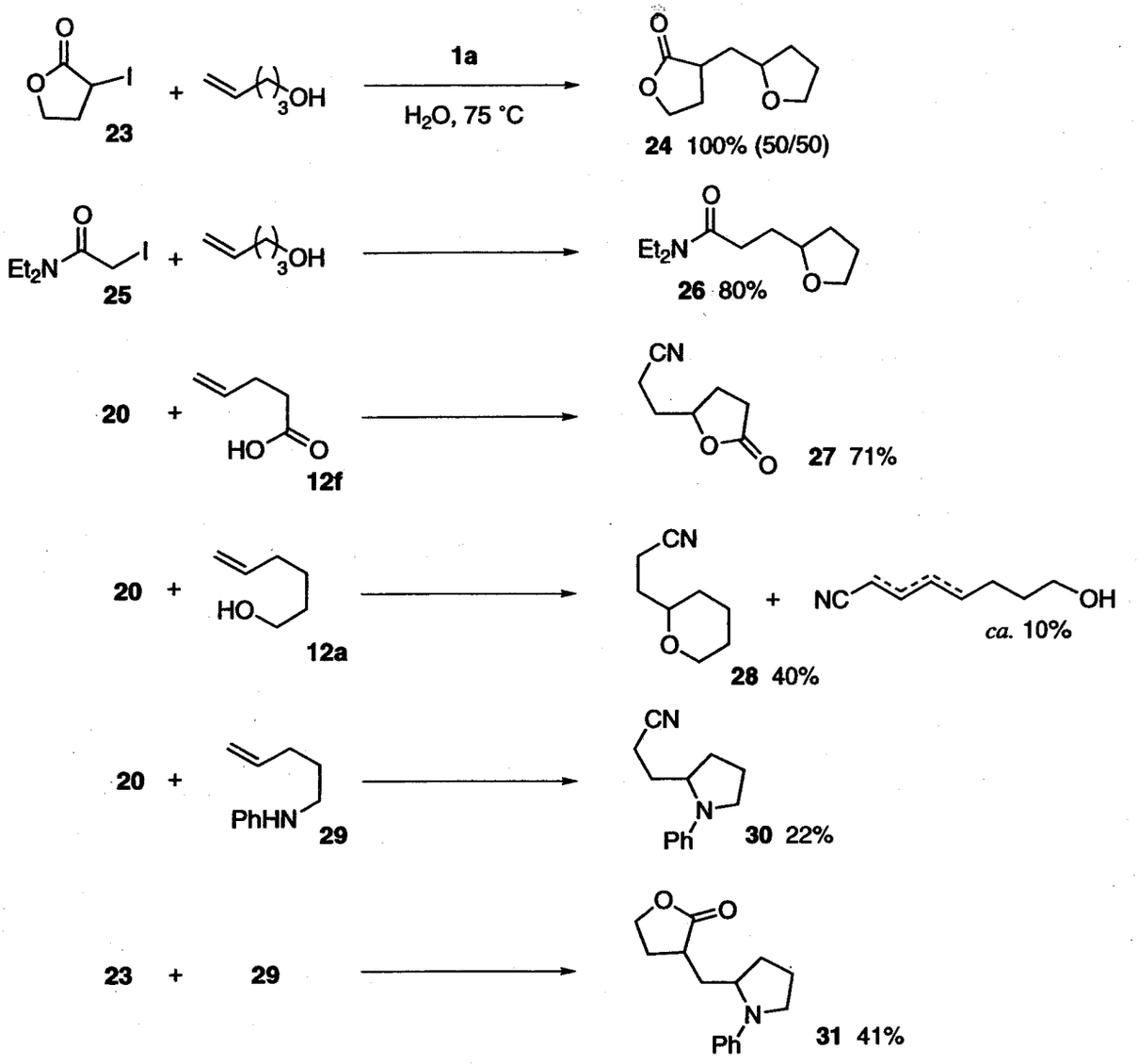
a) 2-Iodoacetamide or 2-iodoacetic acid (1.0 mmol), alkenol (1.5 mmol), and **1a** (0.50 mmol) were employed unless otherwise noted. b) Three molar amounts of alkenol were employed. c) The product was isolated as allyl ester after treatment with allyl bromide in the presence of K_2CO_3 in acetone.

The formation of **19** prompted us to examine the reaction of iodoacetonitrile (**20**) with 4-penten-1-ol (Scheme 5). A mixture of **20** and **12b** was treated under the standard reaction conditions. The anticipated tetrahydrofuran derivative **21** was obtained in 66% yield. The addition of α-iodo-γ-butyrolactone (**23**) or *N,N*-diethyl-2-iodoacetamide (**25**) to 4-penten-1-ol yielded the corresponding product **24** or **26** in excellent yield, respectively (Scheme 6). The addition of **20** to 4-pentenoic acid provided γ-lactone **27** in high yield. Furthermore, 5-hexen-1-ol reacted with **20** to give tetrahydropyran **28** in 40% yield, along with unsaturated ω-hydroxy nitriles. However, synthesis of pyrrolidine using the radical addition-ionic cyclization methodology seems difficult (Scheme 7). Treatment of *N*-(4-pentenyl)aniline (**29**) with **20** or **23** gave the corresponding pyrrolidine **30** or **31** in 22% or 41% yield, respectively.

Scheme 5

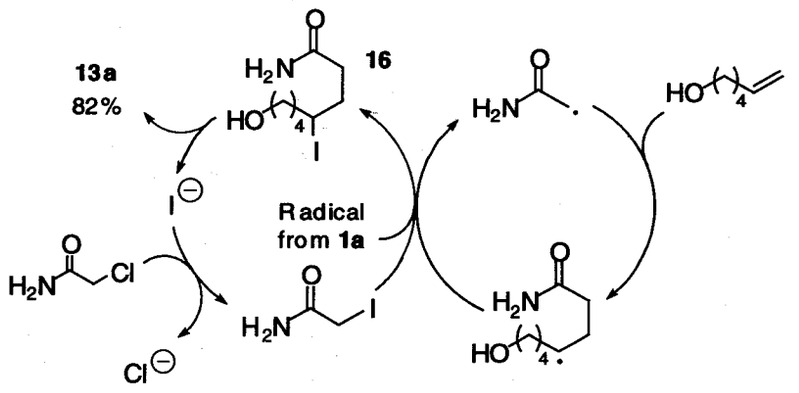


Scheme 6



Iodide was liberated in the transformation of **16** into **13**. Thus, it was anticipated that, by adding a catalytic amount of sodium iodide, the use of 2-chloroacetamide instead of the iodo amide **11a** would provide **13**. It has indeed been found that the radical-ionic tandem reaction of 2-chloroacetamide with 5-hexen-1-ol in the presence of a substoichiometric amount of NaI proceeds smoothly, as shown in Scheme 7. Heating a mixture of 2-chloroacetamide (1.0 mmol), 5-hexen-1-ol (1.5 mmol), and NaI (0.50 mmol)[18] in water (10 mL) at 75 °C for 16 h in the presence of **1a** (0.50 mmol) provided **13a** in 82% yield.

Scheme 7



The author has been interested in radical reactions in aqueous media and have disclosed the attractive solvent effect of water.[5a–5c] Accordingly, the solvent effect on the present reaction was examined. The reaction of *N*-ethyl-2-iodoacetamide (**11d**) with 5-hexen-1-ol in water afforded **13a** in 75% yield. On the other hand, very interestingly, the reaction did not proceed at all in refluxing benzene, and **11d** was almost completely recovered (Scheme 8). The results of further investigations are summarized in Table 2. Benzene, THF, CH_2Cl_2, and acetonitrile were completely ineffective for the synthesis of lactones.[19] In each case, **11d** was recovered, that is, the radical addition step itself did not take place. Employing protic solvents, such as ethanol and methanol, led to some conversion to give γ-decanolactone (**13i**) in 14 % and 26% yields, respectively. Water is the best for this reaction

Scheme 8

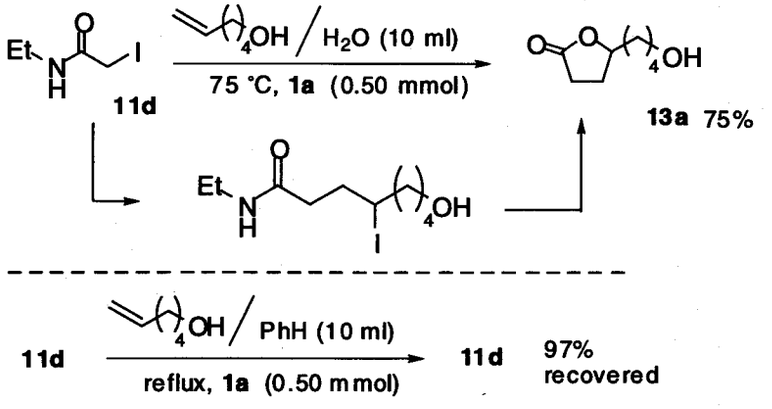
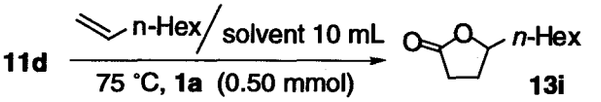


Table 2. Reaction in Various Solvents

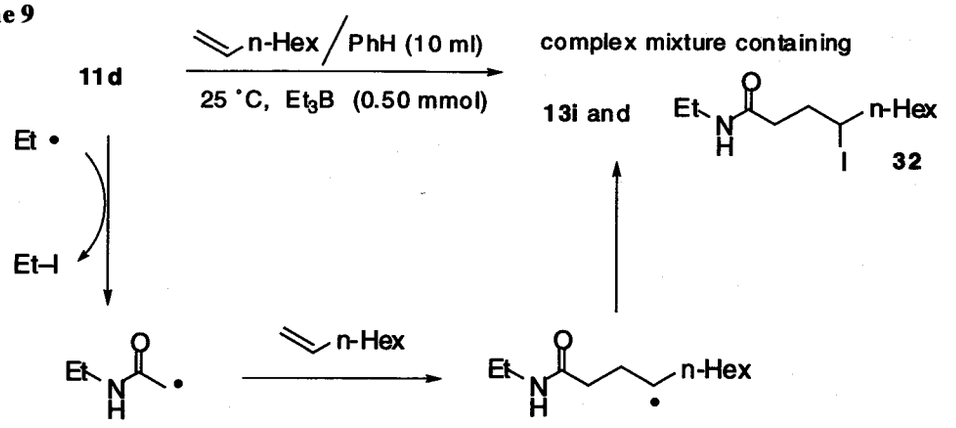


Solvent	Time /h	Yield of **13** /%	Recovered **11d** /%
benzene [1)]	16	0	97
THF[1)]	24	0	89
CH_2Cl_2 [1)]	24	0	100
CH_3CN	24	0	100
MeOH [1)]	40	26	68
EtOH	40	14	77
H_2O [2)]	16	75	0

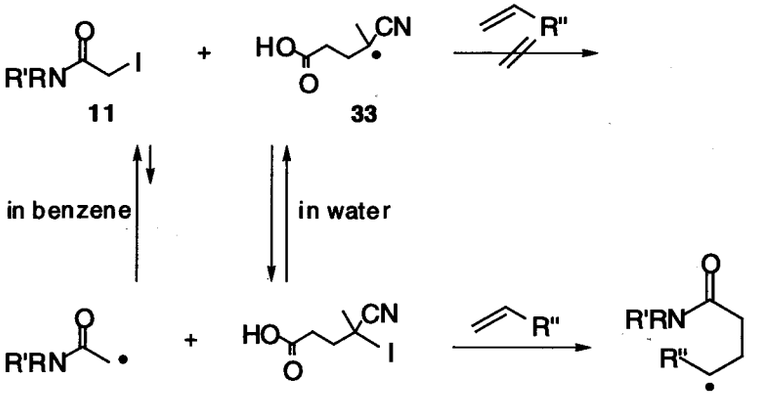
1) Reflux. 2) 5-Hexen-1-ol was used.

To get deeper insight into the solvent effect, the reaction was performed in benzene at room temperature in the presence of triethylborane[20] in place of **1a** (Scheme 9). A mixture of **11d** and 1-octene was treated with triethylborane in benzene at 25 °C. After 3 h, concentration of the reaction mixture yielded a complex mixture containing **13i** and the adduct **32**. The starting iodide **11d** was completely consumed. An ethyl radical, derived from triethylborane by the action of a trace of oxygen, is reactive enough to abstract iodine from iodo amide.[5e] Thus, the reaction was initiated by triethylborane, and the products generated by the radical addition were obtained. The reason for the recovery or the poor conversion of **11d** in organic solvents in the presence of azo initiator **1a** is that the radical **33**, which is generated from **1a** and is stabilized by a cyano group, could not abstract iodine from iodo amide **11** (Scheme 10). The solvent effect of water works in the initiation step. It is assumed that water would enhance the reactivity of radical **33** and activate the carbon-iodine bond in **11** as shown in Chapter 2.

Scheme 9



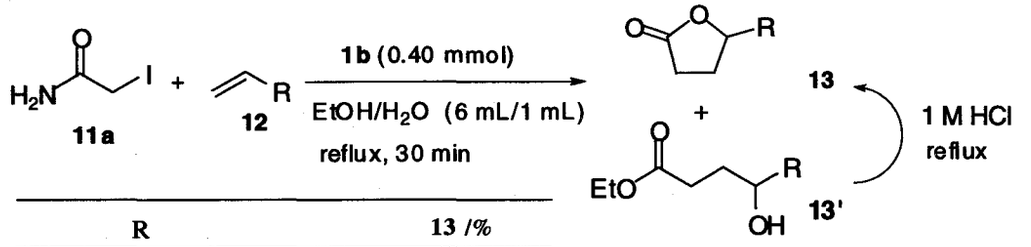
Scheme 10

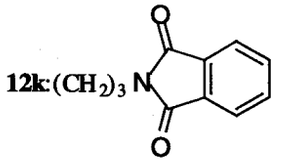


Whereas hydrophilic olefins could be used in the present reaction, hydrophobic compounds such as 1-octene were not suitable. To extend the scope of this reaction, radical reaction in aqueous ethanol was studied. Radical addition-lactonization reaction proceeded less effectively in ethanol than in water in the presence of **1a**, as shown in Table 2. The initiator **1b** was hence tested as an initiator for the reaction in aqueous ethanol. A mixture of iodoacetamide (2.0 mmol) and 1-octene (10 mmol)[21] was heated in $EtOH/H_2O$ (6 mL/1 mL) at reflux in the presence of **1b** (0.20 mmol) for 30 min. Usual workup followed by silica gel column purification provided **13i** in 80% yield in addition to ethyl 4-hydroxydecanoate (**13i'**, 6%), derived from solvolysis of the lactone. Hydroxy ester **13i'** could be easily converted into **13i**. Heating a crude mixture of **13i** and **13i'** in refluxing 1 M HCl for 20 min yielded **13i** in 83% yield after silica gel column purification. The reaction in aqueous ethanol

is summarized in Table 3. Although excess of olefin was necessary,[22] good results were obtained compared with the reaction in water. Water as a cosolvent is essential to give a satisfactory result. For example, the yield of **13i** decreased to 47% on employing anhydrous ethanol (7 mL). The initiator **1b** proved to be more effective than **1a**, for which the author assumes the reason to be as follows. The radical, derived from **1b**, is stabilized with the amide group resulting from hydrolysis of the amidine group. The amide-stabilized radical would be less stable than the radicals produced from AIBN and **1a**, which the cyano groups stabilize,[23] and would be more reactive in iodine abstraction.

Table 3. Synthesis of Lactones in Aqueous Ethanol



R	13 /%
12i: n-C_6H_{13}	**13i**: 83 (0)
12j: $(CH_2)_8OH$	**13j**: 83 (31)
12k: 	**13k**: 79 (0)
12l: $CH_2CH_2COCH_3$	**13l**: 72 (85)

The yields of **13** under the reaction conditions in Table 1 are in parentheses.

In summary, using a water-soluble azo initiator, atom-transfer radical reactions in aqueous media have been developed. Synthesis of γ-substituted γ-lactones has been accomplished by a radical addition-lactonization sequence in a nontoxic solvent. The reaction procedure is simple and safe, and no special technique is necessary. Similar to the previous reports, water as a solvent or a cosolvent accelerates the reaction.

Experimental Section

Typical procedure for synthesis of γ-lactone in water. A water-soluble radical initiator **1a** (0.14 g, 0.50 mmol) was added to a solution of 2-iodoacetamide (**11a**, 0.19 g, 1.0 mmol) and 5-hexen-1-ol (**12a**, 0.15 g, 1.5 mmol) in water (10 mL). After being flushed with argon, the mixture was heated at 75 °C for 16 h, and then cooled to 25 °C. Saturated $NaHCO_3$ (5 mL) was added, and the product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:2) to give 0.15 g of γ-lactone **13a** in 95% yield.

Synthesis of γ-lactone in aqueous ethanol. Iodoacetamide (2.0 mmol) was placed in a pear-shaped flask, and ethanol (6 mL) and water (1 mL) were added to dissolve acetamide. 1-Octene (10 mmol) and **1b** (0.40 mmol) were added, and the whole mixture was heated at reflux (bath temp. 90 °C) for 30 min under argon. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried and concentrated. 1 M HCl was added to the crude oil, and the mixture was heated at reflux for 20 min. Extraction and concentration followed by silica gel column purification provided 0.29 g (1.7 mmol) of γ-decanolactone in 83% yield.

Characterization Data

Compounds **2**,[24] **4**,[25] **9a**,[11h] and **10a**[11h] are found in the literature. Lactone **13i** is commercially available.

1-Acetyl-3-methyl-4-(phenylsulfanylmethyl)-1-pyrrolidine (3, 64/36 mixture of diastereomers. Two rotamers exist for each diastereomer.)**:** Bp 240 °C/0.1 torr; IR (neat) 3432, 2920, 1657, 1464, 1359, 1205, 1088, 1025, 740, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3H × 0.32), 1.02 (d, J = 6.6 Hz, 3H × 0.32), 1.06 (d, J = 6.6 Hz, 3H × 0.18), 1.07 (d, J = 6.6 Hz, 3H × 0.18), 1.93–2.53 (m, 2H), 2.01 (s, 3H × 0.64), 2.02 (s, 3H × 0.32), 2.71–2.89 (m, 1H), 2.92–3.11 (m, 1H), 3.14–3.40 (m, 2H), 3.48–3.60 (m, 1H), 3.62–3.93 (m, 1H), 7.18–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.92, 12.94, 15.96,

16.00, 21.83 (2C), 21.88, 21.92, 32.51, 32.60, 33.88, 35.01, 35.58, 35.75, 37.05, 38.38, 39.70, 41.50, 43.77, 45.55, 48.48, 50.30, 50.53, 51.97, 52.24, 52.32, 54.22, 54.25, 126.23, 126.25, 126.37, 126.39, 128.90 (4C), 128.99 (4C), 129.41 (2C), 129.51 (4C), 129.56 (2C), 135.56, 135.70, 135.74, 135.93, 168.95, 166.03, 169.32, 169.38. Found: C, 67.19; H, 7.75%. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68%.

2-[4-(Phenylsulfanylmethyl)tetrahydrofuran-3-yl]ethanol (5, 60/40 mixture of diastereomers): IR (neat) 3364, 2928, 2864, 1730, 1584, 1481, 1439, 1055, 898, 739, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.63 (m, 1H), 1.69–1.84 (m, 1H), 1.86–2.19 (m, 2H), 2.36–2.52 (m, 1H), 2.79 (dd, *J* = 12.6, 9.6 Hz, 0.6H), 2.92 (dd, *J* = 12.9, 8.1 Hz, 0.4H), 3.06–3.13 (m, 1H), 3.44 (dd, *J* = 8.4, 5.4 Hz, 0.4H), 3.54–3.74 (m, 3H), 3.79 (dd, *J* = 8.7, 4.8 Hz, 0.6H), 3.89–3.98 (m, 1.6H), 4.04 (dd, *J* = 8.7, 6.9 Hz, 0.4H), 7.17–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 29.98, 32.42, 38.77, 41.08, 61.40, 71.94, 71.97, 126.27, 128.98 (2C), 129.49 (2C), 135.96, for minor isomer, δ 35.77, 37.20, 41.80, 44.51, 61.02, 72.62, 73.53, 126.24, 129.00 (2C), 129.28 (2C), 135.93. Found: C, 65.23; H, 7.43%. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61%.

4-(Phenylsulfanyl)-3-buten-1-ol (7, 50/50 mixture of diastereomers): IR (neat) 3335, 2930, 1583, 1479, 1439, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (broad s, 1H), 2.43 (dt, *J* = 7.2, 7.2 Hz, 1H), 2.54 (dt, *J* = 7.2, 7.2 Hz, 1H), 3.65–3.80 (m, 2H), 5.85 (dt, *J* = 9.3, 7.2 Hz, 0.5H), 5.91 (dt, *J* = 15.3, 7.2 Hz, 0.5H), 6.28 (d, *J* = 15.3 Hz, 0.5H), 6.36 (d, *J* = 9.3 Hz, 0.5H), 7.17–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.34, 36.08, 61.38 (2C), 124.03, 125.43, 126.27 (2C), 128.67, 128.78 (2C), 128.84 (2C), 128.92 (4C), 131.70, 135.69, 135.82. HRMS Found: 180.0609. Calcd for $C_{10}H_{12}OS$: 180.0609.

3,4-Bis(phenylsulfanyl)-1-butanol (8): IR (neat) 3346, 2930, 1583, 1479, 1439, 1049, 741, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68–1.83 (m, 2H), 2.21–2.33 (m, 1H), 2.91 (dd, *J* = 14.4, 10.5 Hz, 1H), 3.25–3.35 (m, 2H), 3.87 (dt, *J* = 6.0, 5.4 Hz, 2H), 7.14–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 35.23, 39.48, 45.17, 60.34, 126.38, 127.49, 128.98 (2C), 129.05 (2C), 129.83 (2C), 132.67 (2C), 133.58,

135.47. Found: C, 66.42; H, 6.39%. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25%.

***N,N*-Diallyl-2-iodopropanamide (9b)** was prepared as follows. Chloroacetyl chloride (16 mmol) was added dropwise to a dichloromethane solution (15 mL) of diallylamine (15 mmol) and pyridine (16 mmol) at –78 °C. The resulting mixture was warmed to room temperature and was stirred for 1 h. Usual workup gave a crude oil, which was dissolved in acetone (30 mL). Sodium iodide (30 mmol) was added to the solution at 25 °C. The mixture was stirred for 3 h. Extractive workup followed by silica gel column purification provided **9b** in 83% overall yield. IR (neat) 2976, 2914, 1655, 1459, 1224, 991, 923 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (d, *J* = 6.6 Hz, 3H), 3.61 (dddd, *J* = 15.3, 6.3, 1.2, 1.2 Hz, 1H), 3.78 (dddd, *J* = 18.0, 4.5, 1.8, 1.8 Hz, 1H), 4.09 (dddd, *J* = 18.0, 4.8, 3.0, 1.8 Hz, 1H), 4.38 (dddd, *J* = 15.3, 4.8, 3.0, 1.8 Hz, 1H), 4.52 (q, *J* = 15.3 Hz, 1H), 5.10–5.26 (m, 4H), 5.74–5.92 (m,2H); ^{13}C NMR ($CDCl_3$) δ 13.40, 23.49, 48.16, 49.59, 116.12, 117.00, 132.04, 132.76, 170.85. Found: C, 38.89; H, 5.05%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%.

1-Allyl-4-iodomethyl-3-methylpyrrolidin-2-one (10b): For *trans* isomer (faster moving band, R_f = 0.40, hexane/ethyl acetate = 1/1); IR (Nujol) 2960, 2924, 1689, 1442, 1270, 1241, 1188, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.9 Hz, 3H), 2.08–2.27 (m, 2H), 3.00 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.17 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.41 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.44 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.57–3.99 (m, 2H), 5.16–5.24 (m, 2H), 5.66–5.80 (m,1H); ^{13}C NMR ($CDCl_3$) δ 8.01, 14.63, 42.56, 43.74, 45.02, 51.59, 118.09, 132.12, 175.47. Found: C, 38.88; H, 5.09%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%. For *cis* isomer (slower moving band R_f = 0.34, hexane/ethyl acetate = 1/1); IR (Nujol) 2966, 2926, 1689, 1439, 1266, 1192, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, *J* = 7.8 Hz, 3H), 2.62 (dq, *J* = 7.8, 7.8 Hz, 1H), 2.73–2.86 (m, 1H), 3.08 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.11 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.27 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.46 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.89 (ddd, *J* = 6.0, 1.5, 1.5 Hz, 2H), 5.20 (ddt, *J* = 18.3, 1.5, 1.5 Hz, 1H), 5.21 (ddt, *J* = 9.6, 1.5, 1.5 Hz, 1H), 3.89 (ddt, *J* = 18.3, 9.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 4.22, 10.00, 39.15, 40.99, 45.09, 51.25, 118.29, 132.24, 176.09. Found: C, 38.89; H, 5.11%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%.

1-Allyloxy-2-isopropoxyethane (12e) was prepared from commercially available 2-isopropoxyethanol and allyl bromide by the action of stoichiometric sodium hydride in refluxing THF. Bp 125 °C/50 torr; IR (neat) 2966, 2852, 1648, 1468, 1368, 1080, 995, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.0 Hz, 6H), 3.59 (s, 4H), 3.62 (septet, J = 6.0 Hz, 1H), 4.04 (ddd, J = 6.0 , 1.5, 1.5, Hz, 2H), 5.18 (ddt, J = 10.5, 1.8, 1.5 Hz, 1H), 5.28 (ddt, J = 17.1, 1.8, 1.5 Hz, 1H), 5.93 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.83 (2C), 67.30, 69.62, 71.77, 72.11, 116.86, 134.87. HRMS Found: 129.0911. Calcd for $C_8H_{16}O_2 - CH_3$: 129.0916.

***N*-(4-Pentenyl)phthalimide (12k)** was synthesized by treatment of 1-bromo-4-pentene with an equimolar amount of potassium phthalimide in DMF at 90 °C overnight. IR (neat) 2939, 1771, 1713, 1641, 1396, 1371, 1188, 1072, 993, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (tt, J = 7.2, 7.2 Hz, 2H), 2.13 (dt, J = 7.2, 7.2 Hz, 2H), 3.71 (t, J = 7.2 Hz, 2H), 4.99 (dd, J = 9.9, 1.2 Hz, 1H), 5.06 (dd, J = 17.1, 1.2 Hz, 1H), 5.82 (ddt, J = 17.1, 9.9, 7.2 Hz, 1H), 7.69–7.74 (m, 2H), 7.82–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.43, 30.78, 37.37, 115.25, 123.12 (2C), 132.13, 133.85 (2C), 137.30 (2C), 168.42 (2C). Found: C, 72.60; H, 6.07%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09%.

Hydroxy lactones **13** were silylated with *t*-butyldimethylsilyl chloride in the presence of imidazole in DMF in more than 90% yield to afford analytically pure material.

5-(4-Hydroxybutyl)dihydrofuran-2(3*H*)-one (13a): IR (neat) 3346, 2922, 1752, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.94 (m, 9H), 2.34 (sextet, $J \approx 7$ Hz, 1H), 2.54 (dd, J = 9.3, 6.9 Hz, 2H), 3.67 (t, J = 6.0 Hz, 2H), 4.51 (quintet, $J \approx 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.25, 27.55, 28.52, 31.84, 34.93, 61.87, 80.92, 177.65; MS *m/z* (relative intensity) 157 (M-1, 1), 140 (3), 128 (25), 110 (22), 85 (100).

5-[4-(*t*-Butyldimethylsiloxy)butyl]dihydrofuran-2(3*H*)-one (13a'): IR (neat) 2926, 1777, 1460, 1255, 1180, 1098, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.41–1.67 (m, 5H),

1.70–1.91 (m, 2H), 2.31 (sextet, $J \approx 7$ Hz, 1H), 2.52 (dd, $J = 9.3$, 6.9 Hz, 2H), 3.61 (t, $J = 6.0$ Hz, 2H), 4.48 (quintet, $J \approx 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.58 (2C), 18.09, 21.45, 25.74 (3C), 27.76, 28.62, 32.21, 35.15, 62.63, 80.83, 177.26. Found: C, 62.01; H, 10.44%. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36%.

5-(3-Hydroxypropyl)dihydrofuran-2(3*H*)-one (13b): IR (neat) 3380, 2938, 1749, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.05 (m, 6H), 2.36 (sextet, $J \approx 7$ Hz, 1H), 2.55 (dd, $J = 9.3$, 6.9 Hz, 2H), 3.70 (t, $J = 6.3$ Hz, 3H), 4.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.70, 28.10, 28.59, 31.72, 61.69, 80.91, 177.66.

5-[3-(*t*-Butyldimethylsiloxy)propyl]dihydrofuran-2(3*H*)-one (13b'): IR (neat) 2926, 1768, 1463, 1255, 1181, 1097, 834, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.53–1.92 (m, 5H), 2.33 (sextet, $J \approx 7$ Hz, 1H), 2.53 (dd, $J = 9.3$, 6.3 Hz, 2H), 3.62–3.67 (m, 2H), 4.52 (quintet, $J \approx 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.58 (2C), 18.08, 25.73 (3C), 27.83, 28.27, 28.67, 31.98, 62.33, 80.80, 177.28. Found: C, 60.15; H, 10.10%. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14%.

5-(2-Hydroxyethyl)dihydrofuran-2(3*H*)-one (13c): IR (neat) 3184, 2926, 1753, 1180, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78–1.86 (broad, 1H), 1.87–2.00 (m, 3H), 2.39 (sextet, $J \approx 7$ Hz, 1H), 2.56 (dd, $J = 9.3$, 6.6 Hz, 2H), 3.83 (t, $J = 6.0$ Hz, 2H), 4.71 (quintet, $J \approx 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.06, 28.57, 38.06, 59.12, 78.50, 177.30.

5-[2-(*t*-Butyldimethylsiloxy)ethyl]dihydrofuran-2(3*H*)-one (13c'): IR (neat) 2928, 1774, 1458, 1255, 1179, 1092, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.76–1.99 (m, 3H), 2.35 (sextet, $J \approx 7$ Hz, 1H), 2.53 (dd, $J = 9.3$, 6.9 Hz, 2H), 3.75 (t, $J = 6.0$ Hz, 2H), 4.67 (quintet, $J \approx 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.67 (2C), 18.06, 25.72 (3C), 27.98, 28.63, 38.43, 59.05, 78.06, 177.30. Found: C, 58.74; H, 9.98%. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90%.

5-(6-Methyl-2,5-dioxaheptyl)dihydrofuran-2(3*H*)-one (13e): Bp 155 °C/0.1 torr; IR (neat) 2968, 2868, 1778, 1369, 1128, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.0 Hz, 6H), 2.08–2.79 (m, 4H), 3.54–3.75 (m, 7H), 4.62–4.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.86 (2C), 23.90, 28.22, 67.30, 71.35, 71.86, 72.67, 79.08, 177.52. HRMS Found: 187.0966. Calcd for $C_{10}H_{18}O_4$–CH_3: 187.0970.

Lactone **13f** was quantitatively converted into allyl ester by treatment with allyl bromide (1.5 eq.) and K_2CO_3 (1.5 eq.) in refluxing acetone for 3 h.

5-[2-(Allyloxycarbonyl)ethyl]dihydrofuran-2(3*H*)-one (13f'): IR (neat) 2942, 1774, 1739, 1650, 1439, 1376, 1345, 1264, 1141, 1044, 990, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81–2.10 (m, 3H), 2.37 (sextet, $J \approx 7$ Hz, 1H), 2.45–2.63 (m, 4H), 4.50–4.61 (m, 3H), 5.25 (ddt, J = 10.5, 1.2, 1.2 Hz, 1H), 5.32 (ddt, $J \approx 17.4$, 1.2, 1.2 Hz, 1H), 5.92 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.62, 28.44, 29.85, 30.44, 65.13, 79.46, 118.32, 131.97, 172.29, 176.79. Found: C, 60.61; H, 7.12%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

5-(4-Hydroxybutyl)-3-methyldihydrofuran-2(3*H*)-one (13h, 1/1 mixture of diastereomers): IR (neat) 3347, 2925, 1755, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 1.5H), 1.28 (d, J = 7.2 Hz, 1.5H), 1.42–1.84 (m, 6.5H), 1.96–2.18 (m, 1H), 2.50 (ddd, J = 12.6, 8.4, 5.4 Hz, 0.5H), 2.61–2.90 (m, 2H), 3.67 (t, J = 5.7 Hz, 2H), 4.30–4.40 (m, 0.5H), 4.48–4.57 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ 14.75, 15.50, 21.35, 21.40, 31.82, 31.87, 33.80, 34.84, 34.92, 35.07, 35.66, 36.96, 62.05 (2C), 78.41, 78.62, 179.99, 180.50.

5-[4-(*t*-Butyldimethylsiloxy)butyl]-3-methyldihydrofuran-2(3*H*)-one (13h', 1/1 mixture of diastereomers): IR (neat) 2928, 2856, 1775, 1460, 1250, 1188, 1166, 1097, 1002, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.27 (d, J = 6.9 Hz, 1.5H), 1.28 (d, J = 7.2 Hz, 1.5H), 1.39–1.84 (m, 6.5H), 1.95–2.18 (m, 1H), 2.48 (ddd, J = 12.3, 9.0, 5.4 Hz, 0.5H), 2.59–2.73 (m, 1H),

3.62 (t, J = 6.0 Hz, 2H), 4.29–4.39 (m, 0.5H), 4.46–4.55 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ –5.55 (4C) 14.92, 15.69, 18.12, 21.53, 21.60, 25.76 (7C), 32.21, 32.27, 33.84, 35.03, 35.13, 35.25, 35.74, 37.1(62.68 (2C), 78.28, 78.52, 179.64, 180.12. Found: C, 62.84; H, 10.48%. Calcd for $C_{15}H_{30}O_3Si$: C 62.89; H, 10.55%.

5-(1-Hydroxyethyl)dihydrofuran-2(3*H*)-one (13g, 54/46 mixture of diastereomers): IR (neat) 334(2974, 1753, 1191, 1139, 1021, 986, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 3H × 0.46) 1.27 (d, J = 6.3 Hz, 3H × 0.54), 2.00–2.69 (m, 5H), 3.79 (dq, J = 6.3, 6.3 Hz, 0.5H), 4.08–4.17 (m 0.5H), 4.32–4.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.58, 18.28, 20.79, 23.82, 28.44, 28.52, 67.2(69.60, 83.65, 84.23, 177.71, 178.05.

Acetylation of **13g** (acetic anhydride, pyridine, overnight, 95% yield) provided analytically pur sample **13g'**.

5-[1-(Acetoxy)ethyl]dihydrofuran-2(3*H*)-one (13g', 50/50 mixture of diastereomers): IR (neat 2940, 1780, 1739, 1374, 1242, 1180, 1137, 1074, 1048, 981, 941 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 ((J = 6.6 Hz, 1.5H), 1.31 (d, J = 6.6 Hz, 1.5H), 1.92–2.20 (m, 1H), 2.06 (s, 1.5H), 2.08 (s, 1.5H 2.24–2.36 (m, 1H), 2.46–2.64 (m, 2H), 4.51 (septet, $J \approx 4$ Hz, 1H), 4.96–5.04 (m, 0.5H), 5.04–5.13 (m 0.5H); ^{13}C NMR ($CDCl_3$) δ 15.02, 15.72, 20.84 (2C), 22.46, 23.78, 27.81, 28.00, 70.44, 71.1(80.67, 80.92, 170.09, 170.24, 176.66 (2C). Found: C, 55.79; H, 6.94%. Calcd for $C_8H_{12}O_4$: C 55.81; H, 7.02%.

5-(8-Hydroxyoctyl)dihydrofuran-2(3*H*)-one (13j): Mp 57–59 °C. IR (Nujol) 3402, 3335, 285(1747, 1198, 1182, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26–1.66 (m, 14H), 1.68–1.92 (m, 2H), 2.3 (sextet, $J \approx 7$ Hz, 1H), 2.54 (dd, J = 9.6, 6.6Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 4.49 (quintet, $J \approx 7$ H 1H); ^{13}C NMR ($CDCl_3$) δ 24.93, 25.42, 27.72, 28.61, 28.96, 29.00, 29.11, 32.43, 35.27, 62.57, 80.9 177.54. Found: C, 66.99; H, 10.61%. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35%.

5-(3-Phthalimidopropyl)dihydrofuran-2(3*H*)-one (13k): Mp 76–79 °C. IR (Nujol) 2941, 176'

1715, 1398, 1180, 1047, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61–1.98 (m, 5H), 2.34 (sextet, $J \approx 7$ Hz, 1H), 2.54 (dd, $J = 9.3, 7.2$Hz, 2H), 3.75 (t, $J \approx 6$ Hz, 2H), 4.55 (quintet, $J \approx 7$ Hz, 1H), 7.70–7.67 (m, 2H), 7.81–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.30, 27.53, 28.35, 32.41, 36.96, 79.87, 122.98 (2C), 131.74 (2C), 133.84 (2C), 168.14 (2C), 176.86. Found: C, 65.87; H, 5.53%. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53%.

5-(3-Oxobutyl)dihydrofuran-2(3*H*)-one (13l): IR (neat) 2936, 1771, 1715, 1423, 1358, 1180, 980, 916 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76–1.93 (m, 2H), 1.96–2.08 (m, 1H), 2.18 (s, 3H), 2.37 (sextet, $J \approx$ 7 Hz, 1H), 2.55 (dd, $J = 9.6, 6.9$ Hz, 2H), 2.67 (t, $J \approx 7$ Hz, 2H), 4.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.68, 28.40, 29.02, 29.71, 38.85, 79.64, 176.91, 207.46. Found: C, 61.58; H, 7.84%. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74%.

3-(Tetrahydrofuran-2-yl)propanoic acid (19) was isolated as allyl ester after treatment with allyl bromide in the presence of K_2CO_3 in refluxing acetone.

Allyl 3-(Tetrahydrofuran-2-yl)propanoate (19'): IR (neat) 2932, 2862, 1737, 1648, 1376, 1236, 1158, 1066, 988, 927 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (ddt, $J = 10.5, 7.5, 7.5$ Hz, 1H), 1.77–2.05 (m, 5H), 2.36–2.56 (m, 2H), 3.71 (q, $J \approx 7$ Hz, 1H), 3.80–3.90 (m, 2H), 4.58 (ddd, $J = 5.7, 0.9, 0.9$ Hz, 2H), 5.23 (ddt, $J = 10.5, 1.5, 0.9$ Hz, 1H), 5.31 (ddt, $J = 16.5, 1.5, 0.9$ Hz, 1H), 5.93 (ddt, $J = 16.5, 10.5, 5.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.49, 30.48, 30.86, 30.98, 64.87, 67.54, 78.01, 117.99, 132.30, 173.24. Found: C, 64.93; H, 8.94%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

3-(Tetrahydrofuran-2-yl)propanenitrile (21): IR (neat) 2953, 2872, 2245, 1445, 1427, 1074, 1024, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44–1.57 (m, 1H), 1.72–1.97 (m, 4H), 2.00–2.11 (m, 1H), 2.46 (dd, $J = 7.5, 3.6$ Hz, 1H), 2.48 (dd, $J = 7.8, 2.7$ Hz, 1H), 3.74 (dt, $J = 8.4, 6.9$ Hz, 1H), 3.82–3.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.11, 25.54, 30.95, 31.18, 67.80, 76.98, 119.77. Found: C, 66.99; H, 9.00%. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86%.

3-(Tetrahydrofuran-2-ylmethyl)dihydrofuran-2(3*H*)-one (24, 1/1 mixture of diastereomers)**:** IR (neat) 2941, 1767, 1715, 1398, 1373, 1180, 1047, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.70 (m, 2H), 1.80–2.15 (m, 5H), 2.44–2.54 (m, 1H), 2.58–2.69 (m, 0.5H), 2.75–2.87 (m, 0.5H), 3.68–3.78 (m, 1H), 3.81–3.96 (m, 1.5H), 3.98–4.08 (m, 0.5H), 4.14–4.24 (m, 1H), 4.32–4.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.25, 25.39, 28.58, 29.27, 31.33, 31.43, 35.86, 36.03, 36.65, 37.60, 66.48, 66.53, 67.52, 67.54, 76.20, 77.56, 179.57, 179.72. Found: C, 63.52; H, 8.47%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

***N,N*-Diethyl-3-(tetrahydrofuran-2-yl)propanamide (26):** IR (neat) 2966, 2928, 1640, 1629, 1459, 1380, 1096, 1066, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 4.2 Hz, 3H), 1.17 (t, J = 4.2 Hz, 3H), 1.44–1.56 (m, 1H), 1.70–2.07 (m, 5H), 2.32–2.54 (m, 2H), 3.33 (q, J = 4.2 Hz, 2H), 3.37 (q, J = 4.2 Hz, 2H), 3.72 (q, $J \approx 7$ Hz, 1H), 3.80–3.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.96, 14.20, 25.59, 29.82, 31.17, 31.33, 40.01, 41.83, 67.61, 78.68, 172.04. Found: C, 66.25; H, 10.67%. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62%.

3-(5-Oxotetrahydrofuran-2-yl)propionitrile (27): IR (neat) 2939, 2247, 1771, 1423, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–2.09 (m, 3H), 2.36–2.48 (m, 1H), 2.53–2.62 (m, 4H), 4.54–4.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.85, 27.42, 28.33, 31.23, 78.09, 118.62, 176.24. Found: C, 60.27; H, 6.67%. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52%.

3-(Tetrahydropyran-2-yl)propionitrile (28): IR (neat) 2936, 2849, 2245, 1443, 1090, 1049, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22–1.35 (m, 1H), 1.42–1.64 (m, 4H), 1.71–1.88 (m, 3H), 2.44–2.51 (m, 2H), 3.31–3.47 (m, 2H), 3.94–4.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.32, 23.11, 25.79, 31.48, 31.86, 68.44, 75.32, 119.98. Found: C, 68.78; H, 9.15%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41%.

***N*-(4-Pentenyl)aniline (29)** was prepared by treating a mixture of aniline (20 mmol) and 1-bromo-4-

pentene (10 mmol) with potassium carbonate (20 mmol) in acetone at reflux (32% yield). IR (neat) 3410, 2932, 1603, 1506, 1321, 1259, 912, 748, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (tt, *J* = 7.5, 6.9 Hz, 2H), 2.17 (dt, *J* = 6.9, 6.6 Hz, 2H), 3.13 (t, *J* = 7.5 Hz, 2H), 3.50–3.80 (broad s, 1H), 4.97–5.10 (m, 2H), 5.84 (ddt, *J* = 16.8, 9.9, 6.6 Hz, 1H), 6.60 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.69 (tt, *J* = 7.5, 0.9 Hz, 1H), 7.17 (dd, *J* = 8.7, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.53, 31.19, 43.29, 112.73 (2C), 115.12, 117.19, 129.29 (2C), 138.13, 148.47. Found: C, 81.88; H, 9.55%. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38%.

3-(1-Phenyl-2-pyrrolidinyl)propanenitrile (30): IR (neat) 2936, 2245, 1599, 1504, 1367, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63–1.76 (m, 1H), 1.79–1.86 (m, 1H), 1.95–2.12 (m, 4H), 2.28–2.46 (m, 2H), 3.17 (dt, *J* = 8.7, 8.1 Hz, 1H), 3.44–3.51 (m, 1H), 3.79–3.87 (m, 1H), 6.60 (d, *J* = 8.1 Hz, 2H), 6.70 (t, *J* = 7.5 Hz, 1H), 7.21–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.95, 23.26, 28.51, 29.93, 48.54, 56.86, 112.01 (2C), 116.26, 119.56, 129.42 (2C), 147.00. Found: C, 78.08; H, 8.33%. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05%.

3-(1-Phenyl-2-pyrrolidinylmethyl)dihydrofuran-2(3*H*)-one (31, 1/1 mixture of diastereomers)**:** IR (neat) 2932, 1771, 1599, 1373, 1157, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74–2.26 (m, 7H), 2.36–2.47 (m, 0.5H), 2.48–2.60 (m, 1.5H), 3.13–3.24 (m, 1H), 3.42–3.50 (m, 1H), 3.79–3.88 (m, 0.5H), 4.14–4.53 (m, 2.5H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.64–6.70 (m, 2H), 7.19–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.95, 23.26, 29.10, 29.71, 29.91, 30.08, 33.60, 33.78, 36.49, 37.14, 48.07, 48.40, 55.87, 56.43, 66.43, 66.51, 111.67 (2C), 112.09 (2C), 115.72 (2C), 129.27 (2C), 129.30 (2C), 147.17 (2C), 179.31, 179.50. HRMS Found: 245.1414. Calcd for $C_{15}H_{18}NO$: 245.1416.

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12. Allyl 2-iodoacetate gave the desired γ-lactone in only 38% yield upon heating at 60 °C in H_2O for 10 h in the presence of **1b**. In addition to the γ-lactone, a complex mixture containing acids, which were generated by hydrolysis of the ester group, was obtained.
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16. The use of **1b**, instead of **1a**, also gave the corresponding lactone in good yield. Treatment of a

mixture of iodoacetamide (1.0 mmol) and 5-hexen-1-ol (1.5 mmol) with **1b** (0.5 mmol) at 75 °C for 5 h provided **13a** in 96% yield. However, the product was contaminated with residues derived from **1b** even after silica gel column purification.

17. Reaction in boiling water lowered the yield of lactone (70% yield in the case of **13a**).
18. Reducing the amount of NaI (0.20 mmol) resulted in formation of **13a** in only 39% yield.
19. The use of AIBN, instead of **1a**, also led to recovery of iodo amide.
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22. Non-volatile olefins could be recovered easily.
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CHAPTER 4

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

Treatment of various organic halides with phosphinic acid (hypophosphorous acid) in aqueous ethanol in the presence of a radical initiator and a base furnished the corresponding reduced products in high yields. Addition of a base was 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.

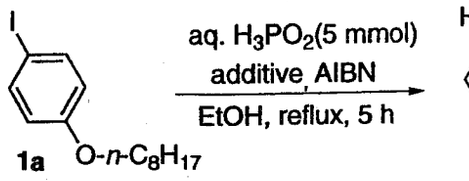
1. Reduction of Organic Halides with Phosphinic Acid in Aqueous Ethanol

During the recent dramatic development of radical methodology in organic synthesis, tributyltin 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 tributyltin 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. The author wishes to describe the details of the radical reduction of various halides with 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

Iodide **1a** was chosen as a model substrate to examine radical reduction with 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 expectations, the desired product **2a** was obtained in only 14% yield, and 85% of **1a** remained unchanged. This reaction was then performed in the presence of sodium hydrogencarbonate (6.0 mmol). Surprisingly, the yield improved sharply up to 98%. Potassium hydroxide or triethylamine was also effective to furnish **2a** in 79% or 96% yield, respectively.[7] On the other hand, addition of hydroiodic acid suppressed the reaction completely.[8] 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.[9,10]

Scheme 1



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)

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, Entries 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 (Entries 5 and 6). Reduction was again sluggish without a base, and no reduced product was obtained in the presence of hydroiodic acid (Entries 7 and 8). Triethylborane, instead of AIBN, acted effectively as a radical initiator at room temperature (Entry 9).[11,12] Reduction did not occur in the absence of a radical initiator.

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

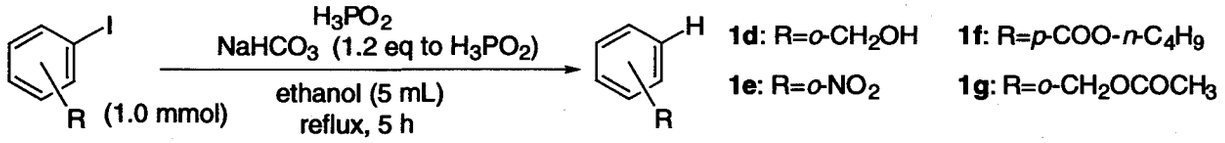
Entry	Substrate	H_3PO_2 /mmol	$NaHCO_3$ /mmol	Time /h	Yield /%[b)]
1	**1b**	10	12	0.5	100
2	**1c**	10	12	0.5	100
3	**1b**	5.0	6.0	0.5	97
4	**1b**	3.0	3.5	1	97
5	**1b**	2.0	2.4	6.5	78 (6)
6	**1b**	1.0	1.2	6.5	38 (57)
7	**1c**	10	0	0.5	31 (69)
8	**1c**	10	0[c)]	0.5	<1 (81)
9	**1b**	5.0	6.0	3	95[d)]

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 25 °C.

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

Table 2. Reduction of Various Aryl Iodides

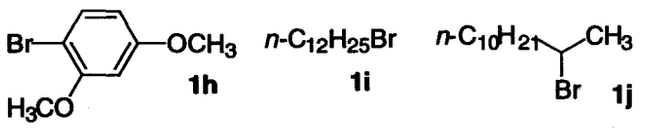


Entry	Substrate	Product	H_3PO_2 /mmol	AIBN /mmol	Yield[b] /%
1	**1d**	**1d**	10	0.10	85
2	**1d**	**1d**	5.0	0.50	100
3	**1e**	**1e**	10	0.50	73
4	**1f**	**1f**	10	0.10	95
5	**1g**	**1g**	5.0	0.10	70
6	**1g**	**1g**	10	2.0[b]	83

a) Benzyl alcohol (23%) was obtained. Reaction time was 3 h. b) Et_3B was used instead of AIBN at 25 °C.

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). It was found that 2,2'-azobis(isobutyramidine) dihydrochloride (AIBA) was more effective than AIBN in reducing alkyl bromide (Entries 3 and 4). Reduction of reactive α-bromocarbonyl 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).

Table 3. Reduction of Other Compounds[a)]

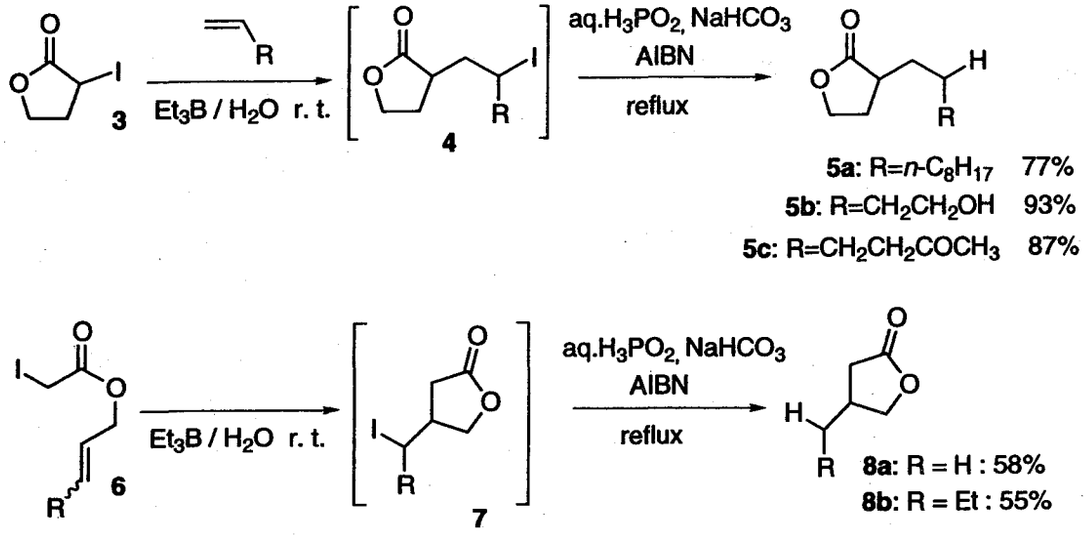


Entry	Substrate	Product	AIBN /mmol	Time /h	Yield /% [b)]
1	**1h**	**2h**	0.50 × 2	5	9 (91)
2	**1i**	**2b**	0.20	5	17 (30)
3	**1i**	**2b**	0.20[c)]	5	84
4	**1j**	**2b**	0.10[c)]	3	80
5	**1k**	**2k**	0.10	2	89
6[d)]	**1l**	**2l**	0.30	2.5	8 (39)
7	**1m**	**2m**	0.20	0.5	100
8	**1m**	**2m**	1.0 × 4[e)]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

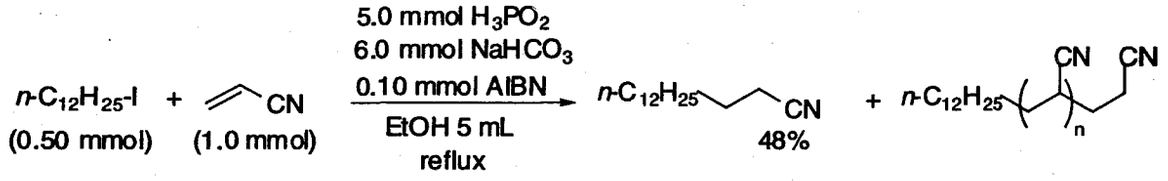
It was recently demonstrated that iodine atom transfer radical reactions proceeded more effectively in water, especially in the case of the cyclization of allyl iodoacetate.[11c] Reduction of the product resulting from iodine atom transfer radical process in water was achieved in the same pot with phosphinate 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.[13] In these cases, ethanol was not used.

Scheme 2



However, reductive radical addition of 1-iodododecane to acrylonitrile did not give a satisfactory result. The best result was obtained when 1-iodododecane (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.

Scheme 3



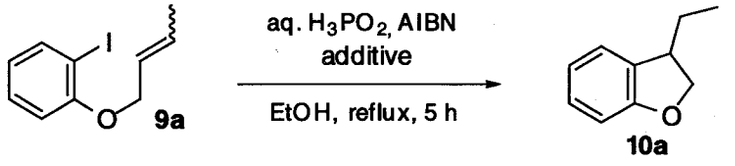
Although these reactions were carried out in nontoxic aqueous ethanol, it is necessary to use organic solvents such as ethyl acetate and hexane in extracting and purifying the products. In order to clear up the contradiction, isolation by distillation was performed. After **1b** (50 mmol) was subjected 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.

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 4

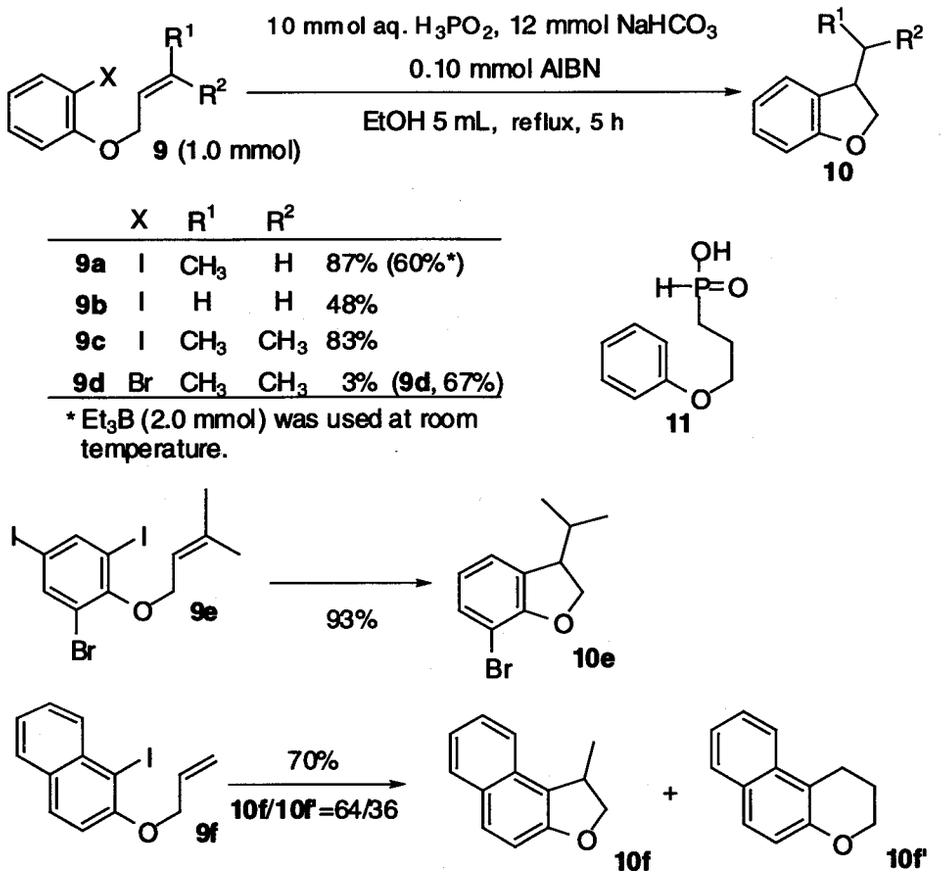


10 mmol $NaHCO_3$	87%		
10 mmol KOH	91%	None	3% (67% recovery)
10 mmol Et_3N	89%	5 mmol aq. HCl	0% (38% recovery)

9a(1.0 mmol), aq. H_3PO_2(1.1 mL 10 mmol), AIBN(0.10 mmol), Ethanol(5 mL)

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 of by-product **11**[14] (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.[15] When allyl ether of iodonaphthol **9f** was employed as a substrate, 6-endo cyclization was observed,[16] in addition to 5-exo cyclization.

Scheme 5

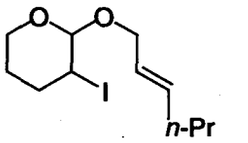
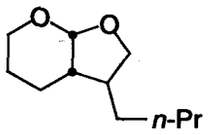
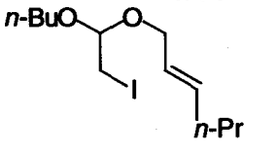
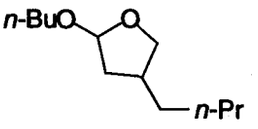
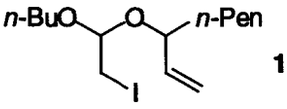
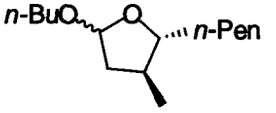
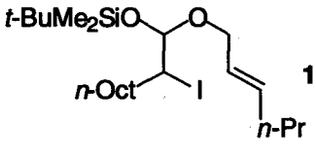
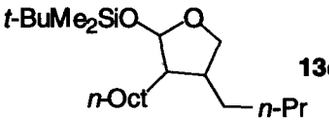
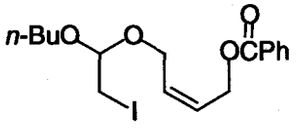
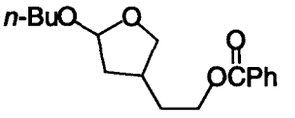
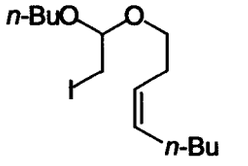
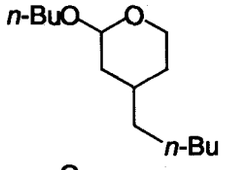
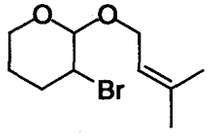
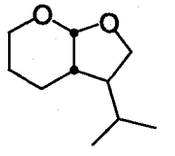
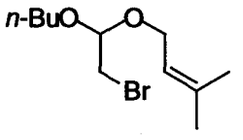
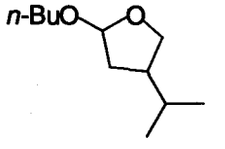


	X	R^1	R^2	
9a	I	CH_3	H	87% (60%*)
9b	I	H	H	48%
9c	I	CH_3	CH_3	83%
9d	Br	CH_3	CH_3	3% (**9d**, 67%)

* Et_3B (2.0 mmol) was used at room temperature.

Next, the author focused on radical cyclization of halo acetals[17] (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 amount 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.[18] (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.

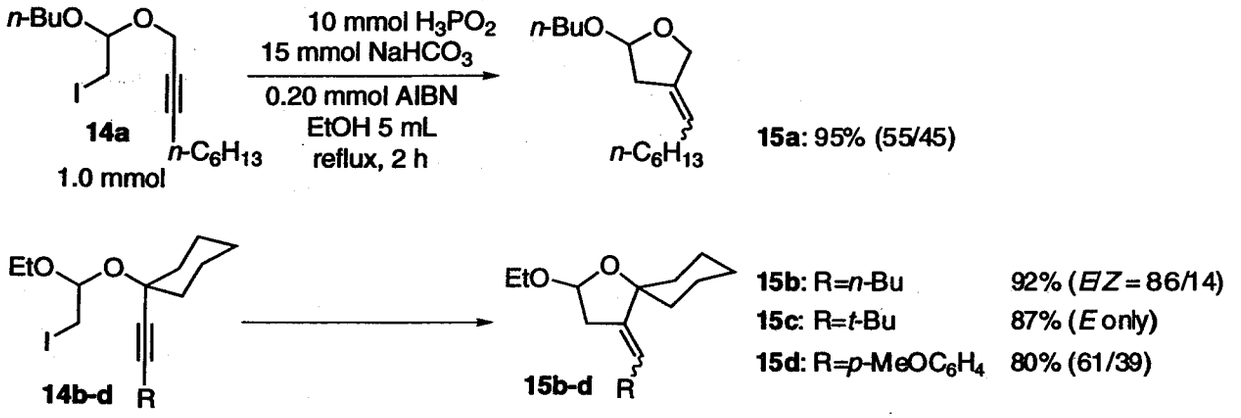
Table 4. Radical Cyclization of Halo Acetals with an H_3PO_2/$NaHCO_3$/EtOH System[a)]

	**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. 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) A solution of H_3PO_2 (10 mmol), $NaHCO_3$ (15 mmol) and 4,4'-azobis(4-cyanopentanoic acid) (0.10 mmol) in water was added to a solution of **12f** in refluxing ethanol 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.

Scheme 6



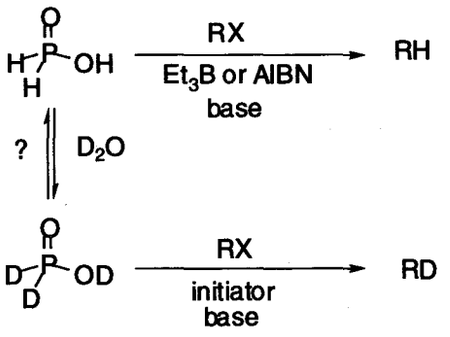
In summary, the phosphinic-acid-mediated radical reaction in aqueous ethanol was demonstrated. Ethanol is cheap and a far less toxic organic solvent than other organic solvents. Phosphinic acid and sodium hydrogencarbonate are probably the cheapest combination for radical reduction, avoid suffering from 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.[19] 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.[20] However, radical reactions using tin deuterides have serious drawbacks when used in the synthesis of biologically active compounds, because the inherent toxicity of organotin derivatives and the difficulty of removal of residual tin compound often prove fatal. Non-toxic and easily removable phosphinic acid effected radical reaction 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).

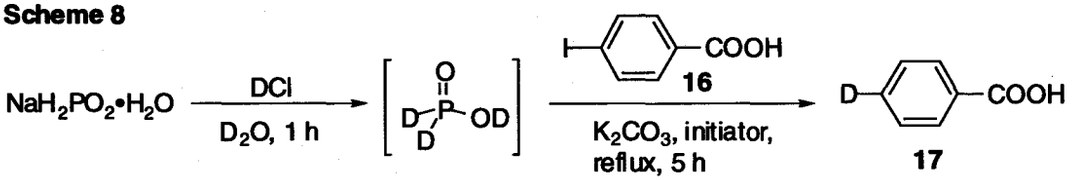
Scheme 7



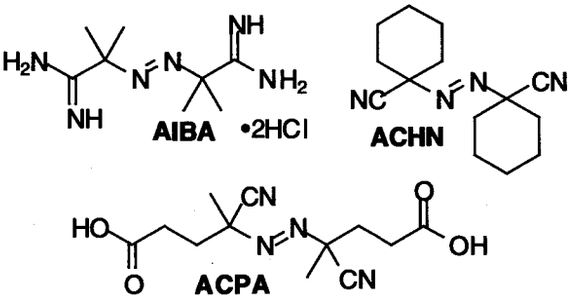
Reduction of *p*-iodobenzoic acid (**16**) in D_2O was examined as a model reaction (Scheme 8). Sodium phosphinate monohydrate ($NaH_2PO_2 \cdot H_2O$, 5.0 mmol) was treated with DCl (37 wt% solution in D_2O, 0.80 mL, 10 mmol) in D_2O (5 mL). After stirring for 1 h, K_2CO_3 (8.0 mmol) was added to the solution to give the deuterated potassium phosphinate, and AIBN (0.10 mmol) and **16** (0.50 mmol) were then added. The resulting mixture was refluxed for 5 h to give benzoic acid

(**17**). The deuterium incorporation at the para position was 85%,[21,22] although the yield was miserable (<10%). In order to improve the yield of **17**, several radical initiators were investigated. Consequently, it was found that 2,2'-azobis(isobutyramidine) dihydrochloride[23] (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)[23] (ACPA) were far inferior to AIBA.

Scheme 8



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)

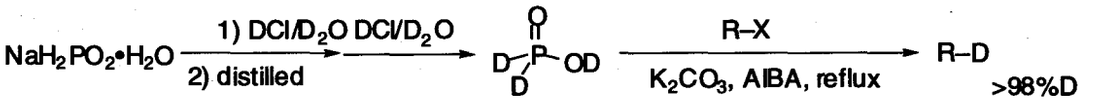


The reason for the uniqueness of AIBA as a radical initiator for deuteration is not clear. In the previous section, AIBN was effective in refluxing aqueous ethanol. Et_3B also acted as an initiator at 25 °C. In the present case, it is obvious that kinetic isotope effects would operate in the initiation 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.[24] 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. The author 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 a 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[25] (50 wt% in D_2O, 5.0 mmol, 0.50 mL) gave the same results.

Scheme 9



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

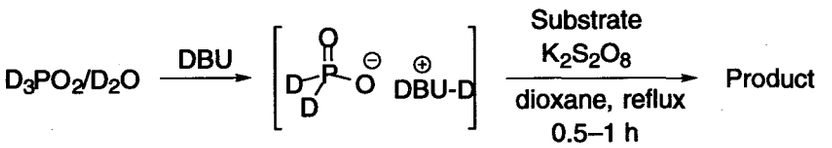
a) The yields using commercially available D_3PO_2 are shown in parentheses

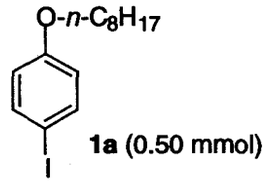
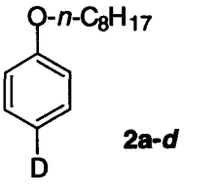
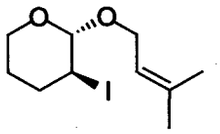
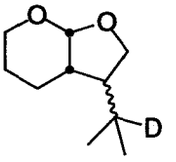
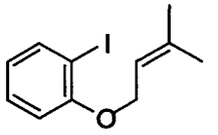
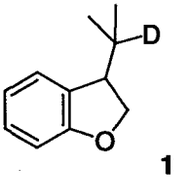
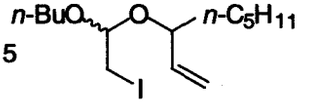
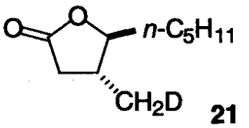
The author also explored the reduction of various hydrophobic organic halides in organic solvents (Table 5). Phosphinic acid-d_3 (10 M solution in D_2O) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[26] and the mixture was stirred for 10 min. A dioxane solution of substrate[27] and $K_2S_2O_8$[28] 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 (Entries 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 heated for 2 h at reflux with vigorous stirring to afford **7g-*d*** in 90% yield (>98%D).[29] 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.

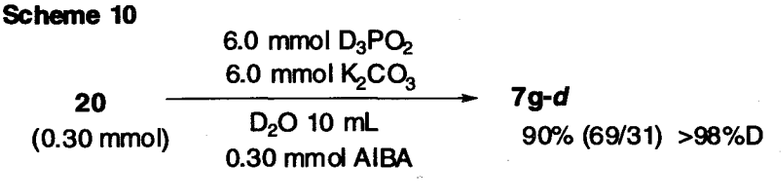
Table 5. D_3PO_2-Mediated Radical Reaction in Dioxane/D_2O[a)]



Entry	Substrate	Product	Yield
1	I–$(CH_2)_{12}$–I **18** (0.40 mmol)	D–$(CH_2)_{12}$–D **19**	94% 91%D
2	 **1a** (0.50 mmol)	 **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	 **12c** (0.70 mmol)	 **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.

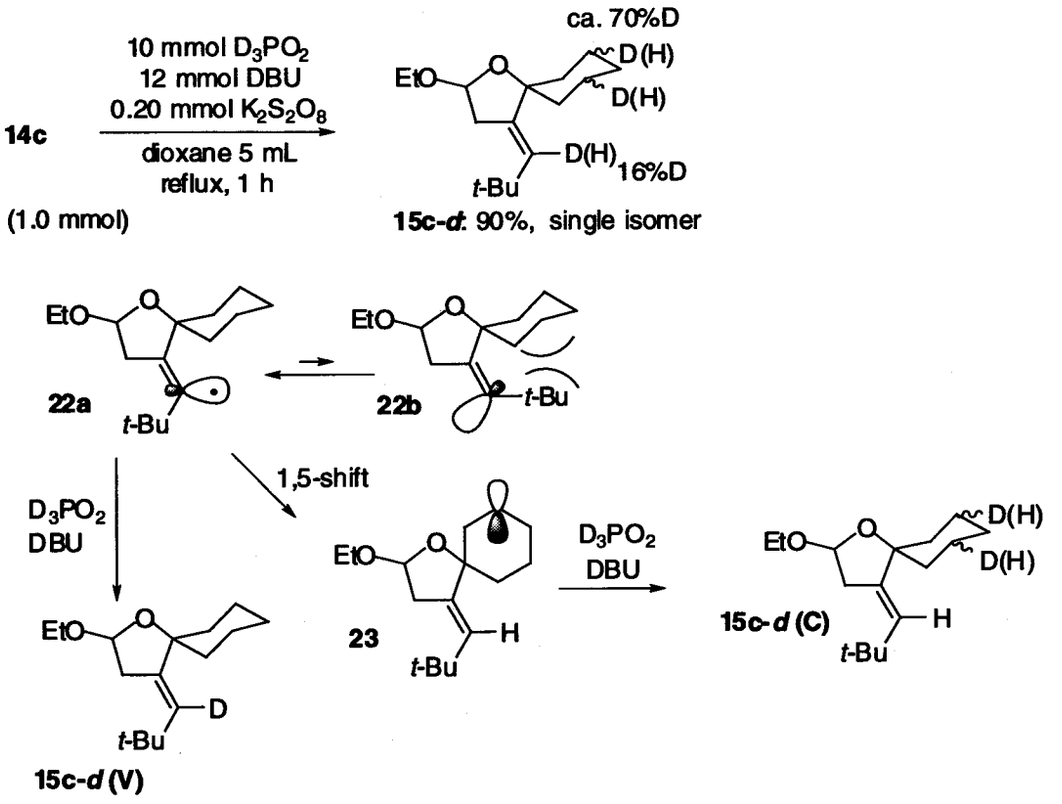
Scheme 10



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 between 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.

Scheme 11


14c
10 mmol D_3PO_2
12 mmol DBU
0.20 mmol $K_2S_2O_8$
dioxane 5 mL
reflux, 1 h
(1.0 mmol)
ca. 70%D
EtO
D(H)
D(H)
D(H)
16%D
t-Bu
15c-d: 90%, single isomer
22a
22b
1,5-shift
23
D_3PO_2
DBU
15c-d (V)
15c-d (C)

Experimental Section

Dioxane was dried over slices of sodium. DBU was distilled from KOH and stored under argon. Halo acetals were prepared according to the literature.[17]

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. Halide **1m** was then 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: An ethanol solution of triethylborane (1.0 M) 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-iododododecane (**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 flashed fire.* 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 1M 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 (50wt%, 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 ^1H 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.[11,16,30]

α-(4-Hydroxybutyl)-γ-butyrolactone (5b): IR (neat): 3260, 2924, 2856, 1744, 1461, 1379, 1148, 1023, 953 cm^{-1}; ^1H 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 Hz, 9.0 Hz, 9.6 Hz, 1H), 4.36 (ddd, J = 3.0 Hz, 9.0 Hz, 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: 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}; ^1H 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 Hz, 9.0 Hz, 1H), 4.35 (dt, J = 3.0 Hz, 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: 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}; ^1H 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: 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}; ^1H 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 = 5 Hz, 1H), 4.47 (dd, J = 5.1 Hz, 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: 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}; ^1H NMR ($CDCl_3$): δ 4.73 (d, J = 2.4 Hz, 2H), 5.32 (dd, J = 10.8 Hz, 1.5 Hz, 1H), 5.56 (dd, J = 17.1 Hz, 1.5 Hz, 1H), 6.04–6.18 (m, 1H), 7.15 (dd, J = 8.7 Hz, 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 Hz, 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: 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 4-butyl-3-octyldihydrofuran-2(3H)-one (a mixture of diastereomers, 80/20) in 78% yield. IR (neat): 2920, 2852, 1776, 1467, 1379, 1164, 1021 cm^{-1}; ^1H 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 Hz, 7.8 Hz 0.8H), 4.07 (dd, J = 9.0 Hz, 3.6 Hz, 0.2H), 4.21 (dd, J = 9.0 Hz, 6.0 Hz, 0.2H), 4.38 (dd, J = 9.0 Hz, 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}; ^1H 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 Hz, 6.6 Hz, 1H), 3.62 (dt, *J* = 9.0 Hz, 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, 129.60, 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}; ^1H 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 Hz, 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, 129.55, 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}; ^1H 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 Hz, 6.9 Hz, 2H), 2.35 (dt, *J* = 6.9 Hz, 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}; ^1H 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 Hz, 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}; ^1H 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 Hz, 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: 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}; ^1H 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: 240.2066, Calcd for $C_{15}H_{28}O_2$: 240.2089.

2-Iodoethanal Ethyl 1-(2-Hexynyl)cyclohexyl Acetal (14b): IR (neat): 2922, 2854, 2230, 1446, 1412, 1372, 1338, 1297, 1176, 1116, 1043, 1002, 938, 905, 614 cm^{-1}; ^1H 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 Hz, 6.6 Hz, 1H), 3.74 (dq, *J* = 9.3 Hz, 6.9 Hz, 1H), 5.06 (dd, *J* = 6.6 Hz, 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}; ^1H 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: 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}; ^1H 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 Hz, 7.2 Hz, 1H), 3.77 (dq, *J* = 9.3 Hz, 7.2 Hz, 1H), 5.02 (dd, *J* = 3.3 Hz, 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}; ^1H 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 Hz, 6.9 Hz, 1H), 3.80 (dq, *J* = 9.9 Hz, 7.2 Hz, 1H), 5.10 (t, *J* = 2.4 Hz, 1H), 5.16 (dd, *J* = 5.1 Hz, 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}; ^1H 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 Hz, 7.2 Hz, 1H), 3.74–3.84 (m, 3H), 3.82 (s, 3H), 5.14 (dd, *J* = 3.9 Hz, 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-[2-(4-Methoxyphenyl)ethynyl]-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}; ^1H 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}; ^1H 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, 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}; ^1H 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 Hz, 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, 2H) 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 (9c-*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 Hz, 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 Hz, 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: 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: 171.1365, Calcd for $C_{10}H_{17}DO_2$: 171.1370.

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6. Reduction of water-soluble substrates in water was reported. Jang, D. O. *Tetrahedron Lett.* **1998**, *39*, 2957–2958.
7. 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.
8. The use of other initiators such as $K_2S_2O_8$ or di-*tert*-butyl peroxide was not effective at all.
9. 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, Jang, D. O.; Song, S. H. *Tetrahedron Lett.* **2000**, *41*, 247–248.

10. The fact that **2a** was obtained in 14% yield without a base is probably due to the equilibrium to generate a small amount of phosphinate anion. Phosphinic acid is highly acidic ($K_1 = 8.0 \times 10^{-2}$). See: the Merck Index, 12th ed., Budavari, S. Ed., Merck & Co., Inc., Whitehouse Station, NJ, 1996, p 836.
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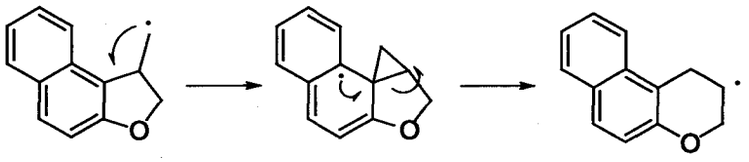
12. The reaction did not go to completion when a catalytic amount of Et_3B was used. The hydrogen abstraction step would be slow at room temperature because of the strong P–H bond.
13. Triethylborane was superior to AIBN in the lactonization step because the reaction at high temperature led to the hydrolysis 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.
14. Phosphorus-centered radical easily adds to terminal olefin (see Ref. 4).
15. The author 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.
16. 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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18. Treatment of **12f** under the standard conditions gave **13f** in 52% yield in addition to the direct reduction product (38% yield).

19. Nnane,I. P.; Hutt, A. J.; Damani,L. A. in *Encyclopedia of Analytical Science*, Townshend, A. Ed., Academic Press, 1995, London, Vol. 2, p. 952.

20. For recent examples of *n*-Bu_3SnD-mediated radical deuteration, see: a) Kawashima, E.; Aoyama, Y.; Sekine, T.; Miyahara, M.; Radwan, M. F.; Nakamura, E.; Kainosho, M.; Kyogoku, Y.; Ishido, Y. *J. Org. Chem.* **1995**, *60*, 6980. b) Shuto, S.; Sugimoto, I.; Abe, H.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 1343. c) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.*, **1999**, *5*, 2866. d) Beckwith, A. L. J.; Duggan, P. J. *Tetrahedron* **1998**, *54*, 6919. e) Nagano, H.; Azuma, Y. *Chem. Lett.* **1996**, 845–846. f) Batey, R. A; Smil, D. V. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1798.

21. The deuterium incorporation was determined by the integration of ^1H NMR.

22. The exchange between hydrogen in H_3PO_2 and deuterium in D_2O proceeds more rapidly in acidic condition 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: Jenkins, W. A.; Yost, D. M. *J. Chem. Phys.*, **1952**, *20*, 538.

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25. Deuterated phosphinic acid is available from Aldrich Chemicals and is sold as 'Hypophosphorus acid–d_3.'

26. DBU was the most effective among the bases 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.

27. 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.

28. 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).

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

30. (a) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039. (b) Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *2*, 651. Compound **5i** was subjected to oxidation by Jones oxidant to give known β-isopropyl-γ-butyrolactone. See, (c) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.

Appendix

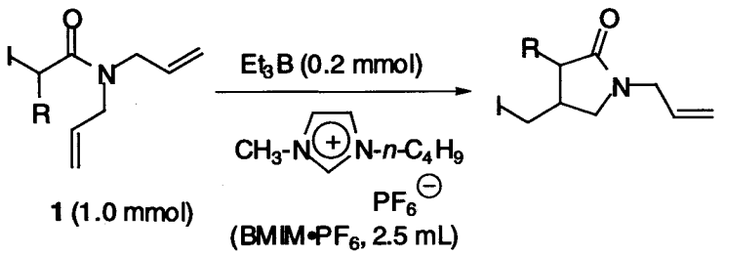
Triethylborane-Induced Radical Reaction in Ionic Liquid

Some triethylborane-induced radical reactions were found to proceed in ionic liquids. The reactions include atom transfer radical cyclization, hydrostannylation of alkyne, and atom transfer radical addition. Ethyl bromoacetate participated in bromine atom transfer reaction to 1-octene in 1-ethyl-3-methylimidazolium tetrafluoroborate to afford the corresponding adduct in excellent yield. The facile bromine atom transfer addition in the ionic liquid indicates that the ionic liquid may have highly polar nature. The ionic liquid used was recyclable in one case, but was not in the other case.

Room temperature ionic liquids have proved to be good solvents for many reactions such as the Diels–Alder reaction, transition metal-catalyzed reactions, and the Friedel–Crafts reactions.[1,2] On the other hand, radical reactions in ionic liquid have been poorly investigated.[3] The author has been interested in solvent effects on radical reactions.[4] Here the results of some radical reactions in ionic liquid is described.

Radical cyclization reaction of *N,N*-diallyl-2-iodoacetamide (**1a**) was first examined. Triethylborane was added to amide **1a** in 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM•PF_6). After stirring under air at 25 °C for 2 h, ether (15 mL) was added to the reaction flask, and the product was extracted (four times). Concentration and silica gel column purification provided γ-lactam **2a** in 82% yield. The reaction was homogeneous. 2-Iodopropanamide **1b** underwent cyclization similarly to afford **2b** in 87% yield. The author investigated the number of times that one could reuse the solvent. After extraction, the ionic liquid was dried at 80 °C in vacuo (0.5 torr) for recycling. As shown in Scheme 1, the decreasing yield was observed in the fifth run.

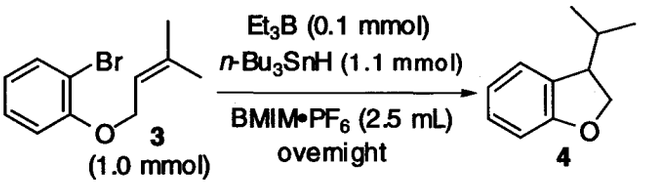
Scheme 1



2a: R = H
1st run: 82% 2nd run: 85%
3rd run: 86% 4th run: 81%
5th run: 67% (**1a**, 27%)
2b: R = CH_3 87% (*c*/*t* = 31/69)

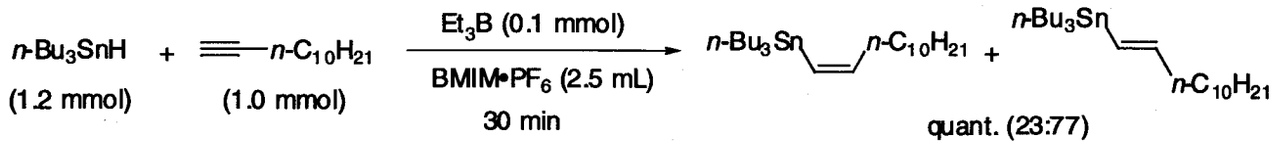
Tributyltin hydride effected reductive cyclization of the prenyl ether of *o*-bromophenol **3**, although the reaction required longer reaction time (Scheme 2). In this case, the system was heterogeneous, and the layer of tributyltin hydride floated on the ionic liquid.

Scheme 2



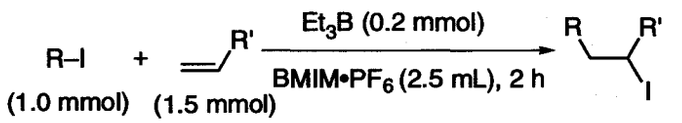
The author then focused on intermolecular radical addition reaction. Hydrostannylation of 1-dodecyne yielded the corresponding 1-alkenyl stannane (*E*/*Z* = 77/23) quantitatively (Scheme 3). Similar reaction was also successful in hexane or without solvent. In regard to the stereoselectivity of the alkenyl stannane, no difference was observed in these three reactions.

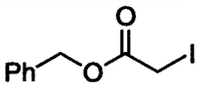
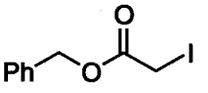
Scheme 3



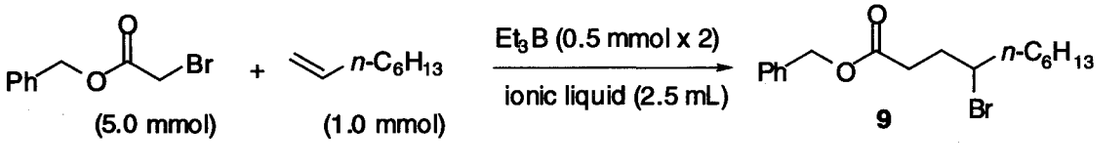
Finally, halogen atom-transfer addition was examined. Perfluoroalkyl iodide and benzyl iodoacetate underwent radical addition smoothly to yield the corresponding adducts (Table 1). The reaction appeared to proceed in a homogeneous phase. On the other hand, addition of benzyl bromoacetate was less efficient (Scheme 4), where a heterogeneous phase, arising from an excess of benzyl bromoacetate, was formed. The reaction in BMIM•PF_6 gave **9** in 34% yield. Several kinds of ionic liquid were surveyed to improve the yield. The use of 1-methyl-3-octylimidazolium hexafluorophosphate (MOIM•PF_6) that has a longer side chain resulted in the lowest yield of **9**. In contrast, reaction in 1-ethyl-3-methylimidazolium tetrafluoroborate (EMIM•BF_4) proceeded very efficiently. The adduct **9** was obtained in 86% yield upon treatment of a mixture of 1-octene and benzyl bromoacetate with triethylborane (0.50 mL × 2) for 6 h. Bromine atom transfer reaction of bromoacetate is usually difficult and requires high temperature. The author and co-workers have reported the reaction proceeded quite efficiently in water, and concluded that the improvement is partly due to the polar nature of solvent.[4a] Thus, the facile bromine atom transfer addition in EMIM•BF_4 indicates that the ionic liquid would have a highly polar nature. Disappointingly, reuse of the ionic liquid was unsuccessful. The second run led to a lower yield (56%).

Table 1. Iodine atom-transfer radical addition in BMIM•PF_6



R–I	R'	yield/%
	n-C_6H_{13}	**5**: 87
	CH_2CH_2OH	**6**: 64
n-C_4F_9–I	n-C_6H_{13}	**7**: 94
n-C_4F_9–I	CH_2CH_2OH	**8**: 74

Scheme 4



R = n-C_4H_9, X = PF_6 (BMIM•PF_6) 34%
R = n-C_4H_9, X = BF_4 (BMIM•BF_4) 25%
R = n-C_8H_{17}, X = PF_6 (OMIM•PF_6) 17%
R = C_2H_5, X = BF_4 (EMIM•BF_4) 86%

Experimental

Most of the substrates and the products are known.[4a,5] BMIM•PF_6 and BMIM•BF_4 were prepared according to the literature.[6,2d] MOIM•PF_6 was prepared in a similar fashion.[6] EMIM•BF_4 and neat triethylborane were purchased from Aldrich.

Radical Cyclization of *N,N*-Diallyl-2-iodoacetamide in BMIM•PF_6 and Recycling of the Ionic Liquid. *N,N*-Diallyl-2-iodoacetamide (**1a**, 265 mg, 1.0 mmol) was placed in an 20-mL reaction flask. BMIM•PF_6 (2.5 mL) was added, and the reaction flask was filled with argon. Triethylborane (0.03 mL, 0.2 mmol) was added to the homogeneous reaction mixture, and the resulting mixture was stirred for 2 h under air. Ether (15 mL) for extraction was added with vigorous stirring. After stirring for 1 min, the upper layer was decanted. This extraction procedure was repeated four times. The combined ethereal solution was evaporated. Purification on silica gel with hexane/AcOEt = 2/1 provided γ-lactam (**2a**, 216 mg, 82% yield). The ionic liquid used was dried in vacuo (0.5 torr) at 80 °C for 3 h. For the second run, the substrate **1a** was added to the ionic liquid in the reaction flask. Amide **1a** was then treated with triethylborane similarly to furnish γ-lactam (225 mg, 85%).

Radical Addition of Benzyl Bromoacetate to 1-Dodecene in EMIM•PF_6. Benzyl bromoacetate (0.79 mL, 5.0 mmol) and 1-octene (0.16 mL, 1.0 mmol) were placed in a 20-mL reaction flask. EMIM•PF_6 (2.5 mL) was added with stirring. The flask was then flushed with argon. Triethylborane (0.07 mL, 0.5 mmol) was added with stirring under argon, and air (10 mL) was introduced to the reaction flask. After stirring for 3 h under air, additional triethylborane (0.07 mL, 0.5 mmol) was added. The resulting mixture was further stirred for 3 h under air. Ether (15 mL) was added to the reaction mixture, and products were extracted (three times). The combined ethereal layer was concentrated in vacuo. Silica gel column purification of the crude oil (hexane/AcOEt = 20/1) provided benzyl 4-bromodecanoate (**9**, 294 mg, 86%).

Benzyl 4-Iododecanoate (5): IR (neat) 2928, 1738, 1167 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 6.6

Hz, 3H), 1.20–1.56 (m, 8H), 1.63–1.75 (m, 1H), 1.81–1.94 (m, 1H), 2.05–2.13 (m, 2H), 2.47–2.70 (m, 2H), 4.06–4.16 (m, 1H), 5.13 (s, 2H), 7.32–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.85, 22.36, 28.22, 29.21, 31.43, 34.20, 35.23, 38.02, 40.52, 66.21, 128.18, 128.23, 128.53, 135.84, 172.46. Found: C, 52.74; H, 6.39%. Calcd for $C_{17}H_{25}IO_2$: C, 52.59; H, 6.49%.

Benzyl 6-Hydroxy-4-iodohexanoate (6): IR (neat) 3427, 2891, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.7 (bs, 1H), 1.89–2.19 (m, 4H), 2.49–2.72 (m, 2H), 3.70–4.00 (m, 2H), 4.23–4.33 (m, 1H), 5.13 (s, 2H), 7.28–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.33, 34.26, 35.46, 42.75, 62.10, 66.46, 128.23, 128.28, 128.56, 135.70, 172.47. Found: C, 45.03; H, 5.09%. Calcd for $C_{13}H_{17}IO_3$: C, 44.85; H, 4.92%.

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Publication List

I. Parts of the present thesis have been published in the following.

Introduction and General Summary

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