

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

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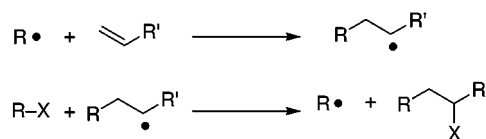
Received June 26, 2001

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, protic solvents such as 2,2,2-trifluoroethanol and 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 the dielectric constant, on the transition states in the bromine atom-transfer and 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 a 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 Kharasch² (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 additions. 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

Scheme 1



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}

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 We have been investigating radical reactions in aqueous media and disclosed the remarkable solvent effects of water.¹⁰ Here, we wish to report the bromine atom-transfer radical addition of α -bromoacetate with 1-alkene in water. The reaction in water could be performed at ambient temperature in the presence of triethylborane¹¹ to yield 4-bromoalkanoate, which will be converted into γ -lactone^{2a,12} or γ -lactam.¹³ We have also investigated the

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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 yields. 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

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Scheme 2

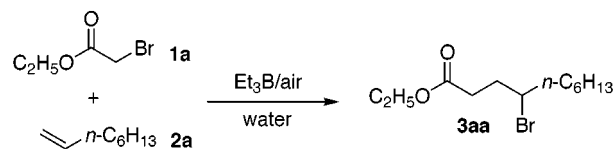


Table 1. Triethylborane-Induced Radical Addition of Ethyl Bromoacetate to Alkenes in Water

entry	2	R	3	yield (%)
1	2a	$n\text{-C}_6\text{H}_{13}$	3aa	80 ^c
2	2b	$n\text{-C}_{10}\text{H}_{21}$	3ab	65 ^c
3	2c	$n\text{-C}_{20}\text{H}_{41}$	3ac	79 ^c
4	2d	$(\text{CH}_2)_4\text{OH}$	3ad	81
5	2e	CH_2OH	3ae	26
6	2f	$\text{CH}_2\text{CH}_2\text{COCH}_3$	3af	84
7	2g	$(\text{CH}_2)_3\text{Br}$	3ag	63
8	2h	$(\text{CH}_2)_8\text{COOCH}_3$	3ah	79
9	2i	$(\text{CH}_2)_4\text{OTHP}$	3ai	69
10	2j	$(\text{CH}_2)_3\text{NPH}^d$	3aj	82
11	2k	cyclohexene	3ak	22 (54/46) ^{c,e}
12	2l	<i>trans</i> -4-octene	3al	10 (1/1) ^{c,e}
13	2m	2-methyl-1-dodecene	3am	77 ^c

^a Ethanol solution (1.0 M). ^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.

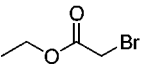
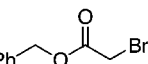
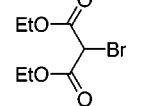
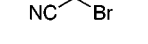
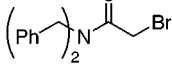
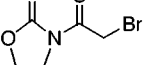
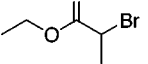
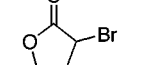
workup followed by silica gel column purification provided ethyl 4-bromodecanoate (**3aa**) in 74% yield (Scheme 2). In contrast to the reaction in water, the reaction proceeded sluggishly in benzene and dichloromethane (12 and 9%, respectively) under similar reaction conditions. When the reaction mixture 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 a 10% yield with stirring for 1.5 h. Employing 5 equiv 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 mol of **1a** with triethylborane (0.50 mmol \times 2) for 3 h. These observations suggest that the rate-determining step in the chain propagation would be the bromine atom-transfer step.

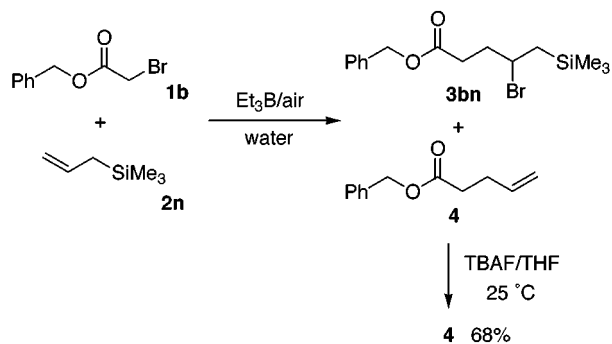
The results of the addition of **1a** (5 equiv) to various olefins in water are summarized in Table 1. A wide range of functionalities in **2d–2j** could survive under the reaction conditions. Interestingly, waxy 1-docosene (**2c**) also reacted with **1a** in an aqueous medium, although the mixture 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**.

Not only ethyl bromoacetate but also other reactive bromides underwent radical addition (Table 2). Bromomalonate **1c** was so reactive⁴ that the addition requires only 1.5 equiv amounts of **1c**. Similar to bromo-

(15) Iodine atom-transfer addition of α -iodo- γ -butyrolactone in water proceeded smoothly to yield the corresponding adduct. In this case, an excess of alkene was used. See ref 3d.

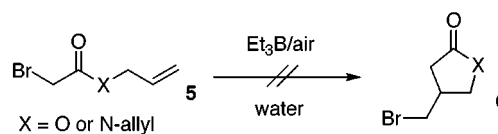
Table 2. Triethylborane-Induced Radical Addition of α -Bromo Carbonyl Compounds to 1-Octene in Water

R-Br + $\text{CH}_2=\text{CH}-n\text{-C}_6\text{H}_{13}$		$\xrightarrow[\text{water (5 mL), 1.5 h}]{\text{Et}_3\text{B (0.50 mmol)}^a, \text{air (10 mL} \times 3)^b}$		R-CH ₂ -CH(Br)-CH ₂ - $n\text{-C}_6\text{H}_{13}$ 3	
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	
5	1e		3ea	N. R. ^c	
6	1f		3fa	<10	
7	1g		3ga	<10	
8	1h		3ha	<10	

^a Ethanol solution (1.0 M). ^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**

acetate, 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).

Radical cyclization of *N,N*-diallyl-2-bromoacetamide or allyl bromoacetate resulted in recovery of the starting

Scheme 4

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.

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

We 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 constant¹⁶ 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 a 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-

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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	entry	solvent	method ^b	yield of 3aa (%) ^c	dielectric constant ^d
1	hexane	A	10	1.88	27	ethylene glycol	C	16	37.7
2	benzene	A	12	2.27	28	2,2,2-TFE ^e	C	73	26.67
3	toluene	A	6	2.38	29	1,1,1,3,3,3-HFP ^f	C	64	
4	chlorobenzene	A	5	5.62	30	water	B	70	79.39
5	dichloromethane	A	9	8.93	31	water	C	50	
6	chloroform	C	3	4.81	32	no solvent	C	12	
7	ether	C	10	4.34	33	0.10 M HCl	B	63	
8	THF	C	4	7.58	34	0.10 M NaOH	B	50	
9	DME	C	23	7.20	35	water ^g	B	8	
10	dioxane	C	24	2.21	36	water ^h	B	2	
11	acetone	C	15	20.56	37	0.10 M NaOH ⁱ	B	14	
12	ethyl acetate	C	18	6.02	38	ethanol/water = 4.5/0.5	B	57	
13	dimethyl carbonate	C	30		39	ethanol/water = 4.0/1.0	B	77	
14	propylene carbonate	C	39	64.92	40	ethanol/water = 3.5/1.5	B	81	
15	formamide	C	16	111.0	41	ethanol/water = 3.0/2.0	B	49	
16	<i>N</i> -methylformamide	C	83	182.4	42	ethanol/water = 2.5/2.5	B	47	
17	<i>N</i> -methylacetamide	C	65	191.3	43	ethanol/water = 2.0/3.0	B	48	
18	DMF	C	67	36.71	44	ethanol/water = 1.5/3.5	B	50	
19	NMP	C	42	33.2	45	ethanol/water = 1.0/4.0	B	43	
20	acetonitrile	C	44	35.94	46	ethanol/water = 0.5/4.5	B	53	
21	HMPA	C	48	29.30	47	THF/water = 4.0/1.0	B	61	
22	DMSO	C	72	46.45	48	THF/water = 2.5/2.5	B	43	
23	methanol	C	36	32.66	49	THF/water = 1.0/4.0	B	46	
24	ethanol	B	35	24.55	50	C ₆ F ₁₄	C	33	
25	isopropyl alcohol	C	35	19.92	51	FC-75 ^j	C	43	
26	<i>t</i> -butyl alcohol	C	48	12.47					

^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 ¹H 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.

trifluoroethanol¹⁷ 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 ($pK_a = 12.8$). Moreover, 1,1,1,3,3,3-hexafluoro-2-propanol ($pK_a = 9.3$) is 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. Thus, 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 perfluoro-hexane 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 fluorinated solvents is not clear because two possibilities, namely, the acceleration by fluorophobic interaction¹⁹ or the high solubility of oxygen in a perfluorinated solvent to improve the efficiency of an initiator,^{18,20} could not be distinguished.

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 fluorinated alcohol, while bromotrichloromethane cannot form such a hydrogen bond that

(17) A radical reaction in 2,2,2-trifluoroethanol is reported. See ref 7c,d. Radical polymerization in perfluorinated alcohols is also reported: Isobe, Y.; Yamada, K.; Nakano, T.; Okamoto, Y. *Macromolecules* **1999**, *32*, 5979–5981.

(18) For a review of reactions in fluorinated media: (a) Betzemeier, B.; Knochel, P. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer-Verlag: Berlin, 1999. (b) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Yamamoto, H., Ed.; Springer-Verlag: Berlin, 2000; Chapter 7.

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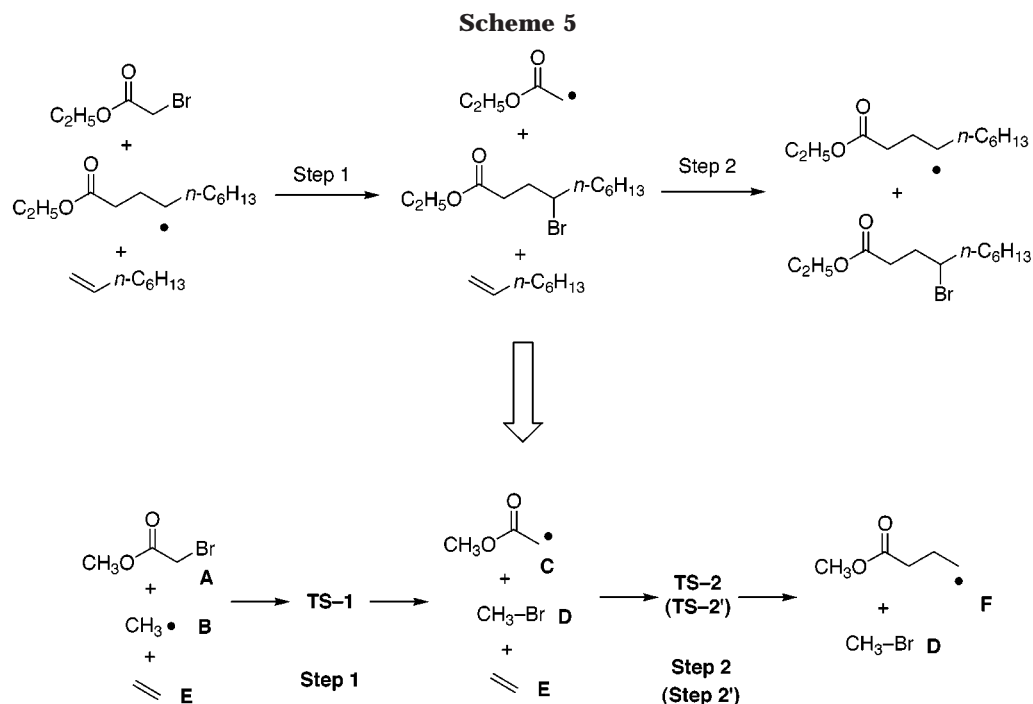
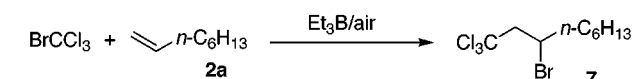


Table 4. Triethylborane-Induced Radical Addition of Bromotrichloromethane to 2a in Various Solvents^a



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	2,2,2-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.

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. We suppose 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.

Ab Initio Calculations and Discussion

To explain these results, we 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 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–Plesset perturbation theory²³ with the 6-31G** basis set at 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 (SCRFF/CPCM)^{24,25} at the B3LYP/6-31G* level. The total energy

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

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

^a Data for step 2. ^b Data for step 2'. ^c Absolute energies are those under vacuum. ^d Solvation energies are those in parentheses.

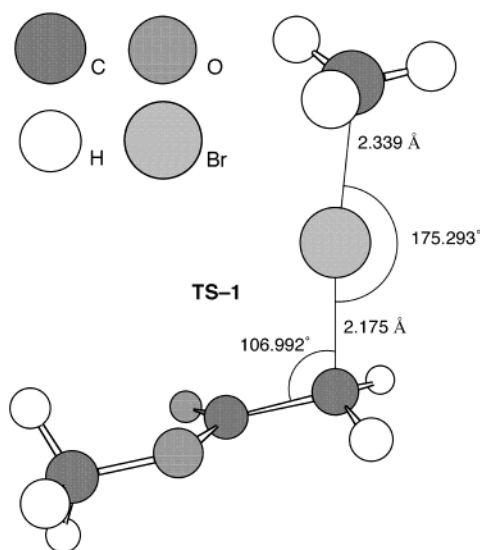


Figure 1. Transition structure of the bromine atom-transfer step (step 1).

value in a solution was obtained as the sum of the energy at the PMP2/6-31G**//B3LYP/6-31G* level, the solvation energy that was obtained at the B3LYP/6-31G* level, and thermodynamic corrections that were 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, we 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. 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

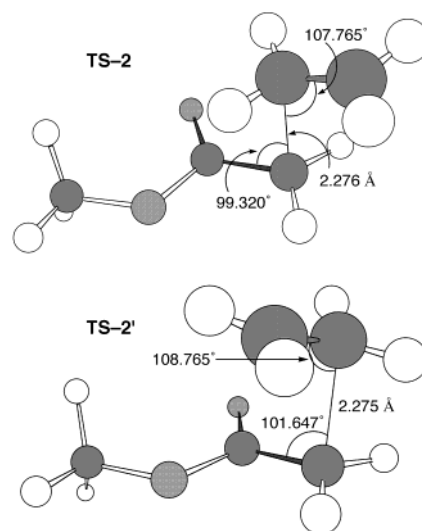


Figure 2. Transition structures of the radical addition step (steps 2 and 2').

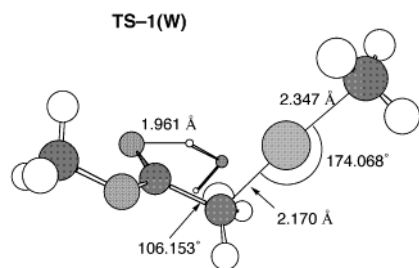
computed activation energies for step 2 and step 2' are 14.57 and 14.47 kcal/mol, respectively. The former, the bromine atom-transfer step, is suggested to be rate-determining, which is consistent with the experiment. We then considered the effect of solvation on the activation energy. As a whole, the 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 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 ($\Delta G^\ddagger_{\text{water}} - \Delta G^\ddagger_{\text{cyclohexane}}$) corresponds to $k_{\text{water}}/k_{\text{cyclohexane}} = 2.44$, according to the equation $k = (k_B T/h) \exp(-\Delta G^\ddagger/RT)$, where k , k_B , h , R , T , and ΔG^\ddagger are the rate constant, Boltzmann constant, Planck constant, gas constant,

(26) Zipse, H.; He, J.; Houk, K. N.; Giese, B. *J. Am. Chem. Soc.* **1991**, *113*, 4324-4325.

Table 6. Calculated Energies with an Explicit Water

	A(W) + B + E	TS-1(W) + E = ΔG^\ddagger for step 1(W)	C(W) + D + E	TS-2(W) + D^a TS-2(W)' + D^b	ΔG^\ddagger for step 2(W) ^a ΔG^\ddagger for step 2'(W) ^b	F(W) + D^a F'(W) + D^b
	-3031.160997	-3031.136158	Absolute Energy (au) ^c			
			-3031.170732	-3031.148611 ^a -3031.149201 ^b		-3031.190085 ^a -3031.189851 ^b
			Relative Energy (kcal/mol) ^d			
under 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

^a Data for step 2. ^b Data for step 2'. ^c Absolute energies are those under vacuum. ^d Solvation energies are those in parentheses.

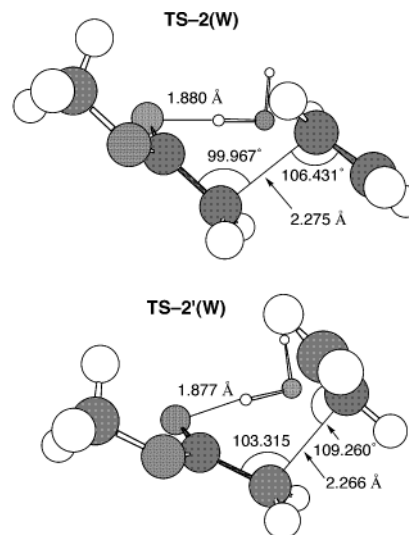
**Figure 3.** Transition structure of step 1 with an explicit water.

temperature (298.15 K here), and activation energy, respectively. However, qualitative discussion would be acceptable.

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 hydroxy groups. 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. We 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.

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

**Figure 4.** Transition structures of steps 2 and 2' with an explicit water.**Table 7. Energies of the HOMO and 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
$\Delta E[\mathbf{A(W)}-\mathbf{A}]$ (eV)	0.0790	0.0260	-0.134
SOMO			
C (au)			-0.41157
C(W) (au)			-0.41444
$\Delta E[\mathbf{C(W)}-\mathbf{C}]$ (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

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, we focused on the electron populations of **A** and **TS-1** (Table 8). The Mulliken charges on the (methoxycarbonyl)methyl moiety of **A** and **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

(27) The solvent effect of water in the Diels-Alder reaction was studied by ab initio computation including calculations on acrolein with explicit water: Evanseck, J. D.; Kong, S. *J. Am. Chem. Soc.* **2000**, *122*, 10418-10427 and references therein.

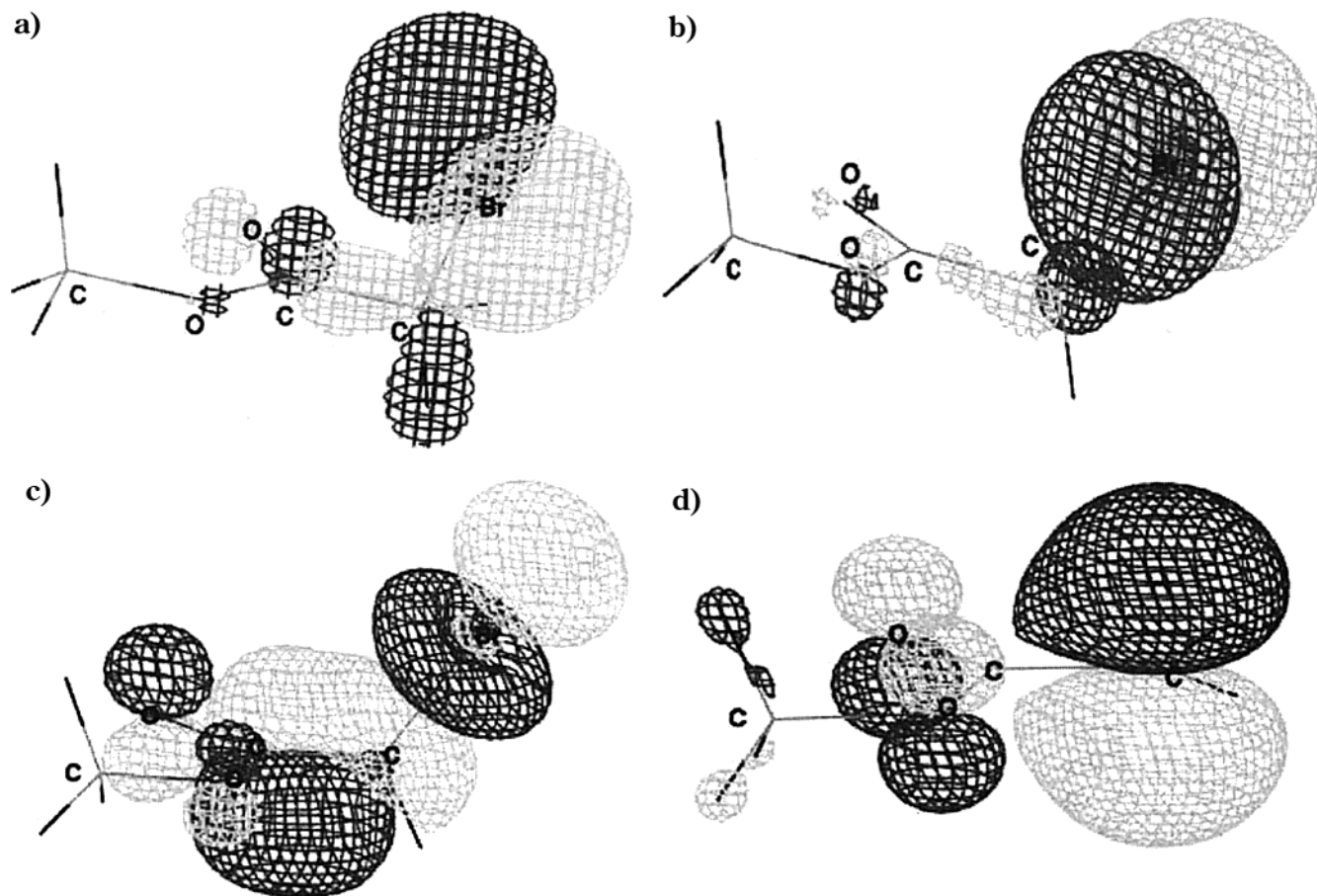


Figure 5. Molecular orbitals of **A** and **C**. (a) HOMO of **A**, (b) HOMO - 1 of **A**, (c) LUMO of **A**, and (d) SOMO of **C**.

Table 9. Stabilization Energies Generated by the Coordination

	energy/au ^a
methyl bromoacetate of A(W)	-2837.023988
water of A(W)	-76.219529
sum of the above two energies $E[\mathbf{A(W)*}]$	-2913.243518
$E[\mathbf{A(W)}]$	-2913.256630
$\Delta E_{\text{coord}}[\mathbf{A(W)}] = E[\mathbf{A(W)}] - E[\mathbf{A(W)*}]$	-0.01311 = -8.23 kcal/mol
TS-1(W) without water	-2876.708310
water of TS-1(W)	-76.219504
sum of the above two energies $E[\mathbf{TS-1(W)*}]$	-2952.927814
$E[\mathbf{TS-1(W)}]$	-2952.941483
$\Delta E_{\text{coord}}[\mathbf{TS-1(W)}] = E[\mathbf{TS-1(W)}] - E[\mathbf{TS-1(W)*}]$	-0.01367 = -8.58 kcal/mol
(methoxycarbonyl)methyl moiety of C(W)	-266.953391 ^b
water of C(W)	-76.220755 ^b
sum of the above two energies $E[\mathbf{C(W)*}]$	-343.174146 ^b
$E[\mathbf{C(W)}]$	-343.194289
$\Delta E_{\text{coord}}[\mathbf{C(W)}] = E[\mathbf{C(W)}] - E[\mathbf{C(W)*}]$	-0.02014 = -12.64 kcal/mol ^b
TS-2(W) without water	-345.263045 ^b
water of TS-2(W)	-76.221187 ^b
sum of the above two energies $E[\mathbf{TS-2(W)*}]$	-421.484232 ^b
$E[\mathbf{TS-2(W)}]$	-421.508705
$\Delta E_{\text{coord}}[\mathbf{TS-2(W)}] = E[\mathbf{TS-2(W)}] - E[\mathbf{TS-2(W)*}]$	-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
sum of the above two energies $E[\mathbf{TS-2'(W)*}]$	-421.484451 ^b
$E[\mathbf{TS-2'(W)}]$	-421.509167
$\Delta E_{\text{coord}}[\mathbf{TS-2'(W)}] = E[\mathbf{TS-2'(W)}] - E[\mathbf{TS-2'(W)*}]$	-0.024716 = -15.51 kcal/mol ^b

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

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. We first obtained the sum of the energy given $E[\mathbf{A(W)*}]$ 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, we

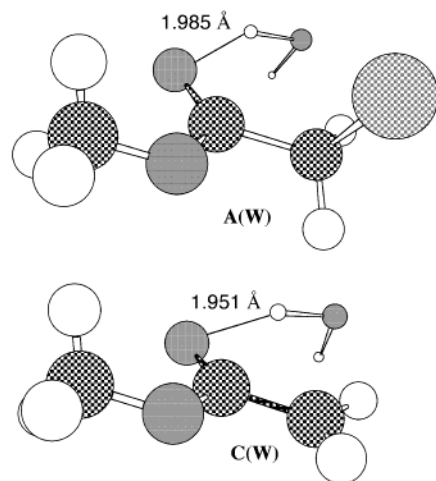


Figure 6. Optimized structures of **A(W)** and **C(W)**.

prescribed the difference between the total energy $E[\mathbf{A(W)^*}]$ and the energy of **A(W)** $E[\mathbf{A(W)}]$ 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 the 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 transfer of an electron 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. We 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 (methoxycar-

Table 10. Results of Radical Addition in a Protic Solvent

$$\text{R}^1\text{-Br} \quad \mathbf{1} + \text{CH}_2=\text{CH-R}^2 \quad \mathbf{2} \xrightarrow{\text{Et}_3\text{B}/\text{Air}} \text{R}^1\text{-CH}_2\text{-CH(R}^2\text{)-Br} \quad \mathbf{3}$$

entry	1	2	solvent ^a	yield (%)	entry	1	2	solvent ^a	yield (%)
1	1a	2a	A	64	10	1a	2g	B	72
2	1a	2a	B	73	11	1a	2h	A	72
3	1a	2d	A	91	12	1a	2h	B	70
4	1a	2d	B	64	13	1a	2a	B ^b	80
5	1a	2e	A	18	14	1a	2a	B ^c	50
6	1a	2e	B	41	15	1a	2a	C ^{d,e}	81
7	1a	2f	A	51	16	1a	2a	C ^{b,d}	94
8	1a	2f	B	53	17	1a	2a	C ^{c,d}	76
9	1a	2g	A	65	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 a solvent. ^c A 1 mL volume of a solvent. ^d Triethylborane was added twice. ^e A 10 mL volume of a solvent.

bonyl)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, we 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 a 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.

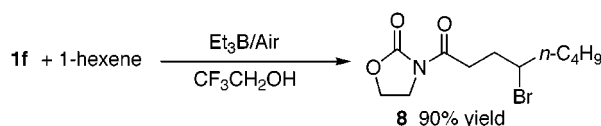
Other Results

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 solvent employed (entries 13–17). The reactions in 3 and 1 mL

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Scheme 6



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 % $\text{Yb}(\text{OTf})_3$. Coordination of **1f** to the solvent enhanced the reaction.

In conclusion, we have 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) and **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 \times 2) every 30 min. The reaction was quenched with 10 mL of hexane, and an organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Silica gel column chromatography of the crude oil (20/1

hexane/ethyl acetate) 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 treated with tetrabutylammonium fluoride (1.0 M THF solution, 2.0 mL, 2.0 mmol) at 25 °C. The temperature of the mixture rose 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. ¹H NMR experiment indicated a 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 ¹H NMR measurement yielded **3aa** in an 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 a 73% yield.

Acknowledgment. We thank Prof. Shigeki Kato (Graduate School of Science, Kyoto University) for helpful suggestions. This work was supported by Grants-in-Aid for Scientific Research (12305058 and 10208208) from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan. H.Y. acknowledges the JSPS Research Fellowship for Young Scientists. H.S. also thanks Banyu Pharmaceutical Co., Ltd.

Supporting Information Available: Characterization data and the Cartesian coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO010652L