tional analysis of natural products and compounds that are available in limited quantity and/or exhibit significant ^{1}H NMR signal overlap.[10] The development of new methods to obtain quantitative ^{1}H-C-C-^{13}C scalar coupling constants from HMBC spectra should increase the power of this tool.[11]

Experimental Section

4-Androstene-3,17-dione (**1**) was purchased from Sigma and purified by column chromatography (silica, ethyl acetate/hexane, 1:1), followed by recrystallization from ethyl acetate. The sample (1.25 mg) was dissolved in 0.5 mL of 80% CD$_3$OD/D$_2$O (Aldrich, 99.5 and 99.8 atom % D, respectively). All of the 2D NMR experiments were performed on a GE GN-500 spectrometer. The temperature was 25 °C, and all experiments were carried out without sample spinning. Proton and carbon chemical shifts were referenced to solvent CD$_3$OD.

The parameters used in this work are as follows. HMQC: 2 × 128 × 1024 data matrix size (two separate sets of data, with 1024 data points in t_2 and 128 data points in t_1); 32 scans (preceded by one dummy scan) per t_1 value; recycle delay = 2.5 s, 800 ms "weft" delay period; broad band (16 W) ^{13}C-decoupling during the acquisition period; 6-Hz Gaussian and 90°-shifted sine bell filtering in t_2 and t_1, respectively. HMBC: 128 × 512 data matrix size; 128 scans (preceded by 2 dummy scans) per t_1 value; recycle delay = 2.5 s; 36 μs 90° ^{13}C pulse width; Δ_1 and Δ_2 durations of 3.5 and 55 ms, respectively (see ref 6 for definitions); sine bell filter and 30-Hz Gaussian filtering in t_2 and t_1, respectively. COSY: 1 × 256 × 1024 data matrix size; 200-ms repitition delay; 32 scans per t_1 increment; sine bell filtering in t_2 and t_1, followed by application of a magnitude calculation.

Acknowledgment. This work was supported by Grant GM 33059 from the National Institutes of Health.

Registry No. 1, 63-05-8.

Supplementary Material Available: 2D NOESY and COSY spectra showing connectivities used to assign signals and perform conformational analyses (5 pages). Ordering information is given on any current masthead page.

---

[10] Kessler et al.[1c] have used COLOC spectroscopy to assign conformations of peptide side chains in a manner similar to that described here, but they used sample sizes of 250–480 mg.

[11] Bermel, K.; Wagner, C.; Griesinger, J. Magn. *Reson.* **1989**, *83*, 223.

New Catalytic Activity of Polymer-Supported Quaternary Onium Salts. Regioselective Addition Reaction of Oxiranes with Active Esters Catalyzed by Insoluble Polystyrene-Bound Quaternary Ammonium and Phosphonium Salts

Tadatomi Nishikubo,* Takashi Iizawa,[†] Moriyasu Shimojo, Tetsuya Kato, and Atsushi Shiina

Department of Applied Chemistry, Faculty of Engineering, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama, 221 Japan

Received October 3, 1989

A new regioselective addition reaction of oxiranes **15–17** with active esters **18** and **19** was carried out to give the adducts **20a–f** using quaternary onium salts on cross-linked polystyrene beads. The catalytic activity of the polystyrene beads was evalulated from rates of the reaction and yields of reaction products. In this reaction, the beads containing pendant benzyltripropyl- or benzyltributylphosphonium chlorides showed the highest catalytic activity among the polymeric catalysts. The beads containing pendant quaternary phosphonium salts also had higher catalytic activity than the beads containing pendant quaternary ammonium salts and the corresponding low molecular weight benzyltrialkylphosphonium salts. Furthermore, it was found from detailed kinetic studies that the rate of addition reaction of oxirane with active ester using polymer-supported quaternary onium salt as a catalyst was proportional to the initial catalyst concentration $[\mathrm{C}]_0$ and the oxirane concentration [O], and was not dependent on the active ester concentration as follows: $d[\mathrm{P}]/dt = k_2[\mathrm{C}]_0[\mathrm{O}]$, where [P] is the product concentration, and k_2 is the second-order rate constant. Given these kinetic results, the reaction mechanism of oxirane with active ester catalyzed by the polymer-supported quaternary onium salts is also assumed.

Quaternary ammonium salts bound to the cross-linked polystyrene beads have been widely used for anion exchange resins, which are typical functional polymers, and very important for the purification of water and various ionic chemicals. Insoluble polymer-supported phase-transfer catalysts were first utilized by Regen,[1] Montanari et al.,[2a] and Brown et al.,[3] independently. A variety of these catalysts containing either pendant quaternary ammonium or phosphonium salts[1-10] or pendant crown ethers[2a,11-14] have been extensively synthesized, and have been widely used in the fields of organic synthesis and organic reactions so far. This insoluble catalyst can be easily separated at the end of a reaction by filtration and can be reused for another run. However, catalytic activities of the polymer-supported phase-transfer catalysts are es-

---

[†] Present address: Department of Chemical Engineering, Faculty of Engineering, Hiroshima University.

[1] (a) Regen, S. L. *J. Am. Chem. Soc.* **1975**, *97*, 5956. (b) Regen, S. L. *Ibid.* **1976**, *98* 2670. (c) Regen, S. L. *J. Org. Chem.* **1977**, *42*, 875. (d) Regen, S. L.; Dulak, L. *J. Am. Chem. Soc.* **1977**, *99*, 623. (e) Regen, S. L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 421.

[2] (a) Cinouini, M.; Colonna, S.; Molinari, H.; Montannari, F. *J. Chem. Soc., Chem. Commun.* **1976**, 394. (b) Molinari, H.; Montanari, F.; Quici, S.; Tundo, P. *J. Am. Chem. Soc.* **1979**, *101*, 3920. (c) Montanari, F.; Tundo, P. *J. Org. Chem.* **1981**, *46*, 2125. (d) Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1981**, *103*, 856.

[3] Brown, J. M.; Jenkins, J. A. *J. Chem. Soc., Chem. Commun.* **1976**, 458.

[4] (a) Tomoi, M.; Ford, W. T. *J. Am. Chem. Soc.* **1981**, *103*, 3821. (b) Tomoi, M.; Ford, W. T. *Ibid.* **1981**, *103*, 3828. (c) Ford, W. T.; Lee, J.; Tomoi, M. *Macromolecules* **1982**, *15*, 1246. (d) Tomoi, M.; Ford, W. T. In *Syntheses and Separations using Functional Polymers*; Sherrington, D. C., Hodge, P., Eds.; Wiley: New York, 1988; pp 181–207.

0022-3263/90/1955-2536$02.50/0

sentially reduced in comparison with those of low molecular weight phase-transfer catalysts.

Recently, Castells and Dunach reported[15] a new catalytic activity of insoluble polymer-supported quaternary ammonium cyanides for benzoin condensation. More recently, we also proposed[16] the utilization of insoluble polymer-supported quaternary ammonium or phosphonium salts as new functional groups. That is, the quaternary onium salts mutually attached to the polystyrene beads having pendant photosensitizing groups act very effectively as substrate-attracting groups. Accordingly, multifunctional photosensitizer beads containing both pendant quaternary onium salts and photosensitizing groups have higher photosensitization efficiency than the corresponding low molecular weight photosensitizers.

Table I. Analytical Data of Polymer-Supported Quaternary Onium Salts[a]

catalyst	Ⓟ-Q^+Cl^-	%, deg of cross-linking[b]	%, yield[c]	mequiv of Cl/g in onium salt	%, conversion[d]
1	$-N^+(Et)_3Cl^-$	0.6	91.0	3.18	100
2	$-N^+(Pr)_3Cl^-$	0.6	78.0	2.62	94.2
3a	$-N^+(Bu)_3Cl^-$	0.6	70.3	1.83	100
3b	$-N^+(Bu)_3Cl^-$	3	89.7	2.45	100
3c	$-N^+(Bu)_3Cl^-$	10	93.7	2.73	100
4	$-N^+(Hex)_3Cl^-$	0.6	59.9	1.72	100
5	$-N^+(Oct)_3Cl^-$	0.6	62.0	1.35	100
6	$-P^+(Et)_3Cl^-$	0.6	89.0	2.90	92.9
7	$-P^+(Pr)_3Cl^-$	0.6	69.0	2.43	97.9
8a	$-P^+(Bu)_3Cl^-$	0.6	87.9	2.17	96.0
8b	$-P^+(Bu)_3Cl^-$	3	87.7	2.40	100
8c	$-P^+(Bu)_3Cl^-$	10	96.3	2.62	100
9	$-P^+(Hex)_3Cl^-$	0.6	70.7	1.95	83.2
10	$-P^+(Oct)_3Cl^-$	0.6	81.1	1.54	88.9

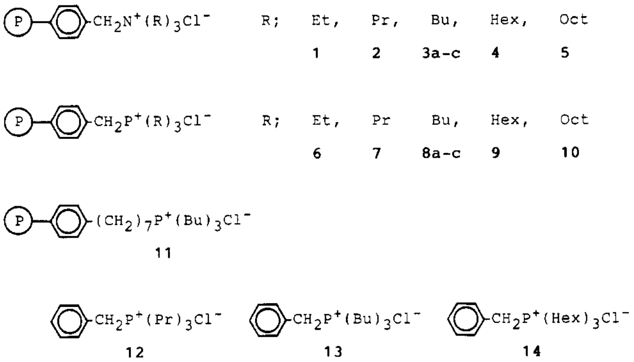
[a] Carried out with 0.02 mol (as Cl) of polystyrene bead and 0.03 mol of tertiary amine or phosphine in 40 mL of DMF at 80 °C for 120 h. [b] Degrees of functionalization of the starting polymers cross-linked with 0.6, 3, and 10% were 5.19, 5.85, and 5.69 mequiv of Cl/g, respectively. [c] Yield of recovered polymer bead. [d] Degree of conversion of pendant chloromethyl group to the quaternary onium salt.

Table II. Results of the Addition Reaction of Oxiranes 15–17 with Active Esters 18, 19 Using Polymer-Supported Catalysts 8b or 11[a]

catalyst	oxirane	active ester	%, yield of adduct[b] **20a–f**	%, yield of adduct[b] **23a–c**
8b	**15**	**18**	**a** 70.8 (65.6)[c]	**a** 21.8
8b	**16**	**18**	**b** 71.8 (62.4)[c]	**b** 18.5
8b	**17**	**18**	**c** 70.8 (63.8)[c]	**c** 20.4
11	**15**	**19**	**d** 88.6 (80.2)[c]	**a** 7.8
11	**16**	**19**	**e** 77.4 (66.5)[c]	**b** 9.8
11	**17**	**19**	**f** 67.0 (62.1)[c]	**c** 13.0

[a] Carried out with 10 mmol of oxirane and 10 mmol of active ester using polymer-supported catalyst (0.5 mmol) in diglyme (5 mL) at 110 °C for 24 h. [b] Determined by GLC. [c] Isolated yield.

Scheme I



On the other hand, oxiranes are widely used materials for synthetic organic chemistry and are very important in the chemical industry. The reactions of oxirane with some reagents such as carboxylic acids, phenols, alcohols, and amines, however, perhaps produce undesirable adducts with hydroxyl groups. We have recently found[17] that the new addition reaction of oxiranes with active esters proceeds very smoothly and regioselectively under relatively mild conditions in the presence of low molecular weight quaternary ammonium or phosphonium salts, or crown ether complexes, although the addition reaction of oxiranes with phenyl ester occurred[18] at elevated temperatures in the presence of tertiary amines or potassium *tert*-butoxide as catalysts. Similar reactions with diphenyl carbonate,[19] acyl halide,[20] alkyl halide,[21,22] carbon dioxide,[23,24] and β-butyrolactone[25] were also found to be stimulated by addition of low molecular weight quaternary ammonium or phosphonium salts as catalysts. These reactions did not produce any hydroxyl groups and are expected to be useful

---

(5) (a) Tomoi, M.; Ikeda, M.; Kakiuchi, H. *Tetrahedron Lett.* **1978**, 3757. (b) Tomoi, M.; Hasegawa, T.; Ikeda, M.; Kakiuchi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1653. (c) Tomoi, M.; Ogawa, E. Hosokawa, Y.; Kakiuchi, H. *J. Polym. Sci., Polym. Chem. Ed.* **1982**, *20*, 3015. (d) Tomoi, M.; Ogawa, E.; Hosokama, Y.; Kakiuchi, H. *Ibid.* **1982**, *20*, 3421. (e) Tomoi, M.; Hosokawa, Y.; Kakiuchi, H. *Makromol. Chem., Rapid Commun.* **1983**, *4*, 227. (f) Tomoi, M.; Yanai, N.; Shiiki, S.; Kakiuchi, H. *J. Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 911. (g) Tomoi, M.; Nakamura, E.; Hosokawa, Y.; Kakiuchi, H. *Makromol. Chem. Rapid Commun.* **1984**, *5*, 281. (h) Tomoi, M.; Shiiki, S.; Kakiuchi, H. *Makromol. Chem.* **1986**, *187*, 357. (i) Tomoi, M.; Kori, N.; Kakiuchi, H. *Ibid.* **1986**, *187*, 2753.

(6) (a) Bernard, M.; Ford, W. T. *J. Org. Chem.* **1983**, *48*, 326. (b) Bernard, M.; Ford, W. T.; Taylor, T. W. *Macromolecules* **1984**, *17*, 1821. (c) Ford, W. T. *J. Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 509. (d) Ford, W. T. In *Crown Ethers and Phase Transfer Catalysis in Polymer Science*; Mathias, L. J., Carraher, C. E., Jr., Eds.; Plenum: New York, 1984; pp 201–226.

(7) Chiles, M. S.; Reeves, P. C. *Tetrahedron Lett.* **1979**, 3367.

(8) Saegusa, T.; Kabayashi, S.; Yamada, A.; Kashimura, S. *Polym. J.* **1979**, *11*, 1.

(9) Ungurenaus, C.; Cotzer, C. *Polym. Bull.* **1985**, *14*, 411.

(10) Okahata, Y.; Ariga, K. *J. Org. Chem.* **1986**, *51*, 5064.

(11) (a) MacKenzie, W. M.; Sherrington, D. C. *Polymer* **1980**, *21*, 791. (b) MacKenzie, W. M.; Sheerington, D. C. *Ibid.* **1981**, *22*, 431. (c) Heffernan, J. G.; MacKenzie, W. M.; Sheerington, D. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 514. (d) Akelah, A.; Sheerington, D. C. *Eur. Polym. J.* **1982**, *18*, 301.

(12) (a) Manecke, G.; Reuter, P. *Makromol. Chem.* **1981**, *182*, 1973. (b) Manecke, G.; Kriamer, A. *Ibid.* **1981**, *182*, 3017.

(13) (a) Smid, J. *Makromol. Chem. Suppl.* **1981**, *5*, 203. (b) Wakui, T.; Xu, W. Y. Chen, C. S.; Smid, J. *Makromol. Chem.* **1986**, *187*, 533.

(14) Anelli, P. L.; Montanari, A.; Quici, S. *J. Org. Chem.* **1986**, *51*, 4901.

(15) Castells, J.; Dunach, E. *Chem. Lett.* **1984**, 1859.

(16) Nishikubo, T.; Uchida, J.; Matsui, K.; Iizawa, T. *Macromolecules* **1988**, *21*, 1583.

(17) (a) Nishikubo, T.; Iizawa, T.; Takahashi, E.; Nono, F. *Polym. J.* **1984**, *16*, 371. (b) Nishikubo, T.; Iizawa, T.; Saita, S. *J. Polym. Sci., Polym. Chem. Ed.* **1986**, *24*, 1685. (c) Nishikubo, T.; Saita, S. *Makromol. Chem.* **1987**, *188*, 799. (d) Nishikubo, T.; Saita, S.; Fujii, T. *J. Polym. Sci., Polym. Chem. Ed.* **1987**, *25*, 1339. (e) Nishikubo, T.; Tanaka, K. *J. Appl. Polym. Sci.* **1987**, *33*, 2821. (f) Nishikubo, T.; Saita, S. *Kobunshi Ronbunshu* **1987**, *44*, 737. (g) Nishikubo, T.; Takehara, E.; Saita, S.; Matsumura, T. *J. Polym. Sci., Polym. Chem. Ed.* **1987**, *25*, 3049. (h) Iizawa, T.; Goto, A.; Nishikubo, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 597. (i) Nishikubo, T.; Iizawa, T.; Matsumura, T. *J. Polym. Sci., Polym. Chem. Ed.* **1989**, *27*, 1975.

(18) (a) Funahashi, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1488. (b) Funahashi, K. *Makromol. Chem.* **1979**, *180*, 501.

(19) Yu, Y.; Bell, J. P. *J. Polym. Sci., Polym. Chem. Ed.* **1988**, *26*, 247.

(20) Nishikubo, T.; Iizawa, T.; Saito, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1983**, *21*, 2291.

(21) Takeda, T.; Yasuhara, S.; Watanabe, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2566.

(22) Gu, X. P.; Ikeda, S.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 397.

(23) Rokicki, G.; Kuran, W.; Marciniak, B. P. *Monatsh. Chem.* **1984**, *115*, 205.

(24) Baba, A.; Nozaki, T.; Matsuda, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1552.

(25) Nishikubo, T.; Iizawa, T.; Iida, M.; Isobe, N. *Tetrahedron Lett.* **1986**, *27*, 3741.

for various fields of synthetic organic chemistry.

Given this background, it seemed reasonable to us[26] that insoluble polymer-supported catalyts containing pendant quaternary onium salts or crown ether complexes might be utilized for the reactions of oxiranes. This paper reports on the regioselective addition reaction of oxiranes with active esters in the presence of cross-linked polystyrene beads containing pendant quaternary ammonium or phosphonium salts having higher catalytic activity than the corresponding low molecular weight quaternary onium salts, and discusses the reaction mechanism using the polymer-supported catalyst.

Result and Discussion

Regioselective Addition Reaction of Oxirane with Active Ester Catalyzed by Insoluble Polymer-Supported Quaternary Onium Salt. Polymer-supported catalysts **1**, **2**, **3a–c**, **4**, and **5** containing pendant quaternary ammonium salts were synthesized by the addition reaction of the cross-linked polystyrene beads with triethylamine, tripropylamine, tributylamine, trihexylamine, and trioctylamine, respectively. The catalysts **6**, **7**, **8a–c**, **9**, and **10** which have pendant quaternary phosphonium salts were also prepared by the reaction of the same polystyrene beads with triethylphosphine, tripropylphosphine, tributylphosphine, trihexylphosphine, and trioctylphosphine, respectively. As summarized in Table I, nearly all addition reactions of the cross-linked polystyrene beads with *tertiary* amines or phosphines proceeded quantitatively to give the corresponding polymer-supported catalysts.

Catalyst **11** was also used for the reaction. It has a heptamethylene chain as a spacer between the polystyrene skeleton and the pendant tributylphosphonium salt, and with 33% of ring substitution, is an inherently hydrophobic polymer-supported phase transfer catalyst.[5e]

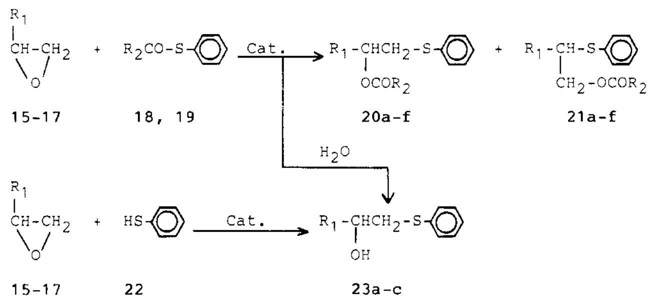
For comparison of activity with the polymer-supported catalysts **1–10**, the reaction of oxirane with active ester was carried out using some corresponding low molecular weight (LMW) catalysts such as benzyltripropylphosphonium chloride (**12**), benzyltributylphosphonium chloride (**13**), and benzyltrihexylphosphonium chloride (**14**) under the same conditions as applied to the polymer-supported quaternary phosphonium salts.

Although reactions of oxiranes (**15–17**) with active esters (**18**, **19**) could be expected to produce two kinds of isomers owing to α-cleavage and β-cleavage of the oxirane ring using polymer-supported catalysts **8b** or **11**, only one kind of isomers (**20a–f**) derived from β-cleavage as obtained in high yield (Table II), and the production of the other kind of isomers (**21a–f**) was not confirmed. Furthermore, small amounts of adducts (**23a–c**) were produced in the reactions as by-products, which were also synthesized by the addition reactions of oxiranes **15–17** with thiophenol **22** as standard compounds for the analysis of the above products. It seems that adducts **23a–c** are hydrolysis products of the reaction of oxiranes **15–17** with active esters **18** and **19** owing to moisture in the reaction system caused by the somewhat hygroscopic nature of the polymer-supported onium salts.

This result means that the addition reaction of oxiranes **15–17** with active esters **18** and **19** occurred regioselectively in high conversions using the polymer-supported quaternary phosphonium salts as catalysts.

The catalytic activities of the polymer-supported quaternary ammonium or phosphonium salts (**1–10**) and LMW quaternary phosphonium salts (**12–14**) were examined from the viewpoint of observed pseudo-first-order rate constant, in which the rate of reaction obeyed first-order kinetics (Table III). When the reaction of oxirane **15** with active ester **18** was accomplished with polymer-supported quaternary ammonium salts, catalyst **3a** showed the highest activity, and the activity of catalysts **1**, **2**, **4**, and **5** was depressed with either decrease or increase of the carbon numer of the trialkyl group on the ammonium salt.

Scheme II



20a, 21a;	R_1=PhOCH$_2$	R_2=Me	23a;	R_1=PhOCH$_2$
20b, 21b;	R_1=MeOCH$_2$	R_2=Me	23b;	R_1=MeOCH$_2$
20c, 21c;	R_1=BuOCH$_2$	R_2=Me	23c;	R_1=BuOCH$_2$
20d, 21d;	R_1=PhOCH$_2$	R_2=Ph		
20e, 21e;	R_1=MeOCH$_2$	R_2=Ph		
20f, 21f;	R_1=BuOCH$_2$	R_2=Ph		

Table III. Catalytic Activity on the Addition Reaction of Oxirane 15 with Active Ester 18[a]

catalyst	%, deg of cross-linking	%, yield of adduct[b] 20a	23a	$k_{obsd} \times 10^{-4}$, s^{-1}
1	0.6	62.7	25.6	0.83
2	0.6	45.9	21.3	0.90
3a	0.6	43.1	21.2	1.13
3b	3	39.2	25.4	0.68
3c	10	26.8	22.4	0.29
4	0.6	37.6	19.9	0.82
5	0.6	36.9	18.1	0.61
6	0.6	85.4	10.0	0.85
7	0.6	87.4	8.0	2.29
8a	0.6	92.5	5.0	1.84
8b	3	79.1	15.8	1.43
8c	10	66.6	22.6	0.73
9	0.6	88.0	5.0	1.30
10	0.6	81.7	8.0	0.84
12		16.8	14.0	0.81
13		25.2	20.3	0.68
14		52.6	14.2	1.09

[a] Carried out with oxirane **15** (4 mmol) and active ester **18** (4 mmol) in the presence of the catalyst (0.2 mmol) and *p*-dichlorobenzene (0.61 g) as an internal staandard in diglyme (2 mL) at 90 °C. [b] Yield at 24 h. [c] Corresponding low molecular weight catalyst.

When the polymer-supported quaternary phosphonium salts were used, catalyst **7** showed the highest catalytic activity, and also the activity of catalysts **6**, **8a**, **9**, and **10** was reduced with either decreasing or increasing of bulkiness of the trialkyl group on the catalyst under the same reaction conditions. That is, the catalysts containing pendant benzyltripropyl or benzyltributyl onium salts have the highest catalytic activity in each polymer-supported catalyst system; also, the polymer-supported quaternary phosphonium salts have higher catalytic activities than the polymer-supported quaternary ammonium salts, when those catalysts have the same alkyl groups.

This result suggests that the catalytic activity of the polymer-supported quaternary onium salts was signifi-

---

(26) Nishikubo, T.; Shiina, A.; Isobe, N. *Chem. Lett.* 1988, 1605.

cantly affected by the hydrophobic interaction between the catalysts and reagents, and the polymers containing pendant quaternary phosphonium salts might be relatively more hydrophobic than the polymers containing quaternary ammonium salts. This consideration was also supported from comparison with the yield of by-product **23a** on the reaction using both polymer-supported cyatalyst systems.

Although increasing the alkyl chain length on the quaternary onium salts increased hydrophobicity of the catalyst, the introduction of bulky alkyl groups such as trihexyl or trioctyl moieties in the polymer-supported catalysts might have cuased steric hindrance from the catalysts and to decrease the catalytic activity.

The activity of catalysts **3b,c** and **8b,c**, which were composed of highly corss-linked polystyrene beads, was compared with those of catalysts **3a** and **8a** with only 0.6% cross-linked beads. The results as shown in Table III suggests that the catalytic activity of polymer-supported onium salts was strongly affected by the degree of cross-linking of the beads, and the activity of polymer-supported onium salts fell gradually with increase of the degree of cross-linking of the beads.

Interestingly enough, the polymer-supported phosphonium salts **7**, **8a**, and **9** showed higher catalytic activities than the corresponding LMW phosphonium catalysts **12**, **13**, and **14** for the addition reaction of oxirane **15** with active ester **18** under the same conditions.

From these results, it might be considered that although the hydrophobicity of the catalyst is a positive factor for high catalytic activity of the polymer-supported quaternary onium salts, there is another reason for high activity especially for the phosphonium salts. That is, the reagents for the reaction were concentrated in the vicinity of the surface of the catalysts or the inside of the cross-linked polymer beads by the polymer-supported quaternary onium salts, which have strong substrate-attracting efficiency due to high hydrophobicity, and the regioselective addition reactions of oxirane with active ester take place smoothly at high concentrations of the reagents.

The catalytic activities of the polymer-supported quaternary onium salts were evaluated from the yields of main product **20a** and hydrolysis product **23a** in Table III. Yields of **20a** and total yields of **20a** and **23a** by using the polymer-supported quaternary phosphonium salts **6–10** were higher than those with the corresponding polymer-supported ammonium salts **1–5** or LMW quaternary phosphonium salts **12–14**, although yields of hydrolysis product **23a** with the former catalysts were lower than those with the latter catalysts.

These results suggest that the polymer-supported quaternary phosphonium salts have higher catalytic activity than the corresponding polymer-supported quaternary ammonium salts and corresponding LMW phosphonium salts for the regioselective addition reaction of oxirane with active ester, because the former catalysts have excellent substrate-attracting efficiency as described concerning the above results of the observed pseudo-first-order rate constants.

It was also suspected that there might be an additional factor for the catalytic activity. That is, catalyst **6** has higher activity than catalyst **2** from the viewpoint of yield of product **20a**, although the observed pseudo-first-order rate constant of reaction with catalyst **2** was faster than with catalyst **6**. Similarly the total yield of adducts **20a** and **23a** by using catalyst **1** was much higher than that by catalyst **3a**, which has a higher rate constant than catalyst **1** under the same conditions.

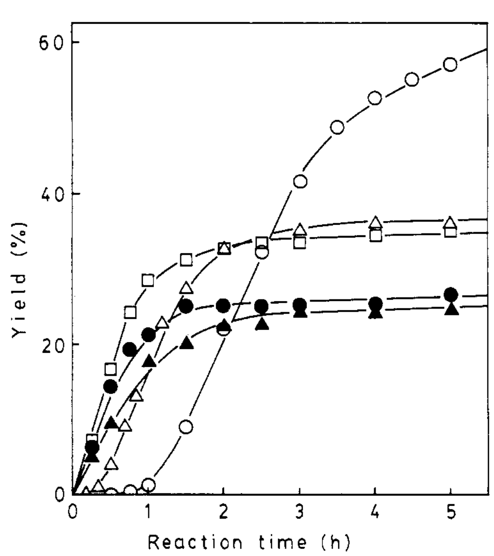


Figure 1. Graph of the percentage yields of adduct **20a** (carried out with oxirane **15** (4 mmol) and active ester **18** (4 mmol) using 1% cross-linked polystyrene beads containing various quaternary ammonium salts (5 mol %) in diglyme (2 mL) at 90 °C): catalyst **1** (○), catalyst **2** (△), catalyst **3a** (□), catalyst **4** (●), catalyst **5** (▲).

These conflicts can be explained after detailed examination of the experimental results, of which a typical example is shown in Figure 1. The observed initial rate of reaction with catalyst **3a** was faster than those with catalysts **2** and **1**; however, the yield of **20a** using catalyst **3a** was almost saturated for 5 h at 90 °C. On the other hand, the yield of **20a** using catalyst **1** gradually increased even after 5 h under the same conditions. This indicates that catalyst **3a** was inactivated by Hofmann's elimination[27] during the short term. That is, the thermal stability of the catalyst is a further important factor for the addition reaction of oxirane with active ester, and the polymer-supported phosphonium salts have higher thermal stability[28] than the corresponding polymer-supported ammonium salts and the LMW quaternary phosphonium salts under the same conditions.

Interesting results can be found in Figure 1. There are remarkeable induction periods of about 1 h and 30 min found on the reaction with catalysts **1** and **2**, respectively. It seems that the swelling rate of catalyst **1** with organic solvent diglyme was lower than that of the other cross-linked polymer-supported quaternary ammonium salts, because catalyst **1**, containing benzyltriethylammonium group, is more hydrophilic than catalysts **2–5**, and the hydrophilicity of catalyst **2** is higher than those of catalysts **3–5**. In addition, the hydrolysis by-product (**23a**) only appeared in the initial stage of the reaction, when hydrophilic onium salt was used as the catalyst. These suggestions about high hydrophilicity of catalyst **1** was supported by comparison with yields of by-product **23a** using these catalysts. That is, when the reaction was catalyzed by **1**, the yield of adduct **23a** was higher than the other runs with catalysts **2–5** under the same conditions.

The possibility of reuse of the polymer-supported quaternary onium salt was examined on the reaction of oxirane **15** with active ester **18** using catalyst **8b**. As summarized in Table IV, it was found that catalyst **8b** can be reused for at least two runs for the addition reaction of oxirane with active ester under 90 °C for 24 h. However, the

---

[27] For example: (a) Patai, S. *The Chemistry of The Amino Group*; Wiley: New York, 1968; p 409. (b) Hojyo, N. *Chelate Resin. Ion Exchange Resin*; Kodansha: Tokyo, 1976; p 168.

[28] Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic Press: New York, 1978; p 64.

Table IV. Activity of the Reused Catalysts 8b on the Addition Reaction of Oxirane 15 with Active Ester 18[a]

	number of cycles of catalyst **8b**			
	1	2	3	4
yield of adduct **20a**,[b] %	79.1	70.5	19.3	0
yield of adduct **23a**,[b] %	15.8	20.4	16.5	4.2

[a] Carried out with equimolecular amounts of oxirane and active ester in the presence of 5 mol % of catalyst **8b** in diglyme (2 mol/L) at 90 °C for 24 h. [b] Determined by GLC.

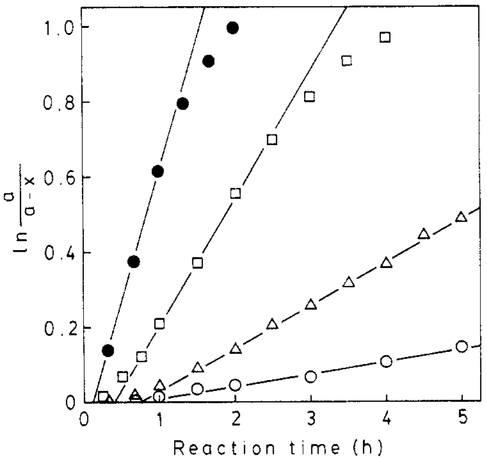


Figure 2. Rate of addition reaction of oxirane **15** with active ester **18** catalyzed by **8a** at various temperatures, at 60 °C (○), 70 °C (△), 80 °C (□), and 90 °C (●).

catalytic activity of polymer-supported quaternary phosphonium salt **8b** declined gradually with increase in the number of cycles, and finally lost all activity. It might be that[27] the pendant quaternary phosphonium salt in the polymer bead is decomposed by long-term heating at elevated temperatures.

Reaction Rate and Reaction Mechanism of Regioselective Addition Reaction of Oxirane with Active Ester Using Polymer-Supported Quaternary Onium Salt. The addition reaction of equimolecular amounts of oxirane **15** with active ester **18** was carried out with 5 mol % of catalyst **8a** in diglyme at various temperatures. The yield of **20a** increased with increasing the reaction temperature, although there is an induction period on the reaction at relatively low temperatures. Furthermore, it was found that the observed rate of reaction obeyed first-order kinetics at various temperatures (Figure 2). The Arrhenium plots based on the observed pseudo-first-order rate constant k_1 of the reaction are shown in Figure 3, and the apparent activation energy of the reaction of oxirane **15** with active ester **18** catalyzed by **8a** was estimated as 103.1 kJ/mol.

The reaction of oxirane **15** with active ester **18** was also conducted under various catalyst concentrations of **8a** in diglyme at 90 °C, and the correlation between the observed pseudo-first-order rate constant k_1 and the catalyst concentration is shown in Figure 4. The observed pseudo-first-order rate constants of the reaction plotted against the catalyst concentrations show a straight line passing through the origin. This means that the addition reaction of oxirane with active ester was proportional to the catalyst concentration.

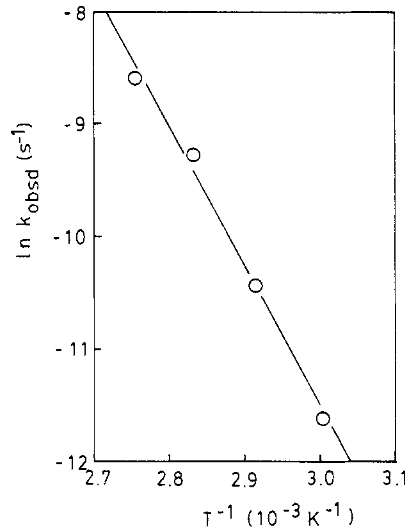


Figure 3. Arrhenius plots of the observed pseudo-first-order rate constant on the reaction of oxirane **15** with active ester **18** catalyzed by **8a**.

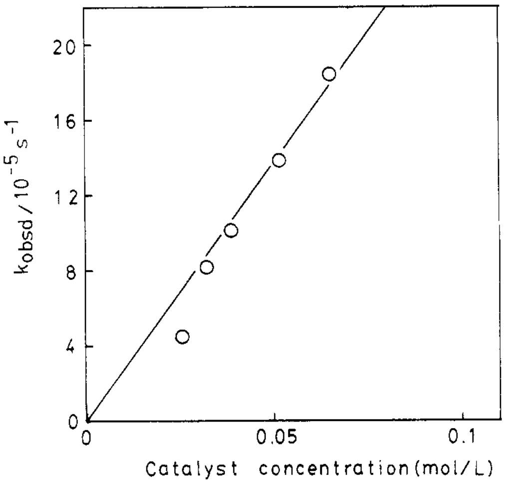


Figure 4. Correlation between the observed pseudo-first-order rate constant and the catalyst concentration (carried out with oxirane **15** (4 mmol) and active ester **18** (4 mmol) using catalyst **8a** in diglyme (2 mL) at 90 °C).

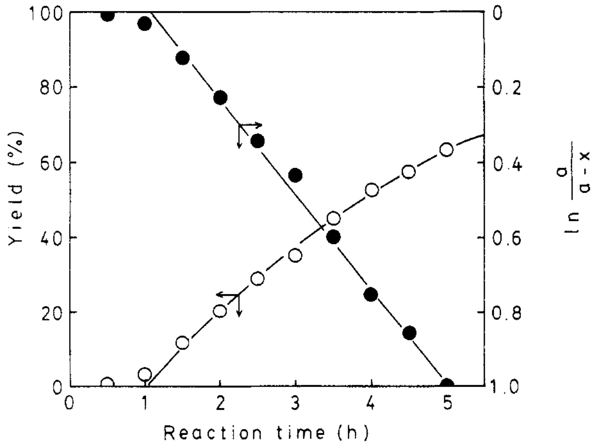


Figure 5. First-order dependence of the reaction in excess amounts of active ester (carried out with oxirane **15** (2 mmol) and active ester **18** (20 mmol) using catalyst **7** (0.2 mmol) at 70 °C). a = [oxirane]$_{\text{initial}}$; x = [oxirane]$_{\text{decreased}}$.

When the reaction of oxirane **15** with excess amounts (multiplets of 10) of active ester **18** was performed using 10 mol % of catalyst **7** to the oxirane at 70 °C, the observed rate of reaction obeyed first-order kinetics and did not make a straight line to the yield of adduct **20a** (Figure 5). That is, the rate of reaction was correlated with the oxirane concentration.

On the other hand, when the reaction of excess amounts of oxirane **15** and active ester **18** was conducted in the

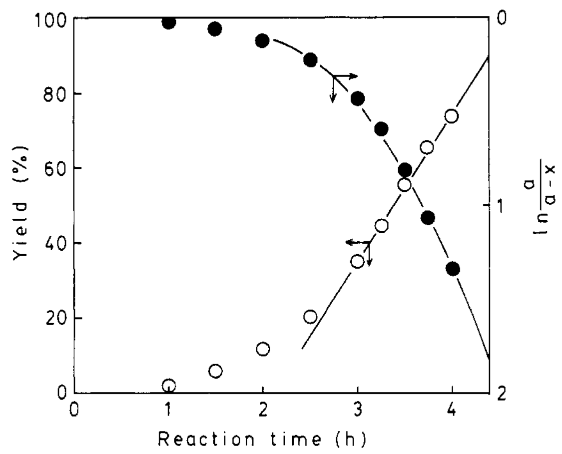


Figure 6. Zero-order dependence of the reaction in excess amounts of oxirane (carried out with oxirane **15** (20 mmol) and active ester **18** (2 mmol) using catalyst **7** (0.2 mmol) at 50 °C). a = [ester]$_{\text{initial}}$; x = [ester]$_{\text{decreased}}$.

Table V. Rates of the Addition Reaction of Various Oxiranes with Active Esters Using Catalyst 7[a]

oxirane	active ester	%, yield of adduct[b] **20**	$k_{\text{obsd}} \times 10^{-4}$, s^{-1}
15	**18**	**a** 73.4	2.29
16	**18**	**b** 25.3	0.18
17	**18**	**c** 21.6	0.18
15	**19**	**d** 4.0	0.03

[a] Carried out with 4 mmol of oxirane and 4 mmol of active ester in the presence of catalyst **7** (5 mol %) and and p-dichlorobenzene (0.61 g) as an internal standard in diglyme (2 mL) at 90 °C. [b] Yield at 5 h.

presence of 10 mol % of catalyst **7** to the active ester at 50 °C, although there was the induction period on the reaction similar to the above reaction, the observed rate of reaction obeyed zero-order kinetics and showed no relation with first-order kinetics (Figure 6). This indicates that the rate of reaction was independent of the active ester concentration. Recently, similar kinetic data have been obtained[29] in the reaction of oxirane **15** with active ester **19** using symmetric LMW quaternary ammonium salts, or crown ether–inorganic or organic salts complexes as catalysts.

Furthermore, as summarized in Table V, the observed rate of addition reaction was strongly affected by the kind of oxirane and active ester. The reactivity of oxirane **15** was higher than that of oxiranes **16** and **17**, and the reactivity of active ester **18** was higher than that of active ester **19** under the same conditions.

From these results, it was established that the rate of addition reaction of oxirane with active ester using polymer-supported onium salt as a catalyst was proportional to the product of initial catalyst concentration [C]$_0$ and oxirane concentration [O], and was not proportional to the active ester concentration [E] as in eq 1:

$$d[P]/dt = k_2[C]_0[O] \tag{1}$$

where k_2 is the second-order rate constant, and [P] is the product concentration.

This may be expressed as follows:

$$E + C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \tag{2}$$

$$I + O \xrightarrow{k_2} P + C \tag{3}$$

where k_1 and k_{-1} are the rate constant of the reaction to produce the intermediate and the rate constant of the reverse reaction from the intermediate, respectively, and [I] is the intermediate concentration.

$$d[I]/dt = k_1[E][C] - k_{-1}[I] - k_2[I][O] \tag{4}$$

Since [C] = [C]$_0$ − [I], it is rewritten:

$$\begin{aligned} d[I]/dt &= k_1[E]([C]_0 - [I]) - (k_{-1} + k_2[O])[I] \\ &= k_1[E]([C]_0 - [I]) - (k_1[E] + k_{-1} + k_2[O])[I] \end{aligned} \tag{5}$$

In the steady state, since d[I]/dt = 0,

$$[I] = k_1[E][C]_0/(k_1[E] + k_{-1} + k_2[O]) \tag{6}$$

From eq 3:

$$d[P]/dt = k_2[I][O] \tag{7}$$

When eq 6 was substituted in eq 7, eq 8 was obtained as:

$$d[P]/dt = k_1k_2[E][C]_0[O]/(k_1[E] + k_{-1} + k_2[O]) \tag{8}$$

In the case of $k_1[E] \gg k_{-1} + k_2[O]$, eq 8 was drawn to eq 1 as $d[P]/dt = k_2[C]_0[O]$.

Given these kinetic results, the reaction of oxirane with active ester catalyzed by the polymer-supported onium salt is assumed to proceed as shown in Scheme III.

The quaternary onium sallt attacks the active ester to give active intermediate **24** (eq 9). The produced intermediate **24** reacts with oxirane to form unstable adduct **25**, and then the adduct **25** decomposes spontaneously to produce adduct **20** and the quaternary onium salt in eq 11. If there are some water molecules present as impurities, which are strong nucleophilic reagents, unstable adduct **25** reacts preferentially with water to give by-product **23** in the reaction of oxirane with the active ester.

Experimental Section

General Methods. All oxiranes (**15**–**17**) and reaction solvents were used after distillation on CaH$_2$. Benzoyl peroxide was recrystallized twice from benzene at 40 °C. Chloromethylated styrene (donated by Seimi Chemical Co.; mixture of 32% meta and 68% para) was distilled twice under reduced pressure. Commercial acetyl chloride, benzoyl chloride, thiophenol, tertiarty amines and phosphines, 55% divinylbenzene, and benzyl chloride were used without further purification. S-Phenyl thioacetate (**18**) (bp 96–97 °C (7 mmHg), and S-phenyl thiobenzoate (**19**) (mp 55.2–56.3 °C) were prepared by the reaction of thiophenol (**22**) with the corresponding acid chlorides and were then purified as reported previously.[30] Chloromethylpolystyrene bead cross-linked with 3% divinylbenzene (5.85 mequiv of Cl/g) and chloromethylpolystyrene bead cross-linked with 10% divinylbenzene (5.69 mequiv of Cl/g) provided by Mitsubishi Kasei Co. were purified by being washed twice with acetone. Chloromethylpolystyrene bead cross-linked with 0.6% divinylbenzene (5.19 mequiv of Cl/g) was prepared[31] in 72% yield by the suspension copolymerization of chloromethylated styrene (76.32 g, 0.5 mol) with divinylbenzene (0.66 g, 2.78 mmol) in water (250 mL) in the presence of 98% saponified poly(vinyl alcohol) (0.84 g) and 88% saponified poly(vinyl alcohol) (0.03 g) using benzoyl peroxide (1.22 g, 5.05 mmol) as radical initiator at 80 °C for 8 h under flowing nitrogen, filtered, washed twice each with water, methanol, and acetone, and dried at 50 °C in vacuo. Asymmetric LMW catalysts benzyltripropylphosphonium chloride (**12**), benzyltributylphosphonium chloride (**13**), and benzyltrihexylphosphonium chloride (**14**) were synthesized by the reaction of benzyl chloride with the corresponding tertiary phosphines, and then recrystallized twice from suitable solvents according to the reported method.[32]

---

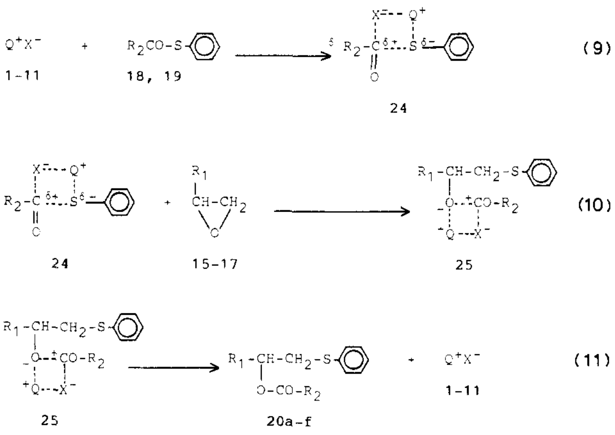
[29] Iizawa, T.; Nishikubo, T.; Shimojo, M., to be published.

[30] Miyaki, K.; Yamagishi, S. *J. Pharm. Soc. Jpn.* **1956**, *76*, 436.

[31] Otsu, T.; Kinoshita, M. *Experimental Method for Polymer Synthesis*; Kagaku Dojin: Kyoto, 1972; p 145.

[32] (a) Henderson, W. A.; Buckler, S. A. *J. Am. Chem. Soc.* **1960**, *82*, 5794. (b) Starks, C. M. *Ibid.* **1971**, *93*, 195.

Scheme III



Q+X-; Polymer-supported quaternary onium salt

Polymer-supported catalyst **11** (2% cross-linked with divinylbenzene; degree of ring substitution, 33% as benzyltributylphosphonium chloride) was obtained from Professor M. Tomoi, Yokohama National University. All boiling and melting points are uncorrected. Column chromatography was performed on silica gel (Merck Co. Kiesegel 60). GLC analyses were carried out on a Shimazu Model GC-9AM gas chromatograph with a 3 mm × 2.6 m column packed with 3% Silicon OV-101 on Shimalite W (AW-DMCS). IR spectra were measured on a JASCO Model A-202 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL Models JNM PS-100 (100 MHz) and JNM FX-200 (200 MHz) instruments in $CDCl_3$ with Me_4Si as internal standard.

Synthesis of the Cross-Linked Polystyrene Beads Containing Quaternary Ammonium Salts (1–5). Catalysts **1–5** were synthesized[2b] by the reaction of the cross-linked chloromethylpolystyrene beads with tertiary amines, employing a typical procedure as follows. A mixture of 3.04 g (0.02 mol as chlorine) of 0.6% cross-linked chloromethylpolystyrene bead and 3.04 g (0.03 mol) of triethylamine was stirred in 40 mL of DMF at 80 °C for 120 h. The polymer bead was filtered, washed twice each in refluxing methanol and acetone, and dried under vacuum at 50 °C. The yield of polymer bead was 4.3 g (91.0% as recovered polymer). The Cl content in the polymer (**1**) was 3.18 mequiv/g (100% conversion). The results of other polymers (**1–5**) are summarized in Table I.

Synthesis of the Cross-Linked Polystyrene Beads Containing Quaternary Phosphonium Salts (6–10). The typical procedure for the synthesis of the polystyrene-supported catalyst having quaternary phosphonium salt was as follows: 3.02 g (0.02 mol as chlorine) of 3% cross-linked chloromethylpolystyrene bead was made to react with 6.07 g (0.03 mol) of tributylphosphine in 40 mL of DMF at 80 °C for 120 h. The polymer bead was purified as described in the above procedure. The yield of recovered polymer **8b**, 6.2 g, was 87.7; (Cl content in **8b**, 2.40 mequiv/g, 100% conversion). The results of other polymers (**6–10**) are summarized in Table I.

Synthesis of 1-Butoxy-3-phenylthio-2-propyl Acetate (20c). 2-Butoxymethyloxirane (**17**) [1.30 g (10 mmol)] and 1.52 g (10 mmol) of *S*-phenyl thioacetate (**18**) were dissolved in 5 mL of diglyme, and then 0.21 g (0.5 mmol as quaternary onium salt) of catalyst **8b** was added to the solution. The mixture was stirred at 110 °C for 24 h, and then the catalyst was filtered off. To the filtrate was added about 30 mL of diethyl ether; the solution washed twice with water, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated in vacuo. The crude product thus obtained was purified by silica gel column using benzene as an eluent: isolated yield of adduct **20c**, 1.80 g, 64.2%; bp 96–100.2 °C (0.03 mmHg); IR (neat) 1740 (C=O), 1240 cm^{-1} (C–O–C, ester); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.0 Hz, CH_3–C), 1.10–1.80 (m, 4 H, C–$(CH_2)_2$–C), 1.95 (s, 3 H, CH_3–CO), 3.19 (d, 2 H, J = 6.7 Hz, CH_2–S), 3.42 (t, 2 H, CH_2–O), 3.60 (d, 2 H, J = 4.8 Hz, O–CH_2), 5.09 (m, 1 H, methine), 7.00–7.60 (m, 5 H, aromatic protons). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.85. Found: C, 63.61; H, 8.03.

Synthesis of 1-Butoxy-3-phenylthio-2-propyl Benzoate (20f). Oxirane **17** (1.30 g, 10 mmol) was made to react with active ester **19** (2.14 g, 10 mmol) in the presence of catalyst **11** (0.35 g, 0.5 mmol) in diglyme (5 mL) at 110 °C for 24 h. The crude product of **20f** was purified by the column using the mixed solvent (4:6 chloroform–carbon tetrachloride): yield 2.14 g, 62.1%; viscous oil; IR (neat) 1720 (C=O), 1270 cm^{-1} (C–O–C, ester); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.0 Hz, CH_3), 1.00–1.70 (m, 4 H, C–$(CH_2)_2$–C), 3.33 (d, 2 H, J = 6.1 Hz, CH_2–S), 3.45 (t, 2 H, J = 4.5 Hz, CH_2–O), 3.72 (d, 2 H, O–CH_2), 5.28 (m, 1 H, methine), 6.80–8.10 (m, 10 H, aromatic protons). Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02. Found: C, 69.68; H, 7.31.

Syntheses of 1-Phenoxy-3-phenylthio-2-propyl Acetate (20a), 1-Methoxy-3-phenylthio-2-propyl Acetate (20b), 1-Phenoxy-3-phenylthio-2-propyl Benzoate (20d), and 1-Methoxy-3-phenylthio-2-propyl Benzoate (20e). Adducts **20a**,[17h] **20b**,[17h] **20d**,[17h] and **20e**[17h] were obtained with 65.6, 62.5, 80.2, and 62.1% yields, respectively, from the reaction of the corresponding oxiranes with active esters using catalysts **8b** or **11** by the same procedure as described above.

Synthesis of 1-Phenoxy-3-phenylthio-2-propanol (23a). Method A. **23a** was normally synthesized in high yield by the addition reaction of oxirane **15** with thiophenol **22** using tetrabutylammonium bromide as a catalyst according to the reported method:[17h] bp 179–180 °C (0.03 mmHg); IR (neat) 3450 cm^{-1} (–OH); ^{1}H NMR ($CDCl_3$) δ 2.76 (d, 1 H, OH), 3.16 (d, 2 H, CH_2–S), 3.90–4.30 (m, 1 H, methine), 4.02 (d, 2 H, CH_2–O), 6.70–7.60 (m, 10 H, aromatic protons). **Method B.** To 15.02 g (100 mmol) of oxirane **15** in 80 mL of diglyme was added 8.56 g (56 mmol) of active ester **18** and 0.56 g (2.01 mmol) of tetrabutylammonium chloride. The mixture was stirred at 90 °C for 1 h. To the solution was added 150 mL of diethyl ether; the solution was washed twice with water, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated in vacuo. The residue was separated by the silica gel column using benzene as an eluent: isolated yield of adduct **23a**, 0.47 g, 2.8%; ratio of **20a**/**23a**, 82.6/17.4 (determined by GLC analysis).

Kinetic Measurement of the Reaction of Oxirane with Active Ester. Appropriate amounts of oxirane, active ester, reaction solvent, and *p*-dichlorobenzene (internal standard for GLC) were charged into a reaction flask, thermostatically kept at the suitable temperature with stirring under flowing nitrogen. To the mixture was added a fixed amount of catalyst at starting time, and the reaction mixture was periodically analyzed by GLC.

Registry No. **12**, 97596-77-5; **13**, 1224-56-2; **14**, 125474-91-1; **15**, 122-60-1; **16**, 930-37-0; **17**, 2426-08-6; **18**, 934-87-2; **19**, 884-09-3; **20a**, 120915-43-7; **20b**, 123295-65-8; **20c**, 125453-81-8; **20d**, 123295-63-6; **20e**, 123295-64-7; **20f**, 125453-82-9; **22**, 108-98-5; **23a**, 84137-77-9; **23b**, 39504-13-7; **23c**, 39504-39-7.