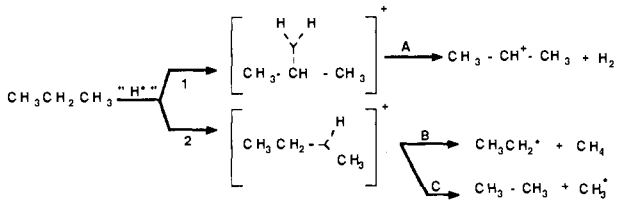
Scheme I



and his group[9] on the relative reactivity of the σ bonds toward the electrophilic proton:

primary C–H ≪ secondary C–H < C–C < tertiary C–H

When the propane–carbon monoxide mixture ($CO:C_3$ molar ratio = 3) was bubbled through $HF\text{-}SbF_5$ under the same conditions as above but after addition of a small amount of sodium bromide (Br^-/Sb:0.5 mol %), the NMR spectrum of the resulting solution showed a selectivity of 95% in IPOC formation with a total conversion of 9% of the propane. The influence of the bromide ion on the selectivity of propane is shown in Figure 1. When the same reaction was carried out on a 20 times larger scale under a pressure of 6 atm in a Hastelloy Autoclave (reaction time: 5 h), the GC analysis of the products obtained by quenching the reaction mixture in ice–water shows a selectivity of 98% in isobutyric acid with a conversion of 80% of the propane. Analysis of the gas phase shows the following product distribution

$$H_2 \gg CH_4 \gg C_2H_6 \text{ (90:10:0)}$$

in agreement with the hydride-abstracting ability of the ethyl cation generated via pathway 2B.

The nature of the bromide salt has little effect on the product distribution as shown by replacing NaBr by tetramethylammonium bromide. The presence of iodide ions shows also an increase in selectivity, whereas the chloride ions have little effect.

The results can be rationalized as follows: When the bromide ion is dissolved in the superacid medium, it is oxidized via protonation of the hydrogen halide. The second step, key step for the observed selectivity, is the electrophilic attack of the secondary C–H bond, as preferred for steric reasons; and in this way HBr is regenerated. The better selectivity observed with the bromide ion seems to be due to the fact that the chloride ion is too difficult to oxidize under the present conditions, whereas the "I^+" ion is less electrophilic.

In contrast to many well defined polyatomic halogen cations[10] such as I_2^+ and Br_2^+ no experimental evidence has been brought for the existence of the monoatomic ions. The Lewis acid assisted generation of "Cl^+" and "Br^+" from chlorine and bromine has been suggested by Olah on the basis of electrophilic chlorination and bromination of alkanes.[11] Bromine itself is easily oxidized in $HF\text{-}SbF_5$ via the Br_2H^+ ions[12] and has been used in selective aromatic bromination.[13] It can also replace the bromide ion in the experiments described above with the same selectivity.

On the other hand, we cannot exclude that CO itself may participate in the key step as [$COBr^+$] analogous to the formyl cation [HCO^+] which has recently been identified in the carbonylation reaction of adamantane or [$COCl^+$] reported as an intermediate in the electrophilic carbonylation of benzene in the liquid SO_2–Br_2–$SbCl_5$–CO system.[14]

The intriguing point in these results is the high selectivity observed with catalytic amounts of bromide ion in a large excess of protonic superacid. This can only be explained by the large rate enhancement as observed. The addition of excess HF leads

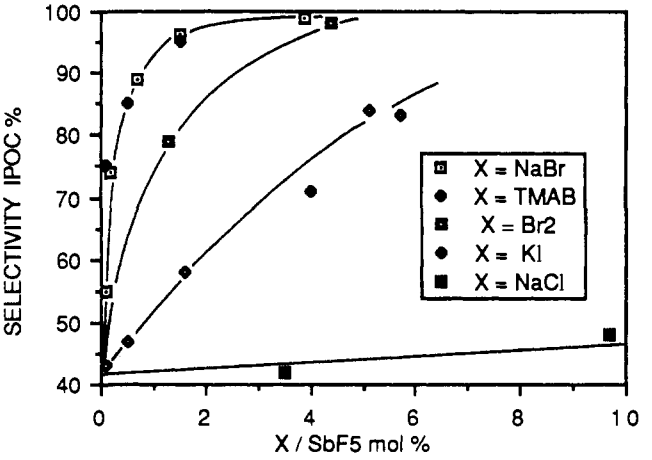
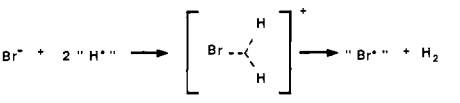
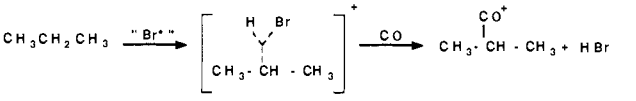


Figure 1. Selectivity in the carbonylation of propane as a function of halide ion concentration in $HF\text{-}SbF_5$.

Scheme II



Scheme III



to the formation of isobutyryl fluoride. In this way the total reaction of carbonylation of propane in $HF\text{-}SbF_5$ can be written as

$$C_3H_8 + HF + CO \rightarrow C_3H_7COF + H_2$$

Acknowledgment. We would like to thank NORSOLOR (subsidiary company of ORKEM) for financial support.

Registry No. C_3, 74-98-6; TMAB, 64-20-0; Br, 24959-67-9; I, 20461-54-5; NaBr, 7647-15-6; Br_2, 7726-95-6; KI, 7681-11-0; isobutyric acid, 79-31-2.

(9) (a) Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251. (b) Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 4960.

(10) (a) Wilson, W. W.; Thompson, R. C.; Aubke, F. *Inorg. Chem.* **1980**, *19*, 1489. (b) Shamir, J. *Struct. Bonding* **1979**, *37*, 141.

(11) (a) Olah, G. A.; Renner, R.; Shilling, P.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 7686. (b) Olah, G. A.; Shilling, P. *J. Am. Chem. Soc.* **1973**, *95*, 7680.

(12) Olah, G. A.; Shen, J. *J. Am. Chem. Soc.* **1973**, *95*, 3582.

(13) Jacquesy, J. C.; Jouannetaud, M. P. *Tetrahedron* **1982**, 23.

(14) Yoshimura, M.; Namba, T.; Tokura, N. *Tetrahedron Lett.* **1973**, 2287.

Convenient Conversion of Aldehydes and Ketones into the Corresponding Alkenes via Hydroboration of Their Enamines. A Remarkably Simple Synthesis of Either [*Z*]- or [*E*]-Alkenes[1a]

Bakthan Singaram, Christian T. Goralski,[1b]
Milind V. Rangaishenvi, and Herbert C. Brown*

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University
West Lafayette, Indiana 47907
Pharmaceuticals Process Research
The Dow Chemical Company
Midland, Michigan 48674

Received July 28, 1988

Aldehydes and ketones are converted into the corresponding alkenes via hydroboration of their enamines. The synthesis of pure [*Z*]- or [*E*]-alkenes is readily achieved from the same acyclic ketone enamine by modification of the hydroboration–elimination procedure: (A) hydroboration of the enamine by 9-borabicyclo[3.3.1]nonane (9-BBN) followed by methanolysis or (B) hy-

* Address correspondence to this author at Purdue University.

(1) (a) Presented in part at the Third Chemical Congress of North America, Toronto, June 5–10, 1988, Abstract ORGN 242. (b) Visiting scientist on leave from the Pharmaceuticals Process Research Laboratory, Michigan Applied Science and Technology Laboratories, The Dow Chemical Company, Midland, Michigan 48674.

0002-7863/89/1511-0384$01.50/0

Table I. Alkenes and Dienes from Aldehyde Enamines

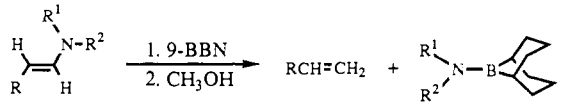
enamine[a]	alkene/diene	yield,[b] %
[*E*]-1-morpholino-1-octene	1-octene	80
[*E*]-1-morpholino-3-phenyl-1-propene	3-phenyl-1-propene	82
(*R*)-(−)-[*E*]-1-pyrrolidino-3,7-dimethyl-1,6-octadiene	*R*-(−)-3,7-dimethyl-1,6-octadiene	75
[*E*]-1-morpholino-1,[*E*]-4-decadiene	1,[*E*]-4-decadiene	82
[*E*]-1-morpholino-1,[*Z*]-4-decadiene	1,[*Z*]-4-decadiene	89
[*E*]-1-hexamethyleneimino-1,10-undecadiene	1,10-undecadiene	72

[a] Prepared from the corresponding aldehyde and secondary amine in cyclohexane in the presence of anhydrous potassium carbonate. [b] Isolated and distilled.

droboration by borane methyl sulfide (BMS) followed by methanolysis and hydrogen peroxide oxidation. The ready availability of stereospecific enamines from acyclic ketones makes this the first general synthesis of either [*Z*]- or [*E*]-alkenes from a single intermediate.[2]

The conversion of carbonyl compounds to alkenes has been of considerable interest in the past, and numerous methods have been developed for this transformation.[3-9] In all of these previous studies, except the desulfurization of vinyl sulfides,[6] only cyclic ketones, in which the stereochemistry of the resulting double bond is fixed, have been investigated. In the course of expanding our studies on the hydroboration of enamines[10] to include dialkylboranes, we discovered a simple hydroboration–elimination reaction of enamines which permits the facile conversion of aldehydes and ketones into the corresponding alkenes.

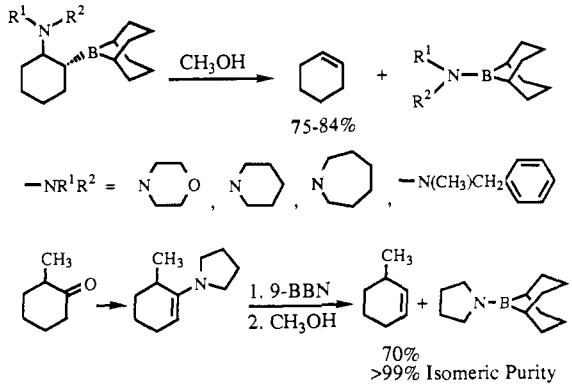
Hydroboration of aldehyde enamines by 9-BBN followed by methanolysis affords the corresponding terminal alkenes in excellent yields (eq 1). Unsaturated aldehyde enamines provide



(1)

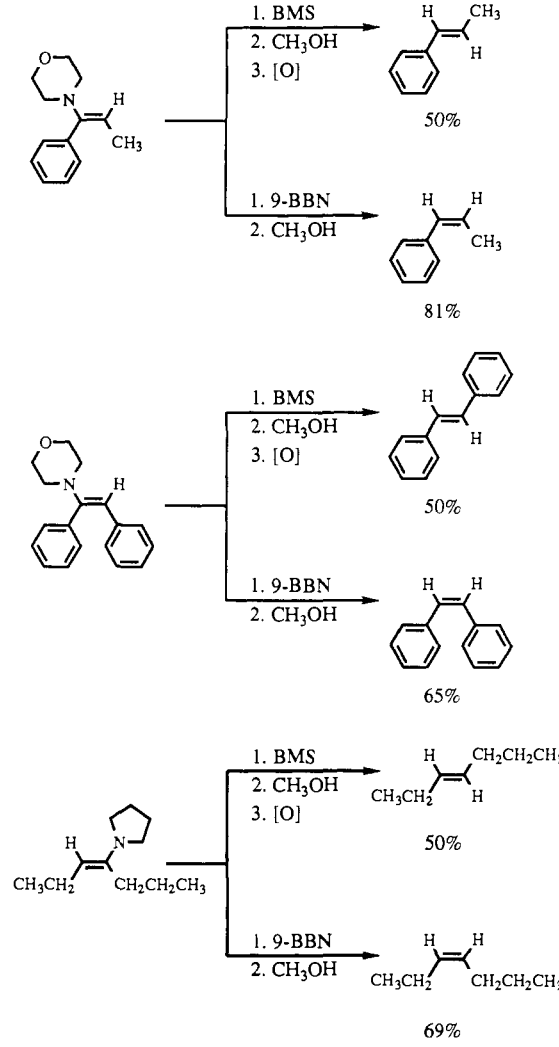
the corresponding dienes under these conditions, demonstrating the remarkable chemoselectivity of the hydroboration reaction for the enamine double bond (Table I).

Enamines from cyclic ketones, e.g., cyclohexanone, give the corresponding cycloalkenes, the elimination reaction being independent of the nature of the secondary amine (eq 2). One can take advantage of the regiospecificity of the pyrrolidine enamine formation with 2-alkylcyclohexanones[11] to produce 3-methylcyclohexene from 2-methylcyclohexanone (eq 3).



(2) (3)

The appropriate selection of hydroboration procedures permits, for the first time, the remarkable conversion of a single acyclic ketone enamine into the corresponding [*Z*]- or [*E*]-alkene at will. Thus, hydroboration of [*E*]-1-morpholino-1-phenyl-1-propene by 9-BBN followed by methanolysis affords an 80% yield of isomerically pure [*Z*]-1-phenyl-1-propene, and hydroboration by BMS followed by methanolysis and oxidation with alkaline hydrogen peroxide gives a 50% yield of [*E*]-1-phenyl-1-propene (eq 4). Similar results are obtained with [*E*]-1,2-diphenyl-1-morpholinoethene (eq 5),[12] [*E*]-1-morpholino-1-(2-thienyl)-1-propene,[13] [*E*]-1-morpholino-1-(4-pyridyl)-1-propene,[13] and [*E*]-4-pyrrolidinyl-3-heptene (eq 6).[14] The results are summarized in Table II.



(4) (5) (6)

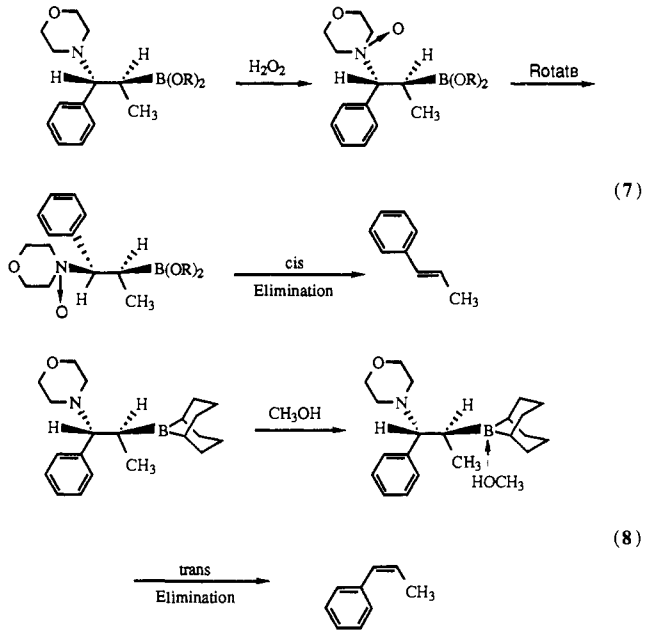
(2) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975, 3363.
(3) (a) Fetizon, M.; Jurion, M.; Anh, N. T. *J. Chem. Soc., Chem. Commun.* **1969**, 112. (b) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. (c) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (d) Ireland, R. E.; Kowalski, C. J.; Tilley, J. W.; Walba, D. M. *J. Org. Chem.* **1975**, *40*, 990. (e) Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 2715.
(4) (a) Pasto, D. J.; Snyder, R. *J. Org. Chem.* **1966**, *31*, 2777. (b) Lewis, J. W.; Pearce, A. A. *Tetrahedron Lett.* **1964**, 2039. (c) Lewis, J. W.; Pearce, A. A. *J. Chem. Soc. B* **1969**, 863. (d) Friary, R. J.; Gilligan, J. M.; Szajewski, R. P.; Falci, K. J.; Franck, R. W. *J. Org. Chem.* **1973**, *38*, 3487. (e) Froborg, J.; Magnusson, G.; Thoren, S. *Tetrahedron Lett.* **1975**, 1621. (f) Montury, M.; Gore, J. *Tetrahedron Lett.* **1977**, *219*. (g) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
(5) (a) Caglioti, L.; Cainelli, G.; Maina, G.; Selva, A. *Gazz. Chim. Ital.* **1962**, *92*, 309. (b) Larson, G. L.; Hernandez, E.; Alonso, C.; Nieves, I. *Tetrahedron Lett.* **1975**, 4005.
(6) Trost, B. M.; Ornstein, P. L. *Tetrahedron Lett.* **1981**, 3463.
(7) (a) Nelson, S. J.; Detre, G.; Tanabe, M. *Tetrahedron Lett.* **1973**, 447. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, 4821.
(8) (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (b) Shapiro, R. H. *Org. React. (N.Y.)* **1975**, *23*, 405. (c) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, 1811. (d) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.
(9) Another approach to the synthesis of [*Z*]- and [*E*]-alkenes from aldehydes based on boron intermediates has reecently been described: Pelter, A.; Buss, D.; Colclough, E. *J. Chem. Soc., Chem. Commun.* **1987**, 297.
(10) Goralski, C. T.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1987**, *52*, 4014.
(11) (a) Gurowitz, W. D.; Joseph, M. A. *Tetrahedron Lett.* **1965**, 4433. (b) Borowitz, I. J.; Williams G. J. *J. Org. Chem.* **1967**, *32*, 4157.
(12) Munk, M. E.; Kim, Y. K. *J. Org. Chem.* **1965**, *30*, 3705.
(13) Stradi, R.; Pocar, D.; Cassio, C. *J. Chem. Soc., Perkin Trans.* **1974**, 2671.
(14) Kuehne, M. E.; Garbacik, T. *J. Org. Chem.* **1970**, *35*, 1555.

Table II. [Z]- and [E]-Alkenes from Acyclic Ketone Enamines

enamine[a]	procedure[b]	alkene[c]	yield,[d] %
[E]-1-morpholino-1-phenyl-1-propene	A	[Z]-1-phenyl-1-propene	80
	B	[E]-1-phenyl-1-propene	50
[E]-1,2-diphenyl-1-morpholinoethene	A	[Z]-1,2-diphenylethene	65
	B	[E]-1,2-diphenylethene	50
[E]-1-morpholino-1-(4-pyridyl)-1-propene	A	[Z]-1-(4-pyridyl)-1-propene	60
	B	[E]-1-(4-pyridyl)-1-propene	30
[E]-1-morpholino-1-(2-thienyl)-1-propene	A	[Z]-1-(2-thienyl)-1-propene	68
	B	[E]-1-(2-thienyl)-1-propene	45
[E]-4-pyrrolidinyl-3-heptene	A	[Z]-3-heptene[e]	69
	B[f]	[E]-3-heptene[e]	50

[a] Prepared from the corresponding ketone and morpholine in toluene. [b] (A) Hydroboration by 9-BBN followed by methanolysis. (B) Hydroboration by BMS followed by methanolysis and oxidation with alkaline hydrogen peroxide. [c] Stereochemical purity of 99% established by capillary GC and ^{13}C NMR analyses. [d] Isolated and distilled. [e] Purity established by capillary GC analysis by comparison with authentic samples purchased from the Aldrich Chemical Company. [f] Neutral hydrogen peroxide was used.

The mechanisms proposed to account for the stereochemical results are shown for [E]-1-morpholino-1-phenyl-1-propene. Hydroboration with BMS followed by methanolysis gives the corresponding dimethylboronate ester. The amino boronate ester on treatment with hydrogen peroxide affords the amine *N*-oxide which undergoes cis elimination to give [E]-1-phenyl-1-propene (eq 7). In contrast, hydroboration with 9-BBN affords the corresponding trialkylborane which on treatment with methanol undergoes a catalyzed trans elimination to produce [Z]-1-phenyl-1-propene (eq 8).



(7)

(8)

The following procedure (A) for the preparation of [Z]-1-phenyl-1-propene is representative. To a stirred suspension of 2.44 g (20.0 mmol) of solid 9-BBN in 2.0 mL of THF at 25 °C was added 4.06 g (20.0 mmol) of [E]-1-morpholino-1-phenyl-1-propene. The suspension became a clear solution after 3 h. The ^{11}B NMR spectrum of the solution indicated the absence of 9-BBN. The THF was removed at 25 °C under reduced pressure (12 Torr). The reaction flask was fitted with a distillation head, and 0.62 g (20.0 mmol) of methanol was added. A mildly exothermic reaction occurred, and the reaction mixture solidified. Upon heating, the solid melted, and 1.90 g (81% yield) of isomerically pure [Z]-1-phenyl-1-propene, bp 62-64 °C (12 Torr), was obtained by distillation. The same procedure is applicable to the preparation of alkenes and dienes from aldehyde enamines.

The following procedure (B) for the preparation of [E]-1-phenyl-1-propene is representative. To a 1.0 M solution of [E]-1-morpholino-1-phenyl-1-propene in THF at 25 °C was added 2.0 mL (20.0 mmol) of 10.0M BMS with stirring. The reaction was stirred at 25 °C for 1 h and then methanolized. The resulting boronic ester was purified by distillation: bp 116-118 °C (0.25 Torr), 80% yield. The boronic ester was oxidized by using solid sodium hydroxide and 30% hydrogen peroxide to give a 50% yield (GLC) of isomerically pure [E]-1-phenyl-1-propene which was purified by distillation: bp 72-74 °C (20 Torr).

Chemoselective Enzymatic Monoacylation of Bifunctional Compounds

Nicolas Chinsky,[†] Alexey L. Margolin,[‡] and Alexander M. Klibanov*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received September 6, 1988

The selective monoprotection of a given function in a heterofunctional molecule constitutes a challenging task in organic synthesis.[1] In particular, it would be highly desirable to have the flexibility of directing the position of monoprotection simply by varying the modifying agent. Recently, the hydrolytic enzymes lipases and proteases have been successfully employed for selective monoacylation of diols[2] and sugars[3] in organic solvents. In the present study, we have found that in heterofunctional compounds, such as aminoalcohols, the chemoselectivity of enzymatic acylation can be readily controlled by the nature of the acyl moiety.

6-Amino-1-hexanol (**1**) was selected as a model bifunctional compound. In the reaction between this aminoalcohol and 2-chloroethyl butyrate (100 mM each, *tert*-amyl alcohol as a solvent, 45 °C), catalyzed by 100 mg/mL *Aspergillus niger* lipase,[4] the initial rate of enzymatic acylation of the OH group was 37 times

[†] On leave from Institut de Chemie des Substances Naturelles, CNRS, Gif sur Yvette, France.

[‡] Present address: Merrell Dow Research Institute, P.O. Box 68470, Indianapolis, IN 46268.

(1) McOmie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum: London, 1973. Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.

(2) Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotechnol.* **1985**, *11*, 401-407. Ramos Tombo, G. M.; Schar, H.-P.; Fernandez, X.; Ghisalba, O. *Tetrahedron Lett.* **1986**, *27*, 5707-5710. Hemmerle, H.; Gais, H.-J. *Tetrahedron Lett.* **1987**, *28*, 3471-3474. Cantacuzene, D.; Guerreiro, C. *Tetrahedron Lett.* **1987**, *28*, 5153-5156. Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127-3129. Riva, S.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 3291-3295.

(3) (a) Therisod, M.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 5638-5640. (b) Therisod, M.; Klibanov, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 3977-3981. (c) Riva, S.; Chopineau, J.; Kieboom, A. P. G.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 584-589.

(4) *Aspergillus niger* lipase (lipase K-30, lot no. LPJ04508) and *Pseudomonas* sp. lipoprotein lipase (LPL lot no. LPL04512) were purchased from Amano International Enzyme Co. (Troy, VA). Porcine pancreatic lipase (Lot No. 74F0470) was obtained from Sigma Chemical Co. (St. Louis, MO). All lipases were suspended in the reaction media without any pretreatment.

0002-7863/89/1511-0386$01.50/0