of 1-phenylpiperazine from **1a** (129 mg, 500 μmol), n-$Bu_4NF{\cdot}3H_2O$ (158 mg, 500 μmol), and **10** (178.5 mg, 1.1 mmol). The reaction was diluted with Et_2O and dried (Na_2SO_4), and then the residue was subjected to flash chromatography (silica gel, EtOAc/benzene/Et_3N 80:19:1), yielding **11a** as a light yellow oil (56 mg, 54%): NMR (360 MHz, $CDCl_3$) δ 2.68–2.73 (m, 5, 4 H; $(CH_2)_2$-NCH_2 + 1 H; NCH_2CH_2F), 2.79 (t, 1, J = 4.9 Hz, NCH_2CH_2F), 3.22 (t, 4, J = 5.0 Hz, $(CH_2)_2NPh$), 4.57 (dt, 2, J = 4.8, 47.7 Hz, CH_2F), 6.83–6.95 (m, 3, aromatic), 7.23–7.28 (m, 2, aromatic); ^{19}F NMR (338 MHz, $CDCl_3$) φ −218.52 (tt, 1, J = 47.7, 28.6 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 50), 202 (27), 175 (92), 160 (17), 132 (76), 105 (58), 42 (100). Anal. Calcd for $C_{12}H_{17}FN_2$: C, 69.20; H, 8.23; F, 9.12; N, 13.45. Found: C, 68.98; H, 8.33; F, 8.96; N, 13.34.

1-(3-Fluoropropyl)-4-phenylpiperazine (11b). The reaction was performed according to the same procedure as **11a** from **10** and **2a** (136 mg, 500 μmol), yielding **11b** as a light brown yellow oil (60 mg, 54%): GLC chromatogram, t_R = 9.54 min (column 2, carrier gas H_2, 0.95mL/min, isothermal 180 °C); NMR (350 MHz, $CDCl_3$) δ 1.83–2.00 (dm, 2, J = 25.6 Hz, $NCH_2CH_2CH_2F$), 2.52 (t, 2, J = 7.4 Hz, $NCH_2CH_2CH_2F$), 2.60 (t, 4, J = 5.0 Hz, $(CH_2)_2NCH_2$), 3.19 (t, 4, J = 5.0 Hz, $(CH_2)_2NPh$), 4.57 (dt, 2, J = 6.0, 47.2 Hz, CH_2F), 6.82–6.93 (m, 3), 7.23–7.27 (m, 2); ^{19}F NMR (338 MHz, $CDCl_3$), φ −220.52 (tt, 1, J =47.3, 25.4 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 95), 175 (100), 147 (16), 132 (44), 105 (51), 70 (63). Anal. Calcd for $C_{13}H_{19}FN_2$: C, 70.24; H, 8.61; F, 8.54; N, 12.60. Found: C, 70.30; H, 8.58; F, 8.35; N, 12.56.

1-(2-Fluoropropyl)-4-phenylpiperazine (11c). A mixture of finely powdered KI (498 mg, 3 mmol) and K_2CO_3 (414 mg, 3 mmol) was placed into a Reacti-Vial. 1-Phenylpiperazine (487 mg, 3 mmol) and a solution of 1-bromo-2-fluoropropane (423 mg, 3 mmol) in 1 mL of acetonitrile were added. The mixture was stirred at 120 °C for 25 min. The reaction was quenched with water and extracted with ether. The organic extract was washed with water and dried (Na_2SO_4). The GLC chromatogram of this solution gave two peaks (Column 2, carrier gas H_2, 0.95 mL/min, isothermal 180 °C, t_R = 5.05 min (**10**, trace), t_R = 7.55 min (**11c**, 99%)). Removal of the solvent and flash chromatography (40% EtOAc in hexane) yielded **11c** as a pale yellow oil (520 mg, 78.1%): NMR (200 MHz, $CDCl_3$) δ 1.35 (dd, 3, J = 23.6, 6 Hz, CH_3), 2.37–2.72 (m, 6, $(CH_2)_3N$), 3.19–3.24 (m, 4, $(CH_2)_2N$), 4.90 (dm, 1, J = 50 Hz, CHF), 6.81–6.95 (m, 3, aromatic), 7.22–7.30 (m, 2, aromatic); ^{19}F NMR (338 MHz, $CDCl_3$) φ −174.15 (dtq, 1, J = 49, 25, 18 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 50), 202 (27), 175 (92), 160 (17), 132 (76), 105 (58), 42 (100). Anal. Calcd for $C_{13}H_{19}FN_2$: C, 70.24; H, 8.61; F, 8.55; N, 12.60. Found: C, 70.00; H, 8.47; F, 8.58; N, 12.71.

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Registry No. **1a**, 103935-47-3; **2a**, 103935-48-4; **2b**, 106114-40-3; **3a**, 762-49-2; **4a**, 352-91-0; **4b**, 462-40-8; **5b**, 106-98-9; **5c**, 109-67-1; **6a**, 1871-72-3; **6b**, 1871-73-4; **6c**, 106114-41-4; **6d**, 1871-74-5; **7**, 749-02-0; **8a**, 106114-42-5; **8b**, 106114-44-7; **8c**, 106114-46-9; **8d**, 106114-47-0; **8e**, 106114-48-1; **8f**, 106114-49-2; **9a**, 106114-43-6; **9b**, 106114-45-8; **10**, 92-54-6; **11a**, 106114-50-5; **11b**, 106114-51-6; **11c**, 106114-52-7; $HO(CH_2)_3I$, 627-32-7; $BrCH_2CHFCH_3$, 1871-72-3; $HO(CH_2)_2Br$, 540-51-2; $Br(CH_2)_3OH$, 627-18-9; ICH_2CHFCH_3, 20174-93-0.

Notes

Use of Aryltrimethylgermanium Substrates for Facile Aromatic Chlorination, Bromination, and Iodination

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The prevalence of halogenated compounds in medicinal chemistry[1] and radiopharmaceutical chemistry[2,3] has generated a need for synthetic methods that yield a single halogenated product and avoid the necessity of separating isomeric mixtures. Silicon[4,5] and tin[6,7] have been used for many years in organic syntheses to direct the specificity of electrophilic reactions, and ipso substitution of aromatic carbon–silicon and –tin bonds has been used to regiospecifically introduce halogens onto aromatic rings. Although both silylated and stannylated arenes have been successfully applied for this purpose, these fourth-group organometallics suffer from various synthetic disadvantages. When silylated arenes are used as halogenation substrates, electron-donating substituents are generally required for high halogenodesilylation yields,[8-11] and in those aromatic rings that are relatively activated toward electrophiles, halogenodeprotonation products predominate.[10,12] Halogenation of stannylated arenes, on the other hand, results in regiospecific substitution of the tin group on aromatic rings that are activated or deactivated toward electrophiles,[13-15] but the great sensitivity of the carbon–tin bond to protolysis[16] or alkaline hydrolysis[17] limits the synthetic utility of this technique.

The intermediate group IVB (group 14)[32] element germanium has a greater covalent radius[18] and a lower car-

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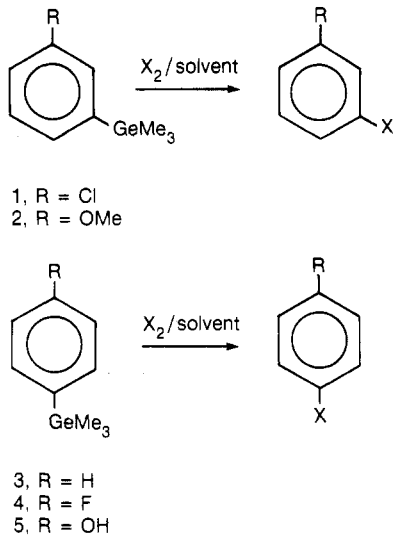
Scheme I



bon–metal bond energy[19] than silicon, so germylated arenes are expected to be more susceptible to electrophilic substitution reactions than arylsilanes. In addition, the aromatic carbon–germanium bond is 4 orders of magnitude less sensitive to acid hydrolysis than that of tin,[16] so the synthesis of germylated precursors for halogenation is less limited than for stannylated substrates. Halogenodegermylation reactions have been shown to be useful for the regiospecific labeling of aromatic rings in high specific activity using in situ oxidized radiobromide and radioiodide.[11,20] This work reports the site-specific halogenation of aromatic rings at the preparative level using aryltrimethylgermanium substrates with elemental chlorine, bromine, and iodine. The high reactivity of fluorine differs from that of the heavier halogens and is the topic of a separate study.[21]

The aromatic substituents on the aryltrimethylgermanium compounds used in this investigation (see Scheme I) were chosen on the basis of the information that the halogenation products would provide concerning the effect of ring activation on electrophilic substitution of the aromatic metallic group and on competitive aromatic halogenodeprotonation reactions. These substituent effects are succinctly described by using the Brown–Okamoto σ^+ substituent constants.[22] Compound **1** is deactivated toward aromatic degermylation ($\sigma_m^+ = 0.399$) as well as competitive halogenodeprotonation ($\sigma_p^+ = 0.114$) reactions, but more so for the former. Substrates **3** and **4** are both nonactivated aromatic systems, with **4** allowing the specificity of the halogenation reaction to be determined. Organometallics **2** and **5** are aromatic rings that are activated toward electrophilic attack. However, in **2** the trimethylgermanium group is deactivated toward electrophilic substitution by the methoxy group ($\sigma_m^+ = 0.047$), while competitive halogenodeprotonation reactions are promoted by this substituent ($\sigma_p^+ = -0.778$). For compound **5**, electrophilic attack is directed to the carbon–germanium bond para to the hydroxyl group ($\sigma_p^+ = -0.92$). Because aromatic hydroxyl and fluoro substituents are ortho–para directors, activation of electrophilic halogenodegermylation in substrates **4** or **5** occurs in competition with statistically favored halogenodeprotonation reactions at the ring position ortho to the substituent.

Table I. Yields for the Regiospecific Halogenodegermylation Reactions $RC_6H_4GeMe_3 + X_2 \rightarrow RC_6H_4X$ in Different Solvents at 25 °C

halogenation substr	yield of RC_6H_4X,[a] %					
	X = Cl			X = Br		
	$MeCO_2H$	MeOH	CCl_4	$MeCO_2H$	MeOH	CCl_4
1	98	98	82	99[b]	81[b]	48[b]
2	99	97	80	80[b]	76[b]	76[b]
3	97	99	98	98	99	88[b]
4	99	99	95	98	97	96
5	99	98	99	99	99	97

[a] Unless otherwise indicated, reaction time = 1 min. [b] Reaction time = 1 h.

Table II. Yields for the Regiospecific Iododegermylation Reactions $RC_6H_4GeMe_3 + I_2$ (ICl) $\rightarrow RC_6H_4I$ in Different Solvents at 25 °C

iodination substr	yield of RC_6H_4I, %					
	I_2[a]			ICl[b]		
	$MeCO_2H$	MeOH	CCl_4	$MeCO_2H$	MeOH	CCl_4
1	70	26	14[c]	98	97	84
2	74	27	51[c]	99	96	82
3	76	28	36[c]	98	98	96
4	99[b]	30	16[c]	99	97	94
5	98[b]	84	70	97	98	95

[a] Unless otherwise noted, reaction time = 1 h. [b] Reaction time = 1 min. [c] Reaction time = 6 h.

Regiospecific incorporation of halogen at the ring position ipso to the trimethylgermanium group occurred upon treatment of compounds **1–5** with molecular halogen. With all substrates, products from competitive halogenodeprotonation were nonexistent. This was true even for organometallic **2**, in which (unlike the corresponding silylated analogue[7,12]) substitution of the germanium moiety at the deactivated meta position takes place in preference to proton displacement at the activated ortho and para positions. The difference in the energies of the aromatic carbon–germanium (74 kcal mol^{-1} [23]) and –hydrogen (110 kcal mol^{-1} [24]) bonds apparently makes halogenodegermylation the favored reaction pathway in each case, so that the electronic effects of ring substituents effects only the rate at which halogen substitution of the metal occurs.

As shown in Figure 1A, using compound **2** as an example, the rate at which the organometallic is halogenated is dependent on the nature of the halogenating species. The yields and rapidity of halogenation increased in the order $I_2 < Br_2 < Cl_2$, in agreement with the rank order for the molecular halogenation of arenes. The rate expressions for the chlorination of arenes are generally first order in chlorine, whereas the rates for bromination and iodination are of higher order in halogen.[25]

The aromatic halogenodegermylation kinetics are also influenced by the reaction solvent, as illustrated in Figure 1B for the bromodegermylation of organometallic **1**. The bromination rate and yield increase as the reaction medium is changed from nonpolar carbon tetrachloride to polar methanol to acidic acetic acid. The latter two solvents probably enhance aromatic bromodegermylation by polarization of bromine, by stabilizatoin of the σ-complex

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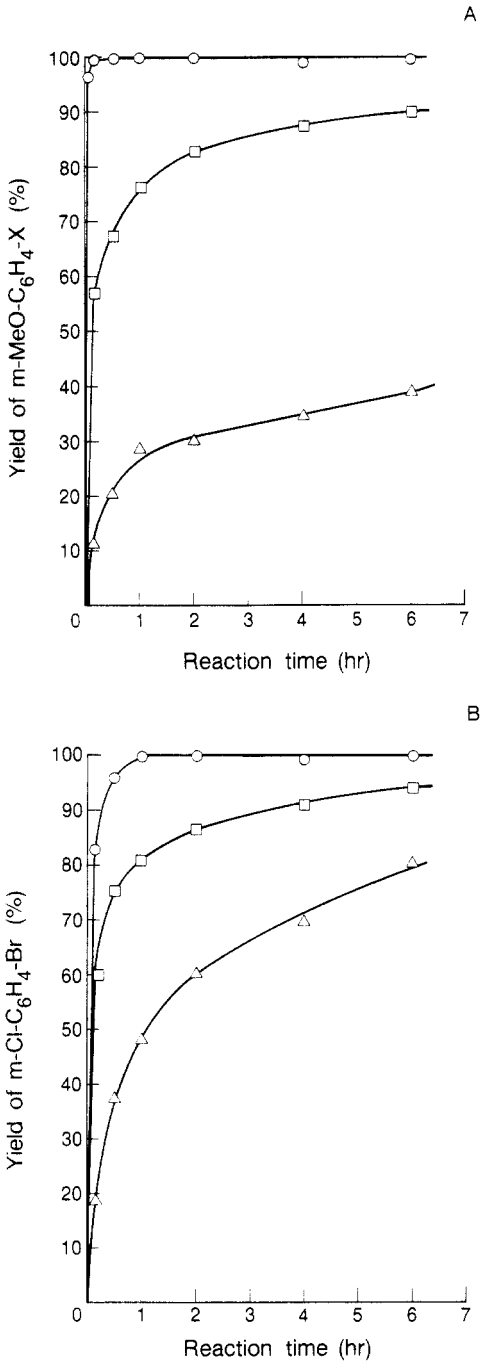

Figure 1. Aromatic halogenodegermylation yields as a function of reaction time. (a) Halogenodegermylation of *m*-anisyltrimethylgermanium with X_2 in methanol. ○, X = Cl; □, X = Br; △, X = I. (b) Bromodegermylation of (*m*-chlorophenyl)trimethylgermanium with Br_2 in various solvents. ○, $MeCO_2H$; □, MeOH; △, CCl_4.

transition state,[26] or by assistance in bromine–bromine bond cleavage.

Similar effects were also noted for the halogenation of the other aryltrimethylgermanium substrates, as summarized in Tables I and II. Table I shows the yields obtained from chloro- and bromodegermylation of organometallics **1–5** in glacial acetic acid, methanol, and carbon tetrachloride at 25 °C. As can be seen, regiospecific chlorination was virtually quantitative within 1 min, even with deactivated aromatic systems in nonpolar carbon tetrachloride. High reactivity was also found with bromination reactions, which show only a moderate response to changes in the aromatic structure. In aromatic rings that are deactivated toward electrophilic attack, reaction times of ca. 1 h were required for optimum bromination yields.

The tendency for lower halogenation reactivity as the seventh group is descended is further supported by the aromatic iododegermylation results compiled in Table II. When elemental iodine is the iodinating species, reaction times of at least 1 h are required unless activated substrates are used in acetic acid. Iodination yields were low in carbon tetrachloride even after 6 h, but useful iodination yields of 41%, 81%, and 42% were achieved using compounds **1**, **3**, and **5**, respectively, over a reaction period of 24 h. In any case, these site-specific iodination yields exceed those that can be obtained by treatment of nonmetalated arenes with iodine.[25] Moreover, as shown in Table II, application of the interhalogen iodine monochloride affords practically quantitative iododegermylation yields within 1-min reaction intervals, independent of the degree of electronic ring activation of reaction solvent. This enhancement of reactivity is expected on the basis of first-order kinetic dependence of aromatic iodination on iodine monochloride concentration.[25] Noteworthy is the fact that only regiospecifically iodinated products were produced with iodine monochloride in carbon tetrachloride, with no chlorinated side products. This indicates that the aromatic iododegermylation process occurs faster than the dissociation of iodine monochloride into iodine and chlorine.[27]

In conclusion, aromatic halogenodegermylation is a useful technique for the site-specific incorporation of halogens onto aromatic rings that are activated or deactivated to electrophilic substitution. Molecular halogens can be used at room temperature without catalysis or oxidizing agents, so sensitive molecules can be halogenated with this technique. The methods described here can be applied by synthetic chemists involved in the preparation of pharmaceuticals, low specific activity radiopharmaceuticals, or other halogenated compounds in which structural constraints are stringent.

Experimental Section

Materials. All reagents employed in these experiments, including the halogenated arenes, which were used as reference compounds in the GC or HPLC analysis of reaction products, were purchased in 98–99% purity from Aldrich or Alfa Chemical Co. Chlorine gas (99.5%) was from Air Products, Inc. All solvents were obtained in analytical quality from Aldrich Chemical Co.

The aryltrimethylgermanium compounds were synthesized via the Grignard compound of the corresponding brominated arene, purified by fractionation, and spectroscopically characterized. Details for the synthesis of the majority of the organometallics have been presented elsewhere,[28] although compounds **1** and **2** are new.

The preparation of organometallic **1** was as follows: The Grignard compound was prepared by dropwise addition of *m*-bromochlorobenzene (19.2 g, 0.1 mol) in 50 mL of dry THF to magnesium metal (2.7 g, 0.11 mol) initiated with 0.5 mL of methyl iodide. This solution was stirred for 2 h at 25 °C under a dry argon atmosphere, then trimethylgermanium chloride (15.3 g, 0.1 mol) in 50 mL of THF was added dropwise, and the resulting mixture was refluxed for 2 h. The vessel contents were then cooled and treated with 5% aqueous ammonium chloride, and the reaction products were extracted into dichloromethane. The organic layer was removed, washed with water, and dried (Na_2SO_4). Fractionation gave pure (*m*-chlorophenyl)trimethylgermanium: 21.1 g (92%); bp 104 °C (24 mm); d^{25} = 1.2290; IR (neat) 3090–2990, 1625, 1420, 1230, 1070, 1000, 860, 815, 760, 665 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.40 (s, 9 H), 7.45 (m, 4 H); MS, *m/e*

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232/230/228/226 (M^+). Anal. Calcd: C, 47.2; H, 5.7. Found: C, 47.4; H, 5.7.

Identical treatment of *m*-bromoanisole produced *m*-anisyltrimethylgermanium: 19.3 g (86%); bp 112 °C (33 mm); d^{25} = 1.1426; IR (neat) 3200–2990, 2850, 1650, 1500, 1280, 1235, 1050, 850, 815, 750, 665 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.38 (s, 9 H), 3.46 (s, 3 H), 7.12 (m, 4 H); MS, *m/e* 226/224/222 (M^+). Anal. Calcd: C, 53.4; H, 7.2. Found: C, 53.2; H, 7.2.

Halogenation Experiments. All halogenation reactions were performed at 25 °C in tightly sealed 100-mL glass reaction vessels equipped with magnetic stirrers. The general sequence used for the halogenodegermylation experiments was to place the aryltrimethylgermanium compound (2–3 mmol) into the vessel and add the reaction solvent (10 mL), followed by addition of 1 equiv of halogen (dissolved in the reaction solvent) while stirring. Stock solutions of the halogens were prepared immediately prior to use. Solutions (0.25 M) of bromine, iodine, and iodine monochloride were obtained by dissolving the calculated amount of halogen in the appropriate volume of solvent. Chlorine solutions were prepared by passing dry chlorine gas through the respective solvents. Concentrations from 0.05 to 0.3 M were obtained, as determined by treatment with excess potassium iodide and subsequent titration for iodine.

Following various reaction intervals (1 min, 5 min, 10 min, 30 min, 1 h, 2 h, 4 h, 6 h, 24 h), a 500-μL aliquot was removed with a glass syringe and transferred to aqueous sodium sulfite (10%, 4 mL) to quench the halogenation reaction. The organic products were extracted into dichloromethane (4 mL), and the organic layer was dried with calcium chloride.

Analysis of Reaction Products. The organic reaction products in 100 μL of the organic layer were analyzed by either gas chromatography or high-performance liquid chromatography. GC analyses were performed using a Hewlett-Packard 5880-A series gas chromatograph with integrator. The isomeric chlorinated, brominated, and iodinated analogues of benzene and chlorobenzene were separated using a $^1/_8$ in. × 13 ft column of 6% Bentone-34 and 20% silicon oil DC-200 on 60/80 Chromosorb W-AW-DMCS,[29] while the corresponding halogenated isomers of anisole and fluorobenzene were separated using a $^1/_8$ in. × 13 ft column of 80% Igepal Co-880 on 60/80 Chromosorb W-AW-DMCS.[30] HPLC analyses were performed with a Waters M-45 solvent delivery system with Model U6K injector and Model 450 variable-wavelength detector connected to a Hewlett-Packard 3390-A reporting integrator. The halogenated isomers of phenol were separated on a stationary phase comprised of 0.5 × 50 cm Lichrosorb Si-60 (Merck) and a mobile phase of 1.5% glacial acetic acid in *n*-heptane.[31] The halogenodegermylation yields were calculated from the GC analyses by comparing the gas chromatograph's thermal conductivity detector response for each product with a calibrated mass–TCD response curve prepared for each of the possible halogenated isomers. A similar approach was used with the UV detector (adjusted to 254 nm) in the HPLC analysis of halogenated phenol products. For both GC and HPLC analyses, complete (98%) passage of the injected mass through the respective detecting devices occurred. This was determined by tracer experiments in which ^{36}Cl-, ^{82}Br-, and ^{131}I-labeled arenes were analyzed, the product peaks collected, and their radioactivities compared to that in a standard sample of the injectate.[2,11]

Acknowledgment. This work was supported in part by the Director, Office of Energy Research, Office of Basic Energy Sciences, Biology and Medicine Division of the U.S. Department of Energy, under Contract No. DE-AC03-76SF00098 and also by the National Institutes of Health, National Heart, Lung, and Blood Institutes, under Grant No. P01-HL25840.

Registry No. 1, 25920-26-7; 2, 31608-56-7; 3, 1626-00-2; 4, 23781-64-8; 5, 105183-09-3; 3-ClC_6H_4Cl, 541-73-1; 3-ClC_6H_4OMe, 2845-89-8; PhCl, 108-90-7; 4-ClC_6H_4F, 352-33-0; 4-ClC_6H_4OH, 106-48-9; 3-BrC_6H_4Cl, 108-37-2; 3-BrC_6H_4OMe, 2398-37-0; PhBr, 108-86-1; 4-BrC_6H_4F, 460-00-4; 4-BrC_6H_4OH, 106-41-2; 3-IC_6H_4Cl, 625-99-0; 3-IC_6H_4OMe, 766-85-8; PhI, 591-50-4; 4-IC_6H_4F, 352-34-1; 4-IC_6H_4OH, 540-38-5; trimethylgermanium chloride, 1529-47-1.

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p-Nitrobenzoate Esters of Epoxy Alcohols: Convenient Synthons for Water-Soluble Epoxy Alcohols

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The recently developed catalytic modification of the asymmetric epoxidation of allylic alcohols has expanded the synthetic utility of the process.[1] Beyond its obvious economic advantage, the catalytic procedure is especially effective for the synthesis of low molecular weight epoxy alcohols since workup and product isolation are now much simpler and in situ derivatization of the product epoxy alcohols is feasible. Sulfonylation, silylation, and esterification have been achieved in situ, following the catalytic asymmetric epoxidation of low molecular weight primary allylic alcohols (Scheme I).[2]

While the sulfonylation and silylation processes provide derivatives that are synthetically advanced over the parent epoxy alcohols, in situ esterification provides products which, depending on the selected conditions for subsequent reactions, are either functionally equivalent or are advanced with respect to the epoxy alcohols.

The functional equivalency between the epoxy esters and the parent epoxy alcohols is achieved under two sets of reaction conditions where initial ester hydrolysis occurs to liberate the free epoxy alcohols, which, in the presence of a nucleophile, then undergo ring-opening. To ensure this equivalency, the ester hydrolysis should take place much faster than ring-opening so that the free epoxy alcohol is the substrate for all the ring-opening reactions. Hence, the nucleophile can be present at the start of the reaction. Two quite different types of reaction conditions were studied in this effort (Scheme II).

When epoxy esters were treated with benzenethiol or 1-naphthol in a solution of *t*-BuOH and aqueous NaOH, ester hydrolysis occurred, as expected, to release the free epoxy alcohols. Under the aqueous basic conditions, the free 2,3-epoxy alcohols **1** underwent isomerization to 1,2-epoxy 3-ols **2** by virtue of the Payne rearrangement.[3] Nucleophilic ring-opening then took place selectively at the C-1 center of the latter isomers to afford a high proportion of the 2,3-diol products (eq 1).[4] The results with

(1) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1952. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(2) (a) Hanson, R. M.; Ko, S. Y.; Gao, Y.; Masamune, H.; Klunder, J. M.; Sharpless, K. B. *J. Am. Chem. Soc.*, in press. (b) In situ opening of glycidol and 2-methylglycidol has also been achieved. See ref 13 and 5b.
(3) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

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