Organic Reactions at Alumina Surfaces.[1] Mild and Selective Opening of Epoxides by Alcohols, Thiols, Benzeneselenol, Amines, and Acetic Acid

Gary H. Posner* and D. Z. Rogers

Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received June 13, 1977*

Abstract: Commercially available Woelm 200 neutral chromatographic alumina catalyzes nucleophilic opening of structurally diverse epoxides by a few equivalents of alcohols, thiols, amines, acetic acid, and benzeneselenol under very mild conditions. The epoxides are opened stereospecifically (trans) and regioselectively with nucleophile incorporation preferentially at the less substituted epoxide carbon atom. Medium-ring cycloalkene oxides give in good yields only the products arising from 1,2 opening, with no products arising from transannular interactions. The mechanism appears to be concerted, involving simultaneous polarization of the C–O bond of the epoxide and activation of the nucleophile by the alumina.

Epoxides are valuable intermediates in organic synthesis partly because their nucleophilic opening leads to 1,2-difunctionalized systems and partly because such cleavages usually occur specifically with trans stereochemistry. However, standard methods for nucleophilic opening of epoxides are often far from ideal. For example, acid-catalyzed scission often leads to mixtures of regioisomers and is unsuitable for molecules with other acid-sensitive functions. Reaction of epoxides with alkoxides or lithium amides often gives only poor yields of nucleophile incorporation, and medium-ring cycloalkene oxides often give products derived from transannular interactions.[2]

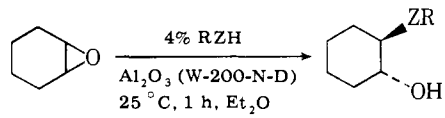
We have found that a stirring slurry of *unactivated, commercially available* Woelm 200 neutral chromatographic alumina (activity "Super I" on the Brockmann scale)[3] catalyzes opening of a wide variety of epoxides by only a few equivalents of nucleophiles under exceedingly mild conditions (25 °C, diethyl ether solvent). Although our initial experiments were done with W-200-N-*Dehydrated* (400 °C, 0.06 Torr, 24 h) alumina,[4] we have recently found that unactivated commercial W-200-N alumina produces very similar results. Nucleophiles which we have found to be incorporated successfully under these conditions include alcohols, thiols, benzeneselenol, amines, and acetic acid. Alumina "doped" with a few equivalents of these nucleophiles opens the epoxides regioselectively and stereospecifically (trans) and gives the corresponding β-functionalized alcohols cleanly and in good yields. The epoxides we have studied include the following types: (1) symmetrical cycloalkene oxides, (2) symmetrical alkene oxides, (3) unsymmetrical epoxides, (4) difunctional epoxides, and (5) miscellaneous epoxides.

The following discussion is organized based on epoxide type.

Results and Discussion

Symmetrical Cycloalkene Oxides. The reaction of epoxides with active alumina has been investigated;[5] in general a mixture of products is obtained in which allylic alcohols are the major component. Cyclohexene oxide is unusual in that the major product of its reaction with *"undoped"* alumina is the trans 1,2-diol.[5]

We have found that if the slurry of alumina is first "doped" by adding enough of an RZH species to equal 4% by weight of the alumina, reaction of cyclohexene oxide with this impregnated alumina for 1 h at 25 °C gives the corresponding trans-2-functionalized cyclohexanol reproducibly in good yield as the *only* product (eq 1). No allylic alcohol, 1,2-diol, or cis

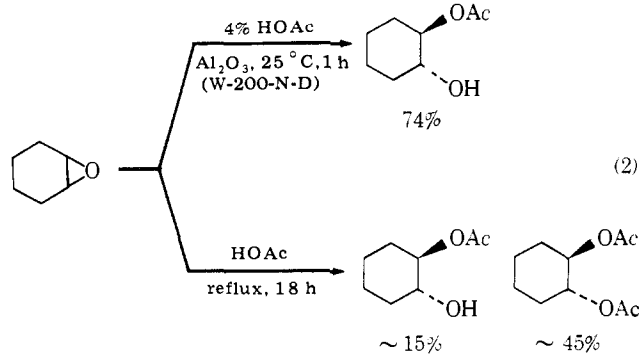


(1)

ZR	% yield (purified)
OMe	66
OCH_2Ph	47
SEt	78
SPn	70
SePh	95
NHBu-*n*	73
	40

isomer is detected. Several grams of epoxide have been successfully opened by heterogeneous reaction on doped alumina.[6]

In several cases cyclohexene oxide reaction with doped alumina is superior to homogeneous methods for synthesis of the corresponding cyclohexanols. *trans*-2-Benzyloxycyclohexanol has been obtained from cyclohexene oxide as a *mixture* containing benzyl alcohol and 1,2-cyclohexanediol;[7] solvolysis of cyclohexene oxide in refluxing acetic acid gave mainly the diacetate (eq 2), and sodium metal in refluxing allyl alcohol was not very successful in opening cyclohexene oxide (eq 3). The formation of *trans*-2-diethylaminocyclohexanol



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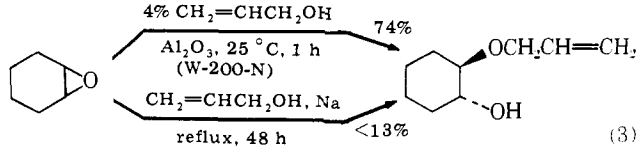
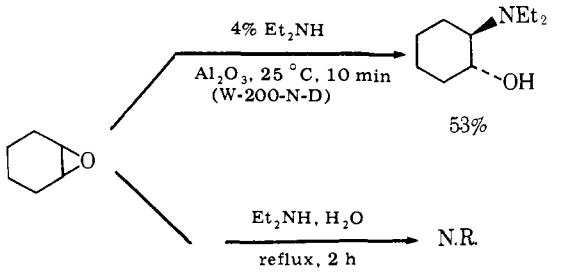


(3)

by refluxing cyclohexene oxide in diethylamine has been reported,[8] but in our hands these conditions gave mostly starting epoxide (eq 4). Likewise homogeneous reaction of cyclohexene



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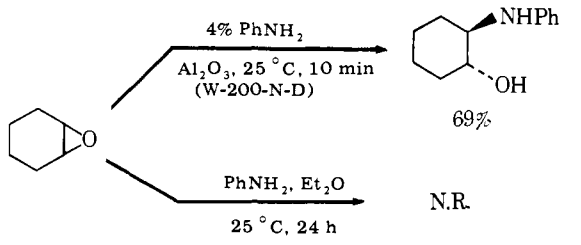
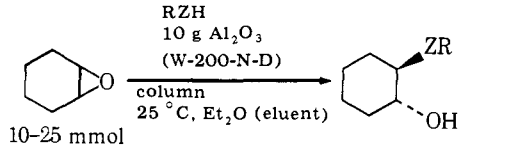
oxide with aniline in ether was much inferior to its heterogeneous reaction with aniline on alumina for production of *trans*-2-anilinocyclohexanol (eq 5).



(5)

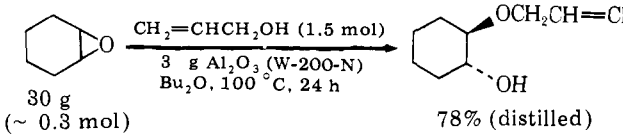
Typically we have found that about 7.5 g of the W-200-N alumina per 1 mmol of epoxide is required for complete reaction.[9] At the current price of W-200-N alumina ($25/500 g), the cost of alumina is 38 cents per mmol of epoxide consumed. To increase the efficiency of this procedure, we have examined the use of glass columns containing W-200-N and W-200-N-dehydrated[4] alumina through which is passed a 1:2 mixture of the epoxide and the doping agent in diethyl ether solvent. W-200-N-D gave only slightly better results than the commercial W-200-N alumina. The best results were obtained with the most reactive epoxides (e.g., cyclohexene oxide) and with the most reactive doping agents (e.g., ROH faster than RNH_2). In these cases, 10 g of alumina was able to consume *20–25* mmol of epoxide. Some results are summarized in eq 6.



(6)

ZR	% yield
OMe	98
$OCH_2CH{=}CH_2$	96
OAc	73
NHBu-*n*	43
N	67

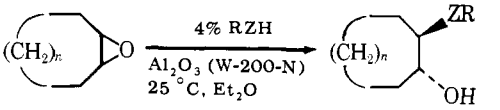
Even more dramatic is our observation that a stirring slurry of allyl alcohol on only *3* g of alumina at 100 °C was able to convert *300* mmol of cyclohexene oxide into the corresponding cyclohexanol (eq 7). Clearly, this type of alumina catalytic process may be very useful for large-scale reactions.

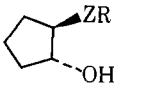
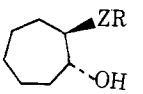
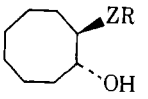
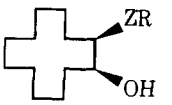


(7)

Symmetrical cycloalkene oxides other than cyclohexene oxide also undergo mild and selective opening by RZH-doped alumina (Scheme I). The results obtained in the reaction of

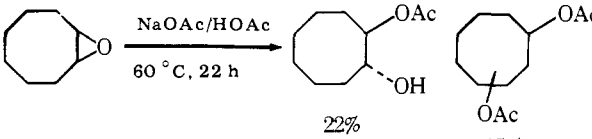
Scheme I. Effect of Ring Size in Opening of Symmetrical Cycloalkene Oxides by RZH-Doped Alumina (% Yield of Purified Products)



ZR =	$OCH_2CH{=}CH_2$	NHBu-*n*	OAc
	76	61	61
	73	64	92
	58	N.R.	82
	57	—	69

cyclopentene oxide and cycloheptene oxide with allyl alcohol, *n*-butylamine, or acetic acid doped alumina are very similar to those for cyclohexene oxide, except that the reaction of cycloheptene oxide with *n*-butylamine-doped alumina required 24 h for completion.

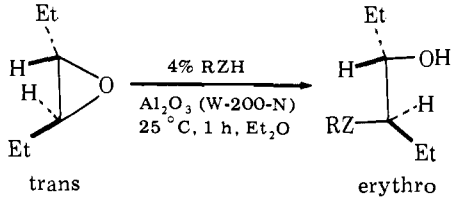
Medium-ring (8–12) cycloalkene oxides are much less reactive than cyclohexene oxides and are difficult to open homogeneously to only 2-functionalized cycloalkanols; direct 1,2-epoxide opening is usually accompanied by substantial amounts of side products derived from transannular interactions.[2] For example, cyclooctene oxide is inert to refluxing alcoholic sodium methoxide and sodium ethoxide,[10] and solvolysis of cyclooctene oxide gives products arising from transannular 1,3- or 1,5-hydride shifts (eq 8).[11] *cis*-Cyclododecene oxide is hydrolyzed only sluggishly with *p*-toluenesulfonic acid in refluxing aqueous dioxane to give *cis*-cyclododecanediol (12%) and starting epoxide (82%). In contrast to these homogeneous reactions, *no* products arising from transannular interactions were found in the RZH-doped alumina-catalyzed opening of these medium-ring cycloalkene oxides, and the yields of pure 1,2-opened products were reproducibly good. These alumina-promoted epoxide openings require 24–48 h and in some cases even such prolonged reactions at 25 °C leave a small amount of unreacted epoxide; allylic alcohols are occasionally observed as minor side products. This mild and clean heterogeneous opening of medium-ring epoxides by RZH-doped alumina appears to be the method of choice for stereospecific conversion of medium-ring cis or trans cycloalkene oxides into the corresponding trans or cis 2-substituted cycloalkanols, respectively.



(8)

Symmetrical Alkene Oxides. Alumina-catalyzed nucleophilic opening is not limited to *cyclo*alkene oxides; *trans*-3-hexene oxide, representing alkene oxides in general, reacted with stirring slurries of RZH-doped W-200-N alumina to

produce *erythro*-β-hydroxyethyl ethers, acetates, sulfides, and amines stereospecifically, as shown in eq 9. The products shown



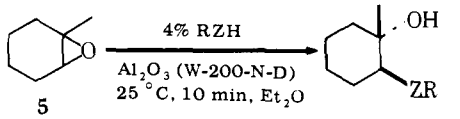
(9)

RZ	% yield (purified)
OMe	74
OAc	59
SEt	69
NHBu-*n*	47 (48-h reaction)

are the only ones observed. As with cycloheptene oxide, reaction of *trans*-3-hexene oxide with *n*-butylamine-doped alumina was much slower than reaction with any other RZH-doped alumina.

Unsymmetrical Epoxides. RZH-doped alumina cleaves unsymmetrical epoxides regioselectively with nucleophile incorporation preferentially at the less substituted epoxide carbon atom. This regioselectivity is more pronounced with diethyl ether than with carbon tetrachloride as solvent.[4] For alcohol-doped alumina, the magnitudes of this regiochemical preference are shown in Scheme II. The largest regioselectivity (6:1) was observed for alcohol attack at the primary center in terminal epoxides **1** and **3**; the basis for the difference in regioselectivity between 1,1-disubstituted epoxides **2** and **3** is not clear at this time. The relatively low regioselectivity observed for the trisubstituted epoxides **4** and **5** suggests that the mechanism of these heterogeneous alumina-promoted reactions is neither of the extreme S_N1 type nor of the extreme S_N2 type; typical homogeneous acid-catalyzed (S_N1) alcoholysis of epoxides **4** and **5** gives mainly tertiary ethers derived from intermediate tertiary carbonium ions, whereas homogeneous alcoholic alkoxide (S_N2) opening of epoxides **4** and **5** gives primarily secondary ethers.[2] Mechanistic analogies from homogeneous reactions to heterogeneous transformations must, of course, be made with caution.

In contrast to the lack of any strong regiochemical preference in *alcohol*-doped alumina opening of trisubstituted epoxide **5**, all other *RZH*-doped alumina reactions involved introduction of the RZ group *regiospecifically* at the less substituted center (eq 10). Even acetic acid on alumina produced



(10)

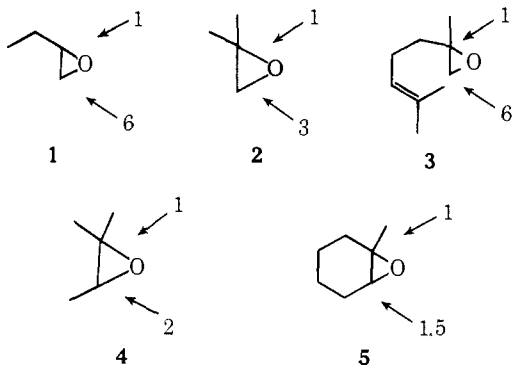
ZR	% yield (purified)
OAc	52
SPh	64
SePh	72

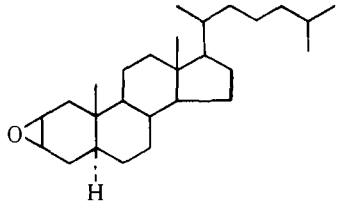
the corresponding *secondary* acetate regiospecifically as the only observed product; no allylic alcohol was detected.

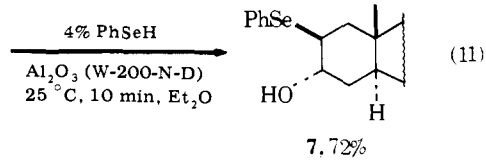
Unsymmetrical steroidal epoxide **6** reacted with benzeneselenol-doped alumina to give trans hydroxyselenide **7** regiospecifically and stereospecifically (eq 11). The preference for axial attack by the benzeneselenol is apparently sufficiently strong so that only isomer **7** was formed, as is the case also for homogeneous benzeneselenolate opening of this epoxycholestane.[12]

Functional Group Stability toward RZH-Doped Alumina. Often it is desirable to open an epoxide in the presence of some other functional groups. To ascertain whether such chemoselective epoxide openings on RZH-doped alumina are possible, we have exposed a series of compounds containing hydroxyl, nitrile, ketone, olefin, ester, and bromide functionalities to a stirring slurry of RZH-doped alumina for 1 h at 25 °C. In most cases, the substrates were recovered and purified in 66–93% yields (Scheme III). Ethyl 11-undecenoate on *n*-butylamine-doped alumina, however, gave a 1:1 mixture of starting ester and the corresponding *n*-butylamide, and 1-bromooctane on *n*-butylamine-doped alumina gave recovered bromide (53%) as well as some *N*-(*n*-butyl)-*N*-octylamine.

Scheme II. Relative Proportions of Unsymmetrical Epoxide Opening with ROH/Al_2O_3 (W-200-N-D)/25 °C/Et_2O

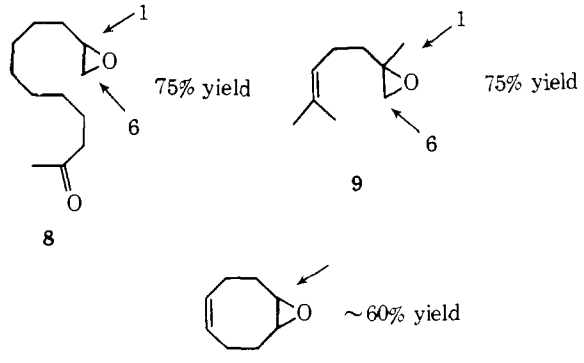






(11)

Several difunctional epoxides were treated with alcohol-doped W-200-N alumina at 25 °C for 1 h in Et_2O. Keto epoxide **8** reacted as if the keto group were not present; regioselective alcohol incorporation occurred at the less substituted epoxide center leading to ring-opened products in 75% yield after purification. Likewise, olefinic epoxides **9** and **10** underwent nucleophilic opening by alcohols on alumina without any apparent participation by the neighboring (**9**) or transannular (**10**) double bond.

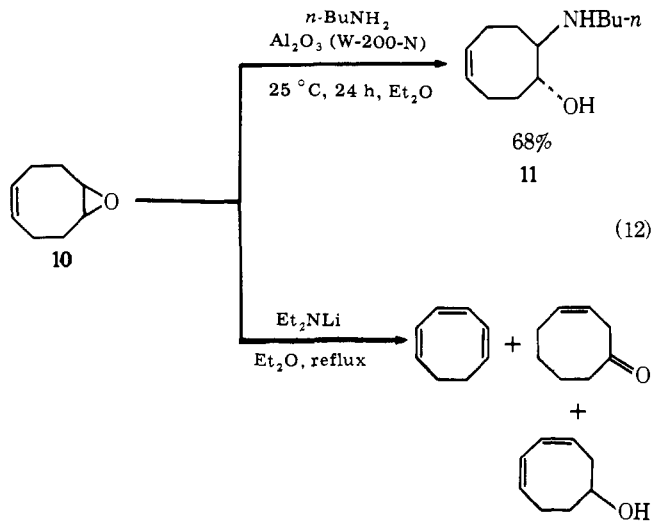


Olefinic epoxide **10** has been reported to react with lithium diethylamide to give the mixture of cyclooctene derivatives

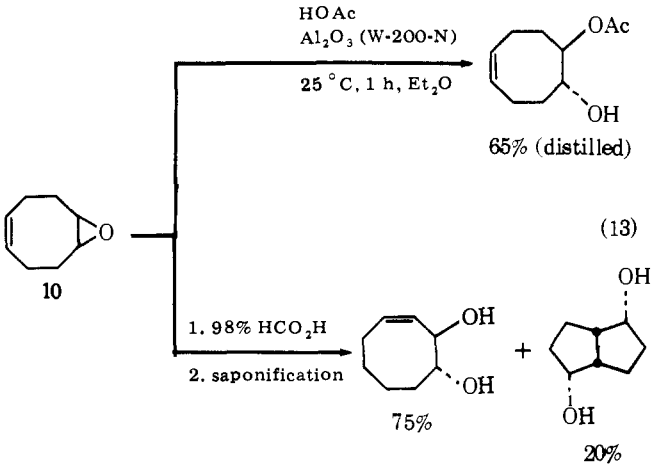
Scheme III. Stability of Functional Groups toward RZH-Doped W-200-N Alumina for 1 h at 25 °C in Et_2O

	RZH	% recovery
$HOCH_2CH_2CN$	MeOH	93
	n-$BuNH_2$	87
	HOAc	46
n-HexCMe (O)	MeOH	66
	HOAc	69
$CH_2{=}CH(CH_2)_8CO_2Et$	MeOH	92
	HOAc	86
	n-$BuNH_2$	47
$CH_3(CH_2)_7Br$	MeOH	70
	HOAc	48
	n-$BuNH_2$	53

shown in eq 12;[13] in contrast, n-butylamine-doped alumina produced analytically pure trans amino alcohol **11** in 68% yield

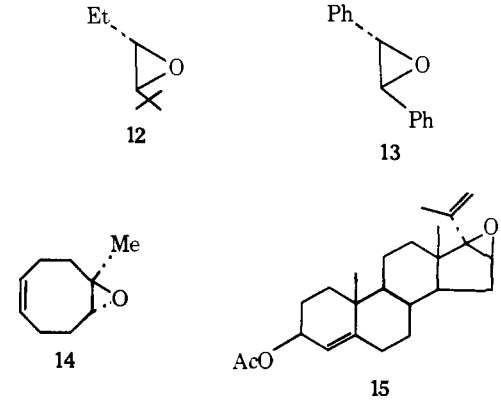


after column chromatographic purification. Likewise, in sharp contrast to homogeneous acidic solvolysis of olefinic epoxide **10** which gave bicyclic products in 20% yield, acetic acid doped alumina gave no bicyclic products (eq 13). These results support the notion that nucleophilic opening of epoxides by RZH-doped alumina is a concerted and not a stepwise process.[15,16]

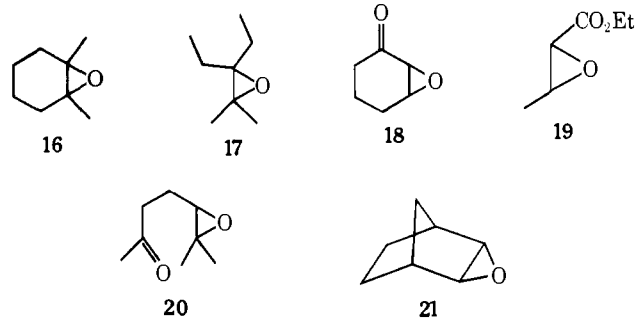


Miscellaneous Epoxides. Epoxides which fail to undergo nucleophilic opening by RZH-doped alumina are of two types: (1) those which are inert (i.e., starting epoxide recovered) and (2) those which react but form products lacking the RZ group. Epoxides inert to RZH-doped alumina include hindered epoxides **12–15.** Presumably the structural environments of the oxirane unit are too encumbered to allow effective oxygen interaction with the Lewis acid sites on the alumina surface.[17] Epoxides **12–15** are recovered intact even after prolonged exposure to RZH-doped alumina.

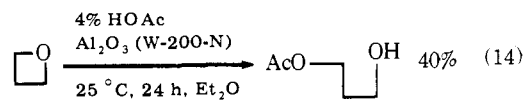
Scheme IV. Epoxides Inert to RZH-Doped Alumina



Epoxides which react on RZH-doped alumina but which form mainly products lacking the RZ group include tetrasubstituted epoxides **16** and **17,** epoxy carbonyl compounds **18–20,** and norbornene oxide **21;** in each case a mixture of products is formed, the main components of which appear to lack the RZ group. These epoxides **16–21** apparently undergo rearrangements faster than nucleophile incorporation on alumina.



Finally, oxacyclobutane reacted with acetic acid doped alumina to give 3-hydroxypropyl acetate in 40% yield (eq 14).



General Comments. Based on a series of control experiments, the following generalizations are important: (1) although Woelm-200 *acidic* and *basic* alumina also gave results similar to those with W-200-*neutral* alumina, W-200-neutral alumina gave ring-opened products uniformly in higher yields; (2) W-200-N-*Dehydrated* alumina offered no general advantage over the commercial W-200-N alumina; (3) reproducible results were obtained even when different batches of Woelm W-200-N alumina were used over the course of a 1-year period; (4) increasing to 6% or decreasing to 2% the amount of doping agent did not raise the yields of ring-opened products; (5) the relative reactivity of symmetrical cycloalkene oxides decreased in the following order of ring sizes: 6 > 8 > 12; and (6) the relative reactivity of doping agents on alumina decreased in the following order: ROH ≈ HOAc ≫ RNH_2.

These epoxide openings effected by alcohols, thiols, benzeneselenol, amines, and acetic acid on commercial W-200-N alumina constitute a new synthetic method. This new procedure is characterized by its clean formation usually of only one

product, by its practical aspects (direct use of commercially available alumina, room temperature conditions, multigram scale reactions, easy product isolation), by its high chemoselectivity, and by its stereospecificity.

Experimental Section

Materials. All substrates, reagents, and standards were the best commercially available reagent grades or were prepared from such. Diethyl ether (Baker reagent grade, anhydrous) was used as received and stored under nitrogen. All other solvents and doping agents were reagent grade and were dried where necessary before use (usually by distillation from the appropriate metal hydride).

Alumina: Woelm 200 neutral, acidic, and basic aluminum oxide (Activity Grade Super I) was purchased from ICN Pharmaceuticals, Inc. (Cleveland, Ohio).

Methods. Preparative vapor phase chromatography (VPC) was performed on a Varian Aerograph Model 90-P3 with a thermal conducitvity detector. Columns used follow (column, liquid phase, solid support): A, 20 ft × ¼ in., 20% SE-30, Chromosorb W (45/60); B, 20 ft × ¼ in., 20% Carbowax C-20M, Chromosorb W (45/60). Column conditions are reported as column (by letter) and temperature. A carrier flow rate of 60–80 mL/min was used throughout.

High-pressure liquid chromatography (HPLC) was performed on a Waters Model 6000A liquid chromatograph, using a Beckman 25 UV–visible spectrometer.

Preparative thin layer chromatography (TLC) was done on 20 × 20 cm Analtech plates coated with 1000 μm of silica gel GF. Visualization of developed plates was by fluorescence quenching (254 nm). Column chromatography was done with Baker chromatographic grade silica gel (60–200 mesh) used as received.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 457-A instrument using thin liquid films or solvent-compensated solutions. Absorptions are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration.

Proton nuclear magnetic resonance (NMR) spectra were run on a JOEL MH-100 instrument using solutions in carbon tetrachloride, deuteriochloroform, or tetradeuteriomethanol with tetramethylsilane as an internal standard. Peak positions are reported as downfield shifts in parts per million (δ) from Me_4Si. Resonances are characterized as a singlet (s), doublet (d), triplet (t), multiplet (m), or a broad band (b). Melting points were taken on a Mel-Temp apparatus and are uncorrected.

General Procedure for Alumina Reactions. A one-neck round-bottom flask equipped with a magnetic stir bar is dried in an oven at ~110 °C for 1 h. The flask is stoppered while hot, allowed to cool, and then tared. The appropriate alumina is then transferred under a dry atmosphere in a glove bag to the flask. The weight of the alumina is determined and enough solvent added to form a slurry. To the stirred slurry is added enough doping agent to equal 4% by weight of the alumina used. Liquid doping agents are measured out by volume (±2%), solids by weight. After 5 min, the substrate (1 mmol of epoxide per 7.5 g of alumina, ±5%) is added in 2–3 mL of solvent. After the appropriate amount of time has elapsed, the slurry is poured into 50–100 mL of methanol and allowed to stand for 4 h. The mixture is then filtered through a Celite pad and the solid washed well with methanol. The solvent is removed from the filtrate in vacuo to give the product.

In the case of acetic acid dopings the crude product is taken up in diethyl ether and washed with saturated aqueous bicarbonate, the organic layer dried over potassium carbonate, and the solvent removed in vacuo to give the intial product mentioned.

In the case of thiophenol dopings enough 1 N methanolic potassium hydroxide is added to the crude filtrate to neutralize the remaining thiophenol. This is then poured into water and extracted three times with diethyl ether. The organic layer is dried over potassium carbonate and the solvent removed in vacuo to give the initial product mentioned.

Cyclohexene Oxide on Thiophenol-Doped Alumina. Cyclohexene oxide (0.1182 g, 1.21 mmol) was allowed to react in diethyl ether with 8.808 g of W-200-N-Dehydrated alumina doped with thiophenol (0.35 g, 3.2 mmol) for 10 min at room temperature. Workup gave 0.3596 g of yellow oil which was placed on a column of 27 g of silica gel in hexane. Elution gave 0.0904 g of diphenyl disulfide: NMR (CCl_4) δ 7.0, 7.2. Continued elution with chloroform gave 0.1751 g (70%) of *trans*-2-thiophenoxycyclohexanol: bp 136–140 °C (1.5 mmHg) (lit.[18] 139 °C (2 mmHg)); NMR ($CDCl_3$) δ 1.2, 1.6, 2.0 (b, CH_2, 8 H), 2.7 (m, CHS, 1 H), 3.2 (s, OH, 1 H), 3.2 (m, CHO, 1 H), 7.1, 7.3 (b, PhH, 5 H); IR (thin film) 3400, 3040, 1580, 1060 cm^{-1}; mass spectrum *m/e* 208 (parent, molecular ion).

Cyclohexene Oxide on Allyl Alcohol Doped Alumina. Cyclohexene oxide (1.0439 g, 10.6 mmol) was allowed to react in diethyl ether with 80.4 g of W-200-N-Dehydrated alumina doped with allyl alcohol (3.22 g, 55.5 mmol) for 10 min at room temperature. Workup gave 1.7320 g of a liquid which was distilled to give 0.9675 g (57%) of *trans*-2-allyloxycyclohexanol: bp 45–45.5 °C (0.2 mmHg) (lit.[19] 59 °C (0.5 mmHg)); NMR ($CDCl_3$) δ 1.2, 1.6, 2.0 (m, CH_2, 8 H), 2.9 (s, OH, 1 H), 3.1 (m, CHOC, 1 H), 3.4 (m, CHOH, 1 H), 4.0 (m, $OCH_2C{=}$, 2 H), 5.2 (b, ${=}CH_2$, 2 H), 5.8 (m, $CH{=}$, 1 H); IR (CCl_4) 3580, 3450, 1230, 1070 cm^{-1}. Because of the discrepancy between the observed and reported boiling points, a combustion analysis was obtained. An analytical sample was prepared by molecular distillation (60 °C, 0.2 mmHg). Anal. Calcd for $C_9H_{16}O_2$: C, 68.35; H, 10.13. Found: C, 68.35; H, 10.48.

Cyclohexene Oxide on Diethylamine-Doped Alumina. Cyclohexene oxide (1.4091 g, 14.4 mmol) was allowed to react in diethyl ether with 106.3 g of W-200-N-Dehydrated alumina doped with diethylamine (4.25 g, 58.2 mmol) for 10 min at room temperature. Workup gave 1.5490 g (63%) of *trans*-2-*N,N*-diethylaminocyclohexanol: NMR ($CDCl_3$) δ 1.0 (t, CH_3, 6 H), 1.1, 1.7, 2.1 (b, CH_2, 8 H), 2.2 (m, CH_2N, 4 H), 2.8 (m, CHN, 1 H), 3.3 (m, CHO, 1 H), 3.9 (s, OH, 1 H); IR ($CHCl_3$) 3400, 1070 cm^{-1}. This material was distilled, bp 102–103 °C (13 mmHg) (lit. 105–110 °C (15 mmHg)), to give 1.3087 g (53%) of *trans*-2-*N,N*-diethylaminocyclohexanol.

General Procedure for Reactions of Epoxides with Columns of Doped Alumina. Alumina is weighed out, a slurry formed, and 4% of the doping agent added as outlined in the general procedure for alumina reactions. Meanwhile a chromatographic column and an addition funnel are dried at 110 °C. The addition funnel is then placed on top of the column via a one-hole rubber stopper and the assembly cooled under a drying tube of calcium chloride. The alumina column is then constructed in the same fashion as a normal column for chromatography, taking care to limit the exposure of the alumina to air. A solution of the doping agent and the epoxide is then placed in the addition funnel. Solvent is eluted from the column at a rate of between 0.5 and 1.0 mL/min and is added to the column at the same rate so as to maintain a constant head pressure. After the epoxide solution has been completely added, an additional 100 mL of solvent is passed over the column to elute any remaining product.

Cyclohexene Oxide on a Column of Methanol-Doped Alumina. A solution of cyclohexene oxide (1.96 g, 20 mmol) and methanol (2.18 g, 40 mmol) was passed over a column of 10.99 g of W-200-N-Dehydrated alumina doped with methanol (4%, 0.44 g). The solvent was removed in vacuo to give 2.5485 g (98%) of *trans*-2-methoxycyclohexanol whose NMR and IR spectra and VPC retention time were identical with those of an authentic sample.

Reaction of Cyclohexene Oxide and Allyl Alcohol on a Small Amount of Alumina. As in the general procedure, 0.44 g of W-200-N alumina was weighed out. To this was added a solution of cyclohexene oxide (1.96 g, 20 mmol) and allyl alcohol (5.8 g, 100 mmol) in 10 mL of diethyl ether. The mixture was stirred for 2 weeks at ambient temperature. Filtration followed by removal of volatile material in vacuo and molecular distillation of the residue (150 °C, 12 mmHg) gave 1.59 g (51%) of *trans*-2-allyloxycyclohexanol whose NMR and IR spectra were identical with those of an authentic sample.

Cyclopentene Oxide on Acetic Acid Doped Alumina. Cyclopentene oxide (0.0797 g, 0.95 mmol) was allowed to react in diethyl ether with 6.995 g of W-200-N-Dehydrated alumina doped with acetic acid (0.28 g, 4.7 mmol) for 10 min at room temperature. Workup gave 0.0840 g (61%) of *trans*-2-hydroxycyclopentyl acetate: NMR ($CDCl_3$) δ 1.7 (m, CH_2, 6 H), 2.05 (s, CH_3, 3 H), 4.0 (s, OH, 1 H), 4.1 (m, *CH*OH, 1 H), 4.8 (m, CHOC, 1 H); IR (thin film) 3440, 1728, 1260, 1035 cm^{-1}. An analytical sample was prepared as the *p*-nitrobenzoate: mp 79.5–80.5 °C (petroleum ether/diethyl ether); mass spectrum *m/e* 293 (parent, molecular ion). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.12. Found: C, 57.34; H, 5.17.

Cycloheptene Oxide on *n*-Butylamine-Doped Alumina. Cycloheptene oxide (0.1146 g, 1.023 mmol) was allowed to react in diethyl ether with 7.876 g of W-200-N alumina doped with *n*-butylamine (0.32 g, 4.1 mmol) for 24 h at room temperature. Workup gave 0.1602 g of an oil which was molecularly distilled (130 °C, 12 mmHg) to give 0.1213 g (64%) of *trans*-2-*n*-butylaminocycloheptanol: NMR

($CDCl_3$) δ 0.9 (t, CH_3), 1.5 (b, CH_2), 2.6 (s, NH, OH), 2.0–2.8 (b, CH_2NCH), 3.2 (m, CHO); IR (thin film) 3450–3100, 1460 cm^{-1}; mass spectrum *m/e* 185 (parent, molecular ion). An analytical sample was obtained as the hydrochloride, mp 218–220 °C dec (ethanol). Anal. Calcd for $C_{11}H_{24}ClNO$: C, 59.59; H, 10.84; N, 6.32. Found: C, 59.98; H, 10.75; N, 6.44.

***cis*-Cyclooctene Oxide on Acetic Acid Doped Alumina.** *cis*-Cyclooctene oxide (0.2509 g, 1.99 mmol) was allowed to react in diethyl ether with 14.900 g of W-200-N alumina doped with acetic acid (0.60 g, 10.0 mmol) for 48 h at room temperature. Workup gave 0.3245 g of an oil which was molecularly distilled (155 °C, 15 mmHg) to give 0.3039 g (82%) of *trans*-2-hydroxycyclooctyl acetate: NMR (CCl_4) 1.3–2.2 (b, CH_2, 12 H), 2.0 (s, CH_3, 3 H), 3.3 (s, OH, 1 H), 3.7 (m, C*H*OH, 1 H), 4.7 (m, CHOC, 1 H); IR (thin film) 3460, 1735, 1720, 1250, 1025 cm^{-1}; mass spectrum *m/e* 186 (parent, molecular ion). The NMR and IR spectra were identical with those of an authentic sample.

***trans*-Cyclododecene Oxide on Acetic Acid Doped Alumina.** *trans*-Cyclododecene oxide (0.3247 g, 1.78 mmol) was allowed to react in diethyl ether with 12.965 g of W-200-N alumina doped with acetic acid (0.52 g, 8.6 mmol) for 94 h at room temperature. Workup gave 0.3659 g of an oil. Column chromatography (50:50 diethyl ether:petroleum ether) gave 0.0683 g (20%) of recovered starting material, 0.0062 g (2%) of 2-cyclododecen-1-ol, and 0.2999 g (69%) of *cis*-2-hydroxycyclododecyl acetate: NMR (CCl_4) δ 1.35 (b, CH_2, 29 H), 2.0 (s, CH_3, 3 H), 2.6 (s, OH, 1 H), 3.7 (m, C*H*OH, 1 H), 4.9 (m, CHOC, 1 H); IR (thin film) 3440, 1740, 1720, 1245, 1030 cm^{-1}; mass spectrum *m/e* 199 (molecular ion − $OCCH_3$). Saponification (aqueous potassium hydroxide, methanol) gave 0.2050 g of *cis*-1,2-cyclododecanediol as white needles, mp 157–159 °C (lit.[20] *cis*- 159–160 °C, *trans*- 105–106 °C).

***trans*-3-Hexene Oxide on Acetic Acid Doped Alumina.** *trans*-3-Hexene oxide (0.1122 g, 1.122 mmol) was allowed to react in diethyl ether with 8.1 g of W-200-N alumina doped with acetic acid (0.32 g, 5.3 mmol) for 1 h at room temperature. Workup gave 0.1364 g of an oil with was molecularly distilled (130 °C, 20 mmHg) to give 0.1065 g (59%) of *erythro*-3-hydroxy-4-hexyl acetate: NMR (CCl_4) δ 0.9 (t, CH_3, 6 H), 1.5 (m, CH_2, 4 H), 2.0 (s, CH_3, 3 H), 2.9 (s, OH, 1 H), 3.5 (m, C*H*OH, 1 H), 4.7 (m, CHOC, 1 H); IR (thin film) 3440, 1730, 1250, 1015 cm^{-1}. Saponification of the ester (aqueous potassium hydroxide, 2-propanol) followed by sublimation (50 °C, 0.5 mmHg) gave 0.0245 g of *erythro*-3,4-hexanediol, mp 87–88 °C (lit.[21] 88 °C).

1-Methylcyclohexene 1,2-Oxide on Thiophenol-Doped Alumina. 1-Methylcyclohexene 1,2-oxide (0.1200 g, 1.07 mmol) was allowed to react in diethyl ether with 7.759 g of W-200-N-Dehydrated alumina doped with thiophenol (0.31 g, 2.8 mmol) for 10 min at room temperature. Workup gave 0.2590 g of yellow oil which was placed on a column of 13 g of silica gel. Elution with hexane gave 0.0773 g of diphenyl disulfide, mp 56–57 °C (lit.[22] mp 60–61 °C). Elution with diethyl ether gave 0.1516 g (64%) of *t*-2-thiophenoxy-1-methyl-*r*-cyclohexanol: NMR ($CDCl_3$) δ 1.2–2.1 (b, CH_2, 8 H), 1.25 (s, CH_3, 3 H), 2.6 (s, OH (D_2O exch), 1 H), 3.0 (m, CHS, 1 H), 7.1–7.4 (b, PhH, 5 H); IR (thin film) 3420, 3050, 1580, 1125, 745 cm^{-1}; $n^{23}D$ 1.5688. An analytical sample was obtained by preparative VPC (column A, 195 °C) followed by molecular distillation (130 °C, 1 mmHg), mass spectrum *m/e* 222 (parent, molecular ion). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 69.91; H, 8.31.

2,3-α-Epoxy-5α-cholestane on Benzeneselenol-Doped Alumina. 2,3-α-Epoxy-5α-cholestane (0.2657 g, 0.69 mmol) was allowed to react in diethyl ether with 11.266 g of W-200-N-Dehydrated alumina doped with benzeneselenol (0.45 g, 2.9 mmol) for 10 min at room temperature. Workup gave 0.6500 g of a yellow solid. Column chromatography gave 0.3535 g of diphenyl diselenide and 0.2718 g (72%) of β-2-phenylselenyl-5α-cholestan-3β-ol which slowly crystallized: mp 124–130 °C; NMR (CCl_4) δ 2.1 (s, OH), 3.2 (m, CHSe), 3.9 (m, CHO), 7.2, 7.4 (b, PhH); IR (KBr pellet) 3340, 3020, 1570, 995, 725 cm^{-1}. The NMR and IR spectra were identical with those of an authentic sample.

***cis,cis*-1,5-Cyclooctadiene Monooxide on Acetic Acid Doped Alumina.** *cis,cis*-1,5-Cyclooctadiene monooxide (0.2009 g, 1.62 mmol) was allowed to react in diethyl ether with 11.431 g of W-200-N alumina doped with acetic acid (0.46 g, 7.7 mmol) for 1 h at room temperature. Workup gave 0.2952 g of an oil which was molecularly distilled (160 °C, 20 mmHg) to give 0.1929 g (65%) of *trans*-2-hydroxy-*cis*-5-cyclooctenyl acetate: NMR (CCl_4) δ 1.7 (b, CH_2, 2 H), 2.0 (s, CH_3, 3 H), 2.05 (s, OH, 1 H), 2.0–2.7 (b, CH_2, 6 H), 3.8 (m, C*H*OH, 1 H), 4.9 (m, CHOC, 1 H), 5.6 (m, CH=CH, 2 H); IR (thin film) 3460, 1730, 1250, 1025 cm^{-1}. An analytical sample was obtained as the *p*-nitrobenzoate, mp 96–97 °C (diethyl ether). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.31; H, 5.70; N, 4.20. Found: C, 61.75; H, 5.85; N, 4.07.

***cis,cis*-1,5-Cyclooctadiene Monooxide on *n*-Butylamine-Doped Alumina.** *cis,cis*-1,5-Cyclooctadiene monooxide (0.1107 g, 0.893 mmol) was allowed to react in diethyl ether with 6.724 g of W-200-N alumina doped with *n*-butylamine (0.27 g, 3.7 mmol) for 24 h at room temperature. Workup gave 0.1362 g of an oil which was placed on a column of 3.5 g of silica gel. Elution with 25:75 diethyl ether–petroleum ether gave 0.0061 g (5.5%) of starting material. Elution with 5:95 methanol–ethyl acetate gave 0.1188 g (68%) of *trans*-2-*n*-butylamino-*cis*-5-cycloocten-1-ol: NMR ($CDCl_3$) δ 0.9 (t, CH_3, 3 H), 1.4 (b, CH_2, 8 H), 2.2 (m, =CCH_2), 2.5 (m, CH_2N) 2.7 (m, CHN), 3.25 (s, OH, NH, 2 H), 3.3 (m, CHO, 1 H), 5.6 (m, CH=CH, 2 H); IR ($CHCl_3$) 3660, 3405, 1650, 1090 cm^{-1}; mass spectrum *m/e* 197 (molecular ion). An analytical sample was obtained as the hydrochloride, mp 142–143 °C (ethyl acetate/ethanol). Anal. Calcd for $C_{12}H_{24}ClNO$: C, 61.67; H, 10.28; N, 5.99. Found: C, 62.09; H, 10.34; N, 5.95.

Oxacyclobutane on Acetic Acid Doped Alumina. Oxacyclobutane (0.0778 g, 1.34 mmol) was allowed to react in diethyl ether with 9.53 g of W-200-N alumina doped with acetic acid (0.38 g, 6.4 mmol) for 24 h at room temperature. Workup gave 0.0633 g (40%) of 3-hydroxypropyl acetate: NMR (CCl_4) δ 1.8 (t, CH_2), 2.0 (s, CH_3), 2.8 (s, OH), 3.6 (t, CH_2OH), 4.2 (t, CH_2OC); IR (CCl_4) 3460, 2960, 1735, 1240, 1050 cm^{-1}; mass spectrum *m/e* 118 (parent, molecular ion).

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Supplementary Material Available: Tables I–V listing physical constants and analytical data for the RZCCOH alcohols discussed in this paper (7 pages). Ordering information is given on any current masthead page.

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Organic Reactions at Alumina Surfaces. Mild and Selective Opening of Arene and Related Oxides by Weak Oxygen and Nitrogen Nucleophiles

Gary H. Posner* and Donald Z. Rogers

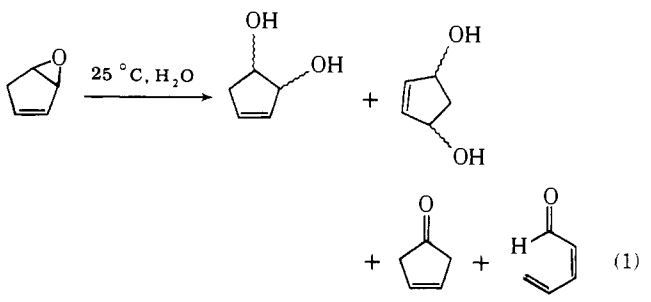
Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received June 13, 1977*

Abstract: Commercially available Woelm 200 basic chromatographic alumina selectively catalyzes the trans opening of both K-region and non-K-region arene oxides by a few equivalents of weak, nonpolarizable oxygen and nitrogen nucleophiles under very mild conditions (25 °C, diethyl ether). Under these conditions nucleophile incorporation competes favorably with aromatization to the corresponding phenol. Vinylic and aryl epoxides are also opened stereo- and regiospecifically by a few equivalents of nucleophiles on neutral alumina.

Metabolism of aromatic hydrocarbons is thought to proceed via arene oxides,[1] and the cytotoxic, mutagenic, and carcinogenic effects of certain polycyclic arenes have been attributed to the covalent binding of the intermediate epoxides to critical cellular macromolecules.[1,2] Much interest, therefore, has been generated concerning the solution chemistry of arene oxides.[3] Recent reports have dealt with the mechanistic details of arene oxide hydrolysis[4] and opening by various nucleophiles;[5] generally, simple arene oxides have been found to undergo aromatization faster than attack by nonpolarizable oxygen and nitrogen nucleophiles.[3] In the accompanying articles, we report that commercially available Woelm 200 chromatographic alumina catalyzes the opening of aliphatic epoxides by a few equivalents of alcohols, thiols, amines, acetic acid, and benzeneselenol.[6] We describe here our finding that this alumina catalyzes trans opening of vinylic epoxides, aryl epoxides, and both K-region and non-K-region arene oxides by a few equivalents of alcohols and amines within 1 h at room temperature.

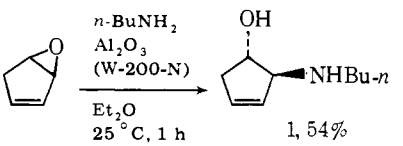
Results and Discussion

Vinylic and Aryl Epoxides. To explore some acid-sensitive and relatively labile oxiranes, we chose two vinylic (cyclopentadiene monooxide and 1,3-cyclohexadiene monooxide) and one aryl epoxide (indene oxide). All three of these epoxides are unusual in that their hydrolysis proceeds via an acid-independent as well as an acid-dependent mechanism.[7] For cyclopentadiene monooxide this acid-independent mechanism leads to rearrangment products as well as diols (eq 1).[8]



(1)

The reactions of cyclopentadiene monooxide with diethyl ether slurries of alumina which had been first "doped" with a few equivalents of 1-butanol or acetic acid gave a mixture of many products. Thus, in the 1-butanol and acetic acid doping the rate of rearrangement appears to be faster than that of nucleophilic attack. In contrast, *n*-butylamine doped alumina was successful in opening the epoxide (eq 2). This success



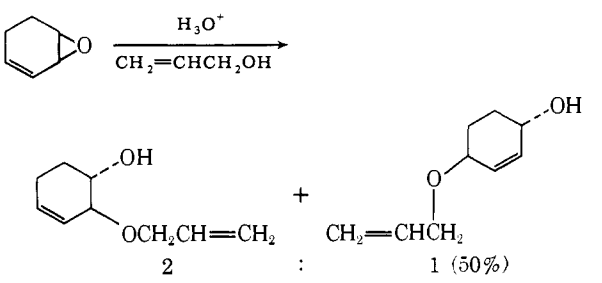
1, 54%

(2)

might be attributed to occupation by the *n*-butylamine of the most acidic sites of the alumina with concomitant reduction in the rate of vinylic epoxide rearrangement.

β-Hydroxy amine **1** was the only product isolated from the reaction shown in eq 2. The regiochemistry of hydroxy amine **1** was assigned from its NMR spectrum, which showed no allylic carbinol proton.

1,3-Cyclohexadiene monooxide reacted not only with alumina carrying a few equivalents of allyl alcohol and *n*-butylamine but also with alumina bearing a few equivalents of acetic acid. In each case, only the homoallylic alcohols **2–4** were obtained and were purified in the yields reported in Scheme I. In our hands, pure allyl ether **2** could be prepared in good yield under *vigorous* homogeneous conditions (sodium in refluxing allyl alcohol), but acid-catalyzed reaction with allyl alcohol gave a mixture of 3,4- and 3,6-dioxygenated cyclohexenes as shown in eq 3. *No 3,6-disubstituted cyclohexenes*



2 : 1 (50%)

(3)