= 2.5 Hz, =CH), 7.5–8.0 (m, 4 H, aromatic H); mass spectrum, m/e (relative intensity) 194 (M$^+$, 100).

Anal. Calcd for $C_{10}H_{10}O_2S$: M_r, 194.0373. Found (high-resolution mass spectrum) M_r, 194.0401.

Registry No. **1d**, 6224-55-1; **1e**, 17347-06-7; **1f**, 87071-05-4; **2b**, 87071-06-5; **3**, 87071-07-6; *threo*-**4**, 87071-08-7; **5**, 78583-20-7; **6**, 87071-09-8; **7**, 87071-10-1; **8**, 87071-11-2; *threo*-**9**, 87071-12-3; *erythro*-**9**, 87071-13-4; (*E*)-**10**, 87071-14-5; 2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide, 14315-13-0; piperidine, 110-89-4.

Copper(I)-Catalyzed Reactions of β,γ-Epoxy Alcohols with Grignard Reagents

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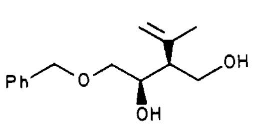
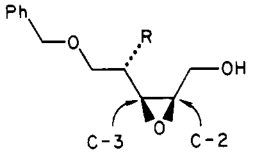
An ongoing synthetic project required the synthesis of diol **1**. A general procedure for the directed cleavage of sterically unbiased epoxy alcohols with copper(I)-catalyzed Grignard reagents will be described. The regiospecific ring opening of epoxy alcohols has been used to great advantage by Kishi and others.[1] Attack on **2** (R = CH_3) by lithium dimethylcuprate takes place specifically and in excellent yield at C-2. The regiochemical preference observed in this case appears to be steric in origin because treatment of **2** (R = H) under identical conditions leads to an indiscriminate reaction in which equal amounts of 1,2- and 1,3-diol are formed.[2] We will show that regioselective reactions at C-2 of **2** and related epoxy alcohols can be observed by judicious choice of reaction conditions.



1



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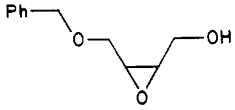

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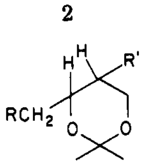

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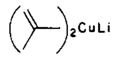
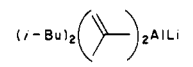
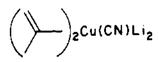
The effect of temperature upon the reaction of **3** with lithium dimethylcuprate in ether was examined. Modest regioselectivity in the desired sense was observed at −20 °C (Table I). Lowering the temperature led to an increase in regioselectivity while greatly diminishing the reaction rate. Diisopropenylcuprate (entry 2) was a more sluggish reagent than dimethylcuprate. An acceptable rate could only be achieved by conducting the reaction at −20 °C. Selectivity and yield were poor. The complex derived from diisobutylaluminum chloride and 2 equiv of 2-propenyllithium[3] (entry 3) showed no selectivity. We were disappointed to find that the higher order cyanocuprate[4] (entry 4) in our hands produced only intractable mixtures of products.

Table I. Reactions of **3** with Carbon Nucleophiles

entry	reagent	conditions	ratio[a] of 1,3-diol:1,2-diol
1	$(CH_3)_2CuLi$	3 equiv, ether; −20 °C, 10 min	1.5:1
		3 equiv, ether; −60 °C, 2 h	2.5:1[b]
2		4 equiv, ether; −20 °C, 4 h; 0 °C, 1 h	2:1
3		4 equiv, hexane; −20 °C, 1 h	1:1[3]
4		4 equiv, THF; −20 °C, 2 h	*c*, ref 4

[a] Ratios were determined by HPLC with a refractive index detector. The ratios determined by product isolation agreed closely with the HPLC ratios. [b] More than 50% of unreacted starting material was also recovered. [c] Complex mixture of products was obtained.

An encouraging result was obtained with the reagent derived from 2-propenylmagnesium bromide and 0.1 equiv of cuprous iodide (Table II). For determination of the scope of the copper-catalyzed Grignard reaction, a series of epoxy alcohol benzyl ethers, **2** (R = H), **4**, and **5**, was prepared, and their reactions with four Grignard reagents were investigated.[5] The choice of epoxy alcohols was made to test the limits of the reaction. All four compounds lack any stereochemical bias for attack of the epoxide and all have potentially troublesome benzyl ethers that could direct the incoming nucleophile to C-3. In all instances the 1,3-diol resulting from nucleophilic attack at C-2 was the major product. The highest selectivity was 7:1, the lowest was 2.2:1. Even in the least selective case the isolated yield of 1,3-diol was 58% so that the method remained preparatively useful. Although it was reasonable to assume inversion of configuration at C-2, alternative mechanisms could not be ruled out.[6] All 1,3-diols were converted to their acetonides **6**.[7] As expected, diols derived from epoxy alcohols **4** and **5** formed acetonides more rapidly than diols derived from **2** and **3**. The vicinal coupling constants for the methine protons were measured by irradiating the exocyclic methylene group of the acetonides in the 300-MHz NMR spectra. All acetonides derived from (*Z*)-epoxy alcohols **2** and **3** had coupling constants of ca. 3 Hz whereas the acetonides derived from **4** and **5** had coupling constants of ca. 10 Hz.[8] These results are consistent with an inversion of configuration at C-2. It seems likely that the epoxy alcohol directs nucleophilic attack at C-2.[1a]

The selectivity of the reaction is maintained only within a narrow range of conditions. Lower temperatures clearly favor the 1,3-diol but diminish the reaction rate. A compromise between selectivity and an acceptable rate is reached by conducting reactions with vinylic Grignard reagents at −20 to −25 °C and reactions with alkyl Grignard

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(1) (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (b) Johnson, M. R.; Kishi, Y. *Ibid.* **1979**, 4347. (c) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (d) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (e) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

(2) Treatment of **2** (R = H) with dimethylcuprate in ether at −40 °C produces a 1:2 ratio of 1,3- and 1,2-diols.

(3) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

(4) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

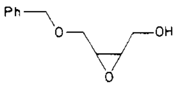
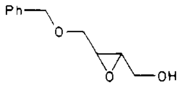
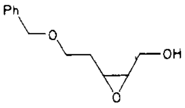
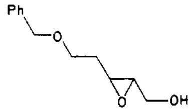
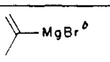
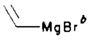
(5) For the preparation of the Grignard reagents, see: Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926.

(6) Equilibration of the epoxy alcohol by base prior to attack by the nucleophile could not be ruled out.[1d]

(7) All compounds gave satisfactory ^{1}H NMR, IR, and mass spectra.

(8) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; pp 286–289, and references cited therein.

Table II. Comparison of Epoxy Alcohols[a]

Grignard reagent	ratio of 1,3-diol:1,2-diol			
	 **3**	 **4**	 **2**	 **5**
 [b]	7:1 87%, 12.5%	c 72%, 0%	4:1 72%, 18%	5.1:1 76%, 15%
 [b]	6.1:1 82%, 13.5%	5.2:1 70%, 13.5%	4.9:1 83%, 17%[d]	4:1 71%, 17.7%
n-BuMgBr[e]	2.6:1 60%, 23%	6:1 75%, 12.5%	3.4:1 68%, 20%	5:1 72%, 14.4%
CH_3MgI[e]	4.8:1 72%, 15%[d]	6:1 72%, 12%[f]	2.2:1 58%, 26%[g]	3.3:1 68%, 20.6%

[a] For all reactions a mixed solvent of tetrahydrofuran and ether, 1:5 to 1:7, was used. Ratios and yields of 1,3-diol:1,2-diol were determined by isolation of both products. [b] Reactions conducted at −20 to −25 °C. [c] None of the 1,2-diol was detected. [d] Yield based on consumed starting material. [e] Reactions conducted at −40 °C. [f] Ratio determined by ^1H NMR. [g] Reaction time was 11 h at −40 °C followed by warming to 23 °C.

reagents at −40 °C. Tetrahydrofuran (THF) was found to be an essential cosolvent. Large amounts of THF inhibited the reaction, possibly because of strong coordination to the metal ions in the reaction medium,[9] but in the absence of THF, mixtures of reaction products were observed. A small percentage of complexing solvent may be necessary to solubilize the reagent.

Our work compliments recent results which show that alanes selectively cleave epoxy alcohols at C-3.[10] The ready availability of enantiomerically pure epoxy alcohols[11] suggests that this procedure will find widespread use in synthesis.

Experimental Section

Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Ultrapure cuprous iodide from Alfa was washed with dry tetrahydrofuran in a Soxhlet extractor for 12 h, was vacuum dried for 8 h, and was stored under argon in a desiccator. Nuclear magnetic resonance (NMR) spectra were recorded either at 100 MHz (Varian XL-100 spectrometer) or at 300 MHz (Oxford magnet, Nicolet data system). Infrared spectra were recorded on a Beckman IR 10 instrument. Electron-impact mass spectra were recorded on a Varian MAT-311 instrument.

General Procedure for Epoxide Ring Opening. To a stirred suspension of 0.57 g (0.03 mol, 0.3 equiv) of cuprous iodide (Alfa, ultrapure) in 100 mL of anhydrous ether under nitrogen at −8 °C was added 0.3 mol of a solution of isopropenyl magnesium bromide in THF (0.43 M, 3 equiv). The light yellow suspension was immediately cooled to −23 °C, and epoxy alcohol **3** (2.0 g, 0.1 mol, 1 equiv) in 5 mL of ether was added slowly via cannula. The yellow heterogeneous mixture was stirred at −23 °C for 8 h. The reaction mixture was partitioned between ether and saturated aqueous NH_4Cl that had been basified to pH 8 by addition of concentrated NH_4OH. The ethereal extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated. The residue was flash chromatographed on silica gel to provide 2.05 g of 1,3-diol (8.67 mmol, 84%) and 0.29 g of 1,2-diol (1.23 mmol, 12%).

^1H NMR of 1,3-diol (**1**) (100 MHz, $CDCl_3$): δ 7.32 (s, 5 H), 4.98 (br s, 1 H), 4.85 (br s, 1 H), 4.54 (s, 2 H), 3.98 (m, 1 H), 3.75–3.40 (m, 4 H), 2.42 (m, 3 H, includes both OH), 1.78 (br s, 3 H). ^1H NMR of 1,2-diol (100 MHz, $CDCl_3$): δ 7.31 (s, 5 H), 4.96 (br s, 1 H), 4.84 (br s, 1 H), 4.50 (s, 2 H), 3.75–2.40 (m, 5 H), 2.51 (m, 1 H), 2.18 (br s, 2 H, both OH), 1.76 (br s, 3 H). The aldehyde derived from cleavage of the 1,2-diol with $NaIO_4$ shows an aldehyde proton in the 100-MHz NMR spectrum at δ 9.57 as a doublet, $J = 2.1$ Hz.

Acknowledgment. We thank the National Institutes of Health (Grant GM 30390-01) for generous financial support. Support from the American Cancer Society, administered by the Cancer Center of Hawaii, Grant IN-145, is also acknowledged. NSF Grant CHE 81-00240 supported the purchase of the 300-MHz NMR spectrometer.

Registry No. **1**, 87116-66-3; **2**, 73814-97-8; **3**, 87172-27-8; **4**, 84621-89-6; **5**, 87205-38-7; CuI, 7681-65-4; $H_2C{=}C(CH_3)MgBr$, 13291-18-4; $H_2C{=}CHMgBr$, 1826-67-1; *n*-BuMgBr, 693-03-8; CH_3MgI, 917-64-6; $(CH_3)_2CuLi$, 15681-48-8; $[H_2C{=}C(CH_3)]_2CuLi$, 21329-14-6; $(i\text{-Bu})_2[H_2C{=}C(CH_3)]_2AlLi$, 87136-17-2; $[H_2C{=}C(CH_3)]_2Cu(CN)Li_2$, 87136-18-3.

Supplementary Material Available: Experimental details of the preparation of epoxy alcohols **2**–**5** and spectroscopic data of the corresponding acetonides (9 pages). Ordering information is given on any current masthead page.

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[10] Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597. Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377.

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Reaction of Some Azolopyrido[2,3-*d*]pyrimidines with Active Methylene Compounds

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Quinazolines or pteridines react with active methylene compounds in several ways. Quinazolines and some pteridines undergo addition of active methylene compounds across the 3,4-double bond. Many adducts have been isolated,[1] but in a further transformation the pyrimidine part is opened, a nitrogen atom is eliminated, and subsequent ring closure gives a condensed pyridine ring. In this way quinazolines were transformed into quinolines[2]

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[1] E. Hayashi and T. Higashino, *Chem. Pharm. Bull*, **12**, 1111 (1964); E. Hayashi and T. Higashino, *ibid.*, **13**, 291 (1965); T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **26**, 3485 (1978); A. Albert and C. F. Howell, *J. Chem. Soc.*, 1591 (1962); A. Albert and J. J. McCormack, *J. Chem. Soc. C*, 1117 (1966); A. Albert and J. J. McCormack, *ibid.*, 63 (1968).

[2] T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull*, **20**, 1544 (1972).

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