Communications to the Editor

Additions of Organocopper Reagents to Allylic Epoxides

Sir:

The reaction of 3,4-epoxy-1-butene (**1**) with alkyl and aryl Grignard reagents, according to an early report[1] and a patent,[2] results solely in 1,4 addition to give allylic alcohols **2**. However, closer examination of this reaction reveals that generally mixtures of alcohols **2**, **3**, **4**, and **5** (Scheme I) are obtained,[3-5] the relative amounts of which are dependent on the nature of the Grignard reagent (see Table I).

Scheme I

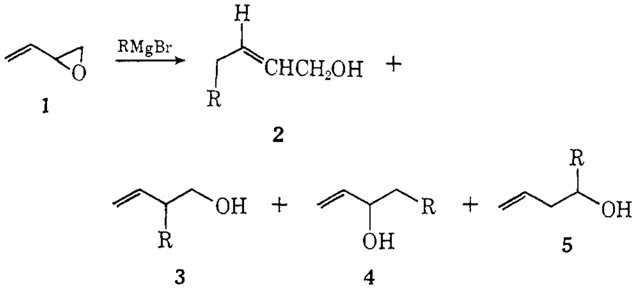


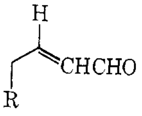
Table I. Results of Reaction of 3,4-Epoxy-1-butene and Grignard Reagents in Diethyl Ether

	Alcohol products, %			
	2	3	4	5[a]
Methyl[b]	Isolated	Isolated		
Ethyl[c]	30[c]	35[c]		22[c]
n-Butyl	56[d,e]	22[d]		19[d]
Phenyl[f]	8	84	8	
α-Naphthyl[g]			58[h]	
α-Thienyl[i]	26[h]			

[a] Derived from initial rearrangement of 3,4-epoxy-1-butene to vinylacetaldehyde and subsequent attack of RMgBr. [b] See ref 3; no yields given. [c] See ref 3 and 4; yield of isolated products. [d] Separated by preparative vpc (15-ft 20% UCON) and characterized by ir and nmr. Total absence of **4** (R = *n*-Bu) was demonstrated by comparison of vpc retention times of authentic **4** (from hexanal and vinyllithium) and the mixture of alcohols. [e] It is interesting that this reaction is also stereoselective for the trans isomer (78:22, trans:cis) as determined by vpc analysis of the corresponding trimethylsilyl ethers. [f] See ref 5; reaction was analyzed by vpc. [g] N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950). [h] Yield of the only isolated product. [i] G. T. Gmitter and F. L. Benton, *J. Amer. Chem. Soc.*, **72**, 4586 (1950); see also ref 1.

In light of the well-documented role of Cu(I) in promoting conjugate additions to α,β-unsaturated carbonyl compounds[6] as well as the reactivity of Cu(I) complexes toward allylic halides[7] and allylic and propargylic acetates,[8] it seemed logical to examine the possibility of a conjugate addition mode of reaction to an allylic epoxide substrate, such as **1**. The realization of this plan is reported here.

As another example of the reaction of a Grignard reagent with **1**, *n*-butylmagnesium bromide was allowed to react with **1** in diethyl ether to give a mixture of three products[9] (see Table I). However, when **1** reacts with di-*n*-butylcopper lithium[10] in diethyl ether or tetrahydrofuran, the product mixture contains 93% of alcohol **2**[11] and 4% of **3**[11a,b] (R = *n*-Bu) along with 3% of an unidentified material (combined yield, 93%). Of interest was the stereochemistry of allylic alcohol **2** (R = *n*-Bu), particularly since reaction of copper(I) complexes with allylic acetates has been reported to be highly stereoselective in a number of cases.[8b] Oxidation of **2** (R = *n*-Bu) with dipyridine–chromium(VI) oxide in methylene dichloride[12] (Collins' reagent) gave cis and trans unsaturated aldehydes **6** (R = *n*-Bu)[13] in the ratio 14:86, respectively.[14] The aldehyde ratio could be obtained both from vpc analysis and from nmr analysis[15] of the aldehyde proton[16] (cis, 10.1 ppm, d, J = 8 Hz; trans, 9.56 ppm, d, J = 8 Hz).



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(1) F. Semeniuk and G. L. Jenkins, *J. Amer. Pharm. Ass., Sci. Ed.*, **37**, 118 (1948).

(2) J. C. Hillyer and J. T. Edmonds, Jr., U. S. Patent 2,583,426 (1952); *Chem. Abstr.*, **46**, P8669*g* (1952).

(3) N. G. Gaylord and E. I. Becker, *Chem. Rev.*, **49**, 413 (1951); for a detailed analysis of the reaction of **1** with methyl Grignard reagents, see the accompanying communication (R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 4979 (1970)). I wish to thank Dr. Carl Johnson for providing me with a copy of his manuscript prior to publication.

(4) R. W. Freedman and E. I. Becker, *J. Org. Chem.*, **16**, 1701 (1951).

(5) C. B. Rose and C. W. Smith, Jr., *Chem. Commun.*, 248 (1969).

(6) For example, see H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966), and references therein.

(7) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967).

(8) (a) P. Rona, L. Tokes, J. Tremble, and P. Crabbe, *Chem. Commun.*, 43 (1969); (b) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970); (c) P. Rona and P. Crabbe, *ibid.*, **90**, 4733 (1968); (d) P. Rona and P. Crabbe, *ibid.*, **91**, 3289 (1969).

(9) This and all subsequently discussed organometallic reactions were done at −10° under an argon atmosphere.

(10) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968).

(11) (a) Separated by preparative vpc; (b) compound gave satisfactory spectral data (ir, nmr); (c) correct elemental analysis obtained.

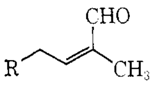
(12) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(13) The 2,4-dinitrophenylhydrazone, recrystallized twice from ethanol, gave mp 125.5–126.5°; lit. mp 125–127° (S. Holand and R. Epsztein, *C. R. Acad. Sci., Ser. C.*, **261**, 4449 (1965)).

(14) Vpc analysis of the trimethylsilyl ethers of **2** (R = *n*-Bu) gave similar values for the cis:trans ratio.

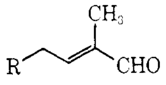
(15) Spectrum obtained using a Varian T-60 spectrometer and deuteriochloroform as solvent with tetramethylsilane as internal reference.

(16) Differences in chemical shift for the aldehyde proton in α,β-unsaturated aldehydes have been observed previously for the cis and trans isomers, i and ii; *e.g.*, K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968); A. F. Thomas and M. Ozainne, *Chem. Commun.*, 46 (1969); A. F. Thomas, *J. Amer. Chem. Soc.*, **91**, 3281 (1969).



i

δ_{CHO} *ca.* 10.1 ppm



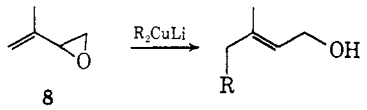
ii

δ_{CHO} *ca.* 9.3 ppm

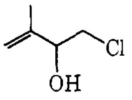
Diphenylcopper lithium[17] in ether–benzene, 5:1, and **1** gave a mixture of **2**[11b,c] (85%, $R = C_6H_5$) and **3**[11b] (15%, $R = C_6H_5$) in an overall yield of 85%. Oxidation of **2** ($R = C_6H_5$) with Collins' reagent to aldehyde **6** ($R = C_6H_5$) and nmr analysis proved the stereoselectivity of the addition again for the trans alcohol **2** over the cis, 90:10. In this instance, the ratio could be determined not only from the aldehyde signal (cis, 10.3 ppm, d, $J = 8$ Hz; trans, 9.58 ppm, d, $J = 8$ Hz) but also from the benzylic methylene (cis, 3.97 ppm, d, $J = 7$ Hz; trans, 3.65 ppm, d, $J = 7$ Hz). This result is again in marked contrast to the reaction of **1** with the corresponding Grignard reagent, phenylmagnesium bromide[5] (see Table I).

A useful extension of this reaction provides a direct method for addition of an isoprenyl unit in a highly stereoselective manner to form the allylic alcohol terminus of many naturally occurring acylic terpenes (see Scheme II). To this end, chloroacetaldehyde was treated with isopropenylmagnesium bromide in tetrahydrofuran to give the relatively unstable 4-chloro-2-methyl-1-buten-3-ol[11b] (**7**; 3,5-dinitrobenzoate,[11b,c] mp 65–66°). Methanolic potassium carbonate action on **7** gave the desired 3,4-epoxy-2-methyl-1-butene (**8**) [ν_{max}^{film} 3065, 1650, 890 cm^{-1} ($H_2C{=}C$); nmr ($CDCl_3$) 1.63 (3 H, d, $J = 1$ Hz, $CH_3C{=}C$), 2.78 (2 H, m, $-CH_2O-$), 3.38 (1 H, m, $=CCHO-$), and 5.03 and 5.17 ppm (2 H, $H_2C{=}C$). *Anal.* Calcd for C_5H_8O: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.51] purified by preparative vpc (15-ft 10% UCON 75-H-90,000; column temperature, 100°). Addition of **8** (1 equiv) to an ether solution of 5 equiv of lithium dimethyl cuprate (0.33 M in $(CH_3)_2CuLi$) at −10° under argon led immediately to allylic alcohol **9**[11b] ($R = CH_3$),[18] again stereoselectively for the trans alcohol product (ratio 92:8). These allylic alcohols were identified (ir, nmr, and vpc) with authentic samples obtained by lithium aluminum hydride reduction of the ester isomers **10**[19] prepared from 2-butanone and sodium triethylphosphonoacetate.

Scheme II



8 **9**



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Thus, when organocopper reagents are utilized for addition to unsaturated epoxide systems, 1,4 addition predominates in a reaction stereoselective for the trans allylic alcohol.

Acknowledgments. Acknowledgment is made to Mr. Loren Dunham of Zoecon Corporation for advice and assistance in the preparative vpc separations, and to Dr. E. E. van Tamelen at Stanford University for providing facilities to complete this work.

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Received April 22, 1970

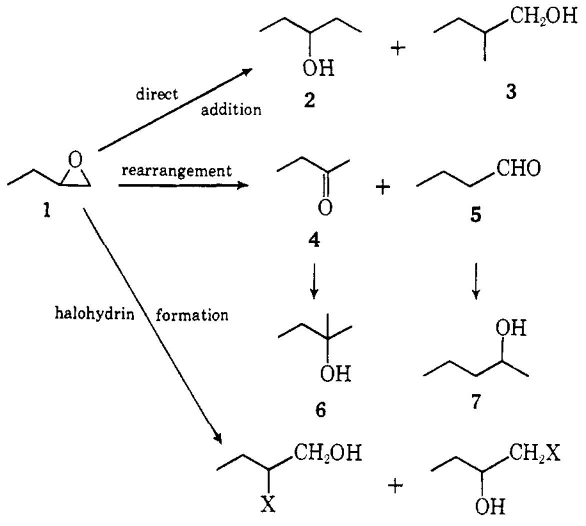
A Comparison of the Reactions of Methylmagnesium, Methyllithium, and Methylcopper Reagents with 1,2-Epoxybutane and 3,4-Epoxy-1-butene

Sir:

We have recently described the nucleophilic ring-opening reactions of oxiranes by organocopper reagents.[1] The synthetic potential of these reactions has encouraged us to make a detailed comparative analysis of the reactions of a simple and a vinyl oxirane with a variety of metallomethyl reagents. The principal substrates chosen for this study were 1,2-epoxybutane and 3,4-epoxy-1-butene.

Organometallic reagents are unique in that they may act as nucleophiles (or bases) or as Lewis acids. In the reactions with oxiranes this ambivalent character can lead to three competing mechanistic pathways, particularly in the case of the Grignard reagents.[2] Possible products resulting from the reactions of metallomethyl reagents with 1,2-epoxybutane (**1**) are shown in Scheme I.

Scheme I



8 (mixture)

The product distributions from the reactions of 1,2-epoxybutane with some metallomethyl reagents are summarized in Table I.[3] An inspection of the results shows that dimethylmagnesium, methyllithium, and lithium dimethylcuprate[4] are far superior to the Grignard reagents with respect to yield of nucleophilic ring-opening product. Lithium dimethylcuprate ap-

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[17] Formed by addition of phenyllithium (Alfa Inorganics, Inc., ether–benzene (30:70) solution) to a suspension of CuI in ether.

[18] A third unidentified product was present in the amount of 4%; overall yield, 97% (determined by vpc using 1-octanol as standard).

[19] Sample was graciously provided by Dr. J. B. Siddall of Zoecon Corporation.

(1) R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 3813 (1970).

(2) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 779 (1959).

(3) Product distribution was observed to be quite sensitive to temperature and mode of addition; see A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part One, A. Weissberger, Ed., Interscience, New York, N. Y. 1964, Chapter 1, p 396.

(4) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. Gilman, R. G. Jones, and L. A. Woods, *ibid.*, **17**, 1630 (1952).