

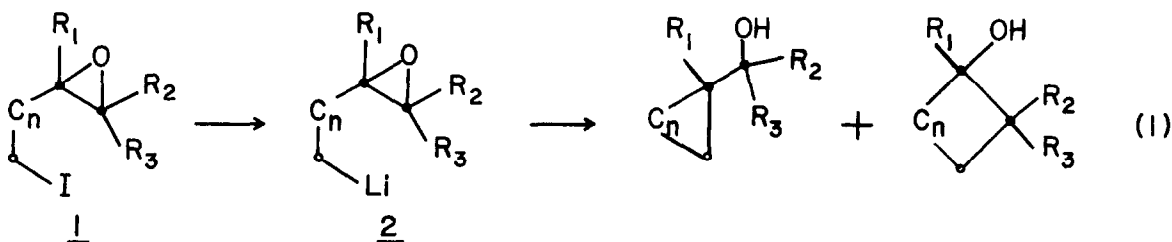
REGIOCHEMISTRY OF THE METAL-HALOGEN EXCHANGE INDUCED
 CYCLIZATION OF ω -IODOEPOXIDES

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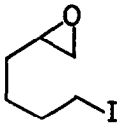
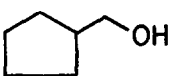
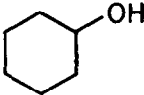
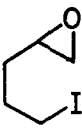
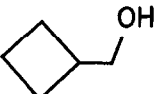
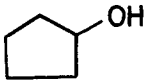
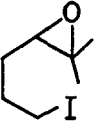
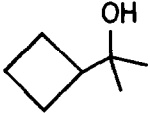
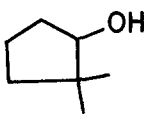
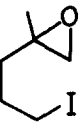
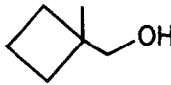
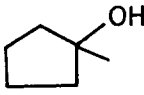
SUMMARY: The regiochemistry of the cyclization reactions of some ω -lithioepoxides as a function of chain length and substitution pattern has been examined. Striking changes in regiochemistry have been observed in the presence of certain Lewis acids and metal halides.

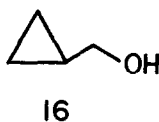
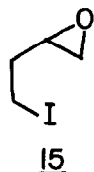
Intramolecular ring-opening reactions of epoxides have received considerable attention in recent years¹ with interest centering on cyclialkylation reactions involving stabilized nucleophilic centers. Less well studied are systems which involve unstabilized carbanionic centers. Bradsher and Reames² and more recently Durst and coworkers³ have shown that intramolecular cyclialkylation reactions of epoxides may be initiated by the lithium-halogen exchange reactions of aromatic halides while Coates and coworkers⁴ similarly have prepared bicyclic carbinols through exchange initiated reactions of bromocyclopropyl epoxides. Very recently Babler and Bauta⁵ described exchange initiated cyclization reactions of 6-bromo and 6-iodo-1,2-epoxyhexane. We wish now to report results of our studies on the regiochemistry of lithium-iodine exchange initiated epoxide openings in a series of ω -iodoepoxides and on the often dramatic effect of additives on the regiochemistry of epoxide opening (eq. 1, Table).



In agreement with Babler and Bauta⁵ we find that **3** undergoes rapid lithium-halogen exchange in Et₂O-pentane at -78°C with *s*-BuLi (or better with 2 equiv. of *t*-BuLi) to give lithiated epoxide **2** (n=3, R=H).⁶ In our hands, this intermediate is relatively stable at -78°C⁷ but rapidly cyclizes upon

TABLE. Metal-Halogen Exchange Induced Cyclization of ω -Iodoepoxides^a

Halide	Additive	(equiv.)	Products ^b	Yield ^c	
 <u>3</u>	—		 <u>4</u>	 <u>5</u>	
	—		10:1	78	
	MgBr ₂	(2)	>100:1	65	
	MeMgBr	(1)	16:1	56	
	BF ₃ ·Et ₂ O	(2.2)	>100:1	40	
CuBr·Me ₂ S	(0.5)	1:4.4	59		
 <u>6</u>	—		 <u>7</u>	 <u>8</u>	
	—		7:1	82	
	MgBr ₂	(2)	1:5.7	60	
	BF ₃ ·Et ₂ O	(2.2)	1:5	24	
CuBr·Me ₂ S	(0.5)	<1:100	30		
 <u>9</u>	—		 <u>10</u>	 <u>11</u>	
	—		18:1	66	
	MgBr ₂	(2)	1:3	49	
BF ₃ ·Et ₂ O	(2.2)	1:2.5	22		
 <u>12</u>	—		 <u>13</u>	 <u>14</u>	
	MgBr ₂	(2)	1:21	45	
—			—	0	

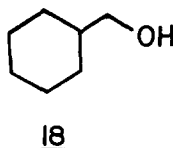
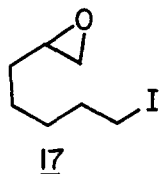


MgBr₂ (2)
CuBr·Me₂S (0.5)

77

77

49



15

a. Halides in Et₂O-pentane (1:1) were treated with 2.2 equiv. of *t*-BuLi at -78°C. Solutions were warmed or treated with additive after 5 min. b. Products were identified by comparison with authentic samples. c. Determined by g.l.c.

warming⁸ to give a 10:1 mixture (78%) of **4** and **5**.⁹ The addition of either 2 equiv. of MgBr₂ or 2.2 equiv. of BF₃·Et₂O¹⁰ results in a dramatic increase in selectivity for 5-membered ring formation while the addition of cuprous salts results in preferential 6-membered ring formation.¹¹

Similarly, treatment of **6** with *t*-BuLi at -78°C followed by warming results in the formation of a 7:1 mixture of carbinols **7** and **8** in 82% yield. The preference for cyclobutane formation in systems of this kind has previously been noted.¹² The addition of MgBr₂, BF₃·Et₂O or CuBr·Me₂S to **2** (*n*=2, R=H) prior to warming results in a reversal of regioselectivity with nearly exclusive cyclopentanol formation in the latter case.

Methyl substitution in **9** increases the preference for 4-membered ring formation giving an 18:1 mixture of **10** and **11**. Again the regiochemistry is reversed when cyclizations are conducted in the presence of MgBr₂ or BF₃·Et₂O. Not surprisingly,⁴ the methyl substitution in **12** results in a strong preference for cyclopentanol (**14**) formation through closure to the least substituted terminal carbon. In this case, carbinols were not obtained when Lewis acids were added.

Epoxide **15** gave only cyclopropyl methanol (**16**) with or without added agents. This is in sharp contrast with results of Erdik¹³ who reported only cyclobutanol formation in cyclizations of the corresponding bromide with Mg or Li in the presence of CuI. In the case of **17** only a low yield of 6-membered ring alcohol **18** was observed with no evidence of any 7-membered ring formation.

While the mode of action of the various additives used to alter the regiochemistry of these cyclizations has not been firmly established, we think it likely that BF₃·Et₂O and MgBr₂ act primarily as Lewis acids to catalyze oxirane opening in the organolithium intermediate (**2**). Catalysis of intermolecular epoxide opening by alkyl lithium reagents with BF₃·Et₂O has recently been reported.¹⁰ Durst

and coworkers³ have previously observed dramatic changes in the regiochemistry of intramolecular epoxide openings in the presence of MgBr₂ (and Grignard reagents) but the effect was shown to be the result of the initial formation of halohydrin derivatives followed by cyclization. This mode of action results in the formation of the larger of the two possible ring sizes in cases involving terminal epoxides in contrast with our results with epoxide **3**. This along with the similarity to the regiochemistry observed with BF₃·Et₂O suggests that MgBr₂ is also acting as a Lewis acid catalyst in our reactions. While the possibility of the formation of an intermediate organomagnesium derivative cannot be ruled out, it is noteworthy that treatment of **3** with Mg in hot THF for prolonged periods gives only **5**, although in very low yield.¹³

In the case of added CuBr organocopper intermediates derived from **2** may be responsible for the general trend towards formation of the larger of the two ring sizes. Similar trends have been observed by Erdik¹³ in haloepoxide cyclizations induced by Mg or Li in the presence of CuI.

Other useful exchange-initiated cyclization reactions are currently under investigation.

Acknowledgment: We thank the National Science Foundation for their support of this work.

References and Notes

1. For a recent review see: J. G. Smith, *Synthesis*, **1984**, 635.
2. C. K. Bradsher and D. C. Reames, *J. Org. Chem.*, **1978**, 43, 3800.
3. (a) K. L. Dhawan, B. D. Gowland and T. Durst, *ibid.*, **1980**, 45, 922; (b) D. Corbel, J. M. Descesare and T. Durst, *Can. J. Chem.*, **1978**, 56, 505; (c) D. Corbel and T. Durst, *J. Org. Chem.*, **1976**, 41, 3648.
4. L. A. Last, E. R. Fretz and R. M. Coates, *ibid.*, **1982**, 47, 3211.
5. J. H. Babler and W. E. Bauta, *Tetrahedron Lett.*, **1984**, 25, 4323.
6. The presence of this intermediate was demonstrated by quenching with MeOH to give 1,2-epoxyhexane (98%) and with (MeO)₂SO₂ to give 1,2-epoxyheptane (46%).
7. Less than 5% cyclization had occurred after 3 hr (at least 20% reported⁵).
8. Highest yields result from rapidly warming solutions to 30-50°C after 5 min exchange time at -78°C.
9. The considerably higher reported⁵ ratio (24:1) is likely the result of an analytical protocol in which a chromatographic purification preceded quantitation.
10. M. J. Eis, J. E. Wrobel and B. Ganem, *J. Am. Chem. Soc.*, **1984**, 106, 3693.
11. In the reported⁵ failure to observe this effect, experimental conditions appear to inadvertently have been employed in which ring closure preceded the addition of CuI.
12. G. Stork and J. F. Cohen, *ibid.*, **1974**, 96, 5270; G. Stork, I. D. Cama and D. R. Coulson, *ibid.*, 5268. See also: J. Y. Lallemand and M. Onaga, *Tetrahedron Lett.*, **1975**, 585.
13. E. Erdik, *Chim. Acta Turc.*, **1981**, 9, 353 (*Chem. Abstr.* 96, 103, 369p).

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