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DIRECT FORMATION OF EPOXYALKYLCOPPER REAGENTS FROM ACTIVATED COPPER AND EPOXYALKYL BROMIDES AND THEIR INTRAMOLECULAR CYCLIZATIONS

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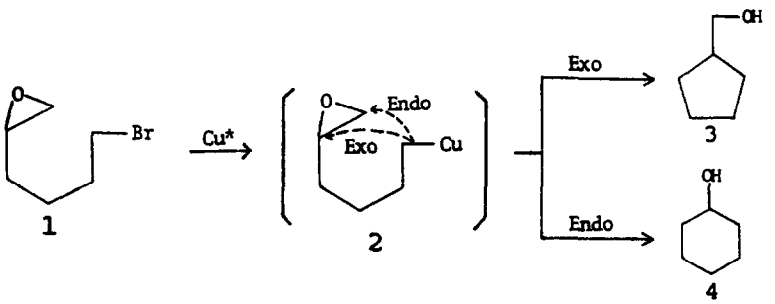
Summary: Epoxyalkylcopper compounds have readily been prepared by the direct oxidative addition of active copper to epoxyalkyl halides. The intramolecular cyclization of the epoxyalkylcopper reagents via an epoxide cleavage process is described. Significantly, many functional groups can be present in the bromoepoxides yielding highly functionalized carbocycles. The regioselectivity of this cyclization is affected by the connecting chain length, substitution pattern, reaction solvent, and the CuI-phosphine complex used to generate the copper.

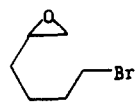
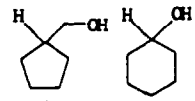
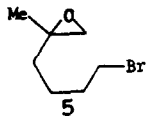
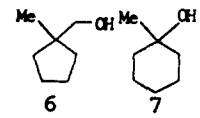
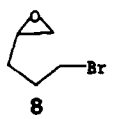
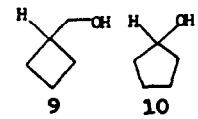
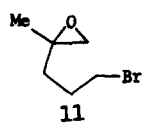
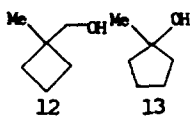
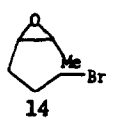
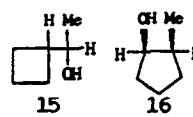
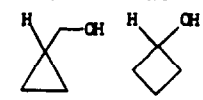
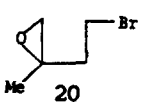
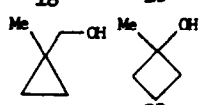
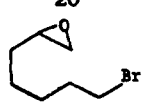
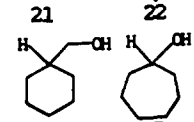
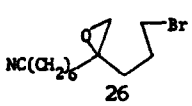
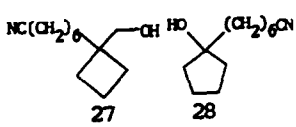
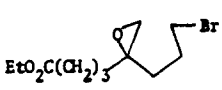
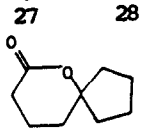
Molecules containing both an epoxide and a nucleophile which can undergo an intramolecular cyclization are synthetically useful. The intramolecular cycloalkylations of epoxynitriles and epoxysulfones via an epoxide cleavage process have been intensively studied during the past decade.[1] More recently, the intramolecular cyclizations of haloepoxides initiated by a lithium-halogen exchange reaction have received considerable attention.[2] Since alkyllithium reagents are generally used for the lithium-halogen exchange, only a few functional groups can normally be tolerated. We have recently reported[3] on the direct formation of organocopper compounds by oxidative addition of highly reactive zerovalent copper to organic halides. Significantly, it has been demonstrated that these organocopper reagents can tolerate a wide range of functionalities, such as nitriles, esters, ketones, chlorides, and epoxides.[3] As part of our continuing interest in this area, we have explored the intramolecular cyclization via an epoxide cleavage process using activated copper (Scheme I).[3a,4]

Scheme I



Treatment of 6-bromo-1,2-epoxyhexane (1) with activated copper in THF at -78 °C formed 5,6-epoxyhexylcopper (2) which cyclized upon warming to give a 1 : 6 mixture of 3 : 4 in 56% yield (entry 1). The predominant formation of cyclohexanol (4) has been observed in the cyclization of 5,6-epoxyhexylcuprate.[5] In contrast, in the absence of Cu(I) salts, the preference of 5-membered ring formation was reported for the lithium-halogen exchange induced cyclization of

Table I. Intramolecular Cyclizations of Bromoepoxides with Activated Copper

Entry	Haloepoxides	PR_3[a]	Solvent	Products[b]	Exo/Endo	%Yield[c]
1	 1	PBu_3	THF	 3 4	1 : 6	56
2		PBu_3	Toluene[d]		1 : 0	45
3		PPh_3	THF		1 : 4	37
4		PPh_3	Toluene[d]		1 : 1.5	62
5	 5	PBu_3	THF	 6 7	0 : 1	35
6		PPh_3	THF		0 : 1	31
7	 8	PBu_3	THF	 9 10	1 : 35	57
8		PPh_3	THF		1 : 37	87(78)[f]
9		PPh_3	Toluene[d]		1 : 7	-[e]
10	 11	PPh_3	THF	 12 13	0 : 1	95
11	 14	PPh_3	THF	 15 16	25 : 1	41
12		PPh_3	Toluene[d]		29 : 1	61
13	 17	PPh_3	THF	 18 19	1 : 0	89(77)[f]
14		PBu_3	THF		1 : 0	51
15		PPh_3	Toluene[d]		6 : 1	-[e]
16	 20	PPh_3	THF	 21 22	1 : 0	96(81)[f]
17		PPh_3	Toluene[d]		1 : 0	-[e]
18	 23	PBu_3	THF	 24 25	0 : 1	10
19		PBu_3	Toluene[d]		0 : 1	(12)
20	 26	PPh_3	THF	 27 28	0 : 1	(83)
21	 29	PPh_3	THF	 30		(50)

[a] $P(n\text{-}Bu)_3$ (2.3 equiv) or PPh_3 (2.0 equiv) was often used. [b] The spectra data of cyclized products are identical to those obtained from authentic samples. All new substances have satisfactory spectroscopic data. [c] Yields reported were mostly determined by gas chromatography analysis. Isolated yields are shown in parenthesis. [d] Activated copper was first generated in THF as usual. Upon the removal of THF in vacuum, toluene was then added. [e] The GC yield could not be determined due to overlap of the product peak with the solvent peak. [f] Isolated as a benzoate derivative; ref. 16.

haloepoxide 1.[6] Significantly, we can reverse the regiochemistry of our cyclization by simply carrying out the reaction in toluene. Cyclization of epoxide 1 with activated copper in toluene gave as the only product, cyclopentylmethanol (3) in 45% yield (entry 2). Also of interest is the decrease in regioselectivity when the PPh_3 complex is used (entries 3 and 4).

Methyl substitution in epoxide 5 gave 1-methylcyclohexanol (7) as a sole product in 35% yield (entries 5 and 6). In accordance with Baldwin's rules,[7] both the endo-mode cyclization to form a 6-membered ring and exo-mode cyclization to give a 5-membered ring are facile processes. Since substitution at the inside position of the epoxide will increase nonbonding interactions for the exo-mode of cyclization, the endo-mode ring closure will then be favored as expected.[8] Similarly, bromoepoxide 11 also gave only 1-methylcyclopentanol (13) in 95% yield (entry 10).

Cyclization of haloepoxide 8 with activated copper in THF yielded a 35 : 1 mixture of cyclopentanol (10) and cyclobutylmethanol (9) in 57% yield (entry 7).[9] It should be pointed out that a small amount of homocoupling of alkyl halides was always observed, when $CuIP(n\text{-}Bu)_3$ was used.[3] The homocoupling of alkyl halides can be completely eliminated by using the PPh_3 complex.[10] The cycloalkylation of epoxide 8 with highly reactive copper, which was generated from the preformed lithium naphthalide and CuI/PPh_3 complex in THF, afforded a 37 : 1 mixture of cyclopentanol (10) and cyclobutylmethanol (9) in excellent yield (87%, entry 8).[4]

Methyl substitution in cis-6-bromo-2,3-epoxyhexane (14) reverses the regioselectivity to undergo preferential exo-mode ring closure to furnish 1-cyclobutylethanol[11] (15) and cis-2-methylcyclopentanol[12] (16) in a 25 : 1 ratio (entry 11). Baldwin's rules were again followed in these medium-size ring cyclizations when both termini of the epoxide are equally substituted.[7,13] Solvent effects are slight for cyclizations of the parent and substituted 5-bromo-1,2-epoxypentane cases (entries 9 and 12).

For a shorter connecting chain, bromoepoxide 17 gave only the 3-membered ring alcohol (18) in 89% yield (entry 13).[14] This observation is also in agreement with Baldwin's rules.[7,13] Cyclization of epoxide 20 gave only the 3-membered ring alcohol (21) in 96% yield (entry 16).

Haloepoxide 23 gave only cycloheptanol (25) in low yield (entries 18 and 19).[15]

Bromoepoxide 26, which contains a cyano group, gave only the 5-membered ring alcohol in 83% yield (entry 20). With an appropriate linkage between epoxide and ester groups, the haloepoxide 29 underwent tandem epoxide-opening/lactonization to form lactone 30 in 50% yield (entry 21).

In conclusion, we have demonstrated that difunctional molecules, containing both an epoxide and a halide, can undergo intramolecular cyclization mediated by the activated copper to generate new carbocycles. Significantly, the haloepoxides can contain other functional groups leading to highly functionalized carbocycles. We are continuing our studies on these intramolecular cyclizations particularly those reactions which exhibit a following second ring closure as entry 21.

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References and Footnotes

1. Smith, J. G. Synthesis 1984, 635 and references cited therein.
2. (a) Cooke, Jr., M. P. and Houpis, I. N. Tet. Lett. 1985, 26, 3643. (b) Babler, J. H. and Bauta, W. E. Tet. Lett. 1984, 25, 4323. (c) Last, L. A.; Fretz, E. R.; Coates, R. M. J.