



Ring opening of disubstituted epoxides linked to a secondary oxygen group with an organocopper reagent



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ABSTRACT

Coupling reactions of epoxide linked to a secondary oxygen group with Gilman reagents were examined. The regiochemical direction depended on whether there is TMS or MOM as a protective group of the secondary alcohol. *anti*-Epoxy alcohol **6** tended to react with Me_2CuLi at the C4 position to generate 1,2-diol **22** as a major component. Epoxide **7** linked to a trimethylsilyloxy group displayed selective formation of 1,3-diol **18**. On the other hand, the reactions of *syn*-epoxy alcohol **12** and the corresponding TMS ether **13** resulted in the selective formation of 1,2-diol **25**.

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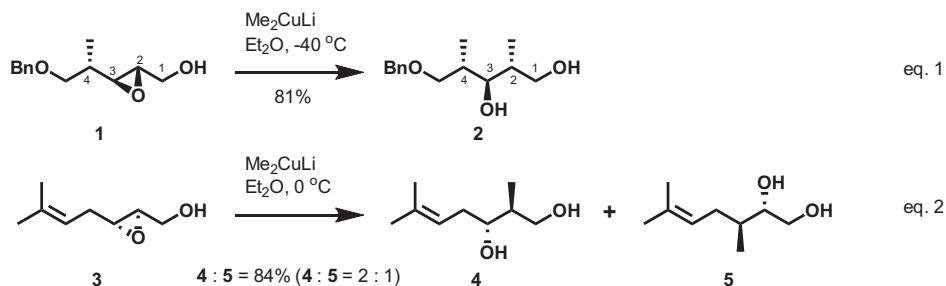
Reactions of organocopper reagents have been considered to be useful synthetic tools in modern organic chemistry.¹ Gilman reagent, which is the most popular organocopper reagent, is soluble in an ethereal solvent and more reactive than the corresponding RCu .^{2,3} It has been frequently used in various types of C–C bond formations such as substitution and conjugated addition.⁴ Epoxides are well known as good substrates that react with Gilman reagent.⁵ Occurring with complete inversion at the reacting center of the epoxide, the substitution has been applied to the syntheses of widespread natural products, particularly those containing a polypropionate part. However, since epoxides can react in either of two directions, their regioselectivity is an important issue. In the case of using epoxides linked to a primary alcohol, the selectivity has been investigated in detail. 2,3-Epoxy alcohols such as **1** having a substituent at the C-4 position react with Me_2CuLi regioselectively to afford 2-methylated 1,3-diol (Scheme 1, Eq. 1).⁶ The regioselectivity is attributed to hindrance from the C-4 methyl group, rather than a chelation effect by the adjacent hydroxyl group. This is because significant regioselectivity cannot be observed in the absence of the alkyl group at the C4 position (Scheme 1, Eq. 2).⁷ On the other hand, there has been very little research on epoxides linked to a secondary alcohol. We report herein critical factors affecting the regioselectivity in the ring opening of epoxides linked to secondary oxygen groups with Gilman reagents: relative configuration of the neighboring

secondary alcohol and protection of the alcohol with a TMS or MOM group.

Ring opening of epoxy alcohols **6–17** with no appendage at the opposite site to a secondary alcohol was first investigated (Table 1). Treatment of *anti*-epoxy alcohol **6** with Me_2CuLi in Et_2O at 0 °C generated a mixture of 1,3-diol **18a** and 1,2-diol **22a** in 75% yield with a ratio of 1:3 (entry 1), which was in contrast to the regioselectivity in Eq. 2 (Scheme 1). Several kinds of additives are well known to accelerate the copper-mediated reaction and control its regio-, stereo-, and chemoselectivity. Interestingly, the coupling reaction of **6** with Me_2CuLi in the presence of TMSCl ⁸ gave a mixture of several silylated compounds, which was further treated with TBAF leading to **18a** and **22a** in 88% yield as a mixture with a ratio of ca. 1.5:1 (entry 2). In the reaction mixture, a part of **6** was probably silylated to form **7**, which undergoes ring opening with a different regiochemical selectivity from that of **6**. We thus performed ring opening of **7** prepared in advance (entry 6). After deprotection of a silyl group, the selectivity was found to increase to 2.5:1 as we expected.⁹ An effect of the TMS group on the regiochemical course was also found when butyl, hexyl, and allyl Gilman reagents were used (entries 3–5 and 7–9). Protection of the hydroxyl group by a bulkier silyl group resulted in a decrease or inversion of regiochemical selectivity (entries 10–13). Thus, small size of the silyl group seems to be essential for selective formation of 1,3-diol. Next, the effects of other types of protecting groups were investigated. Despite the very small size of the protecting group, ring opening of epoxide **10** with a methoxy group resulted in the formation of almost equal amounts of regiochemical isomers

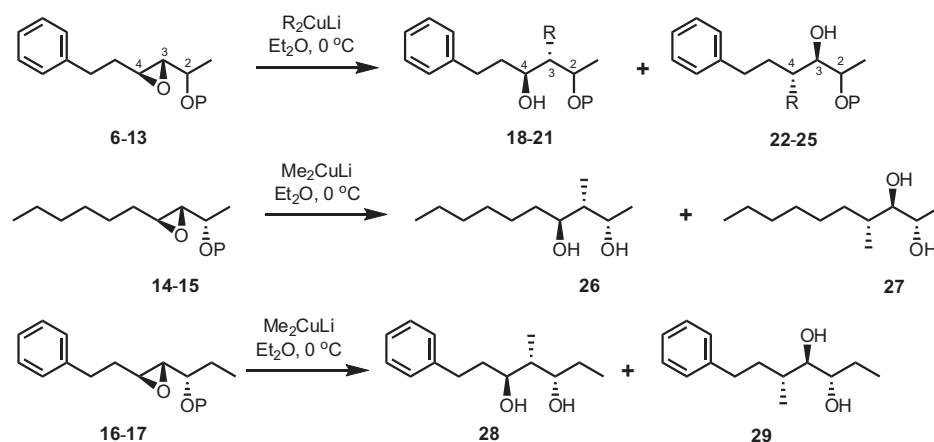
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Scheme 1. Ring opening of epoxides linked to a primary alcohol with Me_2CuLi .

Table 1
Ring opening of epoxides **6–17** with R_2CuLi



Entry	Substrates	Configuration of OP	Reagents	Products	Yields (%)	Ratios (1,3-diol:1,2-diol)
1	6 (P = H)	α	Me_2CuLi	18a, 22a (P = H, R = Me)	75	1:3
2 ^{a,b}	6 (P = H)	α	Me_2CuLi	18a, 22a (P = H, R = Me)	88	1.5:1
3	6 (P = H)	α	<i>n</i> -Bu ₂ CuLi	18b, 22b (P = H, R = <i>n</i> -Bu)	90	1:4.4
4	6 (P = H)	α	(C ₆ H ₁₃) ₂ CuLi	18c, 22c (P = H, R = C ₆ H ₁₃)	87	1:4.4
5	6 (P = H)	α	(CH ₂ = CHCH ₂) ₂ CuLi	18d, 22d (P = H, R = CH ₂ =CHCH ₂)	86	1:1.5
6 ^b	7 (P = TMS)	α	Me_2CuLi	18a, 22a (P = H, R = Me)	81	2.5:1
7 ^b	7 (P = TMS)	α	<i>n</i> -Bu ₂ CuLi	18b, 22b (P = H, R = <i>n</i> -Bu)	60	2.5:1
8 ^b	7 (P = TMS)	α	(C ₆ H ₁₃) ₂ CuLi	18c, 22c (P = H, R = C ₆ H ₁₃)	57	2.2:1
9 ^b	7 (P = TMS)	α	(CH ₂ = CHCH ₂) ₂ CuLi	18d, 22d (P = H, R = CH ₂ =CHCH ₂)	74	2:1
10 ^b	8 (P = TES)	α	Me_2CuLi	18a, 22a (P = H, R = Me)	73	1.5:1
11 ^b	8 (P = TES)	α	<i>n</i> -Bu ₂ CuLi	18b, 22b (P = H, R = <i>n</i> -Bu)	66	1.5:1
12 ^b	9 (P = TBS)	α	Me_2CuLi	18a, 22a (P = H, R = Me)	66	1:1
13 ^b	9 (P = TBS)	α	<i>n</i> -Bu ₂ CuLi	18b, 22b (P = H, R = <i>n</i> -Bu)	78	1:1.5
14	10 (P = Me)	α	Me_2CuLi	19a, 23a (P = Me, R = Me)	86	1:1
15	11 (P = MOM)	α	Me_2CuLi	20a, 24a (P = MOM, R = Me)	92	3:1
16	11 (P = MOM)	α	<i>n</i> -Bu ₂ CuLi	20b, 24b (P = MOM, R = <i>n</i> -Bu)	70	3:1
17	12 (P = H)	β	Me_2CuLi	21a, 25a (P = H, R = Me)	43	1:14
18	12 (P = H)	β	<i>n</i> -Bu ₂ CuLi	21b, 25b (P = H, R = <i>n</i> -Bu)	92	1:20
19 ^b	13 (P = TMS)	β	Me_2CuLi	21a, 25a (P = H, R = Me)	88	1:28
20 ^b	13 (P = TMS)	β	<i>n</i> -Bu ₂ CuLi	21b, 25b (P = H, R = <i>n</i> -Bu)	85	1:20
21	14 (P = H)	α	Me_2CuLi	26, 27	94	1:1.5
22 ^b	15 (P = TMS)	α	Me_2CuLi	26, 27	95	1.5:1
23	16 (P = H)	α	Me_2CuLi	28, 29	97	1:2.5
24 ^b	17 (P = TMS)	α	Me_2CuLi	28, 29	96	2.5:1

^a Entry 2 was carried out in the presence of TMSCl.

^b These ring openings were followed by treatment with TBAF.

19a and **23a** (entry 14). On the other hand, epoxide **11** with a MOM group reacted with Me_2CuLi regioselectively to produce a mixture of **20a** and **24a** in 92% yield with a ratio of 3:1 (entry 15). In the case of using *n*-Bu₂CuLi, the ratio of **20b** and **24b** was also 3:1 (entry 16). Regiochemical inversion by installing a TMS group was also observed in cases of using other *anti*-epoxy alcohol derivatives **14–17** (entries 21–24). We next carried out the

reaction of epoxides **12** and **13** with *syn* configuration. In these cases, highly selective formation of 1,2-diols was observed regardless of whether substrates have a TMS group or not (entries 17–20). An effect of the TMS group on the direction of substitution was thus limited to the reaction of *anti*-epoxy alcohol derivatives.

Next, we carried out ring opening of epoxy alcohols **34–37** and epoxy TMS-ethers **38–41** possessing a methyl substituent at the

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