CO<sub>2</sub>Me

3 (major)

## The Reaction of Methyl (E)-4,5-Epoxypent-2-enoate with Arylcopper: the Unique Role of Boron Trifluoride in determining Regioselectivity

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Excess BF<sub>3</sub> causes regioselectivity reversion in the reaction of methyl 4,5-epoxypent-2-enoate 1 with Ph<sub>2</sub>CuLi; this is rationalised by a two step conversion via methyl 4-bromo-5-hydroxypent-2-enoate 5.

The widely studied nucleophilic opening of epoxides or vinyloxiranes by organocopper reagents is an important methods for the formation of the carbon-carbon bond.<sup>1</sup> Recently the effect of Lewis acids in the epoxy ring opening reaction has attracted much attention.<sup>2</sup> As epoxides are less reactive towards conventional organocopper reagents, the reaction requires a reagent excess per epoxide to proceed at low temperatures. This problem has been solved by using copper reagents with the Lewis acid.<sup>3</sup> Vinyloxiranes usually react with organocopper reagents without the presence of a Lewis acid, but the effect of the Lewis acid on the regioselectivity is interesting. Nucleophilic opening of vinyloxiranes by copper reagents gives the products of either direct (S<sub>N</sub>2) or allylic attack (S<sub>N</sub>2'), depending on the substrate substituents and the type of organocopper reagent. Simple acyclic vinyloxiranes preferentially undergo an S<sub>N</sub>2' addition to form an allylic alcohol.<sup>4</sup> This also occurs using BF<sub>3</sub>.<sup>3</sup> Ibuka et al. also reported that the regiochemistry of the reaction of methyl 4,5-epoxyhex-2-enoate, vinyloxirane linked to an ester group, with methylcopper reagents was directed by the reagents type.<sup>5</sup> The softer copper reagents, e.g. MeCuCNLi and Me<sub>2</sub>CuCNLi<sub>2</sub>, react with the vinyloxirane via an  $S_N 2'$  mechanism and the harder copper reagents, e.g. MeCu and Me<sub>2</sub>CuLi, react via an S<sub>N</sub>2 mechanism. The regioselectivities do not alter with the addition of BF3 in each case.<sup>5</sup> Here we report that BF3 plays an important role in the regioselectivity of the reaction between methyl 4,5-epoxypent-2-enoate 1 and arylcopper reagents.

In the course of our synthetic studies on bisabolane sesquiterpenes,<sup>6</sup> nucleophilic opening of compound 1 by arylcopper reagents aroused our interest. We thus investigated the reaction of  $1^+$  with four different phenylcopper reagents (2 equiv.) at -78 °C, Table 1, entries 1–4. In all the cases,  $\gamma$ substituted 2 and  $\alpha$ -substituted 3 products were formed as a mixture in low yields. All the reactions preferentially proceeded via an  $S_N2$  mechanism to afford compound 2 as the main product. High regioselectivity was especially observed using PhCu (entry 1) and Ph<sub>2</sub>CuLi (entry 2) reagents.

Yields were next enhanced by the addition of BF<sub>3</sub> (Table 1, entries 5-8). The reactivity and regioselectivity when PhCuCNLi (entry 7) and Ph2CuCNLi2 (entry 8) were used were



not influenced by the addition of BF<sub>3</sub>. The BF<sub>3</sub> caused increased yields and reverse regioselectivity when PhCu (entry 5) and Ph<sub>2</sub>CuLi (entry 6) were used. Bromohydrin 4 was also obtained in these cases. It was considered that 4 was formed by BF<sub>3</sub> promoted nucleophilic opening of 1 by LiBr, derived from PhLi and CuBr in situ. This was proved by the following (Scheme 1). Treatment of compound 1 with LiBr in the presence of  $BF_3$ ·Et<sub>2</sub>O yielded 4 (29%) and another bromohydrin 5 (46%), whilst the epoxy ring was not opened without BF3. The fact that 5 was not obtained in entries 5-6 aroused our interest. It can be envisioned that nucleophilic substitution of 5 by the phenylcopper reagent proceeds at low temperatures whilst the reaction of 4 does not. To clarify this point the reactions of 4 or 5 with Ph<sub>2</sub>CuLi in the presence of BF<sub>3</sub> were tested according to a general method. As was expected, 5 was converted to a 1:9 mixture of compounds 2 and 3 in 81% yield, while no reaction was observed in the case of 4.

This finding suggests a mechanism as shown in Scheme 2 for the reversion of regioselectivity in entries 5-6. Basically, 1 tends to react with all phenylcopper reagents via an S<sub>N</sub>2



Scheme 2

CO₂Me

5

HO

Table 1 Reactions of 1 with various ph $\bigcirc CO_2Me  \frac{Ph}{\sqrt{-1}}$	envlcopper reagents -cuprate -78 °C HO	`CO₂Me + HO	Ph CO <sub>2</sub> Me	OH + Br CO2Me
1	2		3	4
Entry	Cuprate <sup>a</sup>	Yield of <b>2 + 3</b> (%)	$2:3^{d}$	Yield of 4 (%)
1	PhCu <sup>b</sup>	27	89:11	0
2	Ph <sub>2</sub> CuLi <sup>b</sup>	40	93:7	0
3	PhCuCNLic	35	68:32	0
4	Ph <sub>2</sub> CuCNLi <sub>2</sub> <sup>c</sup>	48	68:32	0
5	PhCu-BF <sub>3</sub>	54	18:82	22
6	Ph <sub>2</sub> CuLi-BF <sub>3</sub>	56	24:76	24
7	PhCuCNLi-BF3	40	71:29	0
8	Ph2CuCNLi2-BF3	41	59:41	0

<sup>a</sup> All copper reagents were utilised without isolation. All reactions were carried out in Et<sub>2</sub>O at -78 °C under argon and quenched after 30 min. <sup>b</sup> PhCu and Ph<sub>2</sub>CuLi were prepared from CuBr Me<sub>2</sub>S and PhLi. PhCuCNLi and Ph<sub>2</sub>CuCNLi<sub>2</sub> were prepared from CuCN and PhLi. The ratio 2:3 was estimated by comparing the corresponding proton peaks in the <sup>1</sup>H NMR spectrum.

Table 2 Reactions of 1 with various arylcopper reagents

1 Ar <sub>2</sub>	-78 °C	Ar HO <b>Ta-d</b> Ar HO HO HO	Ar 8a-d	CO <sub>2</sub> Me + Ar	H CO <sub>2</sub> Me 9a–d	+ <b>4</b> e	
Entry	Ar		Yield of <b>7a–d + 8</b> a	a-d (%) 7a-d:8a-d	Yield of <b>9a-d</b> (%)	Yield of <b>4</b> (%)	
1	/=<	$\mathbf{6a} \ \mathbf{R}^1 = \mathbf{Me}$	47	21:79	0	26	
2		<b>6b</b> $R^{\dagger} = OMe$	52	17:83	0	38	
3		<b>6c</b> $\mathbf{R}^2$ = Me, $\mathbf{R}^3$ = OMe	98	100:0	0	0	
 4	 R <sup>3</sup>	$\mathbf{6d} \ \mathbf{R}^2 = \mathbf{R}^3 = \mathbf{OMe}$	74	95:5	18	0	

mechanism, but BF<sub>3</sub> promoted addition of LiBr to 1 initially forms two bromides 4 and 5 (entries 5–6). *In situ*, the generated 5 reacts with phenylcopper reagents mostly at the  $\alpha$ -position. Consequently, the reaction of 1 with PhCu or Ph<sub>2</sub>CuLi seemingly proceeds *via* an S<sub>N</sub>2' mechanism in the presence of BF<sub>3</sub>. In other cases, addition of LiBr did not occur due to the absence of BF<sub>3</sub> (entries 1–4) or LiBr (entries 7–8). Therefore, compound 1 reacts with copper reagents directly.

The reaction of compound 1 with four different aryl Gilman reagents **6a–d** in the presence of BF<sub>3</sub> was carried out (Table 2).‡ The reaction with **6a–b** showed a similar result to that obtained using Ph<sub>2</sub>CuLi in the presence of BF<sub>3</sub>. The  $\alpha$ -substituted products **8a–b** were mainly obtained as well as compound 4. The reaction using the arylcopper reagents with two substituents at the *o*-position **6c–d** gave  $\gamma$ -substituted products **7c–d** preferentially and did not yield 4. Furthermore, the  $\delta$ -substituted **9d** was also obtained as a minor product (entry 4). The formation of **9d** is attributable to the direct attack of **1** at the  $\delta$ -position. This was suggested by the fact that the substitution of **4** with **6d** did not proceed.

Two hypothetical paths may be envisioned concerning the  $S_N2$  selectivities for entries 3–4. (*a*) The copper reagents are much more reactive than LiBr and react directly with 1 *via* an  $S_N2$  mechanism to yield  $\gamma$ -substituted products. (*b*) Nucleophilic opening by LiBr with the assistance of BF<sub>3</sub> forms 5 as an intermediate. Then further substitution of 5 with the copper reagents proceeds *via* an  $S_N2$  mechanism to yield  $\gamma$ -substituted products. In each case, compound 5 was not formed as an intermediate because the concomitant 4 was not obtained. Consequently, their regioselectivities can be explained by path

(*a*). We cannot, however, explain the reason why the arylcopper reagents possessing two substituents at the *o*-position are much more reactive than other arylcopper reagents.

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## Footnotes

- † Compound 1 was synthesised by a known method, see reference 6.
- ‡ Satisfactory analytical data were obtained for all new compounds.

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