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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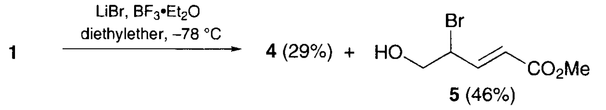
Excess BF_3 causes regioselectivity reversion in the reaction of methyl 4,5-epoxypent-2-enoate **1** with Ph_2CuLi; this is rationalised by a two step conversion *via* methyl 4-bromo-5-hydroxypent-2-enoate **5**.

The widely studied nucleophilic opening of epoxides or vinyloxiranes by organocopper reagents is an important methods for the formation of the carbon–carbon bond.[1] Recently the effect of Lewis acids in the epoxy ring opening reaction has attracted much attention.[2] 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.[3] 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_N2) or allylic attack (S_N2'), depending on the substrate substituents and the type of organocopper reagent. Simple acyclic vinyloxiranes preferentially undergo an S_N2' addition to form an allylic alcohol.[4] This also occurs using BF_3.[3] 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.[5] The softer copper reagents, *e.g.* MeCuCNLi and $Me_2CuCNLi_2$, react with the vinyloxirane *via* an S_N2' mechanism and the harder copper reagents, *e.g.* MeCu and Me_2CuLi, react *via* an S_N2 mechanism. The regioselectivities do not alter with the addition of BF_3 in each case.[5] Here we report that BF_3 plays an important role in the regioselectivity of the reaction between methyl 4,5-epoxypent-2-enoate **1** and arylcopper reagents.

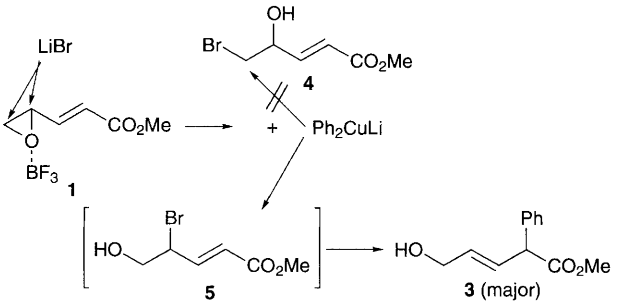
In the course of our synthetic studies on bisabolane sesquiterpenes,[6] nucleophilic opening of compound **1** by arylcopper reagents aroused our interest. We thus investigated the reaction of **1**† with four different phenylcopper reagents (2 equiv.) at −78 °C, Table 1, entries 1–4. In all the cases, γ-substituted **2** and α-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_2CuLi (entry 2) reagents.

Yields were next enhanced by the addition of BF_3 (Table 1, entries 5–8). The reactivity and regioselectivity when PhCuCNLi (entry 7) and $Ph_2CuCNLi_2$ (entry 8) were used were not influenced by the addition of BF_3. The BF_3 caused increased yields and reverse regioselectivity when PhCu (entry 5) and Ph_2CuLi (entry 6) were used. Bromohydrin **4** was also obtained in these cases. It was considered that **4** was formed by BF_3 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 $BF_3 \cdot Et_2O$ yielded **4** (29%) and another bromohydrin **5** (46%), whilst the epoxy ring was not opened without BF_3. 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_2CuLi in the presence of BF_3 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_N2

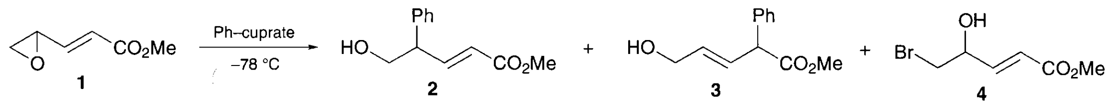


Scheme 1



Scheme 2

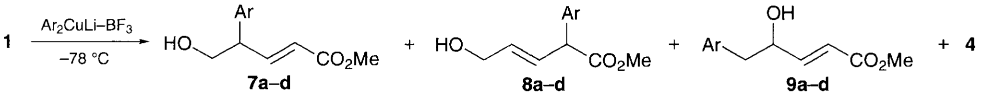
Table 1 Reactions of **1** with various phenylcopper reagents

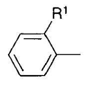
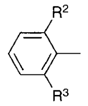


Entry	Cuprate[a]	Yield of **2** + **3** (%)	**2**:**3**[d]	Yield of **4** (%)
1	PhCu[b]	27	89:11	0
2	Ph_2CuLi[b]	40	93:7	0
3	PhCuCNLi[c]	35	68:32	0
4	$Ph_2CuCNLi_2$[c]	48	68:32	0
5	$PhCu\text{-}BF_3$	54	18:82	22
6	$Ph_2CuLi\text{-}BF_3$	56	24:76	24
7	$PhCuCNLi\text{-}BF_3$	40	71:29	0
8	$Ph_2CuCNLi_2\text{-}BF_3$	41	59:41	0

[a] All copper reagents were utilised without isolation. All reactions were carried out in Et_2O at −78 °C under argon and quenched after 30 min. [b] PhCu and Ph_2CuLi were prepared from $CuBr \cdot Me_2S$ and PhLi. [c] PhCuCNLi and $Ph_2CuCNLi_2$ were prepared from CuCN and PhLi. [d] The ratio **2**:**3** was estimated by comparing the corresponding proton peaks in the ^1H NMR spectrum.

Table 2 Reactions of **1** with various arylcopper reagents



Entry	Ar		Yield of **7a–d** + **8a–d** (%)	**7a–d**:**8a–d**	Yield of **9a–d** (%)	Yield of **4** (%)
1		**6a** R^1 = Me	47	21:79	0	26
2		**6b** R^1 = OMe	52	17:83	0	38
3		**6c** R^2 = Me, R^3 = OMe	98	100:0	0	0
4		**6d** R^2 = R^3 = OMe	74	95:5	18	0

mechanism, but BF$_3$ 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 α-position. Consequently, the reaction of **1** with PhCu or Ph$_2$CuLi seemingly proceeds *via* an S$_N$2′ mechanism in the presence of BF$_3$. In other cases, addition of LiBr did not occur due to the absence of BF$_3$ (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$_3$ was carried out (Table 2).‡ The reaction with **6a–b** showed a similar result to that obtained using Ph$_2$CuLi in the presence of BF$_3$. The α-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 γ-substituted products **7c–d** preferentially and did not yield **4**. Furthermore, the δ-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 δ-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$_N$2 selectivities for entries 3–4. (*a*) The copper reagents are much more reactive than LiBr and react directly with **1** *via* an S$_N$2 mechanism to yield γ-substituted products. (*b*) Nucleophilic opening by LiBr with the assistance of BF$_3$ forms **5** as an intermediate. Then further substitution of **5** with the copper reagents proceeds *via* an S$_N$2 mechanism to yield γ-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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