Reaction of Methyl 4,5-Epoxy-(2*E*)-pentenoate with Arylcopper Reagents[1)]

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The reaction of methyl 4,5-epoxy-(2*E*)-pentenoate (1) with various arylcopper reagents was studied. Basically, all arylcopper reagents react with 1 in *S*N2 fashion. However, addition of BF_3 causes reversal of the regioselectivity, which can be rationalized in terms of a two-step conversion by way of methyl 4-bromo-5-hydroxy-2-pentenoate (5).

Key words methyl 4,5-epoxy-2-pentenoate; arylcopper reagent; BF_3; regioselectivity

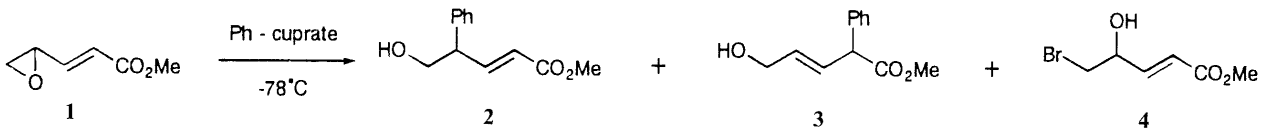
The reaction of epoxides or vinyloxiranes with various nucleophiles is one of the most important methods for the formation of carbon–carbon bonds. Such nucleophilic opening reactions using organocopper reagents compare favorably in yield and mildness of conditions with analogous transformation using other nucleophiles.[2)] The regiochemistry of the nucleophilic opening is of interest. In the cases of simple epoxides, steric factors contribute to the regioselectivity. The reaction of monosubstituted and 1,1-disubstituted epoxides takes place regioselectively at the less hindered site. Vinyloxiranes react with organocopper reagents in an allylic rearrangement (*S*N2′) fashion in competition with direct opening (*S*N2) at the site adjacent to the vinyl function. The regiochemical course (*S*N2 *vs.* *S*N2′) depends upon the steric, electronic and orbital effects in both substrate and reagent. The reaction of 3,4-epoxy-1-butene, the simplest vinyloxirane, with dimethylcopper lithium proceeds in a *S*N2′ manner.[3)] Font *et al.* interpreted this by considering the organocopper reagent as a soft nucleophile.[4)] Ibuka *et al.* reported that the reaction site of methylcopper reagents with methyl 4,5-epoxy-2-hexenoate, vinyloxirane linked to an ester function, was determined by the presence or absence of a CN ligand.[5)] Methylcopper reagents having a CN ligand reacted with the substrate preferentially in *S*N2′ fashion. On the other hand, non-CN type reagents reacted predominantly in a *S*N2 manner. These results can be clearly rationalized by considering methylcopper reagents having a CN ligand as soft nucleophiles and non-CN type reagents as hard nucleophiles. Surprisingly, the effect of the organic group of copper reagents on the regioselectivity of vinyloxirane has not been much discussed. Thus, selection of an aromatic organic copper reagent as a nucleophile for vinyloxirane linked to an ester function has aroused our interest from both theoretical and synthetic[6)] viewpoints. We wish to report here the reaction of methyl 4,5-epoxy-2-pentenoate (**1**) with various arylcopper reagents.

Results and Discussion

First, we examined the reaction of **1**[7)] with various phenylcopper reagents (Table 1, entries 1—4). In all cases, 4-phenylpentenoate (**2**) and 2-phenylpentenoate (**3**) were formed as a mixture after purification by short column chromatography on silica gel in low yields. Each structure was determined on the basis of the spectroscopic data after further separation by preparative TLC (PTLC). The ratio of **2** : **3** was estimated by comparing corresponding proton peaks in the ^{1}H-NMR spectrum of the mixture. All reactions proceeded preferentially in *S*N2 fashion to give **2** as a main product. Especially high regioselectivity was observed in the reaction using non-CN type copper reagents (entries 1 and 2).

An interesting aspect of organocuprate chemistry is the effect of additives on the reactions of organocopper reagents.[8)] The presence of a Lewis acid often increases the yield, rate, regioselectivity and stereoselectivity. To enhance the yield, the addition of BF_3 was examined (Table 1, entries 5—8). The reactivity and the regioselectivity in the cases of PhCuCNLi (entry 7) and $Ph_2CuCNLi_2$ (entry 8) were not influenced by addition of BF_3. However, BF_3 increased the yield and reversed the regioselec-

Table 1. Reaction of **1** with Various Phenylcopper Reagents



1 **2** **3** **4**

Entry	Cuprate	Yield (%) (2+3)	Ratio (2:3)	Yield (%) (4)
1	PhCu	27	89:11	0
2	Ph_2CuLi	40	93: 7	0
3	PhCuCNLi	35	68:32	0
4	$Ph_2CuCNLi_2$	48	68:32	0
5	PhCu–BF_3	54	18:82	22
6	Ph_2CuLi–BF_3	56	24:76	24
7	PhCuCNLi–BF_3	40	71:29	0
8	$Ph_2CuCNLi_2$–BF_3	41	59:41	0

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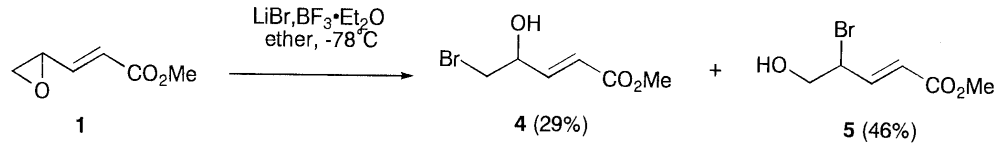


Chart 1

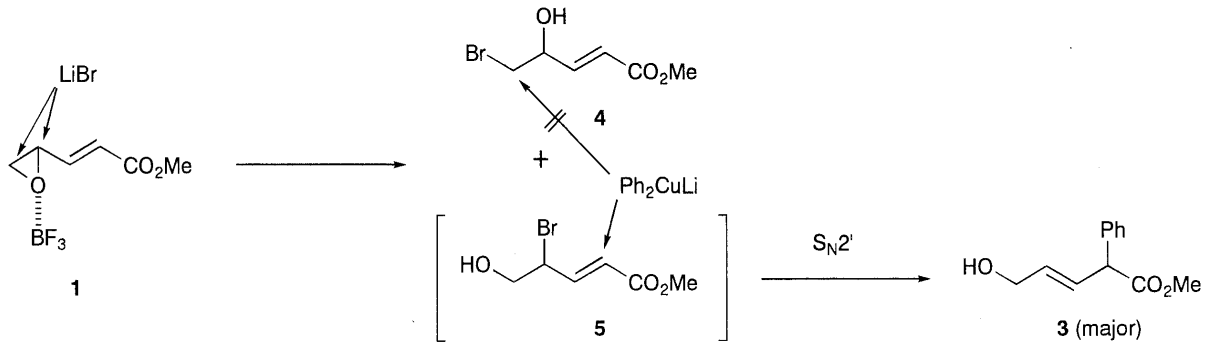


Chart 2

tivity in the cases of PhCu (entry 5) and Ph_2CuLi (entry 6). Interestingly, the 5-bromo-pentenoate (**4**) was also obtained in the cases where **3** was mainly formed.

We thought that the reversal of regioselectivity and the formation of **4** in entries 5 and 6 were attributable to the same cause. To identify the source of bromine in **4**, the reaction of **1** with $CuBr \cdot Me_2S$ or LiBr was carried out (Chart 1). The treatment of **1** with LiBr in the presence of $BF_3 \cdot Et_2O$ gave **4** (29%), along with the 4-bromo-pentenoate (**5**) (46%). The nucleophilic attack of LiBr did not proceed in the absence of $BF_3 \cdot Et_2O$. CuBr did not react with **1** regardless of the presence of $BF_3 \cdot Et_2O$. These findings suggested that $BF_3 \cdot Et_2O$ was involved in the nucleophilic opening of **1** by LiBr, derived from PhLi and CuBr, at the C_5 position as a side reaction in entries 5 and 6. However, it is unclear why **5** was not obtained as a by-product in entries 5 and 6. Possibly **5** undergoes nucleophilic attack of phenylcopper reagent, while **4** does not under the same conditions. Thus, the reactions of **4** or **5** with Ph_2CuLi in the presence of $BF_3 \cdot Et_2O$ were carried out according to the general method. In accord with our expectation, **5** was converted to a 1:9 mixture of **2** and **3** in 81% yield, while no reaction was observed in the case of **4**.

The above results suggest the mechanism shown in Chart 2 for the reversed regioselectivity in entries 5 and 6. Basically, all phenylcopper reagents tend to attack **1** at the C_4 position. In entries 5 and 6, BF_3-promoted addition of LiBr to **1** precedes the nucleophilic opening of **1** by phenylcopper reagents and two bromides **4** and **5** are formed. *In situ*, **5** undergoes attack of phenylcuprates, mainly at the C_2 position. Consequently, the reaction of **1** with PhCu or Ph_2CuLi seemingly proceeds in a *SN*2′ manner in the presence of BF_3. In other cases, addition of LiBr does not proceed because of the absence of BF_3 (entries 1—4) or LiBr (entries 3, 4 and 7, 8). This two-step process in the reaction of vinyloxirane with any kind of organocopper reagent has not been reported previously. In summary, (1) BF_3 plays an important role in the

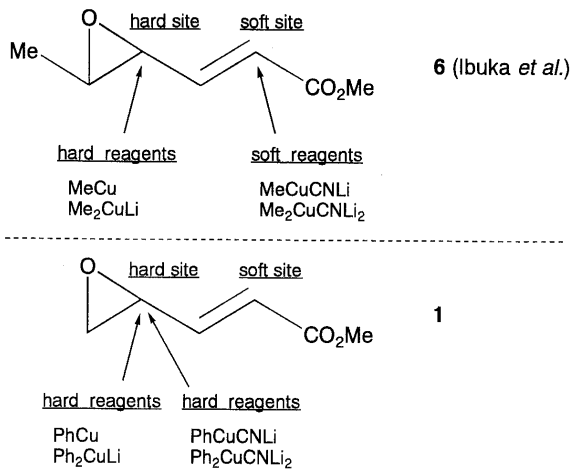


Chart 3

regioselectivity; (2) all phenylcopper reagents react with **1** in a *SN*2 manner selectively, if the participation of BF_3 is precluded.

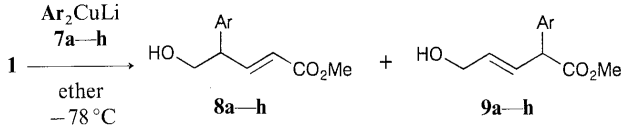
The latter finding arouses our interest because it is different from the finding reported by Ibuka *et al.* that methylcopper reagents having a CN ligand react with methyl 4,5-epoxy-2-hexenoate (**6**) in a *SN*2′ manner.[5] Their results have been clearly explained as following on the basis of the "general perturbation" (GP) equation and the "hard and soft acid and base" (HSAB) concept.[5,9] The CNDO/2 calculations of **6** showed that the charge distribution at the C_4 position was positive, while that at the C_2 position was negative, and the electron density of LUMO at the C_2 position was significantly larger than that at the C_4 position. Therefore, the harder reagents such as MeCu and Me_2CuLi attack selectively at the C_4 position under charge control and the softer reagents such as MeCuCNLi and $Me_2CuCNLi_2$ react predominantly at the C_2 position under orbital control. We carried out PM3 calculation of **6** and **1**.[10] They showed the similar tendencies for the charge distribution and the

electron density of LUMO at the C_2 and C_4 positions. Thus, the difference between our and their findings might be attributed to the nature of the reagents. It can be concluded that PhCuCNLi and $Ph_2CuCNLi_2$ are harder than MeCuCNLi and $Me_2CuCNLi_2$ because of the hardness of the phenyl anion.[9b] Consequently, our finding is compatible with their proposal (Chart 3).

Next, nucleophilic opening of **1** by various aryl Gilman reagents (**7a—h**) was carried out (Table 2). All arylcopper reagents reacted with **1** selectively in S_N2 fashion to give 4-substituted compounds (**8a—h**) as the main products in analogy with Table 1, entry 2. Table 3 summarizes the reaction of **1** with **7a—h** in the presence of BF_3. As we would predict, addition of BF_3 caused at least partial reversal of regioselectivity to afford 2-substituted compounds (**9a—f**) as main products and promoted nucleophilic opening of **1** by LiBr to give **4** in the cases of **7a—f**. These findings can be rationalized in terms of two-step conversion by way of **5**. The reaction using the arylcopper reagents (**7g—h**) possessing two substituents at the *ortho* position gave **8g—h** preferentially in high yield, and did not yield **4**. Furthermore, the 5-substituted compound (**10h**) was also obtained as a minor product in entry 8. The formation of **10h** is attributable to the direct attack on **1** at the C_5-position, which is suggested by the finding that the substitution of **4** with **7h** did not proceed.

Two hypothetical pathways may be envisioned to explain the S_N2 selectivities in entries 7 and 8 (Chart 4). (a) The copper reagents are much more reactive than LiBr and react directly with **1** in a S_N2 manner to yield 4-substituted products. (b) Nucleophilic opening by LiBr

Table 2. Reaction of **1** with Various Aryl Gilman Reagents



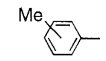
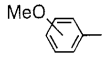
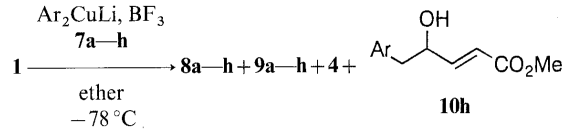
Entry	Ar		Yield (%) (8+9)	Ratio (8:9)
1		**7a** (*o*-Me)	22	80:20
2		**7b** (*m*-Me)	22	89:11
3		**7c** (*p*-Me)	28	89:11
4		**7d** (*o*-MeO)	46	82:18
5		**7e** (*m*-MeO)	46	80:20
6		**7f** (*p*-MeO)	30	84:16
7		**7g** (R^1=Me, R^2=OMe)	95	97: 3
8		**7h** (R^1=R^2=OMe)	32	83:17

Table 3. Reaction of **1** with Aryl Gilman Reagents in the Presence of BF_3



Entry	Reagent	Yield (%) (8+9)	Ratio (8:9)	Yield (%) (4)	Yield (%) (10h)
1	**7a**	47	21:79	26	
2	**7b**	37	33:67	25	
3	**7c**	50	46:54	33	
4	**7d**	52	17:83	38	
5	**7e**	47	44:56	18	
6	**7f**	33	48:52	21	
7	**7g**	98	100: 0	0	
8	**7h**	74	95: 5	0	18

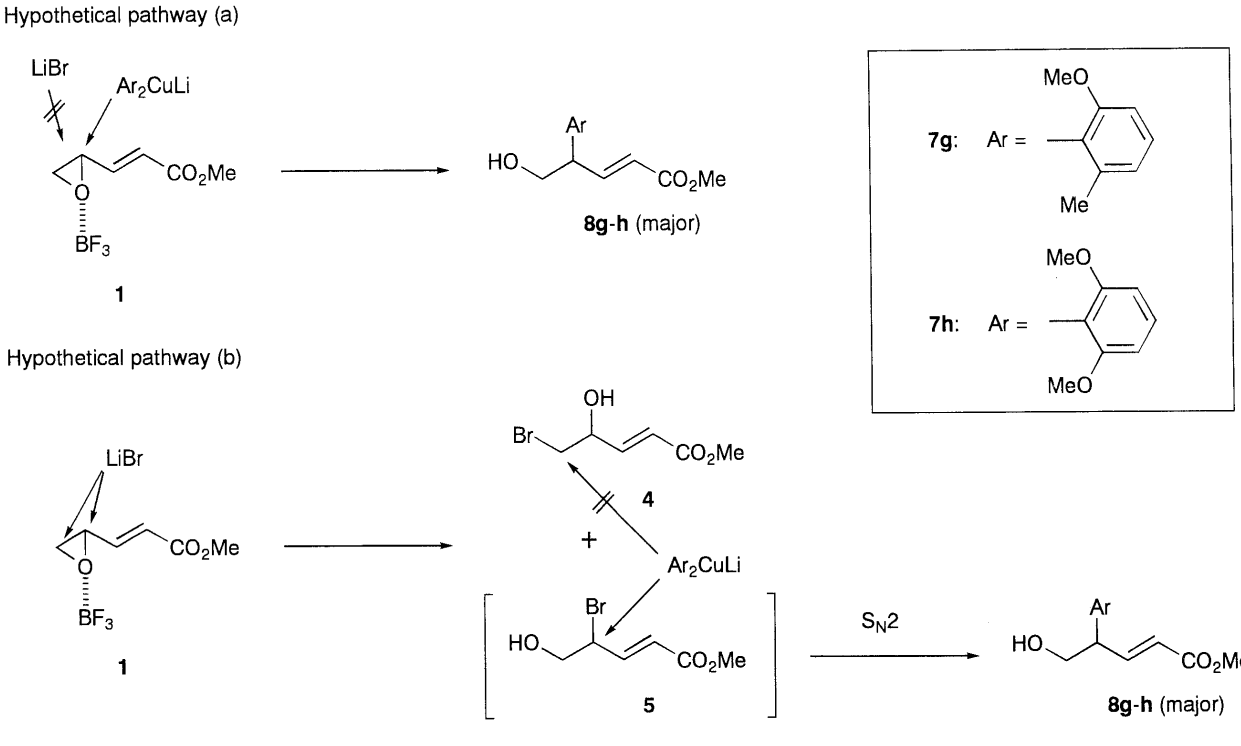


Chart 4

with the assistance of BF_3 forms **5** as an intermediate. Then, substitution of **5** with the copper reagents proceeds in a *SN*2 manner to yield the 4-substituted products.

In each case, **5** should not be formed as an intermediate because **4** was not concomitantly obtained. Consequently, the regioselectivity can be explained in terms of pathway (a). However, we do not know the reason why the aryl-copper reagents possessing two substituents at the *ortho* position are much more reactive than other aryl-copper reagents. Further work is in progress to gain some insight into this question.

Experimental

General Methods The melting points were determined on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO FT/IR-300 spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL JNM-EX400 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were obtained on a JEOL JMS-D300 or JEOL LMS-DX303 spectrometer. Diethyl ether was freshly distilled from sodium under argon. For column chromatography, Silica gel 60 (Merck 7734) was employed. For PTLC, ART. 5744 DC-Fertigplatten Kieselgel 60 F_{254} was used.

Preparation of Arylcopper Reagents PhCu: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (0.95 ml, 1.62 mmol) was added to a stirred solution of 250 mg (1.59 mmol) of bromobenzene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The mixture was further stirred for 30 min at −78 °C.

Ph_2CuLi: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 500 mg (3.18 mmol) of bromobenzene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

PhCuCNLi: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (0.95 ml, 1.62 mmol) was added to a stirred solution of 250 mg (1.59 mmol) of bromobenzene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 145 mg (1.62 mmol) of copper(I) cyanide in 4 ml of ether at −40 °C under argon. The mixture was further stirred for 30 min at −78 °C.

$Ph_2CuCNLi_2$: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 500 mg (3.18 mmol) of bromobenzene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 145 mg (1.62 mmol) of copper(I) cyanide in 4 ml of ether at −40 °C under argon. The solution was further stirred for 30 min at −78 °C.

7a: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 545 mg (3.19 mmol) of 2-bromotoluene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7b: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 545 mg (3.19 mmol) of 3-bromotoluene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7c: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 545 mg (3.19 mmol) of 4-bromotoluene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7d: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 600 mg (3.21 mmol) of 2-bromoanisole in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7e: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 600 mg (3.21 mmol) of 3-bromoanisole in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7f: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 600 mg (3.21 mmol) of 4-bromoanisole in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

7g: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 645 mg (3.21 mmol) of 1-bromo-2-methylanisole in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

The synthesis of 1-bromo-2-methylanisole was carried out as follows. A 17.5% aqueous sodium nitrite (80 ml) was added dropwise to a solution of 25.1 g (183 mmol) of commercially available 2-methoxy-6-methylaniline in 200 ml of 10% HBr at 0 °C and the reaction mixture was filtered. A solution of 20.6 g (144 mmol) of copper(I) bromide in 60 ml of concentrated HBr was added to the filtrate and the resulting mixture was refluxed for 1 h. The reaction mixture was purified by steam distillation and subsequent chromatography with hexane to give 28.4 g (141 mmol, 77%) of 1-bromo-2-methylanisole. Data for ^{1}H-NMR ($CDCl_3$) δ: 7.15 (1H, t, J=8.3 Hz), 6.85 (1H, d, J=8.3 Hz), 6.73 (1H, d, J=8.3 Hz), 3.88 (3H, s), 2.41 (3H, s).

7h: A 1.7 M solution of *tert*-butyllithium in *n*-pentane (1.9 ml, 3.23 mmol) was added to a stirred solution of 440 mg (3.18 mmol) of 1,3-dimethoxybenzene in 4 ml of ether at −30 °C under argon. This solution was stirred for 2 h at 0 °C and was added to a suspension of 330 mg (1.61 mmol) of copper(I) bromide–dimethyl sulfide complex in 4 ml of ether at −30 °C under argon. The solution was further stirred for 30 min at −78 °C.

General Procedure for the Reaction of 1 with Arylcopper Reagents A solution of 100 mg (0.78 mmol) of **1** in 4 ml of ether was added dropwise to a solution of 1.6 mmol of PhCu, Ph_2CuLi, PhCuCNLi, $Ph_2CuCNLi_2$ or other arylcopper reagents in ether at −78 °C under argon. After an additional 30 min of stirring, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography with 10% ethyl acetate in hexane to give the corresponding 4-aryl compound (**2**, **8a**—**g**) and 2-aryl compound (**3**, **9a**—**g**). When separation was difficult, PTLC was carried out. The ^{1}H-NMR spectra of the resulting pure 4-aryl and 2-aryl compounds were measured.

Methyl 4-Phenyl-5-hydroxy-(2*E*)-pentenoate (2) and Methyl 2-Phenyl-5-hydroxy-(3*E*)-pentenoate (3) **2**: ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.22 (5H, m), 7.15 (1H, dd, J=15.6, 6.8 Hz), 5.92 (1H, d, J=15.6 Hz), 3.92 (2H, d, J=6.8 Hz), 3.73 (3H, s), 3.69 (1H, d, J=6.8 Hz), 1.49 (1H, br s); **3**: ^{1}H-NMR ($CDCl_3$) δ: 7.36—7.25 (5H, m), 6.11 (1H, dd, J=15.6, 8.3 Hz), 5.74 (1H, dt, J=15.6, 5.4 Hz), 4.33 (1H, d, J=8.3 Hz), 4.15 (2H, d, J=5.4 Hz), 3.70 (3H, s), 1.49 (3H, s). A mixture of **2** and **3**: IR (neat): 3425 (OH), 1722 (C=O) cm^{-1}. HR-MS m/z Calcd for $C_{12}H_{14}O_3$ 206.1939. Found: 206.0777.

Methyl 4-(*o*-Tolyl)-5-hydroxy-(2*E*)-pentenoate (8a) and Methyl 2-(*o*-Tolyl)-5-hydroxy-(3*E*)-pentenoate (9a) They could not be separated by PTLC. The ratio was estimated by comparing corresponding proton peaks in the ^{1}H-NMR spectrum of the mixture. ^{1}H-NMR ($CDCl_3$) δ: 7.25—7.13 (4H for **8a** and 4H for **9a**, m), 7.11 (1H for **8a**, dd, J=15.6, 6.8 Hz), 6.06 (1H for **9a**, dd, J=15.6, 7.3 Hz), 5.84 (1H for **8a**, d, J=

15.6 Hz), 5.63 (1H for **9a**, dt, J=15.6, 5.4 Hz), 4.54 (2H for **8a**, d, J=7.3 Hz), 4.11 (2H for **9a**, d, J=5.4 Hz), 3.98—3.88 (1H for **8a** and 1H for **9a**), 3.70 (3H for **8a**, s), 3.67 (3H for **9a**, s), 2.33 (3H for **8a** and 3H for **9a**, s), 2.00 (1H for **8a** and 1H for **9a**, br s). IR (neat): 3431 (OH), 1734 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_3$: 220.1095. Found: 220.1128.

Methyl 4-(*m*-Tolyl)-5-hydroxy-(2*E*)-pentenoate (8b) and Methyl 2-(*m*-Tolyl)-5-hydroxy-(3*E*)-pentenoate (9b) They could not be separated by PTLC. The ratio was estimated by comparing corresponding proton peaks in the ^{1}H-NMR spectrum of the mixture. ^{1}H-NMR ($CDCl_3$) δ: 7.24—6.99 (4H for **8b** and 4H for **9b**, m), 7.13 (1H for **8b**, dd, J=15.6, 7.1 Hz), 6.08 (1H for **9b**, dd, J=15.1, 8.3 Hz), 5.89 (1H for **8b**, d, J=15.6 Hz), 5.71 (1H for **9b**, dt, J=15.1, 5.1 Hz), 4.28 (1H for **9b**, d, J=8.3 Hz), 4.11 (2H for **9b**, d, J=5.1 Hz), 3.87 (2H for **8b**, d, J=7.1 Hz), 3.71 (3H for **8b**, s), 3.68 (3H for **9b**, s), 3.62 (1H for **8b**, q, J=7.1 Hz), 2.33 (3H for **8b** and 3H for **9b**), 1.97 (1H for **8b** and 1H for **9b**, br s). IR (neat): 3421 (OH), 1734 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_3$: 220.1095. Found: 220.1111.

Methyl 4-(*p*-Tolyl)-5-hydroxy-(2*E*)-pentenoate (8c) and Methyl 2-(*p*-Tolyl)-5-hydroxy-(3*E*)-pentenoate (9c) **8c**: ^{1}H-NMR ($CDCl_3$) δ: 7.15 (2H, d, J=7.8 Hz), 7.13 (1H, dd, J=15.6, 7.0 Hz), 7.10 (2H, d, J=7.8 Hz), 3.87 (2H, d, J=7.0 Hz), 3.71 (3H, s), 3.64 (1H, q, J=7.0 Hz), 2.33 (3H, s), 1.71 (1H, br s). **9c**: ^{1}H-NMR ($CDCl_3$) δ: 7.17 (2H, d, J=8.3 Hz), 7.09 (2H, d, J=8.3 Hz), 6.07 (1H, dd, J=15.1 , 8.3 Hz), 5.70 (1H, dt, J=15.1, 5.4 Hz), 4.28 (1H, d, J=8.3 Hz), 4.10 (2H, d, J=5.4 Hz), 3.67 (3H, s), 2.31 (3H, s), 2.08 (1H, br s). IR (neat): 3431 (OH), 1725 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_3$: 220.1095. Found: 220.1114.

Methyl 4-(*o*-Anisyl)-5-hydroxy-(2*E*)-pentenoate (8d) and Methyl 2-(*o*-Anisyl)-5-hydroxy-(3*E*)-pentenoate (9d) They could be easily separated by column chromatography. **8d**: ^{1}H-NMR ($CDCl_3$) δ: 7.27—7.13 (3H, m), 6.94 (1H, t, J=7.3 Hz), 6.90 (1H, d, J=8.3 Hz), 5.92 (1H, d, J=15.6 Hz), 4.13 (1H, q, J=6.6 Hz), 3.92 (2H, d, J=6.6 Hz), 3.83 (3H, s), 3.72 (3H, s), 1.64 (1H, br s). IR (neat): 3431 (OH), 1720 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_4$: 236.1044. Found: 236.1017. **9d**: ^{1}H-NMR ($CDCl_3$) δ: 7.28—7.21 (2H, m), 6.94 (1H, t, J=7.8 Hz), 6.88 (2H, d, J=8.3 Hz), 6.07 (1H, dd, J=15.6, 7.8 Hz), 5.70 (1H, dt, J=15.6, 5.4 Hz), 4.63 (1H, d, J=7.8 Hz), 4.13 (2H, d, J=5.4 Hz), 3.81 (3H, s), 3.67 (3H, s), 2.00 (1H, br s). IR (neat): 3444 (OH), 1732 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_4$: 236.1044. Found: 236.1067.

Methyl 4-(*m*-Anisyl)-5-hydroxy-(2*E*)-pentenoate (8e) and Methyl 2-(*m*-Anisyl)-5-hydroxy-(3*E*)-pentenoate (9e) They could not be separated by PTLC. The ratio was estimated by comparing corresponding proton peaks in the ^{1}H-NMR spectrum of the mixture. ^{1}H-NMR ($CDCl_3$) δ: 7.28—7.21 (1H for **8e** and 1H for **9e**, m), 7.12 (1H for **8e**, dd, J=15.6, 7.0 Hz), 6.91—6.75 (3H for **8e** and 3H for **9e**, m), 6.08 (1H for **9e**, dd, J=15.6, 8.3 Hz), 5.90 (1H for **8e**, d, J=15.6 Hz), 5.73 (1H for **9e**, dt, J=15.6, 5.4 Hz), 4.29 (1H for **9e**, d, J=8.3 Hz), 4.12 (2H for **9e**, d, J=5.4 Hz), 3.88 (2H for **8e**, d, J=7.0 Hz), 3.79 (3H for **8e** and 3H for **9e**, s), 3.71 (3H for **8e**, s), 3.68 (3H for **9e**, s), 3.64 (1H for **8e**, d, J=7.0 Hz), 1.92 (1H for **8e** and 1H for **9e**, br s). IR (neat): 3433 (OH), 1726 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_4$: 236.1044. Found: 236.1072.

Methyl 4-(*p*-Anisyl)-5-hydroxy-(2*E*)-pentenoate (8f) and Methyl 2-(*p*-Anisyl)-5-hydroxy-(3*E*)-pentenoate (9f) They could not be separated by PTLC. The ratio was estimated by comparing corresponding proton peaks in the ^{1}H-NMR spectrum of the mixture. ^{1}H-NMR ($CDCl_3$) δ: 7.23—7.09 (3H for **8f** and 2H for **9f**, m), 6.89—6.84 (2H for **8f** and 2H for **9f**, m), 6.08 (1H for **9f**, dd, J=15.6, 8.0 Hz), 5.88 (1H for **8f**, d, J=15.6 Hz), 5.71 (1H for **9f**, dt, J=15.6, 5.3 Hz), 4.28 (1H for **9f**, d, J=8.0 Hz), 4.14 (2H for **9f**, d, J=5.3 Hz), 3.87 (2H for **8f**, d, J=7.5 Hz), 3.792 (3H for **9f**, s), 3.785 (3H for **8f**, s), 3.72 (3H for **8f**, s), 3.68 (3H for **9f**, s), 3.63 (1H for **9f**, q, J=7.5 Hz), 1.68 (1H for **8f** and 1H for **9f**, br s). IR (neat): 3430 (OH), 1725 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{13}H_{16}O_4$: 236.1044. Found: 236.1068.

Methyl 4-(2-Methyl-6-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (8g) and Methyl 2-(2-Methyl-6-methoxyphenyl)-5-hydroxy-(3*E*)-pentenoate (9g) They could be easily separated by column chromatography. **8g**: ^{1}H-NMR ($CDCl_3$) δ: 7.35 (1H, dd, J=15.6, 6.8 Hz), 7.12 (1H, t, J=7.8 Hz), 6.80 (1H, d, J=7.8 Hz), 6.75 (1H, d, J=7.8 Hz), 5.81 (1H, d, J=15.6 Hz), 4.15—4.04 (2H, m), 3.96 (1H, m), 3.77 (3H, s), 3.70 (3H, s), 2.34 (3H, s), 2.27 (1H, br s). IR (neat): 3242 (OH), 1718 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{14}H_{18}O_4$: 250.1200. Found: 250.1205; **9g**: ^{1}H-NMR ($CDCl_3$) δ: 7.14 (1H, t, J=7.8 Hz), 6.80 (1H, d, J=7.8 Hz), 6.74 (1H, d, J=7.8 Hz), 6.13 (1H, dd, J=15.6, 7.3 Hz), 5.53 (1H, dt, J=15.6, 5.9 Hz), 4.54 (1H, d, J=7.3 Hz), 4.07 (2H, d, J=5.9 Hz), 3.75 (3H, s), 3.64 (3H, s), 2.43 (1H, br s), 2.29 (3H, s). IR (neat): 3444 (OH), 1730 (C=O) cm^{-1}. FAB-MS m/z: 251 (M^++1).

Methyl 4-(2,6-Dimethoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (8h) and Methyl 2-(2,6-Dimethoxyphenyl)-5-hydroxy-(3*E*)-pentenoate (9h) They could be easily separated by column chromatography. **8h**: ^{1}H-NMR ($CDCl_3$) δ: 7.34 (1H, dd, J=16.1, 7.3 Hz), 7.19 (1H, t, J=8.3 Hz), 6.56 (2H, d, J=8.3 Hz), 5.84 (1H, d, J=16.1 Hz), 4.43 (1H, q, J=7.3 Hz), 4.05 (1H, dd, J=10.7, 7.3 Hz), 3.94 (1H, dd, J=10.7, 7.3 Hz), 3.79 (6H, s), 3.70 (3H, s), 1.95 (1H, br s). IR (neat): 3242 (OH), 1718 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{14}H_{18}O_5$: 266.1149. Found: 266.1197. **9h**: ^{1}H-NMR ($CDCl_3$) δ: 7.21 (1H, t, J=8.3 Hz), 6.56 (2H, d, J=8.3 Hz), 6.16 (1H, dd, J=15.6, 7.8 Hz), 5.62 (1H, dt, J=15.6, 5.9 Hz), 4.85 (2H, d, J=7.8 Hz), 4.10 (2H, d, J=5.9 Hz), 3.80 (6H, s), 3.65 (3H, s), 2.03 (1H, br s). IR (neat): 3444 (OH), 1734 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_{14}H_{18}O_5$: 266.1149. Found: 266.1180.

The Reaction of 1 with Arylcopper Reagents in the Presence of $BF_3 \cdot Et_2O$ $BF_3 \cdot Et_2O$ (0.2 ml, 1.59 mmol) was added dropwise to a solution of 1.6 mmol of arylcopper reagent in ether at −78 °C under argon. After an additional 30 min of stirring, a solution of 100 mg (0.78 mmol) of **1** in 4 ml of ether was added dropwise. After 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography with 5—10% ethyl acetate in hexane to give **4** and a mixture of the corresponding 4-aryl and 2-aryl compounds. In the case of using **7h**, the 5-aryl compound **10h** was also obtained. **10h**: ^{1}H-NMR ($CDCl_3$) δ: 7.18 (1H, t, J=8.3 Hz), 7.04 (1H, dd, J=15.6, 3.9 Hz), 6.57 (2H, d, J=8.3 Hz), 6.04 ((1H, d, J=15.6 Hz), 4.51 (1H, m), 3.82 (6H, s), 3.72 (3H, s), 3.07 (1H, dd, J=13.7, 4.4 Hz), 2.95 (1H, dd, J=13.6, 7.8 Hz), 2.90 (1H, br s). IR (neat): 3476 (OH), 1722 (C=O) cm^{-1}. FAB-MS m/z: 267 (M^++1).

The Reaction of 1 with Lithium Bromide in the Presense of $BF_3 \cdot Et_2O$ $BF_3 \cdot Et_2O$ (0.45 ml, 3.58 mmol) was added to a suspension of 328 mg (3.78 mmol) of lithium bromide in 3 ml of ether at −78 °C under argon. After an additional 30 min of stirring, a solution of 210 mg (1.64 mmol) of **1** in 4 ml of ether was added dropwise. After 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography with 7—12% ethyl acetate in hexane to give 97.8 mg (0.468 mmol, 29%) of **4** and 158 mg (0.756 mmol, 46%) of **5**. **4**: ^{1}H-NMR ($CDCl_3$) δ: 6.91 (1H, dd, J=15.6, 4.4 Hz), 6.18 (1H, d, J=15.6 Hz), 4.57 (1H, m), 3.76 (3H, s), 3.57 (1H, dd, J=10.7, 3.9 Hz), 3.44 (1H, dd, J=10.7, 6.8 Hz), 3.09 (1H, br s). IR (neat): 3437 (OH), 1712 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_6H_9BrO_3$+H: 208.9810. Found: 208.9759. **5**: ^{1}H-NMR ($CDCl_3$) δ: 6.98 (1H, dd, J=15.6, 9.0 Hz), 6.09 (1H, d, J=15.6 Hz), 4.65 (1H, dt, J=9.0, 5.9 Hz), 3.89 (2H, d, J=5.9 Hz), 3.77 (3H, s), 2.70 (1H, br s). IR (neat): 3430 (OH), 1712 (C=O) cm^{-1}. HR-MS m/z: Calcd for $C_6H_9BrO_3$+H: 208.9810. Found: 208.9776.

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References and Notes

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