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REGIO- AND STEREO-SELECTIVITY IN THE REACTION OF METHYL 4,5-EPOXY-2-HEXENOATE WITH METHYLCOPPER REAGENTS

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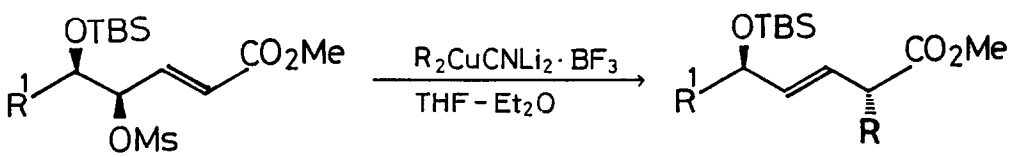
Abstract-The reaction of 4,5-epoxy-2-hexenoate (**3**) with methylcopper, dimethylcuprate, and their BF_3 complexes gave predominantly the γ-methylated product (**5**) via S_N2 process, while the reaction with methylcyanocuprate, higher order dimethylcyanocuprate and their BF_3 complexes afforded preferentially the α-methylated product (**4**) via S_N2' process. Anti-diastereoselectivity was observed regardless of the substitution pattern. The presence of $BF_3 \cdot OEt_2$ decreased the anti-selectivity, and in certain cases the opposite syn-diastereoselectivity was observed in the presence of excess $BF_3 \cdot OEt_2$. These regio- and stereoselectivities were discussed on the basis of CNDO/2 calculations.

We previously reported that the reaction of γ-mesyloxy-(E)-α,β-enoates (**1**) with $R_2Cu(CN)Li_2 \cdot BF_3$ or with $Me_2CuLi \cdot BF_3$ in certain cases gave the α-alkylated product (**2**) with extremely high diastereoselectivity (or enantioselectivity) in an essentially quantitative chemical yield[1] (eq 1).



(1)

1 2

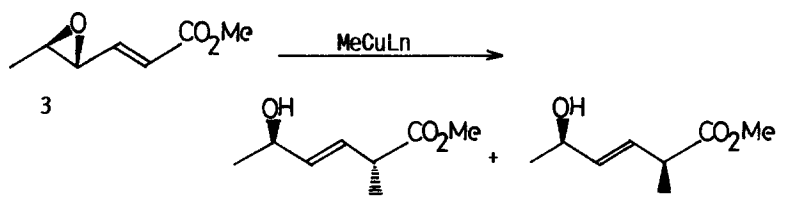
R=R[1]= Me chemical yield, 97 %
diastereoselectivity, > 99 %

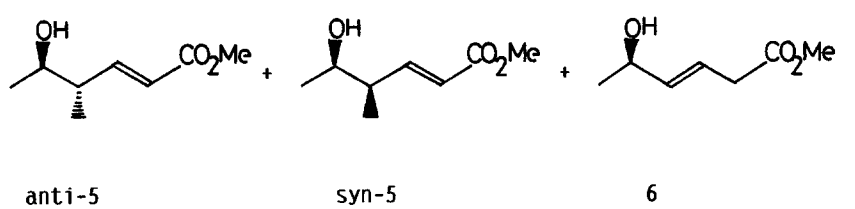
The reaction proceeded in anti-S_N2' manner and the 1,3-chirality transfer approaching 100% diastereomer excess was accomplished with the organocopper-Lewis acid reagent. Recently, this type of 1,3-chirality transfer has also been applied to α-alkyl-γ-mesyloxy-α,β-enoates, and highly efficient synthesis of chiral quaternary carbon center has been achieved.[2] These chiral transfer reactions provide the chiral building blocks useful for the synthesis of certain biologically active natural products.

In connection with our ultimate goal on macrolide synthesis, we required regio- and stereo-selective methylation of γ,δ-epoxy-α,β-unsaturated enoates. We report the regio- and stereo-selectivity in the reactions of methyl 4,5-epoxy-2-hexenoate (**3**) with various methylcopper reagents and other methylmetals, and discuss these selectivities on the basis of CNDO/2 calculations.

Results and Discussion

Reaction of **3** with methylcopper and related reagents. The epoxide (**3**) was prepared by the MCPBA epoxidation of methyl sorbate according to the literature procedure.[3] The reactions of various methylcopper reagents and other methyl-metals were carried out at -78°C under nitrogen atmosphere. The products were isolated by a column chromatography (eq 2), and the product ratio was determined by a capillary GLC. The results are summarized in Table 1.





(2)

Methyl copper, dimethylcuprate, and their BF_3 complexes gave the γ-methylated product (**5**) predominantly (entries 1-4).[4] Trimethylaluminum and the

Table 1. Reactions of **3** with Various Methylmetals

Entry	Reagents (equiv.)	Product ratio			Total yield[a] %	**3** (%)
		Regio-selectivity	Diastereo-selectivity			
		4 : **5**	**4** anti : syn	**5** anti : syn	**4**+**5**+**6**[c]	
1	MeCu (3)	25 : 75	87 : 13	97 : 3	65	2
2	$MeCu \cdot BF_3$ (3)	38 : 62	[b]	47 : 53	42	3
3	Me_2CuLi (3)	21 : 79	71 : 29	96 : 4	58 (39)[c]	-
4	$Me_2CuLi \cdot BF_3$ (1.5)	24 : 76	45 : 55	63 : 37	54 (9)	1
5	MeCuCNLi (3)	68 : 32	99 : 1	97 : 3	71 (12)	3
6	$MeCuCNLi \cdot BF_3$ (3)	61 : 39	80 : 20	89 : 11	53 (7)	-
7	$Me_2CuCNLi_2$ (2)	64 : 36	97 : 3	95 : 5	61 (39)	-
8	$Me_2CuCNLi_2 \cdot 0.5BF_3$ (2)	67 : 33	76 : 24	93 : 7	71 (5)	9
9	$Me_2CuCNLi_2 \cdot BF_3$ (2)	68 : 32	79 : 21	94 : 6	65 (9)	-
10	$Me_2CuCNLi_2 \cdot 2BF_3$ (2)	64 : 36	69 : 31	91 : 9	77 (3)	3
11	$Me_2CuCNLi_2 \cdot 5BF_3$ (2)	79 : 21	30 : 70	54 : 46	84	-
12	Me_3Al/CH_2Cl_2 (2)	11 : 89	45 : 55	83 : 17	47	20
13	$Me_4Al^-Li^+$/ether (2)	21 : 79	44 : 56	90 : 10	73	19

[a] Isolated yield. [b] The ratio was not determined. [c] In the parenthesis, the yield of **6** was indicated. In entries 1,2, and 11-13, **6** was not formed.

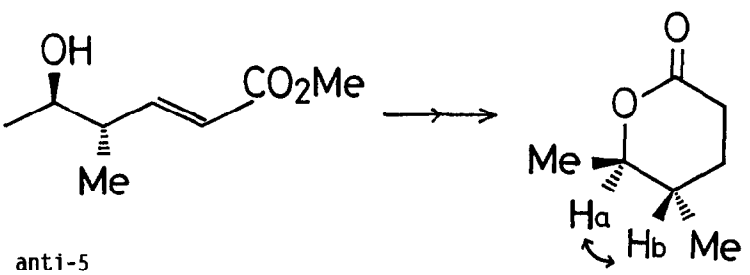
ate complex (Me_4AlLi) also afforded **5** preferentially (entries 12 and 13).[5] On the other hand, methylcyanocuprate, higher order $Me_2CuCNLi_2$, and their BF_3 complexes produced the α-methylated isomer (**4**) predominantly (entries 5-11). It is widely accepted that the reaction of vinyloxiranes with organocopper reagents proceeds through S_N2' pathway.[6] In this respect, the present regioselectivity is interesting; the copper reagents bearing CN ligand react predominantly in S_N2' manner, while the ordinary methylcopper and dimethylcuprate add predominantly in S_N2 manner.

Anti-diastereoselectivity was always observed with MeCu, Me_2CuLi, MeCuCNLi, and $Me_2CuCNLi_2$ regardless of the substitution mode (S_N2' and S_N2) (entries 1, 3, 5, and 7). The presence of $BF_3 \cdot OEt_2$ decreased the extent of anti-diastereoselectivity, and the opposite syn-selectivity became predominant in certain cases (compare entries 1 vs. 2, 3 vs. 4, and 5 vs. 6). The regioselectivity was not so influenced by the presence of $BF_3 \cdot OEt_2$ as shown in entries 1-6. The amount of $BF_3 \cdot OEt_2$ was changed from 0.5 eq to 5 eq in the reaction of $Me_2CuCNLi_2$ (entries 8-11). Here again, the regioselectivity was not so affected, but the anti-diastereoselectivity of **4** and **5** decreased with increase of $BF_3 \cdot OEt_2$. With 5 eq $BF_3 \cdot OEt_2$, the anti-selective formation of **4** was changed to the syn-preference (entry 11). With trimethylaluminum and the ate complex, **5** was produced anti-selectively while **4** was afforded non-stereoselectively (entries 12 and 13).

The anti-diastereoselectivity of **5** in the absence of $BF_3 \cdot OEt_2$ was quite high (>95%). $BF_3 \cdot OEt_2$ coordinates to the oxygen atom of epoxide ring and partially cleaves the ring before the attack of the copper reagents (entries 2 and 4), resulting in low diastereoselectivity.[§] Compared with $MeCu \cdot BF_3$ and $Me_2CuLi \cdot BF_3$, methylcyanocuprate-BF_3 and higher order dimethylcyanocuprate-BF_3 reagents exhibited fairly high anti-selectivity (entries 6, 8-10). This difference is presumably due to the coordination of $BF_3 \cdot OEt_2$ to the nitrogen atom of the CN ligand. The complex between the cyanocopper reagents and $BF_3 \cdot OEt_2$ must be formed in situ and this complex must attack the epoxide. On the other hand, $BF_3 \cdot OEt_2$ and MeCu (or Me_2CuLi) presumably react independently owing to the weak interaction between $BF_3 \cdot OEt_2$ and the copper reagents. Even in the case of $Me_2CuCNLi_2$, use of large excess of $BF_3 \cdot OEt_2$ caused the ring opening, resulting in loss of anti-selectivity (entry 11). Roughly speaking, similar trend was also observed for the diastereoselectivity of **4**.

Significant amounts of the reduction product (**6**) was formed with Me_2CuLi, MeCuCNLi, and $Me_2CuCNLi_2$ (entries 3, 5, and 7). The presence of $BF_3 \cdot OEt_2$ suppressed formation of **6** (entries 4, 6, 8-11), as previously observed in the reaction of **1**.[1] Presumably, **6** arises via an electron transfer to **3** from the cuprate reagents. The presence of $BF_3 \cdot OEt_2$ decreases this electron transfer process and enhances the nucleophilic process.

Determination of stereochemistry. The stereochemistry of **4** was determined by comparison with authentic samples, prepared by the desilylation of the stereodefined **2** and its stereoisomer ($R = R^1 = Me$). The cyclization of anti-**5** was carried out by a sequence of reactions [(i) H_2/10% Pd-C in MeOH; (ii) MeCN-$BF_3 \cdot OEt_2$-HF (98 : 1 : 1)]. The coupling constant of Ha and Hb of the resulting lactone (**7**) was 8Hz, clearly indicating that the starting **5** possessed anti-configuration.

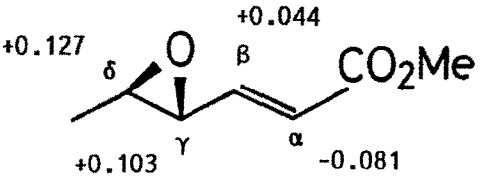


anti-5 7

CNDO/2 calculations. To rationalize the regioselectivity in the reaction of **3** with the copper reagents, we carried out CNDO/2 calculations. Atomic charge distribution and electron densities of LUMO and NLUOMO are summarized in Scheme 1. The charge distribution at the γ-position is positive (+0.103), while that at the α-position is negative (-0.081). Therefore, the harder nucleophiles like MeCu, Me_2CuLi, their BF_3 complexes, Me_3Al, and $Me_4Al^-Li^+$ attack predominantly the γ-position under charge control seeking the most positive center. Although the charge distribution at the δ-position is

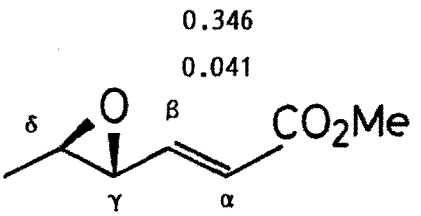
CNDO/2 calculation

Atomic charge distribution



Electron densities of LUMO and NLUMO

LUMO ... 0.049
NLUMO ... 0.183



LUMO ... 2.54 eV
NLUMO ... 6.08 eV

Scheme 1

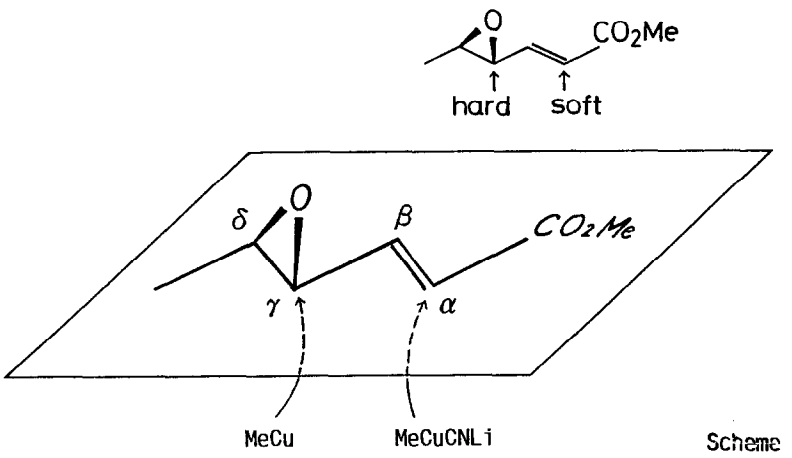
more positive than that at the γ-position, coordination[7] of the reagents to α,β-enoate system must deliver the nucleophiles to the γ-position.

The electron density of LUMO at the α-position (0.225) is significantly larger than that at the γ-position (0.017). Accordingly, the softer copper reagents such as MeCuCNLi, $Me_2CuCNLi_2$, and their BF_3 complexes react predominantly at the α-position under orbital control, producing **4** via S_N2' process. The largest coefficient is at the β-position, but the conjugate addition to the enoate system does not take place. Similarly, γ,δ-dioxygenated α,β-enoates (1) do not undergo the conjugate addition, but undergo S_N2' substitution reaction.[1] The substituent at the γ-position may prevent the addition at the β-position owing to the steric reason.

Since the present discussion does not involve the HOMO level of reagents, it is difficult to explain the regioselectivity quantitatively. However, we can qualitatively understand the regioselectivity on the basis of both the charge distribution and LUMO electron density. MNDO calculations of simple butadiene monoxide have been done quite recently.[8] The present calculation will help to understand the interesting regioselectivity of the methoxycarbonyl substituted analog, though it is CNDO/2. Previously, most organocopper reagents are believed to be a soft nucleophile and react with butadiene epoxide derivatives in S_N2' manner.[6] The present system differentiates the cyanocopper reagents from Me_2CuLi and MeCu. Therefore, it is concluded that the cyanocopper reagents are softer than the cuprate and simple copper reagents.

A delicate shade of difference of softness among the copper reagents is, for the first time, brought to light by the methoxycarbonyl substituted butadiene epoxide derivative. Our conclusion is summarized in Scheme 2.

Acknowledgement. Professor T. Azumi and Mr. K. Maeda are gratefully acknowledged for helping us to perform CNDO/2 calculations. Professor Font and his group are also acknowledged for sending us full computer print out for the MNDO calculations on butadiene monoepoxide.



Scheme 2

Experimental

^{1}H NMR spectra were recorded with a Varian XL-200, Jeol GSX-270 or GX-400 instruments with TMS as an internal standard. IR spectra were recorded with a Hitachi 215 spectrophotometer. Mass spectra were recorded with a Hitachi M-52, Jeol JMS-01SG-2 or DX-303 spectrometer. Elemental analyses were performed by the Tohoku University Microanalytical Center. GLC analyses were performed on a Shimazu GC-14A or GC-4CM by using a capillary column (PEG20M). All temperatures are uncorrected. Reagents and solvents were purified by standard techniques and kept over a drying agent. Cuprous iodide was purchased and purified as described previously.[9] Copper cyanide was purchased and used as such. Methyllithium in ether was a commercial product and titrated by the reported procedure.[10] Other chemicals including methyl sorbate, Me_3Al in hexane, etc., were purchased and used as such.

Reactions of **3** with methylmetals. Methylcopper, dimethylcuprate, and their BF_3 complexes were prepared as described previously.[11] Lithium cyanocuprate, higher order lithium dimethylcyanocuprate, and their BF_3 complexes were prepared according to the literature procedure.[12] To an ether solution of

the methyl copper reagent (0.5mmol) was added **3** (0.5mmol) at -78°C. The reaction was stirred for 3 hr (for 6 hr in the case of MeCu) at this temperature, and then quenched at -78°C with an aqueous NH_4Cl solution in the case of Me_2CuLi and their BF_3 complexes, or quenched with an aqueous NH_4Cl-NH_4OH solution in the case of MeCuCNLi, $Me_2CuCNLi_2$, and their BF_3 complexes. In MeCu addition the reaction was quenched at 0°C. The products were extracted with ether, dried over $MgSO_4$, and filtered through short column of silica gel. In the aluminum reagents, a similar procedure was used. To a hexane solution of Me_3Al (0.5mmol) or to a hexane-ether solution of Me_4AlLi (0.5mmol) was added **3** (0.5mmol) at -78°C. The mixture was stirred for 3 hr at this temperature, and was allowed to warm to room temperature in entry 12. After 12 hr at this temperature, the reaction was quenched with an aqueous NH_4Cl solution. In entry 13, the reaction was allowed to warm to 0°C, and then quenched in a similar way. The product was analyzed by a capillary GLC (PEG, 25m).

anti Methyl 5-hydroxy-2-methyl-3-hexenoate (**anti-4**). ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J=7.2Hz, 3), 1.26 (d, J=6.0Hz, 3), 1.64-1.75 (brs, 1), 3.15 (dq, J=7.2Hz, 7.3Hz, 1), 3.69 (s, 3), 4.31 (dq, J=5.9Hz, 6.0Hz, 1), 5.63 (dd, J=5.9Hz, 15.4Hz, 1), 5.75 (dd, J=7.3Hz, 15.4Hz, 1); IR (CCl_4) 3623, 3450, 1742, 1441, 1170, 1054 cm^{-1}); MS calcd for $C_8H_{14}O_3$ m/z 158.0943, found m/z 158.0931.

anti Methyl-5-hydroxy-4-methyl-2-hexenoate (**anti-5**). ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J=7Hz, 3), 1.20 (d, J=6.3Hz, 3), 1.47-1.71 (brs, 1), 2.36 (dddq, J= 1.2Hz, 6.2Hz, 7Hz, 8.4Hz, 1), 3.74 (s, 3), 3.75 (dq, J=6.2Hz, 6.3Hz, 1), 5.89 (dd, J=1.2Hz, 15.6Hz, 1), 6.96 (dd, J=8.4Hz, 15.6Hz, 1); IR (CCl_4) 3610, 3450, 1725, 1656, 1435, 1095cm^{-1}; MS calcd for $C_8H_{14}O_3$ m/z 158.0943, found m/z 158.0898. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.47; H, 9.10.

trans-4,5-Dimethyl-5-pentanolide (**7**). ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J= 6.3Hz, 3), 1.37 (d, J=6.3Hz, 3), 1.48-1.70 (m, 2), 1.84-1.96 (m, 1), 2.49 (ddd, J=7.2Hz, 9.9Hz, 17.3Hz, 1), 2.64 (ddd, J=4.2Hz, 6.4Hz, 17.3Hz, 1), 4.06 (dq, J=6.3Hz, 9.5Hz, 1); IR (CCl_4) 1728, 1224, 1097cm^{-1}; MS calcd for $C_7H_{12}O_2$ m/z 128.0837; found m/z 128.0829.

Methyl 5-(t-butyldimethylsilyloxy)-3-hexenoate. ^{1}H NMR ($CDCl_3$) δ 0.04 (brs, 6), 0.88 (s, 9), 1.19 (d, J=6.5Hz, 3), 3.04 (d, J=6.5Hz, 2), 3.67 (s, 3), 4.28 (dq, J=4.9Hz, 6.5Hz, 1), 5.57 (dd, J=4.9Hz, 15.2Hz, 1), 5.68 (dt, J=6.5Hz, 15.2Hz, 1); IR (CCl_4) 1743, 1438, 1258, 1165, 1084, 977, 840cm^{-1}. Isolation of **6** in pure form was difficult, and thus the structure was determined as the TBS derivative.[1]

Calculations. The supplementary data in the paper of Font[8] were used to determine the X-, Y-, and Z-coordinates of the transoid and cisoid conformations. The CNDO/2 calculations were carried out by the CNDO/2 program given by Professor Azumi. The calculations of the transoid enoate is shown in Scheme 1. A similar result is also obtained in the case of the cisoid enoate.

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§ As an alternative explanation for the high syn/anti S_N2 ratio with BF_3 coordinated reagents, it is likely that **syn-5** is formed by rearrangement of the σ-complex precursors (**syn-4, anti-4,** and **anti-5**) via the π-complex in accord with the proposals of Goering; H. L. Goering, S. S. Kantner, J. Org. Chem. **1981**, 46, 2144.