# Chelation-Controlled 1,3-Asymmetric Induction in Radical Addition to γ-Hydroxy- and γ-Alkoxy-α-methylenecarboxylic Esters

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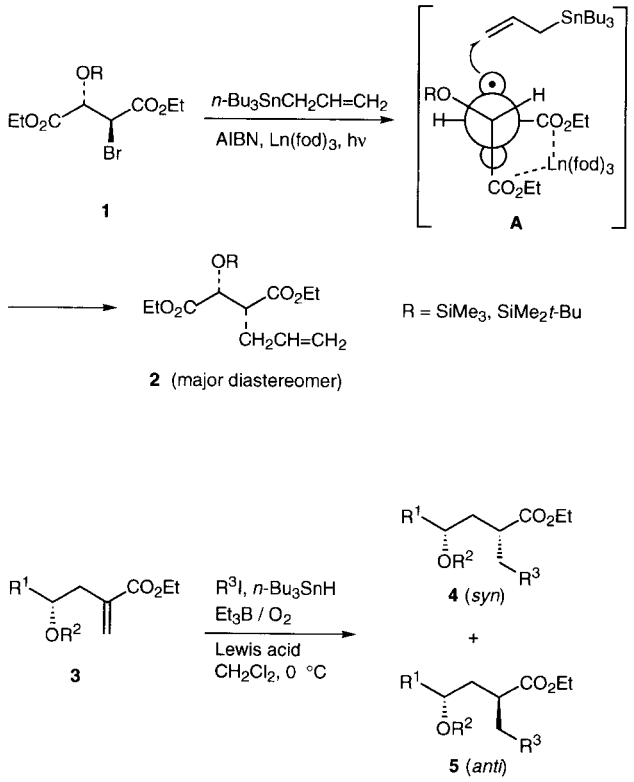
**Abstract:** The radical-mediated reactions of γ-hydroxy- and γ-alkoxy-α-methylenecarboxylic esters **3** ($R^1$ = Ph, *i*-Bu, and *t*-Bu, $R^2$ = H, Me, MOM, and MEM) with isopropyl iodide or cyclohexyl iodide performed in the presence of Lewis acids gave the *syn*-adducts **4** predominantly, whereas the *anti*-adduct **5** was the major product in the reaction of **3** ($R^1$ = Ph, $R^2$ = Me) with *t*-butyl iodide.

**Key words:** radical, 1,3-asymmetric induction, chelation, Lewis acid, γ-alkoxy-α-methylenecarboxylic esters

The chelate ring formation of radical intermediates with Lewis acid plays an important role in the stereochemical control of acyclic radical reactions.[1,2] We have recently shown that the allylation of α-bromo-β-siloxy esters **1** conducted in the presence of Lewis acid proceeded through the transition state model **A** involving a seven-membered chelate ring and yielded the *syn*-product **2** predominantly (Scheme 1).[3] We now report the chelation controlled 1,3-asymmetric induction in radical addition to γ-hydroxy- and γ-alkoxy-α-methylenecarboxylic esters **3**. Little is known about 1,3-asymmetric induction in radical reactions.[4]

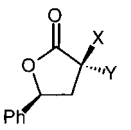
The Reformatsky reaction of aldehydes $R^1$-CH=O ($R^1$ = Ph, *t*-Bu, and *i*-Bu) with ethyl α-bromomethylacrylate gave racemic γ-hydroxy-α-methylenecarboxylic esters **3** in high yields (≥86%).[5,6] Methylation of the alcohol **3** ($R^1$ = Ph, $R^2$ = H) with methyl iodide and silver(I) oxide gave methyl ether **3** ($R^1$ = Ph, $R^2$ = Me) in 56% yield together with γ-lactone **6**. However, methyl ethers of the alcohols **3** ($R^1$ = *t*-Bu, and *i*-Bu, $R^2$ = H) were not obtained due to the formation of the corresponding γ-lactones. Methoxymethyl (MOM) and methoxyethoxymethyl (MEM) ethers **3** ($R^1$ = Ph, *t*-Bu, and *i*-Bu, $R^2$ = MOM and MEM) were prepared from the corresponding alcohols **3** ($R^1$ = Ph, *t*-Bu, and *i*-Bu, $R^2$ = H) following the standard procedures.

After a 10 min complexation time, the alkylation of acrylates **3** was conducted with alkyl iodide $R^3I$ (3 equiv.), *n*-$Bu_3SnH$ (2 equiv.), and $Et_3B$ (0.3 equiv.) as a radical initiator[7] in $CH_2Cl_2$ at 0 °C. The concentration of **3** was 0.07–0.13 mol $dm^{-3}$ in all the reactions. The diastereomer ratios of the products were determined by $^1H$ NMR analysis. The stereochemistry of **4** and **5** was determined as follows. Treatment of the mixture of hydroxy esters **4** and **5** ($R^1$ = Ph, $R^2$ = H, $R^3$ = *i*-Pr; **4** : **5** = 2 : 1) with *p*-toluenesulfonic acid in benzene gave γ-lactones **7** and **8** (**7** : **8** = 2 : 1). The assignment of the γ-lactones was performed by




**Scheme 1**

the comparison of their $^1H$ NMR spectra with those of authentic γ-lactones prepared from α-methylene-γ-lactone **6** following the reported procedures.[8] Methylation of **4** and **5** ($R^1$ = Ph, $R^2$ = H) with methyl iodide and silver(I) oxide gave the corresponding methyl ethers **4** and **5** ($R^1$ = Ph, $R^2$ = Me), respectively. The stereochemistry of **4** and **5** ($R^1$ = *t*-Bu and *i*-Bu, $R^2$ = H, MOM, and MEM) was assigned by comparing their $^1H$ NMR spectral data with those of **4** and **5** ($R^1$ = Ph, $R^2$ = H and Me).[9]




**6** X, Y = $CH_2$
**7** X = H, Y = $CH_2CHMe_2$
**8** X = $CH_2CHMe_2$, Y = H

A summary of the addition reactions is given in Table 1. In the absence of Lewis acid, the reactions of **3** showed poor stereoselectivity (**4** : **5** = 1 : 1.4–1.6, entry 1) except

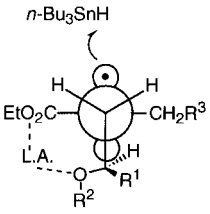
for that of **3** ($R^1$ = *i*-Bu, $R^2$ = MEM; entry 16). The diastereoselectivity was remarkably affected when the reaction was conducted in the presence of Lewis acid. Use of 3 equiv of $MgBr_2 \cdot OEt_2$ reversed the diastereoselectivity of the reaction of alcohol **3** ($R^1$ = Ph, $R^2$ = H; entry 2) with isopropyl iodide,[2k] but low selectivity (entry 2). The reaction of the methyl ether **3** ($R^1$ = Ph, $R^2$ = Me) with isopropyl iodide or cyclohexyl iodide performed in the presence of $MgBr_2 \cdot OEt_2$, $MgBr_2$, $ZnCl_2$, or Eu(fod)$_3$ [= tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium] gave higher selectivities (entries 3–7). As expected from our previous results in the allylation of **1**,[3] La(fod)$_3$ was highly efficient (entry 8). $MgI_2$ was less effective, and tris(2,4-pentadionato)lanthanum and tris(1,3-diphenyl-1,3-propanedionato)-lanthanum] had no effect on the stereocontrol. The reaction of the methyl ether **3** with *t*-butyl iodide performed in the presence of Lewis acid gave the *anti*-product **5** predominately (entries 9 and 10).

The MOM and MEM ethers **3** ($R^1$ = Ph, $R^2$ = MOM and MEM; entries 11, 12, and 15) gave a poorer result than the methyl ether **3**. In the reactions of **3** ($R^1$ = *t*-Bu and *i*-Bu, $R^2$ = MOM and MEM), use of Lewis acid reversed the diastereoselectivity, but the selectivities were low (entries 13 and 16–18) except for **3** ($R^1$ = *t*-Bu, $R^2$ = MOM; entry 14 ).

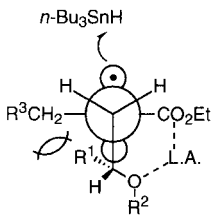
**Table 1.** Radical Reactions of γ-Hydroxy- and γ-Alkoxy-α-methylenecarboxylic Esters **3** with Alkyl Iodides

| entry | $R^1$ | $R^2$ | $R^3$ | Lewis acid (equiv) | Yield (%) | Diastereomer ratio (**4** : **5**) |
|---|---|---|---|---|---|---|
| 1 | Ph | H | *i*-Pr | — | 86 | 1 : 1.4 |
| 2 | Ph | H | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 80 | 2.5 : 1 |
| 3 | Ph | Me | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 96 | 4.3 : 1 |
| 4 | Ph | Me | *i*-Pr | $MgBr_2$ (3) | 92 | 4.5 : 1 |
| 5 | Ph | Me | *i*-Pr | $ZnCl_2$ (3) | 81 | 4.7 : 1 |
| 6 | Ph | Me | *i*-Pr | Eu(fod)$_3$ (1) | 89 | 4.6 : 1 |
| 7 | Ph | Me | *c*-Hex | $MgBr_2 \cdot OEt_2$ (3) | 70 | 3.7 : 1 |
| 8 | Ph | Me | *i*-Pr | La(fod)$_3$ (1) | 90 | 11 : 1 |
| 9 | Ph | Me | *t*-Bu | $MgBr_2 \cdot OEt_2$ (3) | 91 | 1 : 3.8 |
| 10 | Ph | Me | *t*-Bu | La(fod)$_3$ (1) | 99 | 1 : 7.0 |
| 11 | Ph | MOM | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 63 | 2.8 : 1 |
| 12 | Ph | MOM | *i*-Pr | La(fod)$_3$ (1) | 80 | 3.2 : 1 |
| 13 | *t*-Bu | MOM | *i*-Pr | La(fod)$_3$ (1) | 93 | 2.0 : 1 |
| 14 | *t*-Bu | MOM | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 78 | 10 : 1 |
| 15 | Ph | MEM | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 96 | 1.5 : 1 |
| 16 | *i*-Bu | MEM | *i*-Pr | — | 87 | 1 : 2.4 |
| 17 | *i*-Bu | MEM | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 80 | 2.0 : 1 |
| 18 | *t*-Bu | MEM | *i*-Pr | $MgBr_2 \cdot OEt_2$ (3) | 95 | 3.7 : 1 |

In the absence of Lewis acid, *n*-$Bu_3SnH$ would approach equally from the both faces of the radical center in an open-chain transition state model to yield **4** and **5**. In the presence of the Lewis acids, the reaction of **3** with isopropyl iodide or cyclohexyl iodide proceeds probably through the transition state model **B** involving a seven-membered chelate ring. *n*-$Bu_3SnH$ should attack from the less hindered face of the model **B** to yield *syn*-adduct **4**. The transition model **C** yielding *anti*-adduct **5** is less preferable due to the steric repulsion between $R^1$ and $CH_2R^3$ groups. The high *syn* selectivity of **3** ($R^1$ = *t*-Bu, $R^2$ = MOM; entry 14) reflects the very large interaction between the bulky *t*-butyl and *i*-butyl groups in model **C**. The *anti* selectivity in the reaction of **3** ($R^1$ = Ph, $R^2$ = Me) with *t*-BuI (entries 9 and 10) may be ascribable to the shielding of the upper face of model **B** by the bulky neopentyl group. We have shown that the shielding of the upper face of model **A** by the bulky *t*-$BuPh_2SiO$ group lowered the *syn* selectivity in the allylation of **1** (R = $SiPh_2$*t*-Bu).[3]



**B**



**C**

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