# Enantioselective Aldol Reaction Using Bornane-2,3-diol–Aluminum Complex as a Chiral Lewis Acid

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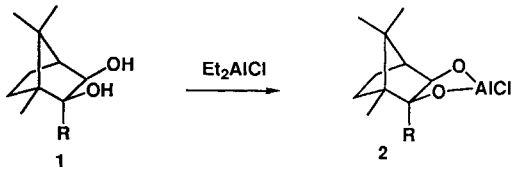
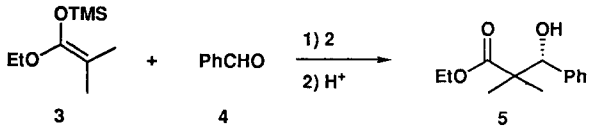
*Dedicated to Professor E. J. Corey in appreciation of his great contribution to organic synthesis*

**Abstract**: β-Hydroxy ester was formed in high enantiomeric excess by the reaction of ketene silyl acetal with aldehyde in the presence of a chiral Lewis acid prepared from diethylaluminum chloride and chiral diol derived from (+)-camphor.

Ready accessibility of camphor in both enanttiomeric forms coupled with recent interest in the creation of asymmetric environment induced by a Lewis acid[1] has prompted us to search for a new chiral Lewis acids. Several years ago Reetz reported that the use of a chiral Lewis acid prepared from (-)-pinanediol and diethylaluminum chloride met with moderate success in the reaction of ketene silyl acetal with aldehyde, and aldol adduct was formed in 15% yield with 66% ee.[2] This observation is quite interesting because the asymmetric induction was possible using a simple aluminum reagent which underwent ready aggregation. Recently remarkable achievement was reported by Yamamoto and Maruoka who used aluminum reagents possessing sterically demanding ligands.[3] High asymmetric induction attained by them may be in part due to the formation of monomeric aluminum reagents effected by such bulky ligands. We have been interested in the use of camphor derivatives as chiral auxiliary and already disclosed β-lactam synthesis and imino pinacol coupling.[4] Considering accessibility and the ease in manipulating their functionalities, we investigated new Lewis acids formed from camphor derivatives, and would like to report herein an asymmetric aldol reaction promoted by chiral Lewis acids derived from bornane-2,3-diols.




a: R = H, b: R = Me, c: R = Et, d: R = $^i$Pr, e: R = Ph




Chiral ligands were readily prepared from (+)-camphor in the following manner: (+)-camphor was oxidized with selenium dioxide to give camphorquinone in 70% yield,[5] and the subsequent reduction with DIBAL gave the diol **1a** in 92% yield,[6] whereas protection of one of the carbonyls with ethylene glycol followed by Grignard addition, deprotection, and reduction afforded alkyl- or phenyl-substituted diols **1b~e** in good overall yields.[7]

First, the effect of substituent was examined. The chiral Lewis acid **2** was prepared by mixing diol **1** and diethylaluminum chloride in toluene at 70 °C for 1.5 h, and the addition reaction was carried out by adding a mixture of ketene silyl acetal **3** and benzaldehyde **4** in toluene at -78 °C ~ room temp. The results are summarized in Table 1.

**Table 1.** The Effects of Substituent in the Aldol Reaction[a]

| Entry | Diol | Time / h | Temp/°C | Yield/%[b] | %ee[c] |
|---|---|---|---|---|---|
| 1 | **1a** | 8 | -78 ~ -3 | 14 | 74 |
| 2 | **1b** | 15 | -78 ~ rt | 21 | 55 |
| 3 | **1c** | 12 | -78 ~ rt | 19 | 50 |
| 4 | **1d** | 10 | -78 ~ rt | 33 | 17 |
| 5 | **1e** | 8 | -78 ~ -3 | 24 | 25 |

[a]The reaction was carried out according to the typical experimental procedure except for the temperature (70 °C for 1.5 h) for the preparation of the chiral Lewis acid. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary column (Daicel OJ), and the absolute configuration was determined by comparison of the optical rotation.[8]

As shown in Table 1, the reaction was sensitive to the steric bulk of the substituent, and *i*-propyl, a sterically demanding group, did not record good enantiofacial discrimination, whereas sterically less-demanding groups provided good discrimination. In particular, when R was H the highest enantiofacial discrimination was observed. These observations suggest that a highly associated active Lewis acid species would be formed in the present reaction. To clarify this hypothesis the molecular weight determination was carried out on the complex formed from diol **1a** and diethylaluminum chloride.[9] An average molecular weight of about 8000 was obtained for the complex, which indicated that a highly associated complex was actually formed in the present reaction medium.

Reaction conditions for the complex formation using diol **1a** and addition steps were examined in order to optimize the present reaction, and Table 2 summarizes the results.

**Table 2.** Comparison of Reaction Conditions[a]

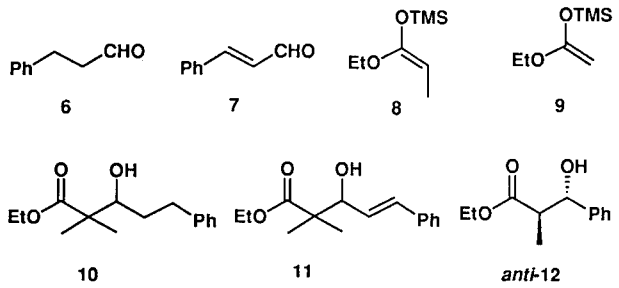
| Entry | Solv | Conctn/M | Temp 1/°C[b] | Temp 2/°C[c] | Yield/%[d] | %ee[e] | Config[f] |
|---|---|---|---|---|---|---|---|
| 1 | $PhCH_3$ | 0.075 | 70 | -78~3 | 14 | 74 | *R* |
| 2 | $PhCH_3$ | 0.075 | rt | -73~23 | 28 | 80 | *R* |
| 3 | $PhCH_3$ | 0.15 | 0 | 0 | 64 | 75 | *R* |
| 4 | $PhCH_3$ | 0.075 | 0 | 0 | 64 | 82 | *R* |
| 5 | $PhCH_3$ | 0.05 | 0 | 0 | 44 | 88 | *R* |
| 6 | $PhCH_3$ | 0.038 | 0 | 0 | 37 | 90 | *R* |
| 7 | $PhCH_3$ | 0.025 | 0 | 0 | 39 | 89 | *R* |
| 8 | $PhCH_3$ | 0.075 | -23 | -23~0 | 17 | 13 | *S* |
| 9 | $PhCH_3$ | 0.075 | -46 | -46 | 34 | 12 | *S* |
| 10 | $CH_2Cl_2$ | 0.05 | 0 | 0 | 46 | 31 | *R* |
| 11 | PhCl | 0.05 | 0 | 0 | 55 | 71 | *R* |
| 12 | PhH | 0.05 | 15 | 15 | 34 | 93 | *R* |

[a]The reaction was carried out according to the typical experimental procedure using **1a** as a chiral auxiliary. [b]Temperature for the preparation of the chiral Lewis acid. [c]Temperature for the addition reaction. [d]Isolated yield. [e]Determined by HPLC analysis using a chiral stationary column (Daicel OJ). [f]Determined by comparison of the optical rotation.[8]

The reaction temperature for the complex formation was crucial both for the product yield and the enantiomeric purity, and the reactions conducted at 0 °C improved the product yield up to 64%.

Concentration of the substrates was also crucial for the enantiofacial selectivity, and the lower concentration produced better enantiomeric excess. Interestingly, the reaction conducted at -23 or -46 °C gave the aldol product of opposite stereochemistry, where *S*-isomer was formed, indicating that the stage of aggregation was highly dependent on the reaction temperature. Among the solvents screened, toluene or benzene was found to be the solvent of choice, where the latter recorded the highest enantifacial discrimination.

The following example represents a typical experimental procedure: to a solution of the diol **1a** (31.9 mg, 0.187 mmol) in toluene (2 mL) was added $Et_2AlCl$ (0.158 mL, 0.95 M in *n*-hexane, 0.150 mmol) at 0°C during 10 min, and the mixture was stirred at 0 °C for 4.8 h. A mixture of the ketene silyl acetal **3** (31.1 mg, 0.165 mmol) and benzaldehyde (15.9 mg, 0.150 mmol) in toluene (2 mL) was added to the resulting mixture at 0 °C during 50 min. After being stirred at 0 °C for 22 h, the reaction mixture was quenched by adding a phosphate buffer solution (2 mL), and the entire mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (5 mL x 3), and the combined extracts were dried over $MgSO_4$. After concentration, the crude oil was purified on preparative TLC to give adduct **5** as a colorless oil (21.5 mg, 64 %). HPLC analysis using a chiral stationary column (Daicel OJ) indicated that the enantiometric purity was 82% ee.




3-Phenylpropanal **6**, and (*E*)-cinnamaldehyde **7** also participated in the present aldol reaction with the ketene silyl acetal **3** to give the aldol adducts **10**, **11** in 50% yield with 58% ee,[10] and 61% yield with 87% ee,[10,11] respectively. The *anti*-selectivity was observed in the reaction of ketene silyl acetal **8** with benzaldehyde, where the ratio of *anti*-(2*R*,3*S*)-**12** : *syn*-(2*S*,3*S*)-**12** was 80 : 20 with 90% ee[12,13] of the major isomer being obtained. However, the ketene silyl acetal **9** derived from simple acetate did not react with aldehydes under the present conditions, and no aldol product was obtained.

In conclusion, the chiral Lewis acid **2a** prepared from bornane-2,3-diol **1a** and diethylaluminum chloride provides a simple entry into β-hydroxy esters in an enantioselective manner. The behavior of a highly associated Lewis acid studied here is of interest in contrast to the well-dissociated counterparts successfully used in a variety of reactions. Since the recovery of the chiral auxiliary from the reaction mixture was simply carried out on TLC in good yield (>85%), the present procedure offers a convenient addition to the existing methodologies of asymmetric aldol reactions.

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(10) Determined by HPLC analysis (Merk Hibar column) of the MTPA derivative.

(11) Determined by GLC analysis using a chiral stationary column (Chiraldex G-TA, 20 m).

(12) Determined by HPLC analysis using a chiral stationary column (Daicel OJ).

(13) Cf. Denmark, S. E.: Griedel, B. D.: Coe, D. M.: Schnute, M. E. *J. Am. Chem. Soc.*, **1994**, *116*, 7026.