Stereoselective Reactions. II.1) Asymmetric Synthesis of 
\( \beta \)-Substituted Aldehydes by Michael Reaction using 
Chiral \( \alpha,\beta \)-Unsaturated Aldimines2)

SHUN-ICHI HASHIMOTO, NOBUYASU KOMESHIMA, SHUN-ICHI YAMADA, 
and KENJI KOGA

Faculty of Pharmaceutical Sciences, University of Tokyo3)

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The Michael reaction of diethyl malonate with chiral \( \alpha,\beta \)-unsaturated aldimines (4), 
prepared from crotonaldehyde and optically active \( \alpha \)-amino acid tert-butyl esters (3), 
was found to give the corresponding \( \beta \)-substituted aldehydes (5) in reasonably high optical 
yields after hydrolysis. A proposed stereoechemical mechanism of the reaction is presented.

Keywords—asymmetric synthesis; asymmetric Michael reaction; \( \alpha \)-amino acid 
ester; stereochemistry; absolute configuration; chelate; bidentate ligand; \( \beta \)-substituted 
aldehyde; \( \alpha,\beta \)-unsaturated aldimine

The Michael reaction is one of the most useful reactions in synthetic organic chemistry,4) 
because the Michael adducts are molecules bearing functional groups and have great potential 
for conversion into various types of compounds by chemical transformations. It is therefore 
highly desirable for the synthesis of optically active compounds such as natural products, 
pharmaceuticals, etc., to devise methods to make this reaction highly asymmetric. Consulting 
references,5) it is surprising to note that this area remains in a relatively primitive state of 
development.6)

In previous papers,1,7) we have reported that 1,4-addition of Grignard reagents to chiral 
\( \alpha,\beta \)-unsaturated aldimines (1), prepared from \( \alpha,\beta \)-unsaturated aldehydes and optically active 
\( \alpha \)-amino acid tert-butyl esters (3), gives the optically active \( \beta \)-substituted aldehydes (2) in 
quite high enantiomeric purities after hydrolysis. It has also been reported that high levels 
of asymmetric induction can be achieved by fixing the reactive conformation by chelation.1,7)
In line with this approach to devise efficient methods for the asymmetric syntheses of a variety 
of chiral and functionalized compounds via chelate formation, the present paper describes 
the asymmetric Michael addition of diethyl malonate to chiral \( \alpha,\beta \)-unsaturated aldimines.

It is known that the Michael addition of a malonate system having two \( \alpha \)-hydrogen 
atoms to \( \alpha,\beta \)-unsaturated aldehydes proceeds to give the corresponding adducts in relatively 
low yields due to the preferential formation of Knoevenagel condensation products.8) Prelimi-

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2) Preliminary communication: S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, Tetrahedron 
3) Location: 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.
N.J., 1971; b) J.W. Scott and D. Valentine, Jr., Science, 184, 943 (1974); c) D. Valentine, Jr. and 
6) For examples of asymmetric Michael reactions, see: a) G. Tsuchihashi, S. Mitamura, S. Inoue, and 
New York, 1959, p. 179.
nary experiments showed that the reaction of an \( \alpha,\beta \)-unsaturated aldimine ((S)-(−)-4a) with the malonate anion is dependent on the conditions employed. Assuming that the malonate anion, a sufficiently soft nucleophile compared with Grignard reagents, might be able to react with \( \alpha,\beta \)-unsaturated aldimines at the soft \( \beta \)-position,\(^9\) experiments were continued under various conditions. It was finally found that Michael adducts of diethyl malonate with \( \alpha,\beta \)-unsaturated aldimines ((S)-(−)-4) are obtained preferentially by the use of more than one equivalent of potassium tert-butoxide as a base in tetrahydrofuran–ethanol (4.5:1).\(^{10}\)

The absolute configuration and maximum rotation of the aldehyde (5) were determined by chemical correlation with the known 3-methylpentanoic acid (8),\(^{12}\) as shown in Chart 3. Thus, the aldehyde ((+)-5) of \([\alpha]_D^{25} +11.6^\circ\) (benzene), obtained by the present asymmetric synthesis (Table I, run 2), was converted to the corresponding dithioacetal (6). A series of reactions involving desulfurization, saponification, and decarboxylation afforded the acid ((+)-8) of \([\alpha]_D^{25} +6.11^\circ\) (neat). Since optically pure (S)-(−)-8 is reported to have \([\alpha]_D^{25} +8.83^\circ\) (neat),\(^{12}\) the above correlation established that (+)-5 belongs to the (S)-series, and the optical rotation of optically pure (S)-(−)-5 can be calculated to be \([\alpha]_D^{25} +16.8^\circ\) (benzene).

The results of reactions of diethyl malonate with aldimines ((S)-(−)-4a, b, and c) prepared from crotonaldehyde and (S)-valine tert-butyl ester ((S)-(−)-3a), (S)-leucine tert-butyl ester ((S)-(−)-3b), and (S)-leucine tert-butyl ester ((S)-(−)-3c) (93.5\% optically pure), respectively, are summarized in Table I, which has several noteworthy features. The first is that the absolute configuration of the aldehyde (5) obtained by the present method using (S)-3 as a chiral source is S in all cases. This means that the stereochemical course


\(^{10}\) The Michael reaction of (S)-(−)-4a in ethanol under conditions B (see Table I) afforded ethyl 1,1,3-butanolactone (i) in 35\% yield; this was identical with an authentic sample\(^{19}\) on the basis of spectral (IR, NMR, and MS) and chromatographic (TLC) comparison. Since i was found to be optically inactive, its formation can be explained as a result of Knoevenagel condensation, followed by 1,6-addition, isomerization, and 1,4-addition.


of the reaction can be predicted on the basis of attack of the malonate anion from the less hindered side of the S-trans conformer of the cyclic complex, as shown in Fig. 1. It is interesting that this stereochemical course is opposite to that of the 1,4-addition of Grignard reagents to the same \( \alpha,\beta \)-unsaturated aldimines (4), reported previously.\(^1\) Detailed investigation of the mechanism of this reaction is a matter of future report.\(^1\) The second point is that the optical yields of 5 obtained by the present method using (S)-\textit{tert}-leucine \textit{tert}-butyl ester ((S)-(\(+)\)-3c) are reasonably high. The third is that (S)-\textit{tert}-leucine \textit{tert}-butyl ester ((S)-(\(+)\)-3c) was recovered from the reaction mixture for reuse without any racemization, while (S)-valine \textit{tert}-butyl ester ((S)-(\(+)\)-3a) or (S)-leucine \textit{tert}-butyl ester ((S)-(\(+)\)-3b) was recovered with partial racemization.

It can be concluded that the optically active \textit{tert}-leucine \textit{tert}-butyl ester (3c) has again\(^1\) been shown to be an excellent chiral reagent as a bidentate ligand for asymmetric synthesis.

\(^{13}\) In order to examine the effect of a metal cation, Michael reaction of (S)-(\(+)\)-4a was carried out as described for run 2 in Table I using bases other than potassium \textit{tert}-butoxide. The results were as follows (chemical yield, optical yield, configuration): lithium ethoxide (23\%, 13\%, \(S\)); sodium ethoxide (29\%, 54\%, \(S\)).
Subsequent papers will describe the results of examinations on the potential of this novel chiral reagent for the development of highly efficient asymmetric syntheses.

**Experimental**

(S)-(+-)4,4-Bis(ethoxycarbonyl)-3-methylbutyraldehyde ([(S)-(+-)-5]—a) Run 2 of Table I: A solution of diethyl malonate (15.38 g, 96 mmol) in THF–EtOH (4.5: 1) (200 ml) was added to a solution of KOH (5.39 g, 48 mmol) in THF–EtOH (4.5: 1) (250 ml) under ice-cooling, and the whole was stirred at room temperature for 30 min under Nz. A solution of (S)-(+-)4a(+-3) (7.21 g, 32 mmol) in THF–EtOH (4.5: 1) (50 ml) was added dropwise under ice-cooling, and the mixture was stirred at room temperature under Nz for 45 hr. The resulting mixture was treated with 2N aq. HCl (25 ml) under ice-cooling, then concentrated to ca. 200 ml. The residue was mixed with 2N aq. HCl (100 ml) under ice-cooling, and the whole was stirred vigorously for 20 min. The mixture was extracted with ether (300 ml×2) and the combined extracts were washed with H2O–satd. aq. NaHCO3 (1: 1) (100 ml×2) and satd. aq. NaCl (100 ml×2). The ethereal solution was dried over MgSO4 and evaporated to dryness in vacuo to give a brown oil (17.28 g), which was distilled to give crude (S)-(+-)-5 as a colorless oil (4.61 g) of bp 95°C (0.05 mmHg) contaminated with a small amount of diethyl malonate. Purification by short-path column chromatography (silica gel, ether–hexane (1: 2) afforded pure (S)-(+-)-5 (3.98 g, y. 54%) as a colorless oil. [x]D+0.5° +11.6° (c=4.56, benzene). IR νmax cm⁻¹: 2820, 2720, 1745, 1725, 1040. NMR (CCl4) δ: 1.05 (3H, d, J=6 Hz, CH3-CH-), 1.29 (6H, t, J=7 Hz, two CH2CH2-), 2.09–2.97 (3H, m, CH2-CH- and CH2-CHO), 3.29 (1H, d, J=6 Hz, CH2COOC2H52), 4.14 (4H, q, J=7 Hz, two CH2CH2-), 9.66 (1H, t, J=1.5 Hz, –CHO), MS m/z: 230 (M+).

2,4-Dinitrophenylhydrazone: mp 88.5–89.5°C (from EtOH). Anal. Calcd. for C12H12N2O6: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.83; H, 5.46; N, 13.85.

From the acidic aq. layer described above, (S)-3a (3.65 g, y. 66%) of bp 76°C (15 mmHg), [x]D+20.9° (neat) (corresponding to 94% optical purity) was recovered by the usual method.³

Run 1: (S)-(+-)-5 had [x]D+10.2° (c=1.22, benzene). Recovered (S)-3a had [x]D+10.2° (neat), corresponding to 40% optical purity.

Run 2: (S)-(+-)-5 had [x]D+9.0° (c=4.12, benzene). Recovered (S)-3b had [x]D+7.95° (c=2.97, EtOH), corresponding to 37% optical purity.

Run 4: (S)-4c of 93.5% optical purity afforded (S)-(+-)-5 in 93° (c=4.93, benzene). Recovered (S)-3c showed [x]D+1.56° (l=0.3 cm, neat), corresponding to 93.5% optical purity.

(S)-4,4-Bis(ethoxycarbonyl)-3-methylbutyraldehyde Ethylenedinitio-acetal ([(S)-6]—A solution of (S)-(+-)-5 (3.80 g, 16 mmol) of [x]D+11.6° (c=4.56, benzene) obtained above and BF3·OEt2 (1.50 g, 10.6 mmol) in ethanediol (11 ml) was stirred at room temperature overnight. The reaction mixture was diluted with ether (400 ml), and the whole was washed with 2N aq. NaOH (80 ml×3) and satd. aq. NaCl. The ether layer was dried over MgSO4 and evaporated to dryness to leave a pale yellow oil, which was purified by column chromatography (silica gel, ether–hexane (1: 4) to give (S)-6 (4.19 g, y. 87.3%) as a colorless oil. IR νmax cm⁻¹: 1735, NMR (CCl4) δ: 1.02 (3H, d, J=7 Hz, CH2CH-), 1.26 (6H, t, J=7 Hz, two CH2CH2-), 1.64–1.98 (2H, m, CH2-CH-), 2.03–2.59 (1H, m, CH2-CH-), 3.19–3.37 (5H, s and d, –S–CH2CH2S– and –CH2COOC2H52), 4.17 (4H, q, J=7 Hz, two CH2CH2-), 4.49 (1H, t, J=7 Hz, –S–CH–S–), MS m/z: 306 (M+).

Diethyl (S)-(2-Butyl)malonate ([(S)-(+-)-7]—A mixture of (S)-6 (1.46 g) and Raney Ni (W-2) (80 ml of sediment in EtOH) in EtOH (250 ml) was stirred under reflux for 3 hr. The insoluble materials were filtered off, and washed well with acetone (100 ml×2). The filtrate and washings were combined and evaporated to dryness in vacuo. The residue was chromatographed (silica gel, ether–hexane (1: 5)) to give (S)-7 (2.68 g, y. 91%) as a colorless oil of bp 92°C (5 mmHg). [x]D+62.3° (c=5.94, benzene). IR νmax cm⁻¹: 1745 (sh), 1735. NMR (CCl4) δ: 0.70–1.08 (6H, m, CH3-CH and CH2CH2-CH-), 1.08–1.41 (2H, m, CH2-CH2-CH-), 1.25 (6H, t, J=7 Hz, two CH2CH2-), 1.67–2.33 (1H, m, CH2-CH-), 3.15 (1H, d, J=7.5 Hz, CH2COOC2H52), 4.13 (4H, q, J=7 Hz, two CH2CH2-). MS m/z: 216 (M+). Anal. Calcd. for C12H22O4: C, 51.09; H, 8.43. Found: C, 51.00; H, 8.50.

14) All melting and boiling points are uncorrected. IR spectra were recorded with a JASCO DS-402G or a JASCO IRA-1 grating infrared spectrometer. NMR spectra were measured with a JNM PS-100 (100 MHz) or a Hitachi R-24 (60 MHz) spectrometer. Tetramethylsilane was used as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured with a Yanaco OR-50 automatic polarimeter. MS were recorded with a JEOL JMS-01 SG-2 mass spectrometer.
(S)-(+) - 3-Methylpentanoic Acid ([(S)-(+) - 8) — A mixture of KOH (2.46 g, 44 mmol) and (S)-(+) - 7 (2.38 g, 11 mmol) in H₂O (15 ml) was vigorously stirred under reflux for 2.5 hr. After cooling, H₂O (25 ml) was added and the whole was washed with ether. The aqueous layer was acidified with 20% aq. HCl to pH 1 and was then extracted with ether (100 ml x 2). The ethereal extracts were washed with satd. aq. NaCl, dried over MgSO₄, and evaporated to dryness to give a colorless semi-solid, which was heated (bath temperature: 160°C) for 5 hr until evolution of CO₂ ceased. The residue was distilled to give (S)-8 (1.06 g, y. 83%) as a colorless oil of bp 110° (33 mmHg). [α]D₂⁰ + 6.11° (neat) [α]D₂⁰ + 0.56° (l=0.1, neat), dₐ = 0.922°. IR νmax cm⁻¹: 1710. NMR (CDCl₃) δ: 0.89 (3H, t, J=6 Hz, CH₃CH₂-), 0.95 (3H, d, J=6 Hz, CH₃CH-), 1.06—1.61 (2H, m, CH₂CH₂-), 1.69—2.45 (3H, m, CH₃CH- and CH₂COOH), 11.91 (1H, s, -COOH). MS m/z: 117 [(M+1)+], 116 (M⁺).


As optically pure (S)-(+) - 8 was reported to have [α]D₂⁰ + 8.83° (neat), (+)-8 obtained here corresponds to 69.2% optically pure S-isomer.