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Stereoselective Reactions. II.[1] Asymmetric Synthesis of β-Substituted Aldehydes by Michael Reaction using Chiral α,β-Unsaturated Aldimines[2]

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

Keywords——asymmetric synthesis; asymmetric Michael reaction; α-amino acid ester; stereochemistry; absolute configuration; chelate; bidentate ligand; β-substituted aldehyde; α,β-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 α,β-unsaturated aldimines (1), prepared from α,β-unsaturated aldehydes and optically active α-amino acid *tert*-butyl esters (3), gives the optically active β-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 α,β-unsaturated aldimines.

It is known that the Michael addition of a malonate system having two α-hydrogen atoms to α,β-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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[1] Part I: S. Hashimoto, S. Yamada, and K. Koga, *Chem. Pharm. Bull.* (Tokyo), **27**, 771 (1979).

[2] Preliminary communication: S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, *Tetrahedron Lett.*, **1977**, 2907.

[3] Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.*

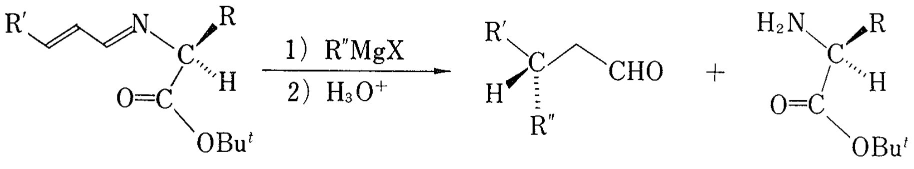
[4] *Cf.* H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Inc., California, 1972, p. 595.

[5] *a*) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N.J., 1971; *b*) J.W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); *c*) D. Valentine, Jr. and J.W. Scott, *Synthesis*, **1978**, 329; *d*) H.B. Kagan and J.C. Fiaud, "Topics in Stereochemistry," Vol 10, ed. by E.L. Eliel and N.L. Allinger, John Wiley and Sons, New York, 1978, p. 175.

[6] For examples of asymmetric Michael reactions, see; *a*) G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, **1973**, 323; *b*) G. Tsuchihashi, S. Mitamura, and K. Ogura, *ibid.*, **1976**, 855; *c*) H. Wynberg and R. Helder, *ibid.*, **1975**, 4057; *d*) K. Hermann and H. Wynberg, *Helv. Chim. Acta*, **60**, 2208 (1977); *e*) T. Mukaiyama, Y. Hirako, and T. Takeda, *Chem. Letters*, **1978**, 461.

[7] S. Hashimoto, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, **98**, 7450 (1976).

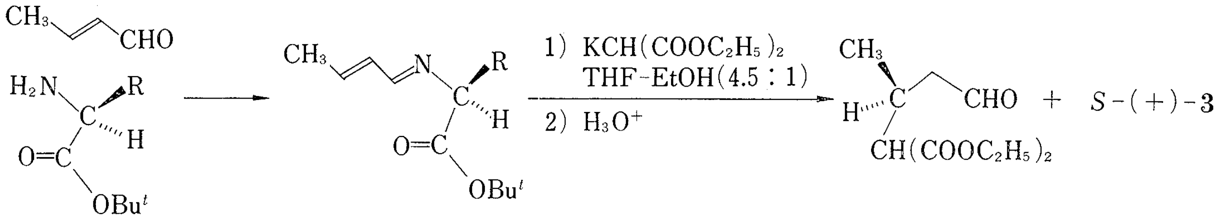
[8] E.D. Bergmann, D. Ginsburg, and R. Pappo, "Organic Reactions," Volume 10, John Wiley and Sons, New York, 1959, p. 179.



1 **2** (*S*)-(+)-**3**

Chart 1

nary experiments showed that the reaction of an α,β-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 α,β-unsaturated aldimines at the soft β-position,[9] experiments were continued under various conditions. It was finally found that Michael adducts of diethyl malonate with α,β-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]



(*S*)-(+)-**3** (*S*)-(−)-**4** (*S*)-(+)-**5**

a: R=iso-Pr; b: R=iso-Bu; c: R=*t*-Bu

Chart 2

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 $[\alpha]_D^{20}$ +11.6° (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° (neat). Since optically pure (*S*)-(+)-**8** is reported to have $[\alpha]_D^{25}$ +8.83° (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 $[\alpha]_D^{20}$ +16.8° (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*)-*tert*-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

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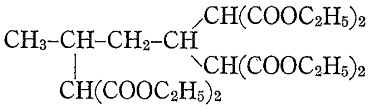
[9] T-L. Ho, *Chem. Rev.*, **75**, 1 (1975).

[10] The Michael reaction of (*S*)-(−)-**4a** in ethanol under conditions B (see Table I) afforded ethyl 1,1,3-butanetriylmalonate (**i**) in 35% yield; this was identical with an authentic sample[11] 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.



$CH_3\text{-}CH(CH(COOC_2H_5)_2)\text{-}CH_2\text{-}CH(CH(COOC_2H_5)_2)_2$

i

[11] E.H. Farmer and T.N. Mehta, *J. Chem. Soc.*, **1931**, 2561.

[12] K.B. Wiberg and T.W. Hutton, *J. Am. Chem. Soc.*, **78**, 1640 (1956).

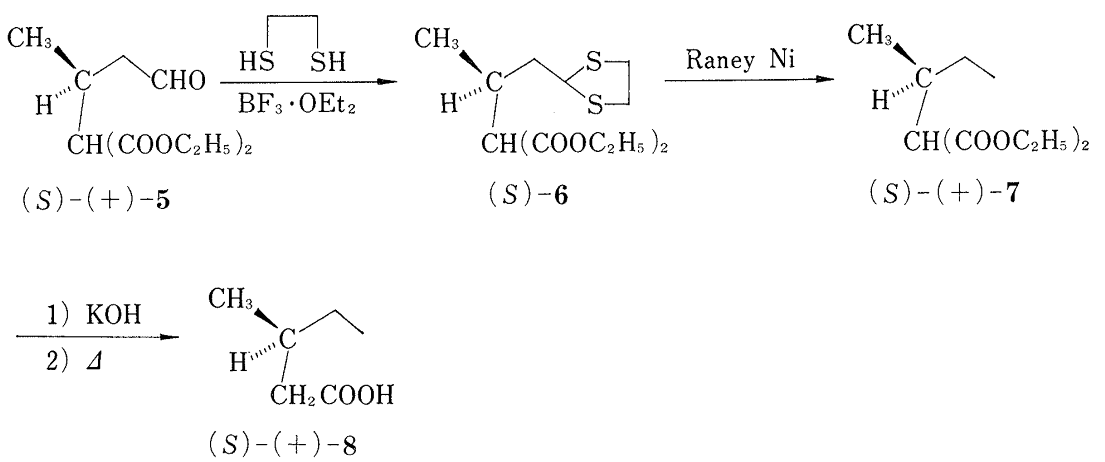


Chart 3

Table I. Asymmetric Michael Addition of Diethyl Malonate to α,β-Unsaturated Aldimines ((S)-(−)-4)

Run	(S)-Aldimine	Reaction conditions[a]	(+)-5 Chem. y.[b]	(+)-5 Opt. y.[c]	(+)-5 Confign.	Recovered (S)-(+)-3 Recovery y.[b]	Recovered (S)-(+)-3 Racemization (%)
1	**4a**	A	46	50	S	61	60
2	**4a**	B	54	69	S	66	6
3	**4b**	B	49	36	S	67	63
4	**4c**	A	26	83[d]	S	68	~0
5	**4c**	B	48	86[d]	S	65	~0

a) A: KOBu^t (1.2 eq.)-$CH_2(COOC_2H_5)_2$ (1.5 eq.); B: KOBu^t (1.5 eq.)-$CH_2(COOC_2H_5)_2$ (3.0 eq.).
b) Isolation yield.
c) Based on $[\alpha]_D^{25}$ +8.83° (neat) for optically pure (S)-(+)-**5**. See the text.
d) Corrected for 93.5% optical purity of (S)-(+)-**3c** used.

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 α,β-unsaturated aldimines (4), reported previously.[1,7] Detailed investigation of the mechanism of this reaction is a matter of future report.[13] The second point is that the optical yields of **5** obtained by the present method using (S)-*tert*-leucine *tert*-butyl ester ((S)-(+)-**3c**) are reasonably high. The third is that (S)-*tert*-leucine *tert*-butyl ester ((S)-(+)-**3c**) was recovered from the reaction mixture for reuse without any racemization, while (S)-valine *tert*-butyl ester ((S)-(+)-**3a**) or (S)-leucine *tert*-butyl ester ((S)-(+)-**3b**) was recovered with partial racemization.

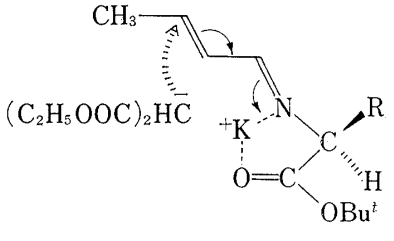


Fig. 1

It can be concluded that the optically active *tert*-leucine *tert*-butyl ester (**3c**) has again[1,7] been shown to be an excellent chiral reagent as a bidentate ligand for asymmetric synthesis.

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[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 *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 chial reagent for the development of highly efficient asymmetric syntheses.

Experimental[14]

(*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 $KOBu^t$ (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 N_2. A solution of (*S*)-(−)-**4a**[1,7] (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 N_2 for 45 hr. The resulting almost clear, yellowish-orange solution was mixed with 2 N aq. HCl (25 ml) under ice-cooling, then concentrated to *ca.* 200 ml. The residue was mixed with 2 N. 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 H_2O–satd. aq. $NaHCO_3$ (1: 1) (100 ml × 2) and satd. aq. NaCl (100 ml × 2). The ethereal solution was dried over $MgSO_4$ 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° (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. $[\alpha]_D^{20}$ +11.6° ($c=4.56$, benzene). IR ν_{max}^{film} cm^{-1}: 2820, 2720, 1745, 1725, 1040. NMR (CCl_4) δ: 1.05 (3H, d, $J=6$ Hz, $C\underline{H}_3$–CH–), 1.29 (6H, t, $J=7$ Hz, two $C\underline{H}_3CH_2$–O–), 2.09—2.97 (3H, m, CH_3–C$\underline{H}$– and –$C\underline{H}_2$–CHO), 3.29 (1H, d, $J=6$ Hz, $C\underline{H}(COOC_2H_5)_2$), 4.14 (4H, q, $J=7$ Hz, two $CH_3C\underline{H}_2$–O–), 9.66 (1H, t, $J=1.5$ Hz, –C$\underline{H}$O), MS *m/e*: 230 (M^+).

2,4-Dinitrophenylhydrazone: mp 88.5—89.5° (from EtOH). *Anal.* Calcd. for $C_{17}H_{22}N_4O_8$: 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° (15 mmHg), $[\alpha]_D^{25}$ +23.9° (neat) (corresponding to 94% optical purity[1]) was recovered by the usual method.[1]

b) Runs 1, 3, 4, and 5 in Table I: The reactions were carried out as described in a) under conditions A or B (see Table I). Data not listed in Table I are given here.

Run 1: (*S*)-(+)-**5** had $[\alpha]_D^{20}$ +8.40° ($c=4.12$, benzene). Recovered (*S*)-**3a** showed $[\alpha]_D^{25}$ +10.2° (neat), corresponding to 40% optical purity.[1]

Run 3: (*S*)-(+)-**5** had $[\alpha]_D^{20}$ +6.05° ($c=3.97$, benzene). Recovered (*S*)-**3b** showed $[\alpha]_D^{25}$ +7.95° ($c=$ 2.97, EtOH), corresponding to 37% optical purity.[1]

Run 4: (*S*)-**4c** of 93.5% optical purity[1] afforded (*S*)-(+)-**5** of $[\alpha]_D^{20}$ +13.0° ($c=4.93$, benzene). Reovered (*S*)-**3c** showed α_D^{20} +1.571° ($l=0.03$, neat), corresponding to 93.5% optical purity.[1]

Run 5: (*S*)-**4c** of 93.5% optical purity[1] afforded (*S*)-(+)-**5** of $[\alpha]_D^{20}$ +13.5° ($c=4.31$, benzene). Recovered (*S*)-**3c** showed α_D^{20} +1.569° ($l=0.03$, neat), corresponding to 93.5% optical purity.[1]

(*S*)-4,4-Bis(ethoxycarbonyl)-3-methylbutyraldehyde Ethylenedithio-acetal ((*S*)-**6**)——A solution of (*S*)-(+)-**5** (3.69 g, 16 mmol) of $[\alpha]_D^{20}$ +11.6° ($c=4.56$, benzene) obtained above and $BF_3 \cdot OEt_2$ (1.50 g, 10.6 mmol) in ethanedithiol (11 ml) was stirred at room temperature overnight. The reaction mixture was diluted with ether (400 ml), and the whole was washed with 2 N aq. NaOH (80 ml × 3) and satd. aq. NaCl. The ether layer was dried over $MgSO_4$ 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 ν_{max}^{film} cm^{-1}: 1735, NMR (CCl_4) δ: 1.02 (3H, d, $J=7$ Hz, $C\underline{H}_3CH$–), 1.26 (6H, t, $J=7$ Hz, two $C\underline{H}_3CH_2$–O–), 1.64—1.98 (2H, m, –$C\underline{H}_2CH$–), 2.03—2.59 (1H, m, CH_3–C$\underline{H}$–), 3.19—3.27 (5H, s and d, –S–$C\underline{H}_2C\underline{H}_2$–S– and C$\underline{H}$-$(COOC_2H_5)_2$), 4.17 (4H, q, $J=7$ Hz, two $CH_3C\underline{H}_2$–O–), 4.49 (1H, t, $J=7$ Hz, –S–C$\underline{H}$–S–), MS *m/e*: 306 (M^+).

Diethyl (*S*)-(2-Butyl)malonate ((*S*)-(+)-**7**)——A mixture of (*S*)-**6** (4.16 g) and Raney Ni (W-2) (80 ml of sediment in EtOH) in EtOH (50 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° (5 mmHg). $[\alpha]_D^{20}$ +6.23° ($c=5.94$, benzene). IR ν_{max}^{film} cm^{-1}: 1745 (sh), 1735. NMR (CCl_4) δ: 0.70—1.08 (6H, m, $C\underline{H}_3$–CH and $C\underline{H}_3CH_2$–CH–), 1.08—1.41 (2H, m, CH_3-$C\underline{H}_2$–CH–), 1.25 (6H, t, $J=7$ Hz, two $C\underline{H}_3CH_2$–O–), 1.67—2.33 (1H, m, CH_3–C$\underline{H}$–), 3.15 (1H, d, $J=7.5$ Hz, $C\underline{H}(COOC_2H_5)_2$), 4.13 (4H, q, $J=7$ Hz, two $CH_3C\underline{H}_2O$–). MS *m/e*: 216 (M^+). *Anal.* Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.40; H, 9.41.

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[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 H_2O (15 ml) was vigorously stirred under reflux for 2.5 hr. After cooling, H_2O (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 × 2). The ethereal extracts were washed with satd. aq. NaCl, dried over $MgSO_4$, and evaporated to dryness to give a colorless semi-solid, which was heated (bath temperature: 160°) for 5 hr until evolution of CO_2 ceased. The residue was distilled to give (*S*)-**8** (1.06 g, y. 83%) as a colorless oil of bp 110° (33 mmHg). $[\alpha]_D^{25}$ +6.11° (neat) (α_D^{25} +0.563° ($l=0.1$, neat), $d_D^{25}=0.922$12)). IR ν_{max}^{film} cm^{-1}: 1710. NMR (CCl_4) δ: 0.89 (3H, t, $J=6$ Hz, $C\underline{H}_3CH_2$–), 0.95 (3H, d, $J=6$ Hz, $C\underline{H}_3CH$–), 1.06—1.61 (2H, m, $CH_3C\underline{H}_2$–), 1.69—2.45 (3H, m, $CH_3C\underline{H}$– and –$C\underline{H}_2COOH$), 11.91 (1H, s, –$COO\underline{H}$). MS *m/e*: 117 $[(M+1)^+]$, 116 (M^+).

Dicyclohexylamine Salt: colorless needles of mp 98—100° (from hexane). *Anal.* Calcd. for $C_{18}H_{35}NO_2$: C, 72.67; H, 11.86; N, 4.71. Found: C, 72.42; H, 11.99; N, 4.74.

As optically pure (*S*)-(+)-**8** was reported12) to have $[\alpha]_D^{25}$ +8.83° (neat), (+)-**8** obtained here corresponds to 69.2% optically pure *S*-isomer.