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Stereoselective Reactions. XXI.[1] Asymmetric Alkylation of α-Alkyl β-Keto Esters to α,α-Dialkyl β-Keto Esters Having Either (*R*)- or (*S*)-Chiral Quaternary Center Depending on the Solvent System

Kaori Ando[2], Yutaka Takemasa, Kiyoshi Tomioka[3], and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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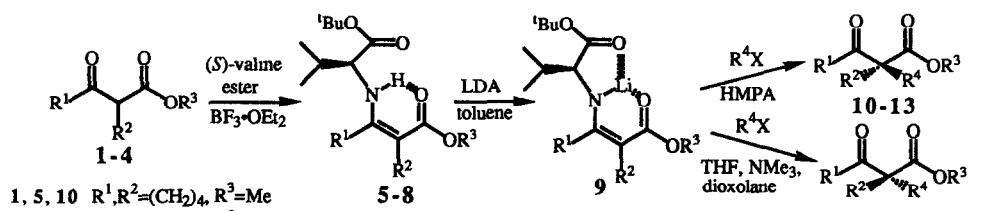
Abstract : Asymmetric alkylation reaction of chiral enamines prepared from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester leading to either enantiomer is described. Lithiated chiral enamines can be alkylated with alkyl halides in a toluene solvent in the presence of HMPA to give, after hydrolysis, α,α-dialkyl β-keto esters in 70-99%ee. The reactions in the presence of THF, dioxolane, or trimethylamine, instead of HMPA, afford the corresponding antipodes with enantiomeric purities of 44-92%ee. The present method provides a procedure for the synthesis of both enantiomers of α,α-dialkyl β-keto esters in high enantiomeric purities starting from the same chiral enamines.

INTRODUCTION

α,α-Dialkyl β-keto esters having a chiral quaternary center are useful starting materials in synthetic organic chemistry. Although several methodological developments had been attained to prepare these compounds enantioselectively,[4] the degrees of asymmetric induction reported were not so high except Cram's Michael addition reaction using a chiral crown ether. Evaluating wide utility of these compounds, we devised a new methodology using an easily available chiral source.

In preliminary communications,[5] we have reported the first results concerning a highly enantioselective asymmetric synthesis of α,α-dialkyl β-keto esters via the alkylation of the lithioenamines derived from α-alkyl β-keto esters and (*S*)-valine *tert*-buty ester (Scheme 1). The most striking characteristic of this reaction is the



Scheme 1

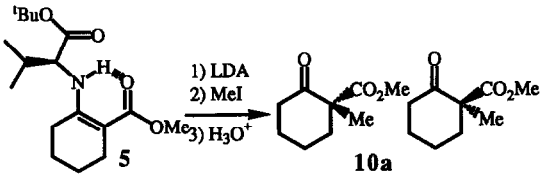
dependence of the diastereoface selection on the solvent system. Asymmetric synthesis of either (*R*)- or (*S*)-enantiomer from the same chiral source is of great importance in organic synthesis, because the chiral sources available are usually limited to one enantiomer. Some sophisticated methodologies have been devised to produce either enantiomer in the formation of a chiral tertiary carbon center.[6] But there has been only few reliable methods to produce either enantiomer bearing a chiral quaternary center.[7,8] Furthermore, relatively little work has been aimed at altering the direction of stereoselectivity. Since the dependence of diastereoface selection on the solvent

system is of both mechanistic and synthetic interest,[9] we would like to report a complete account of our communicated studies on the asymmetric alkylation of α-alkyl β-keto esters.

ASYMMETRIC ALKYLATION OF α-ALKYL β-KETO ESTERS

Chiral enamines **5-8** were prepared from the corresponding β-keto esters **1-4** and (*S*)-valine *tert*-buty ester in the presence of catalytic amount of $BF_3{\cdot}OEt_2$. By direct analogy with earlier studies on the alkylation of enamines derived from simple ketones,[10] the chiral enamine **5** was lithiated with lithium diisopropylamide (LDA) (1.2eq) and methylated with MeI (2eq) in several solvents. Subsequent acid hydrolysis and purification afforded **10a** (Table 1). The sense of asymmetric induction was found to be strongly influenced by the nature of the solvent.[11] For example, a simple change of solvent from THF ((*S*)-**10a**, 58%ee) to toluene leads to the other enantiomer ((*R*)-**10a**, 50%ee). Toluene is a solvent whose coordinating ability to lithium is poor. On the other hand, THF has oxygen lone pair and could coordinate to lithium cation. The results of Table 1 led us to a working hypothesis that if the lithium cation in lithioenamine **9** is coordinated by two ester carbonyl oxygens, tetravalency of lithium cation[12] will be satisfied by the occupation of an external ligand, which may affect the stereochemical course of the reaction.

In order to ascertain the effect of the external ligand, we selected toluene as a solvent, and investigated the effect of several electron donating additives. Table 2 shows the effect of HMPA in a toluene solvent. A toluene solution of the enamine **5** was successively treated with LDA for 30 min, HMPA for 30 min at -78°C, and then MeI. In the absence of HMPA, the alkylation did not proceed below -50°C. However, on addition of 1 equiva-



(Table 1) Solvent Effects on Asymmetric Methylation of Enamine **5**

entry	solvent	temp.(℃)	isolated yield, %	ee, % (config.)
1	THF	-78	77	58 (S)
2	ether	-78	11	41 (S)
3	dioxolane	-78	80	29 (S)
4	DME	-78	60	20 (R)
5	n-hexane	-78 to 0	31	41 (R)
6	toluene	0	30	50 (R)

(Table 2) Effect of HMPA in toluene [a)]

entry	HMPA (eq)	temp.(℃)	isolated yield, %	ee, % (config.)
1	none	-5	57	50 (R)
2	0.1	-78 to -20	55	85 (R)
3	0.5	-78 to -20	62	91 (R)
4	1.0	-55	57	99 (R)
5	3.0	-78 to 0	64	91 (R)

a) **5**→**10a**

(Table 3) Effect of THF in toluene [a)]

entry	THF (eq)	temp. (℃)	isolated yield, %	ee, % (config.)
1	none	-5	57	50 (R)
2	2	-78	63	92 (S)
3	4	-78	67	78 (S)
4	6	-78	74	75 (S)
5	15	-78	67	67 (S)
6	in THF	-78	77	58 (S)

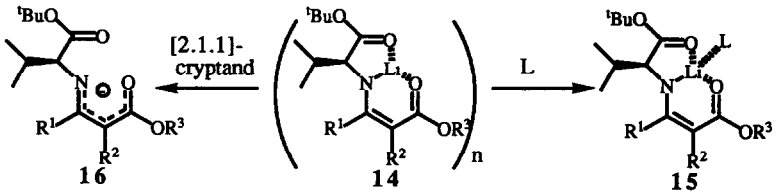
a) **5**→**10a**

(Table 4) Effect of some additives in toluene [a)]

entry	additive(eq)[b)]	temp.(℃)	isolated yield, %	ee, % (config.)
1	none	-5	57	50 (R)
2	HMPA(1)	-55	57	99 (R)
3	18-Crown-6(3)	-78 to -20	78	53 (R)
4	12-Crown-4(3)	-78 to -20	65	52 (R)
5	TMANO(3)	-78 to -20	52	7 (R)
6	TMA(3)	-78	27	3 (R)
7	[2.1.1]-Cryptand(3)	-78	69	14 (S)
8	TMEDA(3)	-78 to -20	70	49 (S)
9	1,4-Dioxane(2)	-78	20	59 (S)
10	1,3-Dioxolane(2)	-78	37	91 (S)
11	THF(2)	-78	63	92 (S)

a) **5**→**10a** b) HMPA: hexamethylphosphoramide; DMPU: N,N'-dimethylpropyleneurea; TMANO: trimethylamine N-oxide; TMA: trimethylamine; TMEDA: tetramethylethylenediamine.

lent of HMPA into a toluene solution of the lithioenamine, the reaction proceeded at -55°C to give (*R*)-**10a** in 99%ee. Even the addition of 0.1 equivalent of HMPA led to the formation of (*R*)-**10a** in 85%ee. The addition of HMPA increased both the reactivity and the diastereoselectivity. These results imply the possibility that the lithioenamine is probably existing in a mixture of aggregates **14** in a toluene solvent, and on addition of HMPA, it might be converted to the reactive species similar to **15** bearing HMPA as the ligand for the lithium cation (Scheme 2).



Scheme 2

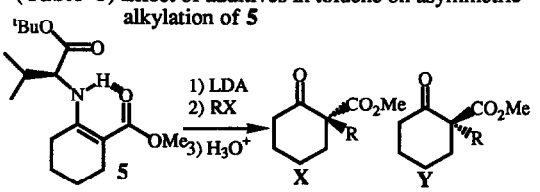
Next we investigated the effect of THF in a toluene solvent (Table 3). The addition of 2 equivalents of THF resulted in the bottom side attack to afford (*S*)-**10a** in 92%ee. The more THF was added, the lower %ee was observed. In this way, the addition of THF effects the high and reversed diastereoface selection. These behavior also imply the possibility that on addition of THF, a mixture of aggregates **14** was converted to the real reactive species similar to **15** bearing THF as the coordinating ligand, which caused the high and the reversed diastereoface selection.

Effects of some electron pair donating additives other than HMPA and THF were also examined in the methylation of the chiral enamine **5** with methyl iodide (Table 4). The ethers, 1,4-dioxane and 1,3-dioxolane showed nearly equal diastereoselectivity to that of THF, and gave (*S*)-**10a** (R=Me). On the other hand, the crown ethers, 18-crown-6 and 12-crown-4, did not affect the diastereoface selectivity. Perhaps these crown ethers can not interact with the lithium cation in this state. However, the addition of [2.1.1]-cryptand did affect both the reaction rate and the diastereoselection to afford (*S*)-**10a** in 14%ee. Since [2.1.1]-cryptand is known to be a powerful host for lithium cation, it will take the lithium off from **14** to generate a disorganized free anion such as **16** (Scheme 2), which should be responsible for the great acceleration of the reaction rate and the significant loss of the diastereoface selection.

In order to make the relation between the nature of the ligand and the diastereoface selection clearer, we also studied the effects of some ligands in the alkylation of **5** with allyl bromide, benzyl bromide and methyl bromoacetate (Table 5). When the alkyl halide attacks the lithioenamine from the front side, **X** is obtained. Alternatively, if the alkyl halide attacks from the back side, the product is **Y**. As a general rule, strongly coordinating ligands such as HMPA favor the front side attack and weakly coordinating ethers or amines favor the back side attack.

Since trimethylamine was found to work as a ligand, our interest was focused on the metallation base. In order to eliminate the effect of diisopropylamine, we used BuLi instead of LDA for metallation of the enamine **5** (Table 6). Even though metallation of the enamine **5** with BuLi was slow at -78°C in toluene, **5** was successfully metallated at -50°C for 45 min. After treatment of the lithioenamine obtained with

(Table 5) Effect of additives in toluene on asymmetric alkylation of **5**



additive	Product (ee, %)			
	MeI	CH_2=$CHCH_2Br$	$PhCH_2Br$	$BrCH_2CO_2Me$
none	Y (50)*			
THF	Y (92)	Y (28)	Y (29)	Y (31)
dioxolane	Y (64)	Y (56)	Y(71)	Y (36)
TMEDA	Y (56)	X (7)	X (51)	Y (10)
NMe_3	X (3)	X (20)	X (35)	Y (74)
DMPU		X (51)***		X (46)
HMPA	X (99)**	X (76)**	X (99)	X (70)

reaction temperature: -78 °C except for * 0°C, ** -55°C, *** -20°C

(Table 6) Asymmetric methylation of enamine **5** by metallation with BuLi in toluene

entry	base	metallation condition	additive (1eq)	reaction temp.(°C)	isolated yield, %	ee, % (config)
1	BuLi	-78°C, 45min	HMPA (1)	-78 to 0	25	84 (R)
2	BuLi	-50°C, 45min	HMPA (1)	-55	57	99 (R)
3	LDA	-78°C, 30min	HMPA (1)	-55	57	99 (R)
4	BuLi	-50°C, 40min	THF (1)	-78	35	54 (S)
5	BuLi	-78°C, 3h	THF (1)	-78	48	81 (S)
6	LDA	-78°C, 30min	THF (1)	-78	18	90 (S)

HMPA (1eq) and MeI, (*R*)-**10a** was formed by the same chemical yield and enantiomeric excess as the case of LDA (57%, 99%ee) (Entries 2 and 3). When **5** was metallated with BuLi at -50°C, and treated with THF (1eq) at -78°C, and then MeI at -78°C, (*S*)-**10a** was obtained in 54%ee. If metallation was conducted at -78°C, the enantiomeric excess of (*S*)-**10a** increased to 81%ee (Entry 5). From these data, we have found that replacing LDA with BuLi has little effect on the diastereoselectivity but the metallation temperature has an effect on it in toluene-THF system. Since the metallation time for LDA (~30 min) was more convenient than BuLi (~3 h) at -78°C, we routinely used LDA as a metallation base.

The best results for the asymmetric alkylation of enamines **5-8** are listed in Table 7. There are some general trends in this reaction. First, an opposite sense of asymmetric induction is found in the solvent system of toluene-HMPA on one hand and systems toluene-THF, -dioxolane, or -trimethylamine on the other hand, with the former system exhibiting a somewhat greater selectivity. Second, the appropriate combination of alkylating agent and ligand is of great importance in order to realize a high level of asymmetric induction from the back side attack. The appropriate combinations were found to be THF for methyl iodide, dioxolane for allyl bromide and benzyl bromide, and trimethylamine for methyl bromoacetate. Third, asymmetric alkylation to each enantiomer can be realized regardless of whether cyclic or acyclic β-keto esters are involved. For example, the acyclic enamine **7** was alkylated with benzyl bromide to give (*R*)-**12c** (92%ee) for the toluene-HMPA system and (*S*)-**12c** (90%ee) for the toluene-dioxolane system (Entries 12 and 13). Fourth, the alkoxy moiety of β-keto esters has a small effect on the diastereoselectivity. That is, the methyl ester **5** was alkylated with allyl bromide in toluene-HMPA system to give (*S*)-**10b** in 76%ee (Entry 3), while the ethyl ester **6** gave (*S*)-**11b** in 85%ee under

(Table 7) Asymmetric alkylation of enamine **5-8** leading to **10-13** (Scheme 1)

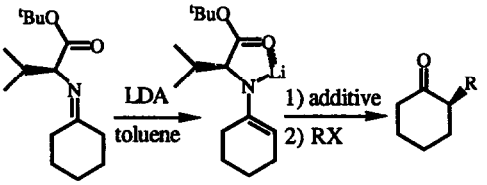
entry	enamine	R^4X (equiv.)	additive (equiv.)	Product	isolated yield,%	ee, % (config)
1	**5**	MeI (1.2)	HMPA (1.0)	**10a**	57	≥99 (R)
2	**5**	MeI (5.0)	THF (2.0)	**10a**	63	92 (S)
3	**5**	$CH_2CH{=}CH_2Br$ (1.3)	HMPA (1.0)	**10b**	71	76 (S)
4	**5**	$CH_2CH{=}CH_2Br$ (5.0)	dioxolane (1.2)	**10b**	56	56 (R)
5	**5**	$PhCH_2Br$ (2.0)	HMPA (1.0)	**10c**	77	≥99 (S)
6	**5**	$PhCH_2Br$ (5.0)	dioxolane (1.6)	**10c**	48	71 (R)
7	**5**	$BrCH_2CO_2Me$ (2.0)	HMPA (1.0)	**10d**	59	70 (S)
8	**5**	$BrCH_2CO_2Me$ (2.0)	TMA (3.0)	**10d**	78	74 (R)
9	**6**	$CH_2CH{=}CH_2Br$ (2.0)	HMPA (1.0)	**11b**	87	85 (S)
10	**7**	$CH_2CH{=}CH_2Br$ (2.0)	HMPA (1.0)	**12b**	68	94 (S)
11	**7**	$CH_2CH{=}CH_2Br$ (2.0)	dioxolane (2.0)	**12b**	20	47 (R)
12	**7**	$PhCH_2Br$ (2.0)	HMPA (1.0)	**12c**	90	92 (S)
13	**7**	$PhCH_2Br$ (5.0)	dioxolane (2.0)	**12c**	83	90 (R)
14	**7**	$BrCH_2CO_2Me$ (2.0)	HMPA (1.0)	**12d**	81	76 (S)
15	**7**	$BrCH_2CO_2Me$ (2.0)	TMA (3.0)	**12d**	76	44 (R)
16	**8**	MeI (2.0)	HMPA (1.0)	**13a**	54	95 (R)
17	**8**	MeI (2.0)	THF (1.6)	**13a**	66	78 (S)

the similar condition (Entry 9). Furthermore, the chiral auxiliary, (*S*)-valine *tert*-butyl ester, was recovered for recycling since no racemization took place during the entire sequence.

ASYMMETRIC ALKYLATION OF CYCLOHEXANONE IMINE

In order to get more information about the reaction transition state, the alkylation of the lithioenamine derived from cyclohexanone and (*S*)-valine *tert*-butyl ester was carried out under the similar conditions (HMPA, THF, or TMEDA in toluene). The sense of diastereoselectivity did not change, giving the products arising from the front side attack of the alkyl halids in 64-98%ee (Table 8). These data mean that the chelated structure shown in **9** is essential for the reversal of the diastereoface selection.

(Table 8) Asymmetric alkylation of cyclohexanone imine



entry	additive(eq)	RX	%ee (config)
1	HMPA (2)	MeI	64 (S)[13]
2	THF (2)	MeI	78 (S)
3	TMEDA (2)	MeI	98 (S)
4	HMPA (2)	$PhCH_2Br$	68 (R)[14]
5	THF (2)	$PhCH_2Br$	92 (R)
6	TMEDA (2)	$PhCH_2Br$	74 (R)

DISCUSSION

It is of interest to speculate on the reaction mechanism of this novel asymmetric alkylation. As previously mentioned, the lithioenamine **9** is probably existing as a mixture of aggregates **14** in a toluene solvent. On addition of electron donating additives, it would be converted to the definitely organized reactive species similar to **15** bearing an additive as the ligand for the lithium cation. Now, let us look more closely at the structure of **15**. About the five-membered chelated structure, the nitrogen lone pair should be exclusively cis to the bulky isopropyl substituent on the chiral carbon for steric reasons.[15] This means that the nitrogen lone pair is fixed cis to the isopropyl group. If this nitrogen lone pair retains a conjugation with the enamine double bond, a favorable structure of **15** would be **A** in Figure 1. The bulky and powerful ligand, HMPA, would coordinate to the lithium cation to satisfy the tetravalency and this coordination would increase the nucleophilicity of the enamine system, block the bottom side attack, and result in the top side attack of alkyl halides. On the other hand, weak ligands, ethers or amines, would not activate the enamine system enough to simply react with alkyl halide intermolecularly. Instead, the external ligand L would be replaced by alkyl halide, which reacts from the bottom side in the complex. Alternatively, partial breaking of the chelate structure **15** by HMPA may occur to form the species **B** or **C**.[16] The alkyl halides access from the less hindered side of **B** or **C**, which results in the top side attack. We could not get any information about the structures of real reactive species, but we prefer the structure **A** at present. When asymmetric alkylation of **5** with MeI was performed in the presence of HMPA (1eq) in THF, the bottom side attack occured to give (*S*)-**10a** in 41%ee. This result implys that THF and HMPA have opposite effects and compete each other, and supports the structure **A** rather than **B** or **C**.

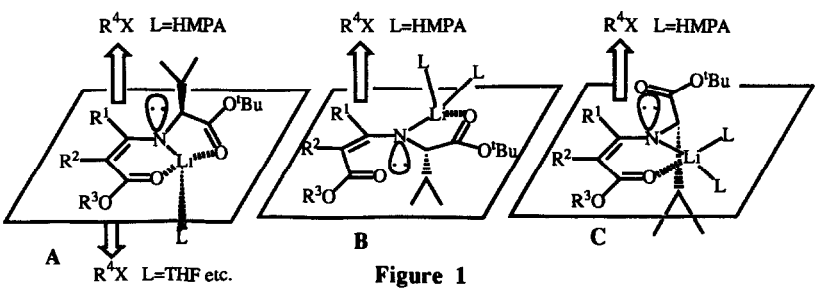
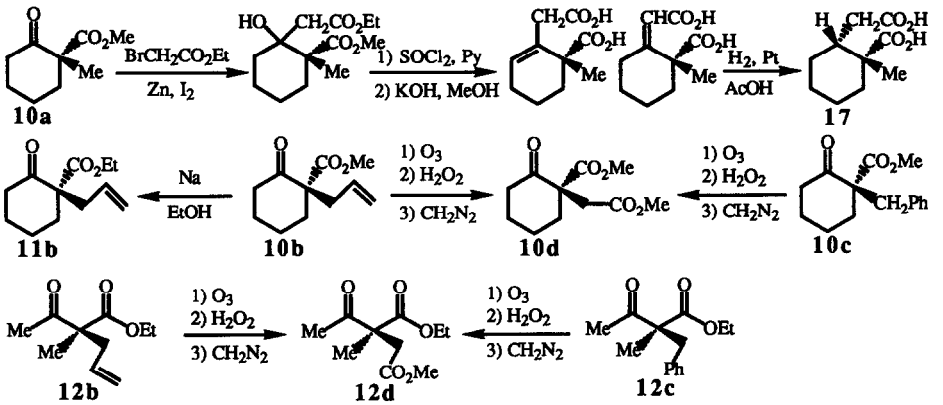


Figure 1

DETERMINATION OF THE ABSOLUTE CONFIGURATIONS AND OPTICAL PURITIES

Since the chiral α,α-dialkyl β-keto esters except **11b**[17] and **12b**[18] had not been previously described in enantiomerically pure form, it was necessary to determine the absolute configuration as well as the degree of asymmetric induction. These chiral β-keto esters were converted into known compounds and their absolute configurations were determined by comparing their optical rotations (Scheme 3). That is, **10a** and **10b** were converted into the known compounds **17**[19] and **11b**, respectively. Both **10b** and **10c** were treated with ozone to give **10d** after esterification. Similarly, both **12b** and **12c** were converted to **12d**. The optical purities were further confirmed by the ^1H NMR analysis in the presence of chiral shift reagent (Eu(hfc)$_3$).



Scheme 3

CONCLUSION

In summary, asymmetric alkylation of the chiral enamines **5-8** in toluene in the presence of HMPA as the ligand takes place preferentially from the front side of **9**, while in the presence of THF, dioxolane, or trimethylamine as the ligand it takes place from the back side of **9**. This method provides a procedure for the synthesis of both enantiomers of α,α-dialkyl β-keto esters with a predictable absolute configuration in high enantiomeric purities starting from the same chiral enamines. We believe that the results described above have implications for other systems which could be a tridentate ligand for lithium cation. The methodology outlined herein will be of considerable utility in chiral compound synthesis.

EXPERIMENTAL SECTION

All dry solvents were distilled under argon. Toluene, THF, and ethyl ether were distilled from sodium/benzophenone just before use. Diisopropylamine was distilled from calcium hydride. All reactions were conducted under an argon atmosphere unless otherwise stated. Boiling points and melting points are uncorrected. Kugelrohr distillation boiling points refer to the external air bath temperature. Column chromatography was performed on SiO_2. The ^1H NMR spectra were recorded in $CDCl_3$ at 100 MHz (JNM-PS) or 60 MHz (Hitachi R-24B), the chemical shifts are expressed in ppm relative to TMS. Optical rotations were measured on a Jasco DIP-181 Digital Polarimeter. Areas of *R* and *S* proton signals in the presence of Eu(hfc)3 were determined by cutting and weighing expanded spectra.

***N*-(2-Carbomethoxy-1-cyclohexen-1-yl)-(*S*)-valine *tert*-butyl ester (5).** To a solution of methyl 2-oxocyclohexanecarboxylate (9.80ml, 70mmol) and optically pure (*S*)-valine *tert*-butyl ester[20a] (bp 91-92°C/23mmHg, $[\alpha]_D^{25}$ +25.6°(neat),[20b,10] $[\alpha]_D^{21}$ +32.8°(C 1 65, EtOH)) (13 39ml, 70mmol) in benzene (300ml) was added BF_3•OEt_2 (0.45ml, 3.5mmol), and the resulting solution was heated to reflux using a Dean-Stark apparatus for 13 h This reaction mixture was washed with aq $NaHCO_3$ and dried

over K_2CO_3. Removal of the solvent gave a yellow oil (21.90g), which was distilled to give **5** (20.05g, 92%) as a colorless oil of bp 140°C (0.08mmHg). $[\alpha]_D^{25}$ +139.0° (C 1.47, benzene). ^{1}H NMR δ 0.99 (6H, d, J=7Hz), 1.39 (9H, s), 1.40-1.80 (5H, m), 2.00-2.90 (4H, m), 3.70 (3H, s), 3.80 (1H, dd, J=6Hz, 9Hz), 9.13 (1H, brd, J=9Hz). IR (film) 3250, 1730, 1650, 1600 cm^{-1}. MS (m/e): 311 (M^+). HRMS calcd for $C_{17}H_{29}O_4N$: 311.2096, found: 311.2123.

***N*-(2-Carboethoxy-1-cyclohexen-1-yl)-(*S*)-valine *tert*-butyl ester (6).** **6** was prepared in the same way as **5** using ethyl 2-oxocyclohexanecarboxylate. Recrystallization from EtOH yielded **6** in 81% yield as colorless needles. mp 81.5-82.0°C. $[\alpha]_D^{24}$ +141.8°(C 1.36, benzene). ^{1}H NMR δ 1 00 (6H, d, J=6Hz), 1.25 (3H, t, J=7Hz), 1.45 (9H, s), 1.45-2.45 (9H, m), 3.77 (1H, dd, J=6Hz, 10Hz), 4.15 (2H, q, J=7Hz), 9.17 (1H, brd, J=10Hz). IR (film) 3230, 1725, 1657, 1603 cm^{-1}. MS (m/e): 325 (M^+). Anal. calcd for $C_{18}H_{31}O_4N$: C, 66.43; H, 9.60; N, 4.30; found: C, 66.38; H, 9.75; N, 4.46.

***N*-(3-Carboethoxy-2-buten-2-yl)-(*S*)-valine *tert*-butyl ester (7).** **7** was prepared in the same way as **5** using ethyl 2-methylacetoacetate in 84% yield as a colorless oil of bp 117°C (0.04mmHg). $[\alpha]_D^{25}$ +153 4° (C 2.13, benzene). ^{1}H NMR δ 1.02 (6H, d, J=7Hz), 1.26 (3H, t, J=7Hz), 1 46 (9H, s), 1 79 (3H, s), 1.88 (3H, s), 1.70-2.38 (1H, m), 3.78 (1H, dd, J=5Hz, 9Hz), 4.12 (2H, q, J=7Hz), 9.46 (1H, brd, J=9Hz). IR (film) 3260, 1729, 1640, 1600 cm^{-1}. MS (m/e): 299 (M^+). HRMS calcd for $C_{16}H_{29}O_4N$: 299.2098, found: 299.2112.

***N*-(3-Carboethoxyhexa-2,5-dien-2-yl)-(*S*)-valine *tert*-butyl ester (8).** **8** was prepared in the same way as **5** in 85% yield as a colorless oil of bp 128°C (0.05mmHg). $[\alpha]_D^{24}$ +140 3° (C 1.42, benzene). ^{1}H NMR δ 1.02 (6H, d, J=7Hz), 1.25 (3H, t, J=7Hz), 1 46 (9H, s), 1.87 (3H, s), 1.75-2.35 (1H, m), 3.01 (2H, d, J=5Hz), 3.80 (1H, dd, J=5Hz, 9Hz), 4.15 (2H, q, J=7Hz), 4.70-5.23 (2H, m), 5.40-6.10 (1H, m), 9.58 (1H, brd, J=9Hz). IR (film) 3400, 1739, 1643, 1600 cm^{-1}. MS (m/e): 325 (M^+). HRMS calcd for $C_{18}H_{31}O_4N$: 325.2254, found: 325.2263.

Methyl (*R*)-1-methyl-2-oxocyclohexanecarboxylate (*R*-10a). (entry 1 in Table 7) **(Procedure A)** LDA solution was prepared from diisopropylamine (0 21ml, 1.50mmol) in toluene (1.5ml) and 1.6M BuLi in hexane (0.94ml, 1.50mmol) at -78°C for 30 min. This LDA solution was added to a solution of **5** (0.389g, 1.25mmol) in toluene (5.5ml) at -78°C, and the resulting mixture was stirred for 30 min. HMPA (0 26ml, 1.50mmol) was next added , and 30 min later MeI (0.09ml, 1.50mmol) was added dropwise. The resulting mixture was stirred at -55±5°C for 3 h. 4% HCl (30ml) was added to the mixture and the whole was stirred vigorously at 0°C for 30 min, and then extracted with ether (30ml×3) The combined ethereal extracts were washed with aq. $NaHCO_3$, 5% $Na_2S_2O_3$, water, and then brine, and dried ($MgSO_4$) and concentrated Column chromatography (hexane-ether (6:1)) provided 0.120g (57% yield) of the product as a colorless oil. $[\alpha]_D^{24}$ -108° (C 1.94, EtOH) (≥99%ee). ^{1}H NMR δ 1.29 (3H, s), 1.30-2.15 (5H, m), 2.25-2.65 (3H, m), 3.73 (3H, s). IR (film) 1743, 1732, 1718 cm^{-1}. MS (m/e): 170 (M^+). HRMS calcd for $C_9H_{14}O_3$: 170 0943, found. 170.0944.
To the above acidic aqueous layer was added aq. K_2CO_3 to adjust to pH 9. After saturation with NaCl, the whole alkaline mixture was extracted with ether (50ml×3), and the combined organic layers were dried over K_2CO_3. Removal of the solvent followed by Kugelrohr distillation (110°C/15mmHg) gave (*S*)-valine *tert*-butyl ester (0 132g, 61% yield). $[\alpha]_D^{21}$ +32.5° (C 1.53, EtOH).

Methyl (*S*)-1-methyl-2-oxocyclohexanecarboxylate (*S*-10a). (entry 2 in Table 7) **(Procedure B)** To a solution of **5** (0 398g, 1.28mmol) in toluene (3.5ml) was added LDA solution (prepared by the same method as the procedure A) (1.66mmol) at -78°C, and the resulting mixture was stirred for 30 min. THF (0.27ml, 3.32mmol) was next added and 1 h later MeI (0 39ml, 6 40mmol) was added dropwise. The resulting mixture was stirred at -78°C for 25 h. 4% HCl (30ml) was added to the mixture and the whole was stirred at 0°C for 30 min, and then extracted with ether (30ml×3). The combined ethereal extracts were washed with aq. $NaHCO_3$, 5% $Na_2S_2O_3$, water, and then brine and dried ($MgSO_4$) and concentrated. Column chromatography (hexane-ether (5:1)) provided 0 137g (63% yield) of the product as a colorless oil $[\alpha]_D^{24}$ +99.6° (C 1.85, EtOH) (92%ee).

Methyl (*S*)-1-allyl-2-oxocyclohexanecarboxylate. (*S*-10b) (entry 3 in Table 7) This compound was prepared by the procedure A using allyl bromide (1.3eq) in 71% yield as a colorless oil $[\alpha]_D^{25}$ -102.0° (C 1.81, EtOH) (76%ee). ^{1}H NMR δ 1.20-2.80 (10H, m), 3 73 (3H, s), 4 90-5.21 (2H, m), 5.51-6.03 (1H, m). IR (film) 1748, 1734, 1724, 1716, 1641 cm^{-1}. MS (m/e): 196 (M^+) HRMS calcd for $C_{11}H_{16}O_3$: 196.1100, found: 196.1096.

Methyl (*R*)-1-allyl-2-oxocyclohexanecarboxylate (*R*-10b). (entry 4 in Table 7) This compound was prepared by the procedure B using dioxolane (1 2eq) instead of THF and allyl bromide (5.0eq) in 56% yield as a colorless oil $[\alpha]_D^{25}$ +75.2° (C 1.10, EtOH) (56%ee)

Methyl (*S*)-1-benzyl-2-oxocyclohexanecarboxylate (*S*-10c). (entry 5 in Table 7) This compound was prepared by the procedure A using benzyl bromide (2.0eq) at -78°C in 77% yield as a colorless oil. $[\alpha]_D^{25}$ -111° (C 1.64, EtOH) (≥99%ee). ^{1}H NMR δ 1.05-2.55 (8H, m), 2.85 (1H, d, J=13Hz), 3.33 (1H, d, J=13Hz), 3.63 (3H, s), 6.90-7.40 (5H, m). IR (film) 1743, 1721, 1710, 721, 695 cm^{-1}. MS (m/e): 246 (M^+). Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. found: C, 73.27; H, 7.44.

Methyl (*R*)-1-benzyl-2-oxocyclohexanecarboxylate (*R*-10c). (entry 6 in Table 7) This compound was prepared by the procedure B using dioxolane (1.6eq) instead of THF and benzyl bromide (5.0eq) in 48% yield as a colorless oil. $[\alpha]_D^{25}$ +77.0° (C 1.20, EtOH) (71%ee).

Methyl (*S*)-1-carbomethoxy-2-oxocyclohexylacetate (*S*-10d). (entry 7 in Table 7) This compound was prepared by the procedure A using methyl bromoacetate (2.0eq) at -78°C in 59% yield as a colorless oil. $[\alpha]_D^{25}$ -64.9° (C 1.35, EtOH) (70%ee). ^{1}H NMR δ1.40-2.90 (8H, m), 2.73 (2H, s), 3.63 (3H, s), 3.73 (3H, s). IR (film) 1755, 1742, 1735, 1718, 1710, 1440, 1360 cm^{-1}. MS (m/e): 228 (M^+). HRMS calcd for $C_{11}H_{16}O_5$: 228.0995, found: 228.0987.

Methyl (*R*)-1-carbomethoxy-2-oxocyclohexylacetate (*R*-10d). (entry 8 in Table 7) This compound was prepared by the procedure B using trimethylamine (3.0eq) instead of THF and methyl bromoacetate (2.0eq) in 78% yield as a colorless oil. $[\alpha]_D^{25}$ +69.2° C 1.26, EtOH) (74%ee).

Ethyl (*S*)-1-allyl-2-oxocyclohexanecarboxylate (*S*-11b). (entry 9 in Table 7) This compound was prepared by the procedure A using the enamine **6** and allyl bromide (2.0eq) at -78°C in 87% yield as a colorless oil. $[\alpha]_D^{22}$ -111° (C 0.81, $CHCl_3$) (85%ee) (lit [17] $[\alpha]_D^{22}$ -131° (C 0 76, $CHCl_3$)). ^{1}H NMR δ 1.25 (3H, t, J=7Hz), 1.40-2.80 (10H, m), 4.20 (2H, q, J=7Hz), 4.89-5.22 (2H, m), 5.51-6 05 (1H, m). IR (film) 1738, 1725, 1710, 1640 cm^{-1}. MS (m/e): 210 (M^+). HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found: 210.1265.

Ethyl (*S*)-2-acetyl-2-methyl-4-pentenoate (*S*-12b). (entry 10 in Table 7) This compound was prepared by the procedure A using the enamine **7** and allyl bromide (2.0eq) at -78°C in 68% yield as a colorless oil. $[\alpha]_D^{22}$ -27.9° (C 0.91, $CHCl_3$) (94%ee) (lit [18] $[\alpha]_D^{22}$ -29.6° (C 0.83, $CHCl_3$)). ^{1}H NMR δ 1.26 (3H, t, J=7Hz), 1.33 (3H, s), 2.17 (3H, s), 2.30-2.70 (2H, m), 4.21 (2H, q, J=7Hz), 4.93-5.26 (2H, m), 5.43-5.94 (1H, m). IR (film) 1740, 1723, 1710, 1640 cm^{-1}. MS (m/e): 184 (M^+). HRMS calcd for $C_{10}H_{16}O_3$: 184.1099, found: 184.1097.

Ethyl (*R*)-2-acetyl-2-methyl-4-pentenoate (*R*-12b). (entry 11 in Table 7) This compound was prepared by the procedure B using the enamine **7**, dioxolane (2.0eq) instead of THF, and allyl bromide (2.0eq) in 20% yield as a colorless oil. $[\alpha]_D^{22}$ +14.0° (C 1.26, $CHCl_3$) (47%ee).

Ethyl (*S*)-2-benzyl-2-methyl-3-oxobutyrate (*S*-12c). (entry 12 in Table 7) This compound was prepared by the procedure A using enamine **7** and benzyl bromide (2.0eq) at -78°C in 90% yield as a colorless oil. $[\alpha]_D^{22}$ -58.2° (C 0.90, $CHCl_3$) (92%ee) ^{1}H NMR δ 1.23 (3H, t, J=7Hz), 1.27 (3H, s), 2.14 (3H, s), 3.03 (1H, d, J=14Hz), 3.23 (1H, d, J=14Hz) 4.14 (2H, q, J=7Hz), 6.81-7 36 (5H, m) IR (film) 1740, 1724, 1709, 739, 693 cm^{-1}. MS (m/e). 234 (M^+). HRMS calcd for $C_{14}H_{18}O_3$: 234.1253, found: 234.1247

Ethyl (*R*)-2-benzyl-2-methyl-3-oxobutyrate (*R*-12c). (entry 13 in Table 7) This compound was prepared by the procedure B using the enamine **7**, dioxolane (2.0eq) instead of THF, and benzyl bromide (5.0eq) in 83% yield as a colorless oil. $[\alpha]_D^{22}$ +57.0° (C 0.89, $CHCl_3$) (90%ee)

Ethyl methyl (*S*)-2-acetyl-2-methylsuccinate (*S*-12d). (entry 14 in Table 7) This compound was prepared by the procedure A using the enamine **7** and methyl bromoacetate (2.0eq) at -78°C in 81% yield as a colorless oil. $[\alpha]_D^{22}$ -30.6° (C 1.07, $CHCl_3$) (76%ee). ^{1}H NMR δ 1.25 (3H, t, J=7Hz), 1.48 (3H, s), 2.22 (3H, s), 2.89 (2H, s), 3 65 (3H, s), 4 21 (2H, q, J=7Hz). IR (film) 1740, 1712 cm^{-1}. MS (m/e): 216 (M^+). HRMS calcd for $C_{10}H_{16}O_5$: 216.0995, found: 216.0994.

Ethyl methyl (*R*)-2-acetyl-2-methylsuccinate (*R*-12d). (entry 15 in Table 7) This compound was prepared by the procedure B using the enamine **7**, trimethylamine (3.0eq) instead of THF, and methyl bromoacetate (2.0eq) in 76 % yield as a colorless oil. $[\alpha]_D^{22}$ +17 7° (C 0.88, $CHCl_3$) (44%ee)

Ethyl (*R*)-2-acetyl-2-methyl-4-pentenoate (*R*-13a). (entry 16 in Table 7) This compound was prepared by the procedure A using the enamine **8** and methyl iodide (2.0eq) at -78°C in 54% yield as a colorless oil. $[\alpha]_D^{22}$ +28.2° (C 1.02, $CHCl_3$) (95%ee).

Ethyl (*S*)-2-acetyl-2-methyl-4-pentenoate (*S*-13a). (entry 17 in Table 7) This compound was prepared by the procedure B using the enamine **8** in 66% yield as a colorless oil. $[\alpha]_D^{22}$ -23.2° (C 0.97, $CHCl_3$) (78%ee).

Conversion of 10a to 17. Zinc powder was washed successively with 10% HCl, distilled water, and dry ether, and then dried in a vaccume desicator. To a suspension of the obtained zinc powder (1.00g, 15.3mmol) in benzene (4ml) and ether (4ml) was added a piece of iodine. A solution of methyl 1-methyl-2-oxocyclohexanecarboxylate **10a** ($[\alpha]_D^{24}$ -104° (C 1.82, EtOH) (96%ee)) (0.400g, 2.35mmol) in ether (2ml) and ethyl bromoacetate (0.54ml, 9.70mmol) were added to the above suspension and the whole was heated to reflux for 5h. After adding MeOH-AcOH (1:1) (30ml), the resulting mixture was poured into water and extracted with benzene (10ml×3). The combined extracts were washed with water (30ml×3), and then brine, and dried over $MgSO_4$. Removal of the solvent gave the Reformatsky products as a pale yellow oil (0.580g, 96% yield). ^1H NMR δ 1.27 (3H, t, J=7Hz), 1.29 (3H, s), 1.2-2.1 (9H, m), 2.20-2.60 (2H, m), 3.69 (3H, s), 4.13 (2H, q, J=7Hz). IR (film) 3450, 1735, 1725, 1710 cm^{-1}. MS (m/e): 258 (M^+).
To the Reformatsky product thus obtained (0.580g, 2.24mmol) in ether (4ml) was added pyridine (1.79ml, 22.4mmol) and thionyl chloride (1.64ml, 22.4mmol) at 0°C. The mixture was surred for 2h at room temperature and poured into water (50ml) and extracted with ether (20ml×2). The combined extracts were washed with 10% HCl, water, and brine, and dried over $MgSO_4$. Removal of the solvent followed by column chromatography (hexane-ether (5:2)) gave a pale yellow oil (0.297g, 56% yield). ^1H NMR δ 5.60-5.80 (1H, brs). IR (film) 1640 cm^{-1}. MS (m/e): 240 (M^+).
To a solution of the above oil (0.297g, 1.23mmol) in MeOH (2.5ml) was added KOH (0.300g, 5.35mmol) and the mixture was heated to reflux for 12h. The resulting potassium salt was filtered and washed with ether (10ml×2). 10% HCl (10ml) was added to the above salt and the whole was extracted with ether (20ml×3). The combined ethereal extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a colorless oil (0.155g, 63% yield). ^1H NMR δ 1.37 (3H, s), 1.10-2.80 (8H, m), 5.75 (1H, brs), 10.35 (2H, brs). IR (film) 1700 cm^{-1}. MS (m/e): 198 (M^+).
To a suspension of PtO_2 (0.010g, 0.044mmol) in AcOH (1ml) was bubbled hydrogen gas for 30 min and added a solution of the above oil (0.123g, 0.62mmol) in AcOH (2ml) and surred for 3 h under hydrogen atomosphere. 10% NaOH (10ml) was added to the reaction mixture and extracted with ether (20ml×3). The combined ethereal extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent followed by column chromatography (ether) gave **17** as a white solid (0.106g, 85% yield), which was recrystalized from hexane-acetone provided colorless needles of mp 162-163°C. $[\alpha]_D^{27}$ +8.97° (C 1.07, acetone) (~100%ee, *R,R*) (lit.[17] mp 161-163°C, $[\alpha]_D$ +9° (C 1.0, acetone)). ^1H NMR δ 1.22 (3H, s), 1.10-2.10 (9H, m), 2.35-2.65 (2H, m), 8.00-9.50 (2H, brs). IR (film) 1700, 1690 cm^{-1}. MS (m/e): 182 (M^+-H_2O). HRMS calcd for $C_{10}H_{14}O_3$ (M^+-H_2O): 182.0943, found: 182.0937.

Conversion of 10b to 11b. To a solution of a piece of Na metal in EtOH (5ml) was added a solution of methyl 1-allyl-2-oxocyclohexanecarboxylate **10b** ($[\alpha]_D^{25}$ -97.8° (C 1.55, EtOH) (73%ee)) (0.070g, 0.36mmol) in EtOH (2ml) at 0°C and the mixture was surred at room temperature for 3 h and poured into cold aq NH_4Cl (50ml), followed by the extraction with ether (20ml×3). The combined ethereal extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent followed by column chromatography (ether-hexane (1:5)) gave a colorless oil (0.030g, 40% yield). $[\alpha]_D^{26}$ -88.9° (C 1.28, $CHCl_3$) (67%ee, *S*).

Conversion of 10b to 10d. A solution of methyl (*S*)-1-allyl-2-oxocyclohexanecarboxylate **10b** ($[\alpha]_D^{25}$ -101° (C 1.66, EtOH)) (75%ee) (0 393g, 2.00mmol) in AcOH-H_2O (5:1)(30ml) was treated with a stream of ozone at room temperature for 4 h. Excess ozone was then removed by passing a stream of N_2 through the solution and the mixture was treated with 10% H_2O_2 (12ml) at 0°C and stirred for 12 h at room temperature. After removal of the solvent, the mixture was treated with a solution of excess CH_2N_2 in ether at 0°C. 1 h later, 3N AcOH was added until the yellow color was discharged. This mixture was washed with aq. 5% $Na_2S_2O_3$ and brine, and then dried over $MgSO_4$. Removal of the solvent followed by column chromatography (hexane-ether (5:2)) gave a colorless oil (0.155g, 34% yield). $[\alpha]_D^{25}$ -65.5° (C 2.04, EtOH).

Conversion of 10c to 10d. A solution of methyl 1-benzyl-2-oxocyclohexanecarboxylate **10c** ($[\alpha]_D^{25}$ -111°(C 1.64, EtOH)) (≥99%ee) (0.575g, 2.33mmol) was subjected to the standard ozonolysis procedure described just above to give methyl (*S*)-1-carbomethoxy-2-oxocyclohexylacetate as a colorless oil (0.162g, 31% yield). $[\alpha]_D^{25}$ -87.5°(C 1.11, EtOH) (100%ee, *S*).

Conversion of 12b to 12d. A solution of ethyl (*S*)-2-acyl-2-methyl-4-pentenoate **12b** ($[\alpha]_D^{22}$ -27.9° (C 0.91, $CHCl_3$)) (94%ee) (0.102g, 0.55mmol) was subjected to the standard ozonolysis procedure described above to give ethyl methyl (*S*)-2-acyl-2-methylsuccinate as a colorless oil (0.039g, 33% yield). $[\alpha]_D^{22}$ -37.8° (C 0.65, $CHCl_3$).

Conversion of 12c to 12d. A solution of ethyl 2-benzyl-2-methyl-3-oxobutyrate **12c** ($[\alpha]_D^{22}$ -58.2° (C 0.90, $CHCl_3$)) (92%ee) (0.201g, 0.86mmol) was subjected to the standard ozonolysis procedure described above to give ethyl methyl (*S*)-2-acyl-2-methylsuccinate as a colorless oil (0.103g, 55% yield). $[\alpha]_D^{22}$ -36.9° (C 0.96, $CHCl_3$) (92%ee, *S*).

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