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Stereoselective Reactions. XXIV.[1] Chlorotrimethylsilane Promoted Asymmetric Michael Reaction of Chiral Lithioenamines Derived from α-Alkyl β-Keto Esters

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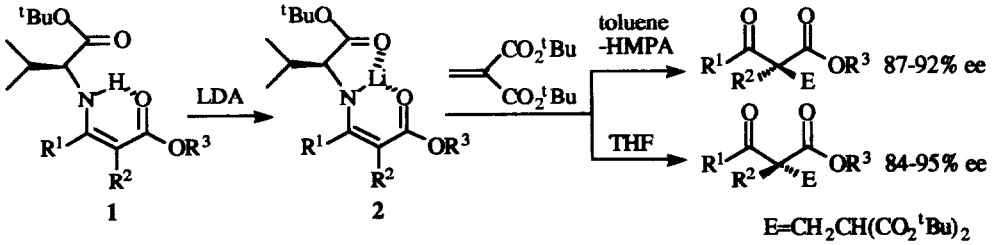
Abstract : Chlorotrimethylsilane promoted asymmetric Michael reaction of the chiral lithioenamines derived from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester is described. Complementary asymmetric syntheses producing either enantiomers from the same starting material have been realized by changing the solvent system. That is, the lithioenamines react with methyl vinyl ketone or ethyl acrylate in THF in the presence of chlorotrimethylsilane to give, after hydrolysis, the Michael adducts in 57-90% ee. On the other hand, the reaction using toluene-HMPA as a solvent system, instead of THF, affords the corresponding antipodes with enantiomeric purities of 41-77% ee.

The Michael addition reaction is one of the most powerful and widely employed carbon-carbon bond forming reactions in organic synthesis. Accordingly, its asymmetric version has attracted widespread attention for the last two decades.[4] In previous publications,[5] we have reported asymmetric Michael reaction of the chiral lithioenamines, derived from α-alkyl β-keto esters and (*S*)-valine *tert*-buty ester, with di-*tert*-butyl methylenemalonate (Scheme 1). The diastereoselectivity of this reaction is highly sensitive to the solvent system. Thus the reactions in toluene-HMPA gave α,α-dialkyl β-keto esters in 87-92% ee after hydrolysis. On the other hand, the reaction in THF gave the corresponding antipodes in 84-95% ee. However, the reaction attempted with a weakly activated Michael acceptor, such as methyl vinyl ketone (MVK) or ethyl acrylate, failed to afford products. To overcome the problem of low reactivity with the chiral lithioenamines **2**, the activation of Michael acceptors by Lewis acid catalysts was investigated. We have found that the asymmetric Michael reaction of the chiral lithioenamines **2** with MVK or ethyl acrylate can be promoted by chlorotrimethylsilane (TMSCl) to give either enantiomer of the corresponding Michael adducts **3** and **4** in good enantioselectivities.[6] In this paper, we report a full detail of chlorotrimethylsilane promoted asymmetric Michael reaction of the chiral lithioenamines **2**.

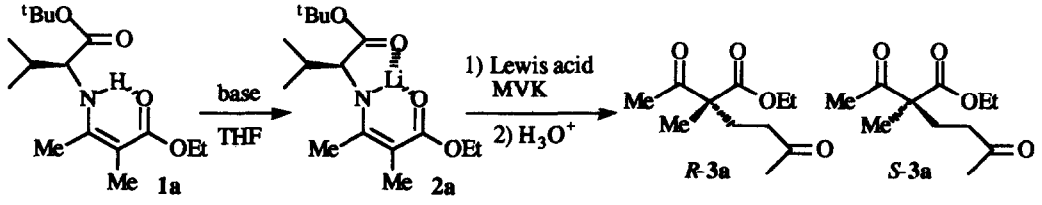


Scheme 1

ASYMMETRIC MICHAEL REACTION IN THE PRESENCE OF LEWIS ACID

The asymmetric Michael reaction of the acyclic lithioenamine **2a** with MVK in the presence of several Lewis acids was studied in THF, and the results are summarized in Table 1. The lithioenamine **2a** was prepared by treatment of **1a** with lithium diisopropylamide (LDA) or *n*-BuLi in THF. The reaction of **2a** with MVK did not occur at -78 °C, whereas it started when MVK was added to a mixture of **2a** and BF_3•OEt_2 (2 eq) (Method A) to give, after hydrolysis, the corresponding Michael adduct *R*-**3a** (23% ee) in 69% yield. The order and way of mixing of the reagents affect strongly both the product yield and the enantioselectivity. Thus when BF_3•OEt_2 was added to a THF solution containing **2a** and MVK (Method B), only trace amount of product was obtained (Entry 3). Among the examined Lewis acids, TMSCl exhibited profound effect on the enantioselectivity (Entries 12-15). It is essential to add the lithioenamine solution to a mixture of MVK and TMSCl (5 eq) (Method C) in order to obtain a practical yield and a good selectivity. Thus *R*-**3a** was obtained in 65% yield and 73% ee (Entry 14). As expected, the enantiomeric excess increased to 87% when the temperature was decreased to -100 °C (Entry 15). It is interesting to note that *S*-**3a** was obtained by Method B (Entry 13). The reversal of the stereoselection was also observed in the presence of $ZnCl_2$ depending on the

Table 1. Michael reaction of **2a** with MVK in the presence of Lewis acids in THF



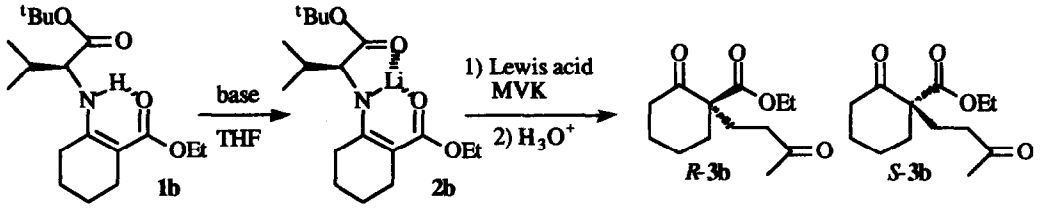
Entry	base	Temp (°C)	Lewis acid (eq)	Method[a]	yield (%)	ee (%)	*R*/*S*
1	LDA	-78→0	none		trace		
2	LDA	-78	BF_3•OEt_2 (2)	A	69	23	*R*
3	BuLi	-78	BF_3•OEt_2 (1)	B	trace		
4	LDA	-78	$TiCl_4$ (2)	A	—	—	—
5	BuLi	-78	$ZnCl_2$ (1)	C	39	47	*R*
6	LDA	-78	$ZnCl_2$ (2)	D	28	18	*S*
7	BuLi	-78	$MgCl_2$ (1)	C	31	9	*R*
8	BuLi	-78	LiCl (2)	A	2	52	*R*
9	BuLi	-78	LiI (2)	A	46	23	*R*
10	BuLi	-78	$SnCl_4$ (1)	A	40	24	*R*
11	LDA	-78	$AlCl_3$ (2)	A	27	18	*R*
12	LDA	-78	TMSCl (1)	A	22	59	*R*
13	LDA	-78	TMSCl (1)	B	12	17	*S*
14	LDA	-78	TMSCl (5)	C	65	73	*R*
15	LDA	-100	TMSCl (5)	C	66	87	*R*

a) A: MVK was added to a mixture of **2a** and Lewis acid after 20 min; B: Lewis acid was added to a mixture of **2a** and MVK; C: The lithioenamine solution was added to a mixture of MVK and Lewis acid: D: A mixture of MVK and Lewis acid (1 eq) was added to a mixture of **2a** and Lewis acid (1 eq).

mixing method (Method C and D; see the footnote of Table 1), though the selectivities were low to moderate (Entries 5 and 6).

Further we examined the effect of some Lewis acids in detail in the Michael reaction of the cyclic lithioenamine **2b** with MVK in THF (Table 2). In the absence of Lewis acid, the reaction of **2b** with MVK hardly takes place. However, when MVK was added to a THF solution containing **2b** and $BF_3 \cdot OEt_2$ (2 eq) after 20 min mixing duration at -78 °C (Method A), the reaction occurred to give the Michael adduct *R*-**3b** (79% ee) in 90% yield (Entry 4). The reduction of the mixing period has only a slight effect (Entry 2), but the decrease of the quantity of $BF_3 \cdot OEt_2$ has a strong effect on the chemical yield (Entry 3). The experiment at -100 °C (Entry 6) was not up to our expectations and resulted in just a reduced yield. Again the reversal of the stereoselection was observed by changing the mixing order (Method B) (Entry 7). The use of *n*-BuLi as a lithiating reagent was inferior to that of LDA in both the chemical yield and the enantioselectivity (Entries 8, 9). TMSCl, the best Lewis acid for the acyclic lithioenamine **2a**, gave the moderate selectivity for **2b** at -78 °C

Table 2. Michael reaction of **2b** with MVK in the presence of Lewis acids in THF



Entry	base	Temp (°C)	Lewis acid (eq)	Method[a]	yield (%)	ee (%)	*R/S*
1	LDA	-78→0	none		trace		
2	LDA	-78	$BF_3 \cdot OEt_2$ (2)	A'	87	76	*R*
3	LDA	-78	$BF_3 \cdot OEt_2$ (1)	A'	34	76	*R*
4	LDA	-78	$BF_3 \cdot OEt_2$ (2)	A	90	79	*R*
5	LDA	-78	$BF_3 \cdot OEt_2$ (3)	A	91	72	*R*
6	LDA	-100	$BF_3 \cdot OEt_2$ (2)	A	46(88)[b]	79	*R*
7	LDA	-78	$BF_3 \cdot OEt_2$ (1)	B	50	29	*S*
8	BuLi	-78	$BF_3 \cdot OEt_2$ (1)	A	19	60	*R*
9	BuLi	-78	$BF_3 \cdot OEt_2$ (1)	B	15	11	*S*
10	LDA	-78	TMSCl (5)	C	60	55	*R*
11	LDA	-78	TMSCl (5)	C'	60	42	*R*
12	LDA	-78	TMSCl (5)	A"	19	52	*R*
13	LDA	-100	TMSCl (5)	C	67	90	*R*
14	LDA	-78	TMSOTf (2.5)	C	75	77	*R*
15	BuLi	-78	$ZnCl_2$ (1)	C	14	39	*R*

a) A: MVK was added to a mixture of **2b** and Lewis acid after 20 min; A': MVK was added to a mixture of **2b** and Lewis acid immediately; A": A mixture of **2b** and Lewis acid was added to MVK; B: Lewis acid was added to a mixture of **2b** and MVK; C: **2b** was added to a mixture of MVK and Lewis acid; C': A mixture of MVK and Lewis acid was added to **2b**. b) Yield based on consumed **1b** in parentheses.

(Entries 10-12). Fortunately, the enantioselectivity was dramatically improved by lowering the reaction temperature to -100 °C to give 90% ee of *R*-**3b** in 67% yield (Entry 13).

Thus the reaction of the lithioenamines **2** and MVK in THF was found to be promoted by several Lewis acids, especially TMSCl to give *R*-adducts highly selectively. *S*-Adducts were also obtained by changing the mixing order of reagents in some cases, but the selectivities were low (11-29% ee).

DIASTEREOFACIAL CONTROL BY SOLVENT SYSTEM

We turned our attention to the control of the diastereoselectivity by solvent system. By a direct analogy with a previous study on asymmetric Michael reaction with di-*tert*-butyl methylenemalonate,[5] the reaction of **2b** with MVK was performed in toluene using HMPA as a ligand, expecting to get the *S*-adduct (Table 3). However, an excess quantity of $BF_3 \cdot OEt_2$ over HMPA afforded *R*-**3b** and an excess of HMPA over $BF_3 \cdot OEt_2$ failed to afford the product (Entries 1, 2). HMPA appears to play a role as Lewis base for $BF_3 \cdot OEt_2$ and remove it from the reaction. Using THF as a ligand in toluene also leads to *R*-adduct in a slightly reduced selectivity compared to the result in a THF solvent (Entry 3). A small excess of TMSOTf over HMPA also affords *R*-**3b** (Entry 4). Fortunately, three molar excess of TMSCl over HMPA resulted in the formation of *S*-**3b** (Entries 5-7). This means TMSCl and HMPA are independently playing their roles as an activator for MVK and as a diastereocontroling ligand to the lithium cation of **2b**, respectively. Lowering the reaction temperature was not fruitful, but the decrease of the quantity of HMPA brought some improvement to

Table 3. Michael reaction of **2b** with MVK in toluene using HMPA as a ligand

Entry	base	Ligand (eq)	Temp (°C)	Lewis acid (eq)	Method[a]	yield (%)	ee (%)	Product
1	LDA	HMPA (1)	-78	$BF_3 \cdot OEt_2$ (2)	A'	54	61	*R*-**3b**
2	LDA	HMPA (4)	-78	$BF_3 \cdot OEt_2$ (2)	A'	trace		
3	LDA	THF (8)	-95	$BF_3 \cdot OEt_2$ (2)	A'	29	40	*R*-**3b**
4	LDA	HMPA (2)	-78	TMSOTf (2.5)	C	44	40	*R*-**3b**
5	LDA	HMPA (2)	-78	TMSCl (5)	C	35	48	*S*-**3b**
6	LDA	HMPA (2)	-95	TMSCl (5)	C	35	45	*S*-**3b**
7	LDA	HMPA (1)	-95	TMSCl (5)	C	48	60	*S*-**3b**

a) A': MVK was added to a mixture of **2b** and Lewis acid immediately; C: **2b** was added to a mixture of MVK and Lewis acid.

Table 4. Michael reaction of **2a** with MVK in toluene using HMPA as a ligand

Entry	base	Ligand (eq)	Temp (°C)	Lewis acid (eq)	Method[a]	yield (%)	ee (%)	Product
1	LDA	HMPA (2)	-78	TMSCl (5)	C	29	39	*S*-**3a**
2	LDA	HMPA (7)	-78	TMSCl (6)	C	11	27	*R*-**3a**
3	LDA	HMPA (1)	-78	TMSCl (5)	C	38	39	*S*-**3a**
4	LDA	HMPA (1)	-95	TMSCl (5)	C	38	50	*S*-**3a**

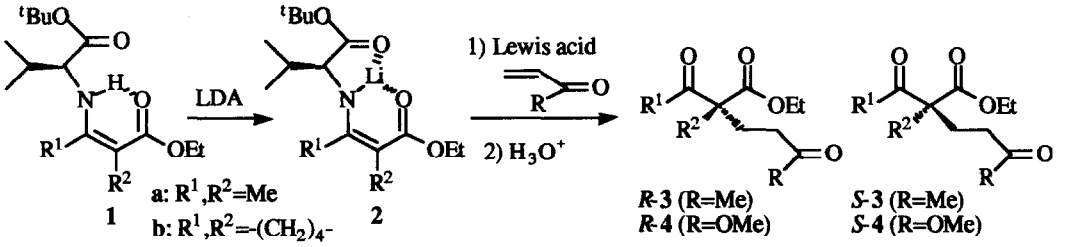
a) C: **2a** was added to a mixture of MVK and Lewis acid.

give 60% ee of *S*-3b.

The results from the reaction of 2a and MVK in toluene using HMPA and TMSCl were summarized in Table 4. A similar tendency was observed and 50% ee of *S*-3a was obtained in the presence of one equivalent of HMPA and five equivalents of TMSCl at -95 °C (Entry 4).

Based on the data obtained above, asymmetric Michael reaction of 2 with ethyl acrylate was carried out in the presence of five equivalents of TMSCl by Method C. The results are collected in Table 5 along with the best data of the reaction with MVK. Either enantiomer 4 could be prepared in good enantiomeric purities from the same chiral enamines 1 simply by changing the solvent system.[7]

Table 5. Asymmetric Michael reaction of 2 promoted by TMSCl[a]



Entry	2	R	solvent-Ligand (eq)	Temp (°C)	yield (%)	ee (%)	Product
1	2a	Me	THF	-100	66	87	*R*-3a
2	2a	Me	toluene-HMPA (1)	-95	38	50	*S*-3a
3	2b	Me	THF	-100	67	90	*R*-3b
4	2b	Me	toluene-HMPA (1)	-95	48	60	*S*-3b
5	2a	OEt	THF	-100	43	79	*R*-4a
6	2a	OEt	toluene-HMPA (1)	-95	16	41	*S*-4a
7	2b	OEt	THF	-100	53	57	*R*-4b
8	2b	OEt	toluene-HMPA (1)	-95	23	77	*S*-4b

a) The lithioenamine 2 was added to a mixture of MVK and Lewis acid (Method C).

DISCUSSION

Lewis acids can be assumed to enhance the reactivity of α,β-unsaturated carbonyl compounds by the coordination to their carbonyl oxygen atoms. In fact, several Lewis acids accelerated this asymmetric Michael reaction. Especially TMSCl not only gives the practical yields and good enantioselectivities but also can be compatible with HMPA. Thus the use of TMSCl as a reaction promoting reagent permits the diastereocontrol by solvent system. It is well known TMSCl accelerates conjugate addition of Gilman cuprate reagents. However, the principle of the acceleration by TMSCl has still been unclear and there are considerable debates.[8] In our Michael reaction, involvement of TMS azaenolate as an active species is unlikely. Treatment of 2b with TMSCl at -78 °C for 3 h followed by the addition to MVK afforded 3b in a significantly decreased yield (Entry 12 in Table 2). Therefore it is plausible to assume that TMSCl acts as Lewis acid. Coordination of TMSCl to α,β-unsaturated carbonyl compounds as Lewis acid lowers their LUMO energy and enhances their reactivity

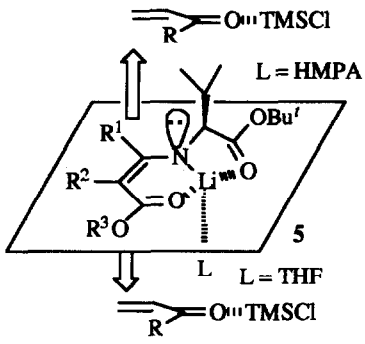


Figure 1

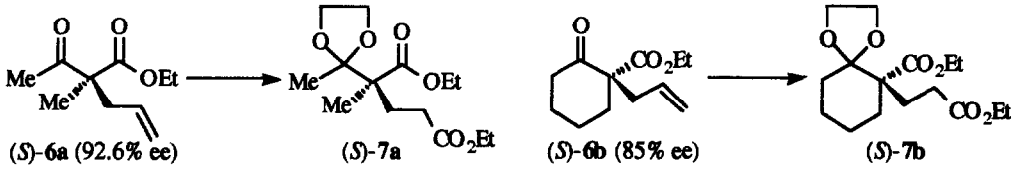
toward Michael reaction. This asymmetric Michael reaction can be seen as the one between the lithioenamines **2** and Michael acceptors activated by TMSCl.

The results from this asymmetric Michael reaction can be rationalized by consideration of the *trans*-fused chelated structure **5**[9,10] (Figure 1), which we proposed before.[5,7] The bulky and powerful ligand HMPA not only increases the nucleophilicity of the lithioenamines **2**, but also blocks the bottom face. Therefore the reaction occurs from the top face. On the other hand, the weak and small ligand THF might be replaced by TMSCl and the reaction occurs from the bottom face. Alternatively the direction of the nitrogen lone pair might be responsible for the bottom face reaction.

DETERMINATION OF THE ABSOLUTE CONFIGURATIONS AND OPTICAL PURITIES

The absolute configuration and the enantiomeric purity of the Michael adduct **3a** were determined from the reported value for *S*-**3a** ($[\alpha]_D^{22}$ -8.3° ($CHCl_3$), 86% ee).[11] In a similar way, the absolute configuration of **3b** was determined. But the reported optical rotation for enantiomerically pure *R*-**3b** was significantly different ($[\alpha]_{578}^{r.t.}$ +81° (CCl_4)[12] and $[\alpha]_{578}^{22}$ +97° (CCl_4)[13]). Therefore the enantiomeric excess of **3b** was confirmed by the ^1H NMR analysis in the presence of chiral shift reagent Eu(hfc)$_3$. Thus the rotation for optically pure *R*-**3b** was determined to be $[\alpha]_{577}^{22}$ +85.0° (CCl_4).

The Michael adducts **4a** and **4b** had not been previously described in enantiomerically pure forms in the literature. Fortunately, we had obtained *S*-**4a** ($[\alpha]_D^{23.5}$ -10.5° (C 1.00 in $CHCl_3$) (92.6% ee)) and *S*-**4b** ($[\alpha]_D^{25}$ -64.9° (C 1.39 in $CHCl_3$) (85% ee)) as by-products in the chemical transformations of **6a,b** into **7a,b** (Scheme 2).[14] The optical purities of **4a** and **4b** were further confirmed by ^1H NMR analysis in the presence of the chiral shift reagent [Eu(hfc)$_3$].



Scheme 2

CONCLUSION

Asymmetric Michael reaction of the chiral lithioenamines **2** derived from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester was promoted by chlorotrimethylsilane. The stereochemistry of the products can be controlled by choosing the solvent system. Thus, the reaction of **2** with Michael acceptors in THF in the presence of TMSCl (5 eq) takes place preferentially from the bottom face of the complex **5** and affords, after hydrolysis, the Michael adducts in 57-90% ee. While using toluene-HMPA (1 eq) as a solvent system affords the corresponding antipodes in 41-77% ee. The sense of asymmetric induction in this Michael reaction can be

predicted by assuming the *trans*-fused chelated structure **5**. This method provides a procedure for the synthesis of both enantiomers of α,α-dialkyl β-keto esters with a predictable absolute configuration in good enantiomeric purities starting from the same chiral enamines.

EXPERIMENTAL SECTION

All dry solvents were distilled under argon. Toluene and THF 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. 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 internal tetramethylsilane. 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.

Michael reaction of N-*[2-ethoxycarbonyl-1-methylprop-1-enyl]*-S-*valine* tert-*butyl ester* **1a** *with MVK (Entry 1 of Table 5) (Procedure 1)* An LDA solution was prepared from diisopropylamine (0.30 ml, 2.1 mmol) in THF (3 ml) and *n*-BuLi (1.55 M in hexane, 1.36 ml, 2.1 mmol) at -78 °C for 30 min. A solution of **1a**[7a] (0.61 g, 2.0 mmol) in THF (7 ml) was added to this, and the resulting solution was stirred for 30 min. This lithioenamine solution was added to a solution of MVK (0.25 ml, 3.0 mmol) and TMSCl (1.27 ml, 10.0 mmol) in THF (10 ml) at -100 °C and the whole was stirred at -100 °C for 5 h. The reaction was quenched by 10% HCl (40 ml) and the whole mixture was stirred vigorously at room temperature for 1 h and was then extracted with AcOEt (30 ml × 3). The combined extracts were washed successively with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane : AcOEt = 8 : 1) provided *R*-**3a** (0.29 g, 66%) as an oil. $[\alpha]_D^{22}$ +8.38° (C 1.29 in $CHCl_3$) (87% ee). ^1H NMR δ 1.26 (3H, t, J=7.1 Hz), 1.33 (3H, s), 1.80-2.61 (4H, m), 2.11 (3H, s), 2.13 (3H, s), 4.15 (2H, q, J=7.1 Hz). IR (neat, film) 1730, 1715, 1705 cm^{-1}. MS (m/e): 214 (M^+), 144 (M^+ − MVK). Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47; found: C, 61.40; H, 8.32.

(Entry 2 of Table 5) (Procedure 2) An LDA solution was prepared from diisopropylamine (0.30 ml, 2.1 mmol) in toluene (3 ml) and *n*-BuLi (1.55 M in hexane, 1.34 ml, 2.1 mmol) at -78 °C for 30 min. After the addition of HMPA (0.38 ml, 2.2 mmol), a solution of **1a** (0.60 g, 2.0 mmol) in toluene (7 ml) was added to this mixture, and the resulting solution was stirred for 1 h. This lithioenamine solution was added to a solution of MVK (0.25 ml, 3.0 mmol) and TMSCl (1.27 ml, 10.0 mmol) in toluene (8 ml) at -95 °C and the whole was stirred at -95 °C for 5 h. The reaction mixture was worked up in the same way as Procedure 1 to give *S*-**3a** (0.16 g, 38%) as an oil. $[\alpha]_D^{22}$ -4.84° (C 1.29 in $CHCl_3$) (50% ee).

Michael reaction of N-*[2-(ethoxycarbonyl)cyclohex-1-enyl]*-S-*valine* tert-*butyl ester* **1b** *with MVK (Entry 3 of Table 5)* This reaction was performed by Procedure 1 by using **1b**[7a] to give *R*-**3b** (67%) as an oil. $[\alpha]_{577}^{22}$ +76.4° (C 1.03 in CCl_4) (90% ee). ^1H NMR δ 1.28 (3H, t, J=7.1 Hz), 1.43-2.71 (12H, m), 2.13 (3H, s), 4.20 (2H, q, J=7.1 Hz). IR (neat, film) 1730, 1715, 1705 cm^{-1}. MS (m/e): 240 (M^+), 170 (M^+ − MVK). Anal. calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; found: C, 64.74; H, 8.50.

(Entry 4 of Table 5) This reaction was performed by Procedure 2 by using **1b** to give *S*-**3b** (48%) as an oil. $[\alpha]_{577}^{22}$ -51.3° (C 1.03 in CCl_4) (60% ee).

Michael reaction of N-*[2-ethoxycarbonyl-1-methylprop-1-enyl]*-S-*valine* tert-*butyl ester* **1a** *with ethyl acrylate (Entry 5 of Table 5)* This reaction was performed by Procedure 1 by using **1a** and ethyl acrylate (8 eq) to give *R*-**4a** (43%) as an oil. $[\alpha]_D^{23.5}$ +8.96° (C 1.00 in $CHCl_3$) (79% ee). ^1H NMR δ 1.25 (3H, t, J=7.1 Hz), 1.27 (3H, t, J=7.1 Hz), 1.35 (3H, s), 1.8-2.4 (4H, m), 2.17 (3H, s), 4.13 (2H, q, J=7.1 Hz), 4.20 (2H, q,

J=7.1 Hz). IR (neat, film) 1735, 1710 cm^{-1}. MS (m/e): 245 (M^+ + 1), 171 (M^+ - CO_2Et). HRMS calcd for $C_{12}H_{21}O_5$ (M^+ + 1): 245.1389, found: 245.1392.

(Entry 6 of Table 5) This reaction was performed by Procedure 2 by using **1a** and ethyl acrylate (8 eq) to give *S*-**4a** (16%) as an oil. $[\alpha]_D^{23.5}$ -4.64° (C 1.00 in $CHCl_3$) (41% ee).

Michael reaction of N-*[2-(ethoxycarbonyl)cyclohex-1-enyl]*-S-*valine* tert-*butyl ester* **1b** *with ethyl acrylate (Entry 7 of Table 5)* This reaction was performed by Procedure 1 by using **1b** and ethyl acrylate (5 eq) to give *R*-**4b** (53%) as an oil. $[\alpha]_D^{25}$ +43.4° (C 1.39 in $CHCl_3$) (57% ee). ^1H NMR δ 1.22 (3H, t, J=7.1 Hz), 1.26 (3H, t, J=7.1 Hz), 1.4-2.7 (12H, m), 4.03 (2H, q, J=7.1 Hz), 4.14 (2H, q, J=7.1 Hz). IR (neat, film) 1735, 1710, cm^{-1}. MS (m/e): 270 (M^+). HRMS calcd for $C_{14}H_{22}O_5$: 270.1467, found: 270.1466.

(Entry 8 of Table 5) This reaction was performed by Procedure 2 by using **1b** and ethyl acrylate (8 eq) to give *S*-**4b** (23%) as an oil. $[\alpha]_D^{25}$ -58.5° (C 1.39 in $CHCl_3$) (77% ee).

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