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Catalytic asymmetric synthesis of β-hydroxy-α-amino acid esters by direct aldol reaction of glycinate Schiff bases

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Abstract—A catalytic asymmetric synthesis of β-hydroxy-α-amino acid esters was developed using the direct aldol reaction of glycinate Schiff bases with aldehydes. The reaction was catalyzed by heterobimetallic asymmetric complexes without preformation of enol silyl ethers from glycinate Schiff bases. *anti*-β-Hydroxy-α-amino acid esters were obtained as the major diastereomer in most cases, and moderate enantiomeric excess (up to 76% ee) was achieved for the first time for this type of reaction. Various substrates were also examined to investigate the effects of the protective groups for the amine or for the carboxylic acid moiety in glycine.

1. Introduction

β-Hydroxy-α-amino acids are the constituents of numerous biologically active compounds. For example, the vancomycin class of antibiotics[1] contains either an *erythro*- or *threo*-β-arylserine moiety, and a wide range of other antibiotics incorporate β-hydroxy-α-amino acids. β-Hydroxy-α-amino acids also occur in other classes of biologically important compounds such as (+)-lactacystin[2] and cyclosporin. Moreover, β-hydroxy-α-amino acids serve as versatile precursors for other types of building blocks: reduction of the carboxylic acid gives a 2-amino-1,3-diol,[3] which is the key component of sphingosine, and conversion of the β-hydroxyl group leads to an efficient synthesis of β-lactams.[4] Some chiral ligands are also synthesized from β-hydroxy-α-amino acids.[5]

A number of methods have been reported for the enantioselective synthesis of β-hydroxy-α-amino acid derivatives using different types of strategies, including epoxidation/amination,[6] aminohydroxylation of cinnamates,[7] dihydroxylation of α,β-unsaturated esters,[8] alkylation of α-amino-β-oxyaldehydes,[9] hydrogenation of β-oxyacetamidoacrylates,[10] hydrogenation of 2-(*N*-acetylamino)-3-oxoalkanoates,[11] addition of acetylide to a nitrone,[12] Strecker reactions,[13] rearrangements,[14] aldol reactions,[15] etc. Among these methods, aldol reactions of glycine equivalents with aldehydes provide an efficient and direct access to β-hydroxy-α-amino acid derivatives, because the process involves the formation of a C–C bond and construction of vicinal stereogenic centers. A few elegant methods for the aldol strategy have been reported employing only catalytic amounts of chiral sources. Ito and Hayashi et al. reported the use of gold catalysts for the aldol reaction of α-isocyano acetates with aldehydes.[16] This system works with small amounts of catalysts and gives *trans*-4-alkoxycarbonyl-2-oxazolines in a highly stereoselective manner, which are easily transformed into *syn*-β-hydroxy-α-amino acid esters. Corey et al. developed a Mukaiyama-type aldol reaction of ketene silyl acetals derived from glycinate Schiff bases.[17] The reaction was catalyzed by a cinchonidine-derived ammonium salt to afford mostly *syn*-β-hydroxy-α-amino acid esters as the major diastereomer. Recently, aluminum catalysts were reported for the stereoselective synthesis of *cis*-4-alkoxycarbonyl-2-oxazolines,[18] which are precursors to *anti*-β-hydroxy-α-amino acid esters. While these catalysts provide an efficient approach to the synthesis of *anti*-β-aryl-β-hydroxy-α-amino acid esters from aromatic aldehydes, aliphatic aldehydes were not suitable substrates. An enzymatic approach was extensively studied by Wong et al., and several types of aldolases give β-hydroxy-α-amino acid esters.[19] Although this process realizes ideal atom efficiency by employing glycine as a donor substrate, there some limitations remain, such as substrate generality.

During the past few years, we developed enantioselective direct aldol reactions of unmodified ketones using several types of heterobimetallic asymmetric catalysts.[20–22] These processes exclude the necessity of preforming enol ethers from carbonyl compounds for enantioselective catalytic aldol reactions.[23] The use of methyl ketones and hydroxy ketones as substrates enables efficient catalytic asymmetric syntheses of β-hydroxy ketones[20c–e] and α,β-dihydroxy

Keywords: direct aldol reaction; heterobimetallic asymmetric catalyst; glycinate Schiff base; β-hydroxy-α-amino acid; lanthanide; vancomycin; benzophenone imine; glycine.

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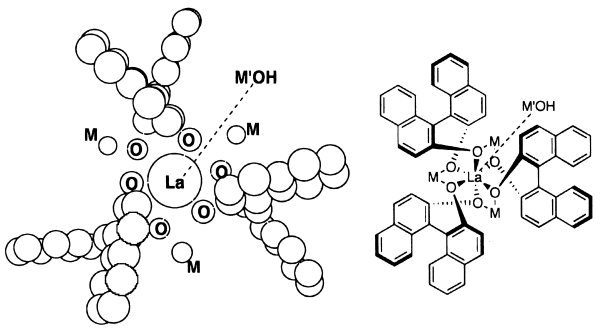
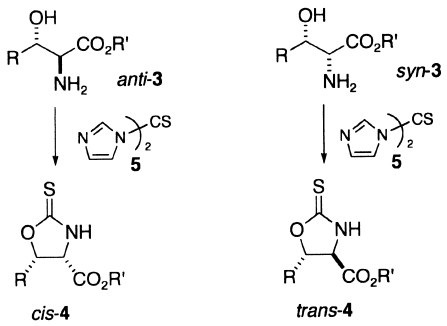


Figure 1. Heterobimetallic catalysts $M_3[La(S\text{-binol})_3]$.



Scheme 1. Determination of enantiomeric excess.

ketones.[20a,b] This article focuses on the development of catalytic asymmetric synthesis of β-hydroxy-α-amino acid derivatives using the direct aldol reaction.

2. Results and discussion

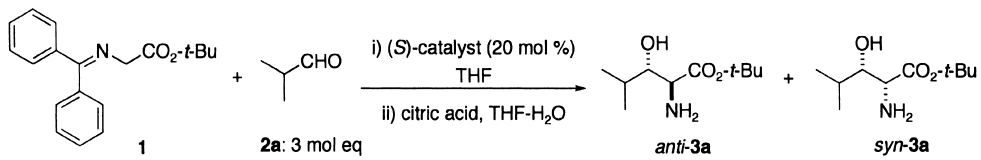
2.1. Catalyst screening

Glycinate Schiff bases were used as glycine equivalents for the donor substrate because they can be enolized under mildly basic conditions.[24] Thus, a series of heterobimetallic lanthanide complexes (Fig. 1),[22] which were developed in our group, were screened in the direct aldol reaction of isobutyraldehyde (**2a**) with Schiff base **1** derived from *tert*-butyl glycine ester and benzophenone (Table 1). The reaction was conducted in THF, and the crude product was treated with aqueous citric acid to hydrolyze the benzophenone imine moiety of the aldol adducts, giving β-hydroxy-α-amino acid esters **3a** as a mixture of diastereomers. The diastereomers (*anti*-**3a** and *syn*-**3a**) were isolated by silica gel column chromatography, and the enantiomeric excess was determined by HPLC after conversion to the corresponding oxazolidinethione (**4**) by treatment with thiocarbonyl diimidazole (**5**) (Scheme 1).[17] As a result, LLB (M=Li, Fig. 1) gave the *anti*-product (*anti*-**3a**) in 19% ee (Table 1, entry 1), whereas two other complexes (M=Na or K, Fig. 1) afforded racemic products (Table 1, entries 5 and 6). To improve the chemical yield, we attempted to improve the LLB catalyst by addition of a catalytic amount of bases (Table 1, entries 2–4) that can activate LLB.[25] We previously reported that a heteropolymetallic catalyst, prepared from MOH (M=alkali metal), H_2O, and LLB, is an effective promoter for the direct aldol reactions of methyl ketones[20d] and α-hydroxy ketones.[20a,b] In those cases, the addition of KOH rather than LiOH or NaOH gave the best results in terms of reactivity and stereoselectivity. In the present system, the addition of such bases also accelerated the aldol reaction to afford the products in much higher chemical yields. In contrast to the previous cases, a catalyst prepared from LLB, LiOH, and H_2O gave the best result (yield 78%, *anti*/*syn*=67:33) (Table 1, entry 2). Moreover, the enantiomeric excess of the *anti*-isomer was greatly improved to 54%.

2.2. Effects of substituents on the benzophenone imine moiety

In the direct aldol reactions previously reported by our group, the acidity of the α-proton of the carbonyl compounds was a crucial factor.[20d] In this regard, we examined the benzophenone imine moiety in the present system. Thus, we synthesized glycinate Schiff bases possessing an electron-withdrawing or electron-donating diarylmethylene moiety, attempting to vary the acidity of the donor substrate (Table 2). As a result, the reaction was accelerated when electron-withdrawing substituents were introduced. This phenomenon is consistent with the expected increase in the acidity of the α-proton of the glycinates. Moreover, the enantiomeric excess of the *anti*-isomer (*anti*-**3a**) was further improved to 74% when chloro-substituted benzophenone imine **8** was used as a

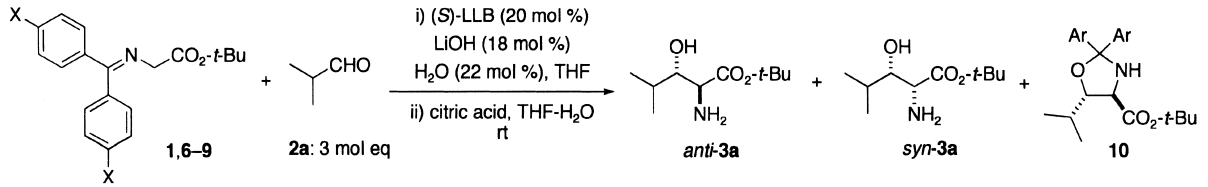
Table 1. Direct aldol reactions of glycinate Schiff base **1** with isobutyraldehyde (**2a**) promoted by heterobimetallic catalysts



Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)[a]	*anti*/*syn*[b]	ee of *anti* (%)[c]	ee of *syn* (%)[c]
1	LLB ($Li_3[La(S\text{-binol})_3]$)	−50	65	12	58:42	19	1
2	LLB+LiOH (0.9)+H_2O (1.1)	−50	65	78	67:33	54	1
3	LLB+NaOH (0.9)+H_2O (1.1)	−50	65	79	66:34	21	5
4	LLB+KOH (0.9)+H_2O (1.1)	−50	65	52	63:37	45	0
5	LSB ($Na_3[La(S\text{-binol})_3]$)	−40	123	42	64:36	0	0
6	LPB ($K_3[La(S\text{-binol})_3]$)	−40	123	97	37:63	0	−1

[a] Yield of isolated amino acid esters **3a**.
[b] Determined by ^1H NMR of the crude mixture of amino acid esters **3a** after hydrolysis of the imine moiety of the aldol adducts.
[c] Determined by HPLC after conversion to thioxooxazolines **4**.

Table 2. Direct aldol reaction of glycinate Schiff bases with *p*,*p*′-disubstituted benzophenone imine moiety



Entry	X	Temperature (°C)	Time (h)	Yield (%)[a]	*anti*/*syn*	ee of *anti* (%)[b]	ee of *syn* (%)[b]
1	CH_3 (**6**)	−40	23	85 (0)	63:37[c]	42	0
2	H (**1**)	−40	36	94 (0)	62:38[c]	47	3
3	F (**7**)	−50	26	87 (0)	53:47[c]	64	8
4	Cl (**8**)	−50	16	93 (19)	59:41[d]	74	20
5	CF_3 (**9**)	−60	5	72 (22)	56:44[d]	61	43
6	CF_3 (**9**)	−50	1	89 (46)	44:56[d]	68	51

[a] Combined yield of amino acid esters **3a** and oxazolidine **10**. Isolated yield of **10** is given in parentheses.
[b] Determined by HPLC after conversion to thioxooxazolines **4**.
[c] Determined by ^{1}H NMR of the crude mixture of amino acid esters **3a** after hydrolysis of the imine moiety of the aldol adducts.
[d] Determined by calculation on the basis of the isolated **3** and **10**.

substrate (entry 4).[26] As shown in entries 5 and 6, the introduction of trifluoromethyl groups significantly accelerated the aldol reaction, affording the products (**3a**) in good yield after 5 h at −60°C (entry 5) or after 1 h at −50°C (entry 6). This substrate (**9**) is interesting because the enantiomeric excess of the *syn*-adduct (*syn*-**3a**) was also largely improved (51% ee, entry 6). In the case of imines with electron-withdrawing substituents, portions of *syn*-adducts underwent cyclization to afford the corresponding *trans*-oxazolidines (**10**)[27] after treatment with aqueous citric acid at room temperature (entries 4–6). In the experiments presented in Table 2, these oxazolidines were isolated by flash silica gel column chromatography. Nevertheless, conducting the hydrolysis at 40°C successfully transformed the oxazolidines (**10**) to the principal *syn*-amino acid esters (*syn*-**3**).

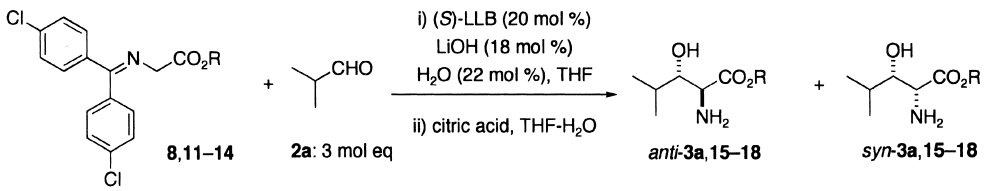
2.3. Effects of the protective group for the carboxylic acid in glycine

With the best imine moiety in the substrates, we examined the effects of the protective group for the carboxylic acid (Table 3). Methyl ester **11** had higher reactivity in the aldol reaction (entry 1), compared with the *tert*-butyl ester (**8**) (entry 3), affording the aldol adducts in good yield. The subsequent hydrolysis was performed at lower temperature (20°C) due to the lability of the methyl ester (**15**), and the corresponding *trans*-oxazolidine was isolated in 29% yield. The desired amino acid esters (**15**) were obtained in 58% yield with 38% ee (*anti*). Diphenylmethyl ester **12** was also highly reactive to give the corresponding amino acid esters (**16**) with moderate enantiomeric excess (*anti*, 47% ee; *syn*, 42% ee) (entry 2). Amide **14** also reacted with **2a** rapidly to afford the *syn*-product as the major diastereomer (*anti*/*syn*=20:80), albeit with very low enantiomeric excess (3%) (entry 5). In contrast to the above-mentioned substrates, phenacyl ester **13** did not react with isobutyraldehyde (**2a**) even at a higher temperature (entry 4). This result is likely due to the ability of the phenacyl ester moiety to inactivate the catalyst by forming a tight chelate complex.

2.4. Catalyst amounts and solvents

Because the present system is highly reactive, the catalyst

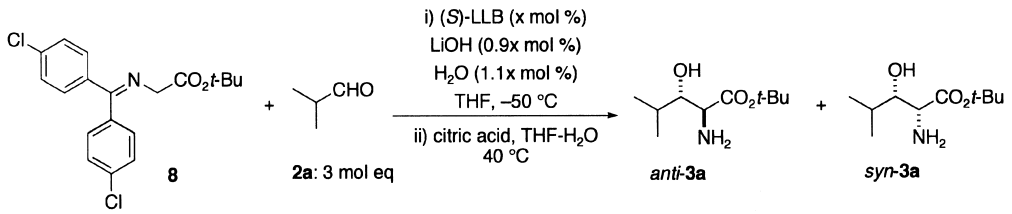
Table 3. Direct aldol reaction of glycinate Schiff bases with different protective groups for the carboxylic acid



Entry	R	Product	Temperature (°C)	Time (h)	Yield (%)[a]	*anti*/*syn*[b]	ee of *anti* (%)[c]	ee of *syn* (%)[c]
1	CH_3 (**11**)	**15**[d]	−50	2	58 (29)	89:11	38	ND
2	$CHPh_2$ (**12**)	**16**[d]	−50	1	56[e]	78:22	47	42
3	*t*-Bu (**8**)	**3a**	−50	16	93	59:41	74	20
4	CH_2COPh (**13**)	**17**	−20	16	0	–	–	–
5	$N(CH_3)OCH_3$ (**14**)	**18**[d,f]	−40	14	98	20:80	33	3

[a] Isolate yield of amino acid esters. Figure in parenthesis shows the isolated yield of oxazolidine.
[b] Determined by ^{1}H NMR of the crude mixture of amino acid esters after hydrolysis of the imine moiety of the aldol adducts.
[c] Determined by HPLC after conversion to thioxooxazolines **4**.
[d] The absolute configuration was not determined.
[e] The formation of oxazolidine **10** was observed on TLC, but was not isolated.
[f] The hydrolysis was conducted with HCl in MeOH/H_2O.

Table 4. Effects of catalyst amounts and solvents



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[a]	*anti*/*syn*[b]	ee of *anti* (%)[c]	ee of *syn* (%)[c]
1	5	THF	14	93	52:48	45	16
2	10	THF	14	98	56:44	62	23
3	20	THF	16	93	59:41	74	20
4	20	Ether	18	90	51:49	29	13
5	20	DME	18	94	60:40	10	36
6	20	Toluene	50	91	49:51	12	4

[a] Isolate yield of amino acid esters **3a**.
[b] Determined by ^{1}H NMR of the crude mixture of amino acid esters **3a** after hydrolysis of the imine moiety of the aldol adducts.
[c] Determined by HPLC after conversion to thioxooxazolines **4**.

amount could be reduced. The reaction proceeded smoothly in the presence of less catalyst and gave the product in excellent yield with as little as 5 mol% of the catalyst (Table 4, entries 1 and 2). The selectivity was maintained at a moderate level with 10 mol% of the catalyst (entry 2), whereas a significant deterioration of the stereoselectivity was observed after reducing the catalyst amount to 5 mol% (entry 1). Among several solvents tested, tetrahydrofuran (THF) gave the best result (entry 3).

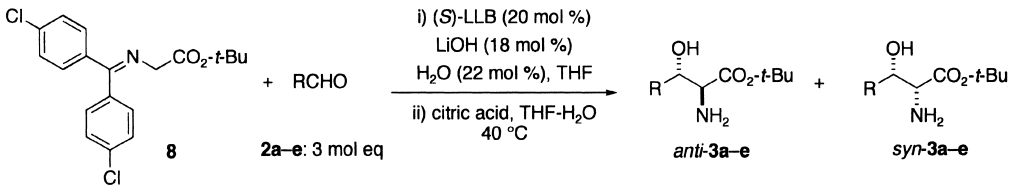
2.5. Generality of aldehydes

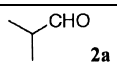
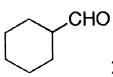
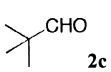
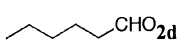
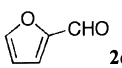
Using **8** as the best donor substrate, the range of applicable aldehydes was investigated (Table 5). Cyclohexanecarboxaldehyde (**2b**) afforded the amino acid esters (**3b**) in 73% yield in a better diastereomeric ratio (70:30) with a comparable enantiomeric excess (*anti*: 69% ee) (entry 2). Pivalaldehyde (**2c**) had a much better diastereoselectivity (*anti*/*syn* 86:14) and gave the *anti*-adduct with 76% ee (entry 3). Hexanal (**2d**), an enolizable aldehyde, also reacted with **8** cleanly to afford the corresponding products in 89% yield (entry 4). The diastereoselectivity was opposite to that of the other cases, and the *syn*-adduct (*syn*-**3d**) was obtained as the major diastereomer with poor enantiomeric excess. Furfural (**2e**) also underwent a smooth conversion to afford the products in good yield, albeit with poor enantiomeric excess (entry 5).

2.6. Reaction mechanism

The present reaction probably proceeds with the aid of the Lewis acidity and the Brønsted basicity of the catalyst,

Table 5. Direct aldol reaction of glycinate Schiff base **8** with aldehydes



Entry	Aldehyde	Product	Temperature (°C)	Time (h)	Yield (%)[a]	*anti*/*syn*[b]	ee of *anti* (%)[c]	ee of *syn* (%)[c]
1	 **2a**	**3a**	−50	16	93	59:41	74	20
2	 **2b**	**3b**[d]	−50	23	73	70:30	69	18
3	 **2c**	**3c**[d]	−50	23	71	86:14	76	ND
4	 **2d**	**3d**[d]	−50	13	89	28:72	42	1
5	 **2e**	**3e**[d]	−50	18	82	61:39	19	2

[a] Isolate yield of amino acid esters **3**.
[b] Determined by ^{1}H NMR of the crude mixture of amino acid esters **3** after hydrolysis of the imine moiety of the aldol adducts.
[c] Determined by HPLC after conversion to thioxooxazolines **4**.
[d] The absolute configuration was not determined.

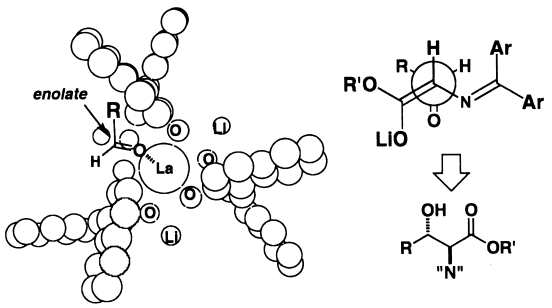


Figure 2. Working model.

similar to previously reported direct aldol reactions with methyl ketones[20c–e] and α-hydroxy ketones.[20a,b] Especially in the latter case, both diastereomers of the aldol products possessed identical stereochemistry at the α-position, which led us to propose the formation of a chelate complex between the enolate and the central lanthanide metal of the catalyst.[20a] In the present system, however, a different tendency was observed for the stereochemical outcome of amino acid esters (2*S*,3*S*)-**3a** and (2*R*,3*S*)-**3a**. Hence the 'chelation model' is not applicable to the present system. Based on this fact, we propose the working model presented in Fig. 2, wherein the catalyst permits an enolate to attack the *Re*-face of the aldehyde by shielding the *Si*-face. Whereas the *Z*-enolate is presented in the working model, a small amount of the *E*-enolate could also be involved in the transition state, giving rise to the moderate stereoselectivities (no more than 76% ee and 72% de). In this regard, the geometry of the enolates remains to be investigated to predict the precise mechanism.

3. Conclusions

We report a direct aldol reaction of glycinate Schiff bases with aldehydes using heterobimetallic asymmetric complexes as a catalyst. *anti*-β-Hydroxy-α-amino acid esters were obtained as the major diastereomers with moderate enantiomeric excess in the case of α-substituted aliphatic aldehydes. To the best of our knowledge, this is the first successful example of the direct aldol reaction of glycinate Schiff bases with aldehydes, achieving moderate to good stereoselectivity.[28] Further investigation to improve the efficiency and the generality, and mechanistic studies are currently ongoing in our laboratory.

4. Experimental

4.1. General methods and materials

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to report multiplicities: 's' (singlet), 'd' (doublet), 'dd' (doublet of doublets), 't' (triplet), 'm' (multiplet), 'br' (broad). Optical rotations were measured on a JASCO P-1010 polarimeter. EIMS were measured on a JEOL JMS-BU20 GCmate. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Preparative thin layer chromatography (preparative TLC) was performed on Merck Art. 5715, Silica gel 60 F_{254} plates. The enantiomeric excess was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UVIDEC-100-IV, measured at 254 nm; column, DAICEL CHIRALPAK AS or AD; mobile phase, hexane-2-propanol; flow rate, 0.3–1.5 mL/min. Reactions were performed in dry solvents under an argon atmosphere. THF was distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Lanthanum triisopropoxide ($La(O\text{-}i\text{-}Pr)_3$) was purchased from Kojundo Chemical Laboratory Co., Ltd, 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +(81)-492-84-1351). Other reagents were purified using standard methods.

4.2. Synthesis of glycinate Schiff bases

Glycinate Schiff bases were prepared according to the reported procedure.[29]

4.2.1. *tert*-Butyl *N*-(diphenylmethylene)glycinate (1). This compound was reported in Ref. 29.

4.2.2. *tert*-Butyl *N*-[bis(*p*-methylphenyl)methylene]glycinate (6). ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J=8.2 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.12 (d, J=7.8 Hz, 2H), 7.06 (d, J=7.8 Hz, 2H), 4.11 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 1.46 (s, 9H). LRMS (EI) m/z 323 (M^+), 222 ($M^+-CO_2CH_3$).

4.2.3. *tert*-Butyl *N*-[bis(*p*-fluorophenyl)methylene]glycinate (7). Colorless solid. Mp 86.5°C. ^{1}H NMR ($CDCl_3$) δ 7.65–7.61 (m, 2H), 7.17–7.16 (m, 4H), 7.03–6.99 (m, 2H), 4.09 (s, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 169.6, 169.4, 164.3 (d, J=250 Hz), 162.8 (d, J=249 Hz), 135.5 (d, J=3.0 Hz), 131.6 (d, J=4.1 Hz), 130.7 (d, J=8.2 Hz), 129.7 (d, J=8.2 Hz), 115.8 (d, J=21.7 Hz), 115.1 (d, J=21.6 Hz), 81.3, 56.2, 28.1. FTIR (KBr) ν 1741, 1227 cm^{-1}. LRMS (EI) m/z 331 (M^+), 230 (M^+-CO_2t-Bu, base peak). Anal. Calcd for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23. Found: C, 68.88; H, 5.89; N, 4.04.

4.2.4. *tert*-Butyl *N*-[bis(*p*-chlorophenyl)methylene]glycinate (8). Colorless solid. Mp 93.5°C. ^{1}H NMR ($CDCl_3$) δ 7.59–7.56 (m, 2H), 7.46–7.44 (m, 2H), 7.31–7.29 (m, 2H), 7.13–7.11 (m, 2H), 4.09 (s, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 169.4, 169.3, 137.4, 136.8, 135.1, 133.8, 129.9, 129.1, 129.1, 128.3, 81.4, 56.2, 28.8. FTIR (KBr) ν 1747 cm^{-1}. LRMS (EI) m/z 365 (M^++2), 363 (M^+), 262 (M^+-CO_2t-Bu). Anal. Calcd for $C_{19}H_{19}Cl_2NO_2$: C, 62.65; H, 5.26; N, 3.85. Found: C, 62.74; H, 5.52; N, 3.80.

4.2.5. *tert*-Butyl *N*-[bis(*p*-(trifluoromethyl)phenyl)methylene]glycinate (9). Pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J=8.0 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 6.70 (d, J=8.0 Hz, 2H), 4.01 (s, 2H), 1.34 (s, 9H). LRMS (EI) m/z 431 (M^+), 330 (M^+-CO_2t-Bu), 57 (t-Bu^+).

4.2.6. Methyl *N*-[bis(*p*-chlorophenyl)methylene]glycinate (11). Pale yellow solid. Mp 85–86°C. ^{1}H NMR

($CDCl_3$) δ 7.58–7.56 (m, 2H), 7.47–7.45 (m, 2H), 7.32–7.30 (m, 2H), 4.19 (s, 2H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.6, 169.7, 137.2, 136.9, 135.2, 133.6, 130.0, 129.2, 129.1, 128.4, 55.5, 52.1. FTIR (KBr) ν 1758 cm^{-1}. LRMS (EI) *m/z* 323 (M^++2), 321 (M^+), 262 (M^+-CO_2t-Bu). Anal. Calcd for $C_{16}H_{13}Cl_2NO_2$: C, 59.65; H, 4.07; N, 4.35. Found: C, 59.72; H, 4.23; N, 4.15.

4.2.7. Diphenylmethyl *N*-[bis(*p*-chlorophenyl)methylene]-glycinate (12). Colorless solid. Mp 95–96°C. ^1H NMR ($CDCl_3$) δ 7.59–7.56 (m, 2H), 7.41–7.38 (m, 2H), 7.34–7.28 (m, 12H), 7.07–7.05 (m, 2H), 6.95 (s, 1H), 4.30 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 169.9, 169.2, 139.8, 137.3, 137.0, 135.2, 133.6, 130.0, 129.2, 129.0, 128.5, 128.4, 128.0, 127.2, 77.4, 55.7. FTIR (KBr) ν 1742, 1173 cm^{-1}. LRMS (EI) *m/z* 475 (M^++2), 473 (M^+), 167 (Ph_2CH^+, base peak). Anal. Calcd for $C_{28}H_{21}Cl_2NO_2$: C, 70.89; H, 4.46; N, 2.95. Found: C, 70.89; H, 4.62; N, 2.86.

4.2.8. *N*-Methoxy-*N*-methyl 2-[*N*-bis(*p*-chlorophenyl)-methyleneamino]acetamide (14). Colorless solid. Mp 94°C. ^1H NMR ($CDCl_3$) δ 7.58–7.56 (m, 2H), 7.46–7.44 (m, 2H), 7.31–7.29 (m, 2H), 7.18–7.16 (m, 2H), 4.34 (s, 2H), 3.66 (s, 3H), 3.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.7, 169.4, 137.5, 136.6, 135.0, 133.8, 129.9, 129.3, 129.0, 128.3, 61.4, 54.5, 32.3. FTIR (KBr) ν 1665 cm^{-1}. LRMS (EI) *m/z* 321 (M^++2−OCH_3), 319 (M^+-OCH_3), 264 (M^++2−$CON(OCH_3)CH_3$), 262 ($M^+-CON(OCH_3)CH_3$). Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 58.24; H, 4.78; N, 7.79.

4.3. Direct aldol reaction of glycinate Schiff bases promoted by a heterobimetallic catalyst

4.3.1. Preparation of (*S*)-LLB (Li_3[La(*S*-binol)$_3$]). A 200 mL flask equipped with a 3-way tap was charged with solid La(O-*i*-Pr)$_3$ (4.61 g, 14.57 mmol) in a glove box. Addition of dry THF (72.8 mL) via syringe under argon atmosphere gave a 0.2 M solution of La(O-*i*-Pr)$_3$ (NOTE: We recommend preparing the solution immediately before use; otherwise, it must be stored below −20°C under argon atmosphere. The decomposition of La(O-*i*-Pr)$_3$ was observed at higher temperatures in THF). A separate 100 mL flask was charged with (*S*)-BINOL (6.78 g, 24.0 mmol), equipped with a 3-way tap and a magnetic stirrer, and heated at 45°C under reduced pressure for 2 h. After the BINOL was dissolved in dry THF (21 mL) under argon, the La(O-*i*-Pr)$_3$ solution (40.0 mL, 8.0 mmol) was added at 0°C, and the resulting pale yellow solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure at room temperature by using a vacuum pump, and the resulting residue was further dried at the same temperature under reduced pressure for 1 h. The residue was dissolved in dry THF (65.7 mL), and a solution of *n*-BuLi in hexanes (14.3 mL, 24.0 mmol, 1.68 M) was added at 0°C. Stirring for another 12 h at room temperature gave a pale yellow solution of (*S*)-LLB (0.1 M), which can be stored at room temperature under argon atmosphere for 6 months without loss of activity. The flask containing the LLB was also shielded from light during storage.

4.3.2. Representative procedure for catalytic asymmetric aldol reaction of glycinate Schiff bases promoted by the LLB·LiOH complex. A solution of BuLi in hexane (33.3 μL, 0.054 mmol, 1.62 M) was added to a stirred solution of H_2O in THF (0.12 mL, 0.12 mmol, 1 M) at 0°C. The resulting mixture was stirred at the same temperature for 20 min, and a solution of (*S*)-LLB in THF (0.6 mL, 0.06 mmol, 0.1 M) was added. After stirring for 30 min at 0°C, the mixture was cooled to −50°C, and a solution of imine **1** (0.3 mmol) in THF (0.9 mL) was added. The resulting solution was stirred at the same temperature for 15 min, and aldehyde **2a** (0.9 mmol) was added via syringe. The reaction mixture was stirred until the starting imine was consumed as determined by TLC analysis and quenched by adding a solution of AcOH in ether (3 mL, 0.25 M). Water was added, and the aqueous layer was extracted with ether (×3). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The hydrolysis was performed according to a procedure similar to that reported in Ref. 17: the solvent was evaporated, and the resulting residue was dissolved in THF (4 mL). Aqueous citric acid (0.5 M, 2.22 mL) was added, and the resulting mixture was stirred for 5 h at room temperature and for 13 h at 40°C. After evaporation of THF, the resulting mixture was washed with ether (×2), and sodium bicarbonate ($NaHCO_3$, 450 mg) was carefully added to the aqueous layer. The aqueous layer was saturated by addition of NaCl and extracted thoroughly with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. Evaporation of solvents gave β-hydroxy-α-amino acid esters **3a** as a mixture of diastereomers, which were purified by silica gel column chromatography (CH_2Cl_2/MeOH 50:1 (v/v)) to afford *anti*-**3a** (32.4 mg, 53%) and *syn*-**3a** (25.5 mg, 42%).

4.3.3. Methyl (2*S*,3*S*)-2-amino-3-hydroxy-4-methylpentanoate (*anti*-15). Colorless oil. 38% ee. ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.58 (d, *J*=4.9 Hz, 1H), 3.40 (dd, *J*=5.5, 4.9 Hz, 1H), 2.13 (br-s, 3H), 1.81–1.74 (m, 1H), 0.95 (d, *J*=5.6 Hz, 3H), 0.93 (d, *J*=5.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.9, 78.5, 55.6, 52.0, 30.5, 19.4, 17.8. FTIR (KBr) ν 1737 cm^{-1}. $[\alpha]_D^{25}$+9.9 (*c* 1.2, $CHCl_3$). LRMS (EI) *m/z* 162 (M^++1), 118 (M^+−*i*-Pr, base peak), 102 ($M^+-CO_2CH_3$). HRMS (EI) calcd for $C_7H_{16}NO_3$ (M^++1) 162.1130, found 162.1126.

4.3.4. Diphenylmethyl (2*S,3*S**)-2-amino-3-hydroxy-4-methylpentanoate (*anti*-16).** Colorless oil. 47% ee. ^1H NMR ($CDCl_3$) δ 7.36–7.27 (m, 10H), 6.94 (s, 1H), 3.70 (d, *J*=5.0 Hz, 1H), 3.48 (dd, *J*=6.4, 5.0 Hz, 1H), 1.87 (br-s, 3H), 1.74–1.64 (m, 1H), 0.91 (t, *J*=6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 173.7, 139.7, 139.5, 128.6, 128.5, 128.1, 128.1, 127.2, 78.4, 77.7, 57.1, 30.5. FTIR (neat) ν 1733, 1169 cm^{-1}. $[\alpha]_D^{25}$=−3.6 (*c* 0.5, $CHCl_3$). LRMS (EI) *m/z* 314 (M^++1). HRMS (EI) calcd for $C_{19}H_{24}NO_3$ (M^++1) 314.1756, found 314.1762.

4.3.5. Diphenylmethyl (2*R,3*S**)-2-amino-3-hydroxy-4-methylpentanoate (*syn*-16).** Colorless solid. 42% ee. ^1H NMR ($CDCl_3$) δ 7.36–7.27 (m, 10H), 6.93 (s, 1H), 3.63 (d, *J*=4.2 Hz, 1H), 3.54 (dd, *J*=6.5, 4.2 Hz, 1H), 1.86 (br-s, 3H), 1.75–1.67 (m, 1H), 1.00 (d, *J*=6.4 Hz, 3H), 0.94 (d, *J*=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.7, 139.7, 139.6, 128.6, 128.1, 128.1, 127.1, 127.0, 77.8, 56.3, 30.6, 19.4, 17.7. FTIR (KBr) ν 1727, 1241 cm^{-1}. $[\alpha]_D^{24}$+4.4 (*c* 0.4,

$CHCl_3$). LRMS (EI) *m/z* 314 (M^++1). HRMS (EI) calcd for $C_{19}H_{24}NO_3$ (M^++1) 314.1756, found 314.1758.

4.3.6. *tert*-Butyl (2*S*,3*S*)-2-amino-3-hydroxy-4-methylpentanoate (*anti*-3a). The absolute configuration was determined by comparison of the optical rotation with the reported one.[17]

4.3.7. *tert*-Butyl (2*R*,3*S*)-2-amino-3-hydroxy-4-methylpentanoate (*syn*-3a). The absolute configuration was determined after conversion to the corresponding oxazolidine.[17]

4.3.8. (2*R,3*S**)-2-Amino-3-hydroxy-4-methylpentanoic acid *N*-methoxy-*N*-methylamide (*syn*-18).** This compound was transformed into the corresponding N^{α}-(*tert*-butoxycarbonyl) amide, which was identified by comparison of the ^1H and ^{13}C NMR with reported ones.[16a] The absolute configuration was not determined.

4.3.9. *tert*-Butyl (2*S,3*S**)-2-amino-3-cyclohexyl-3-hydroxypropanoate (*anti*-3b).** Colorless solid. 69% ee. Mp 47–49°C. ^1H NMR ($CDCl_3$) δ 3.49 (d, *J*=4.2 Hz, 1H), 3.40 (dd, *J*=6.9, 4.2 Hz, 1H), 2.06 (br-s, 3H), 1.95–1.90 (m, 1H), 1.78–1.60 (m, 4H), 1.50–1.42 (m, 1H), 1.47 (s, 9H), 1.26–0.98 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 173.8, 81.7, 78.0, 56.6, 40.7, 29.5, 28.5, 28.0, 26.3, 26.1, 25.9. FTIR (KBr) ν 3187, 1732, 1155 cm^{-1}. $[\alpha]_D^{24}$+12.7 (*c* 1.3, $CHCl_3$). LRMS (EI) *m/z* 244 (M^++1).

4.3.10. *tert*-Butyl (2*R,3*S**)-2-amino-3-cyclohexyl-3-hydroxypropanoate (*syn*-3b).** Colorless oil. 18% ee. ^1H NMR ($CDCl_3$) δ 3.45–3.42 (m, 2H), 1.96–1.91 (m, 1H), 1.90 (br-s, 3H), 1.81–1.73 (m, 2H), 1.68–1.60 (m, 2H), 1.47 (s, 9H), 1.47–1.37 (m, 1H), 1.30–1.04 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 174.0, 81.5, 76.5, 55.9, 40.5, 29.6, 28.0, 26.3, 26.0. FTIR (neat) ν 1773, 1156 cm^{-1}. $[\alpha]_D^{23}$=−3.4 (*c* 0.6, $CHCl_3$). LRMS (EI) *m/z* 244 (M^++1). HRMS (EI) calcd for $C_{13}H_{26}NO_3$ (M^++1) 244.1913, found 244.1918.

4.3.11. *tert*-Butyl (2*S,3*S**)-2-amino-3-hydroxy-4,4-dimethylpentanoate (*anti*-3c).** Colorless solid. 76% ee. Mp 74–76°C. ^1H NMR ($CDCl_3$) δ 3.40 (d, *J*=3.0 Hz, 1H), 3.33 (d, *J*=3.0 Hz, 1H), 2.08 (br-s, 3H), 1.46 (s, 9H), 0.93 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 175.2, 82.9, 82.0, 55.2, 35.1, 27.9, 26.4. FTIR (KBr) ν 3188, 1733, 1150 cm^{-1}. $[\alpha]_D^{25}$+14.7 (*c* 1.0, $CHCl_3$). LRMS (EI) *m/z* 218 (M^++1), 116 (M^+-CO_2t-Bu), 57 (*t*-Bu^+).

4.3.12. *tert*-Butyl (2*S,3*S**)-2-amino-3-hydroxyoctanoate (*anti*-3d).** Colorless oil. 42% ee. ^1H NMR ($CDCl_3$) δ 3.77–3.73 (m, 1H), 3.45 (d, *J*=4.3 Hz, 1H), 1.99 (br-s, 3H), 1.54–1.24 (m, 8H), 1.46 (s, 9H), 0.89–0.86 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 173.2, 81.6, 72.2, 59.0, 32.0, 31.7, 28.0, 25.4, 22.5, 14.0. FTIR (neat) ν 1731, 1156 cm^{-1}. $[\alpha]_D^{25}$=−1.3 (*c* 1.0, $CHCl_3$). LRMS (EI) *m/z* 232 (M^++1). HRMS (EI) calcd for $C_{13}H_{26}NO_3$ (M^++1) 232.1913, found 232.1910.

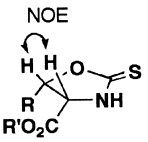
4.3.13. *tert*-Butyl (2*R,3*S**)-2-amino-3-hydroxyoctanoate (*syn*-3d).** Colorless oil. 1% ee. ^1H NMR ($CDCl_3$) δ 3.68–3.64 (m, 1H), 3.21 (d, *J*=4.7 Hz, 1H), 2.15 (br-s, 3H), 1.52–1.40 (m, 8H), 1.46 (s, 9H), 0.89–0.86 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 173.6, 81.6, 72.2, 58.8, 33.9, 31.8, 28.0, 25.3, 14.0. FTIR (neat) ν 1731, 1157 cm^{-1}. LRMS (EI) *m/z* 232 (M^++1). HRMS (EI) calcd for $C_{13}H_{26}NO_3$ (M^++1) 232.1913, found 232.1914.

4.3.14. *tert*-Butyl (2*S,3*S**)-2-amino-3-(1-furyl)-3-hydroxypropanoate (*anti*-3e).** Colorless oil. 19% ee. ^1H NMR ($CDCl_3$) δ 7.33 (d, *J*=1.8 Hz, 1H), 6.31 (dd, *J*=3.0, 1.8 Hz, 1H), 6.27 (d, *J*=3.0 Hz, 1H), 4.96 (d, *J*=5.1 Hz, 1H), 3.74 (d, *J*=5.1 Hz, 1H), 2.30 (br-s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 171.8, 153.6, 142.1, 110.1, 107.6, 82.0, 68.0, 58.6, 27.9. $[\alpha]_D^{21}$=−3.1 (*c* 1.0, $CHCl_3$). LRMS (EI) *m/z* 228 (M^++1). HRMS (EI) calcd for $C_{11}H_{18}NO_4$ (M^++1) 228.1236, found 228.1231.

4.3.15. *tert*-Butyl (2*R,3*S**)-2-amino-3-(1-furyl)-3-hydroxypropanoate (*syn*-3e).** Colorless oil. 2% ee. ^1H NMR ($CDCl_3$) δ 7.38–7.37 (m, 1H), 6.35–6.31 (m, 2H), 4.77 (d, *J*=5.1 Hz, 1H), 3.77 (d, *J*=5.1 Hz, 1H), 2.31 (br-s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.0, 153.8, 142.2, 110.2, 107.7, 82.0, 68.7, 58.1, 27.8. LRMS (EI) *m/z* 228 (M^++1). HRMS (EI) calcd for $C_{11}H_{18}NO_4$ (M^++1) 228.1236, found 228.1239.

4.4. Conversion of amino acid esters to oxazolidinethiones

The β-hydroxy-α-amino acid esters were converted to the corresponding oxazoline-2-thiones to determine the enantiomeric excess.[17] The relative configuration was assigned by ^1H NOE.



4.4.1. (4*S,5*S**)-5-Isopropyl-2-thioxooxazolidine-4-carboxylic acid methyl ester (from *anti*-15).** Colorless solid. 38% ee. Mp 103–104°C. ^1H NMR ($CDCl_3$) δ 7.90 (br-s, 1H), 4.70 (dd, *J*=8.3, 7.8 Hz, 1H), 4.60 (d, *J*=8.3 Hz, 1H), 3.81 (s, 3H), 2.02–1.92 (m, 1H), 1.05 (d, *J*=6.2 Hz, 3H), 1.03 (d, *J*=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 190.4, 168.4, 89.9, 60.6, 53.0, 29.1, 19.1, 17.9. FTIR (KBr) ν 3185, 1736 cm^{-1}. $[\alpha]_D^{24}$=−7.9 (*c* 1.2, $CHCl_3$). LRMS (EI) *m/z* 203 (M^+, base peak), 144 ($M^+-CO_2CH_3$). HRMS (EI) calcd for $C_8H_{13}NO_3S$ (M^+) 203.0616, found 203.0613. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 0.3 mL/min; t_R 42.4 min (major) and 49.9 min (minor).

4.4.2. (4*S,5*S**)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic acid diphenylmethyl ester (from *anti*-16).** Colorless solid. 47% ee. Mp 126–128°C. ^1H NMR (C_6D_6) δ 7.41–7.32 (m, 4H), 7.18–6.96 (m, 6H), 6.95 (s, 1H), 6.30 (br-s, 0.28H), 6.16 (br-s, 0.72H), 3.58 (dd, *J*=9.4, 7.7 Hz, 0.72H), 3.58 (m, 0.28H), 3.44 (d, *J*=7.7 Hz, 0.28H), 3.43 (d, *J*=7.2 Hz, 0.72H), 1.46–1.38 (m, 1H), 0.69 (d, *J*=6.3 Hz, 3H), 0.46 (d, *J*=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 190.9, 166.9, 138.7, 138.6, 128.7, 128.6, 128.6, 128.4, 127.5, 126.9, 90.4, 79.1, 61.0, 28.7, 19.0, 18.1. FTIR (KBr) ν 3170, 1748, 1184 cm^{-1}. $[\alpha]_D^{24}$=−11.8 (*c* 0.6, $CHCl_3$). LRMS (EI)

m/z 355 (M^+), 167 (Ph_2CH^+, base peak). HRMS (EI) calcd for $C_{20}H_{21}NO_3S$ (M^+) 355.1242, found 355.1228. HPLC: column, Chiralpak AS; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.5 mL/min; t_R 28.5 min (minor) and 41.6 min (major).

4.4.3. (4*R* *,5*S* *)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic acid diphenylmethyl ester (from *syn*-16). Colorless solid. 42% ee. ^1H NMR ($CDCl_3$) δ 7.53 (br-s, 1H), 7.39–7.30 (m, 10H), 6.94 (s, 1H), 4.72 (t, J=5.5 Hz, 1H), 4.32 (d, J=5.5 Hz, 1H), 2.14–2.05 (m, 1H), 1.05 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 189.3, 167.8, 138.6, 128.8, 128.8, 128.6, 128.5, 127.1, 126.8, 89.9, 79.3, 59.6, 32.4, 17.1, 16.7. FTIR (KBr) ν 3340, 1742, 1496 cm^{-1}. $[\alpha]_D^{23}=-9.5$ (*c* 0.3, $CHCl_3$). LRMS (EI) *m/z* 355 (M^+), 167 (Ph_2CH^+, base peak). HRMS (EI) calcd for $C_{20}H_{21}NO_3S$ (M^+) 355.1242, found 355.1255. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 0.7 mL/min; t_R 22.0 min (major) and 25.9 min (minor).

4.4.4. (4*S*,5*S*)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *anti*-3a). This compound was reported in Ref. 17. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 7.2 min (major) and 10.1 min (minor).

4.4.5. (4*R*,5*S*)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *syn*-3a). The absolute configuration was determined by comparison of the optical rotation with the reported one.[17] HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 7.4 min (minor) and 10.6 min (major).

4.4.6. (4*S* *,5*S* *)-5-Cyclohexyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *anti*-3b). Colorless solid. 69% ee. ^1H NMR ($CDCl_3$) δ 7.83 (br-s, 1H), 4.68 (dd, J=8.4, 7.7 Hz, 1H), 4.46 (d, J=8.4 Hz, 1H), 1.98–1.94 (br, 1H), 1.80–1.64 (m, 5H), 1.49 (s, 9H), 1.26–1.10 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 190.4, 167.0, 89.1, 84.1, 61.1, 38.4, 29.3, 27.9, 25.8, 25.5, 25.2. FTIR (KBr) ν 3330, 2928, 1719, 1507, 1478 cm^{-1}. $[\alpha]_D^{25}=-4.4$ (*c* 1.4, $CHCl_3$). LRMS (EI) *m/z* 285 (M^+, base peak), 184 (M^+-CO_2t-Bu). HRMS (EI) calcd for $C_{14}H_{23}NO_3S$ (M^+) 285.1398, found 285.1404. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 7.1 min (major) and 10.5 min (minor).

4.4.7. (4*R* *,5*S* *)-5-Cyclohexyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *syn*-3b). Colorless solid. 18% ee. Mp 115–116°C. ^1H NMR ($CDCl_3$) δ 7.66 (br-s, 1H), 4.72 (t, J=5.6 Hz, 1H), 4.18 (d, J=5.6 Hz, 1H), 1.89–1.67 (m, 6H), 1.48 (s, 9H), 1.30–1.05 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 189.1, 167.6, 89.5, 84.2, 60.1, 41.9, 27.9, 27.5, 27.1, 26.0, 25.5, 25.3. FTIR (KBr) ν 3185, 2927, 1751, 1511 cm^{-1}. $[\alpha]_D^{25}=-14.1$ (*c* 0.6, $CHCl_3$). LRMS (EI) *m/z* 285 (M^+), 184 (M^+-CO_2t-Bu), 57 (t-Bu^+, base peak). HRMS (EI) calcd for $C_{14}H_{23}NO_3S$ (M^+) 285.1398, found 285.1396. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 9.3 min (minor) and 12.8 min (major).

4.4.8. (4*S* *,5*S* *)-5-*tert*-Butyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *anti*-3c). Colorless solid. 76% ee. Mp 164°C. ^1H NMR ($CDCl_3$) δ 7.96 (br-s, 1H), 4.64 (d, J=8.0 Hz, 1H), 4.36 (d, J=8.0 Hz, 1H), 1.49 (s, 9H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 190.9, 167.6, 93.2, 84.4, 61.3, 33.4, 28.9, 25.8, 25.3. FTIR (KBr) δ 3244, 2979, 1731, 1480 cm^{-1}. $[\alpha]_D^{25}+26.4$ (*c* 2.0, $CHCl_3$). LRMS (EI) *m/z* 259 (M^+), 158 (M^+-CO_2t-Bu), 57 (t-Bu^+, base peak). HRMS (EI) calcd for $C_{12}H_{21}NO_3S$ (M^+) 259.1242, found 259.1249. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 6.5 min (major) and 10.1 min (minor).

4.4.9. (4*S* *,5*S* *)-5-Pentyl-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *anti*-3d). Colorless solid. 42% ee. ^1H NMR ($CDCl_3$) δ 7.58 (br-s, 1H), 5.02–4.97 (m, 1H), 4.46 (d, J=8.9 Hz, 1H), 1.76–1.28 (m, 8H), 1.49 (s, 9H), 0.91–0.87 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 190.1, 166.7, 84.8, 84.2, 61.4, 31.3, 30.2, 28.0, 25.1, 22.4, 13.9. FTIR (KBr) ν 3160, 1735, 1180 cm^{-1}. $[\alpha]_D^{26}=-10.5$ (*c* 0.8, $CHCl_3$). LRMS (EI) *m/z* 273 (M^+), 172 (M^+-CO_2t-Bu), 57 (t-Bu^+). HRMS (EI) calcd for $C_{13}H_{23}NO_3S$ (M^+) 273.1398, found 273.1391. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 6.8 min (major) and 9.8 min (minor).

4.4.10. (4*R* *,5*S* *)-5-Pentyl-2-thiooxooxazoline-4-carboxylic acid *t*-butyl ester (*syn*-3d). Colorless solid. 1% ee. Mp 67°C. ^1H NMR ($CDCl_3$) δ 7.89 (br-s, 1H), 4.88 (dt, J=6.6, 5.4 Hz, 1H), 4.11 (d, J=6.6 Hz, 1H), 1.91–1.76 (m, 2H), 1.58–1.41 (m, 2H), 1.36–1.30 (m, 4H), 1.48 (s, 9H), 0.92–0.87 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 189.1, 167.2, 85.6, 84.3, 62.6, 34.8, 31.1, 27.9, 24.0, 22.3, 13.9. FTIR (KBr) ν 3198, 1743 cm^{-1}. LRMS (EI) *m/z* 273 (M^+), 57 (t-Bu^+, base peak). HRMS (EI) calcd for $C_{13}H_{23}NO_3S$ (M^+) 273.1398, found 273.1398. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 7.1 min and 11.1 min.

4.4.11. (4*S* *,5*S* *)-5-(1-Furyl)-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *anti*-3e). Pale yellow solid. 19% ee. Mp 177–180°C. ^1H NMR ($CDCl_3$) δ 7.43 (d, J=1.7 Hz, 1H), 7.31 (br-s, 1H), 6.53 (d, J=3.2 Hz, 1H), 6.39 (dd, J=3.2, 1.7 Hz, 1H), 6.00 (d, J=9.8 Hz, 1H), 4.82 (d, J=9.8 Hz, 1H), 1.25 (s, 9H). FTIR (KBr) ν 3165, 1737 cm^{-1}. LRMS (EI) *m/z* 269 (M^+), 57 (t-Bu^+, base peak). HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 17.2 min (major) and 31.1 min (minor).

4.4.12. (4*R* *,5*S* *)-5-(1-Furyl)-2-thiooxooxazoline-4-carboxylic acid *tert*-butyl ester (from *syn*-3e). Colorless solid. 2% ee. ^1H NMR ($CDCl_3$) δ 7.49 (d, J=1.8 Hz, 1H), 7.33 (br-s, 1H), 6.58 (d, J=3.1 Hz, 1H), 6.42 (dd, J=3.1, 1.8 Hz, 1H), 5.90 (d, J=5.6 Hz, 1H), 4.72 (d, J=5.6 Hz, 1H), 1.49 (s, 9H). FTIR (KBr) ν 1732, 1515 cm^{-1}. LRMS (EI) *m/z* 269 (M^+), 57 (t-Bu^+, bae peak). HRMS (EI) calcd for $C_{12}H_{15}NO_4S$ (M^+) 269.0722, found 269.0717. HPLC: column, Chiralpak AD; eluent, hexane/2-propanol 9:1 (v/v); flow, 1.0 mL/min; t_R 19.6 and 23.6 min.

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References

1. For a review, see: (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152. (b) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004–10011. (c) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862–1871. (d) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584–2601. (e) Nicolaou, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J. M.; Bräse, S.; Solomon, M. E. *Chem. Eur. J.* **1999**, *5*, 2602–2621. (f) Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem. Eur. J.* **1999**, *5*, 2622–2647. (g) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. Eur. J.* **1999**, *5*, 2648–2667. (h) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700–2704.
2. For a stereoselective total systhesis of (+)-lactacystin, see: Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Ōmura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590.
3. For a recent example of a diastereoselective synthesis of γ-hydroxy-β-amino alcohols from a serine derivative, see: Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709–1713.
4. For pioneer works, see: (a) Mattingly, P. G.; Kerwin, Jr. J. F.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983–3985. (b) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 5160–5167. (c) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548–554. (d) For a recent example, see: Jackson, B. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reinhard, M.; Kroeff, E. P.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y. *Tetrahedron* **2000**, *56*, 5667–5677.
5. Buono, G.; Siv, C.; Peiffer, G.; Triantaphylides, C.; Denis, P.; Mortreux, A.; Petit, F. *J. Org. Chem.* **1985**, *50*, 1781–1782.
6. Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401–13408. See also Ref. 2.
7. Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507–2510. (b) Park, H.; Cao, B.; Joullié, M. M. *J. Org. Chem.* **2001**, *66*, 7223–7226. See also Ref. 1e.
8. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 4317–4320. (b) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582–2583. See also Ref. 1e.
9. Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631–3646. (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204. (c) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673–11694.
10. Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499–3503.
11. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.
12. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489–3496.
13. Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663–7666.
14. Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
15. Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghiyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481–485. (b) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963–5966. (c) Felice, P. D.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2191–2201. (d) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089–6098. (e) Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T. W.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malley, M. F.; Gougoutas, J. Z. *Synlett* **1998**, 664–666. (f) Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 677–680. (g) Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735–6738. (h) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367–5378. (i) Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497–498. (j) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42. (k) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (l) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252–4259. (m) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091. (n) Nakatsuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 279–282, See also Ref. 16–19.
16. (a) Sawamura, M.; Nakayama, Y.; Kato, T.; Ito, Y. *J. Org. Chem.* **1995**, *60*, 1727–1732. (b) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253–5262. (c) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235–238. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
17. Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.
18. Suga, H.; Ikai, K.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 869–879. (b) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884–1888.
19. Kimura, T.; Vassilev, V. P.; Shen, G.-J.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11734–11742.
20. Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556–2565. (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467. (c) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569–2579. (d) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178. (e) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871–1873.

21. For a review of catalytic asymmetric direct aldol reactions, see: Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601.
22. For reviews of enantioselective transformations catalyzed by heterobimetallic complexes, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2209. (b) Shibasaki, M.; Yamada, K.-i.; Yoshikawa, N. *Lewis Acids in Organic Synthesis*, Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2. Chapter 20. (c) Shibasaki, M. *Enantiomer* **1999**, *4*, 513–527. (d) Shibasaki, M. *Chemtracts-Org. Chem.* **1999**, *12*, 979–998. (e) Shibasaki, M.; Iida, T.; Yamada, Y. M. A. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 344–356. (f) Shibasaki, M.; Sasai, H.; Arai, T.; Iida, T. *Pure Appl. Chem.* **1998**, *70*, 1027–1034. (g) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256.
23. For recent reviews of aldol reactions of modified carbonyl compounds (Mukaiyama aldol reaction), see: (a) Carreira, E. M. In *Catalytic Asymmetric Synthesis*. 2nd ed. Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8B2. (b) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*. 2nd ed. Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8B1. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389. (e) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141.
24. For catalytic asymmetric alkylations of glycinate Schiff bases, see: (a) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507–4518. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229, and references cited therein.
25. Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368–1372. See also Refs. 20a,b,d and 22.
26. The use of heterobimetallic complexes containing other lanthanide (Pr, Sm, Gd, Dy, or Yb) gave similar results, in contrast to the previous report: Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657–2660.
27. The enantiomeric excess of the oxazolidines was comparable to that of *syn*-**3**. Corey et al. also reported the formation of oxazolidines in aldol reactions. See Ref. 17.
28. Miller et al. have obtained 12% ee. See Ref. 15h.
29. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666. (b) Pickard, P. L.; Tolbert, T. L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V. pp 520–522.