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Published on Web 07/16/2004

Development of Highly Diastereo- and Enantioselective Direct Asymmetric Aldol Reaction of a Glycinate Schiff Base with Aldehydes Catalyzed by Chiral Quaternary Ammonium Salts

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Abstract: A highly efficient direct asymmetric aldol reaction of a glycinate Schiff base with aldehydes has been achieved under mild organic/aqueous biphasic conditions with excellent stereochemical control, using chiral quaternary ammonium salt **1b** as a phase-transfer catalyst. The initially developed reaction conditions, using 2 equiv of aqueous base (1% NaOH (aq)), exhibited inexplicably limited general applicability in terms of aldehyde acceptors. The mechanistic investigation revealed the intervention of an unfavorable yet inevitable retro aldol process involving the chiral catalyst. On the basis of this information, a reliable procedure has been established by use of a catalytic amount of 1% NaOH (aq) and ammonium chloride, which tolerates a wide range of aldehydes to afford the corresponding *anti*-β-hydroxy-α-amino esters almost exclusively in an essentially optically pure form.

Introduction

Optically active β-hydroxy-α-amino acids are an extremely important class of amino acids as structural components of many complex biologically active cyclic peptides and enzyme inhibitors.[1] For example, D-*allo*-threonine is found in the antibiotics katanosins[2a,b] and accurninaturn.[2c] (+)-Lactacystin[3a] and cyclosporin[3b] contain a β-hydroxyleucine moiety. Furthermore, these minutely functionalized compounds are useful chiral building blocks in organic synthesis, as exemplified by their transformations into β-lactams,[4] β-halo-α-amino acids,[5] and aziridines.[6]

Accordingly, numerous methods for the asymmetric synthesis of β-hydroxy-α-amino acids have been elaborated on the basis of different strategies.[7,8] Among them, a catalytic asymmetric protocol for the aldol reaction of glycine equivalents and aldehydes is considered to be one of the most efficient and powerful strategies because it allows the direct construction of the primary structure of β-hydroxy-α-amino acids with the correct relative and absolute stereochemistries. A few successful examples based on this approach have been reported. Ito, Hayashi, and co-workers utilized gold catalysts for the aldol reaction of α-isocyano acetates with aldehydes to give *trans*-4-alkoxycarbonyl-2-oxazolines with high stereoselectivities, which are readily transformed into *syn*-β-hydroxy-α-amino esters.[9] Corey and co-workers developed a Mukaiyama-type aldol coupling of ketene silyl acetal derived from glycinate Schiff base **2**[10] with aldehydes catalyzed by cinchonidine-derived ammonium bifluoride.[11] While this procedure affords mostly *syn*-β-hydroxy-α-amino esters with good to excellent enantioselectivities, preactivation of the substrate as an unstable ketene

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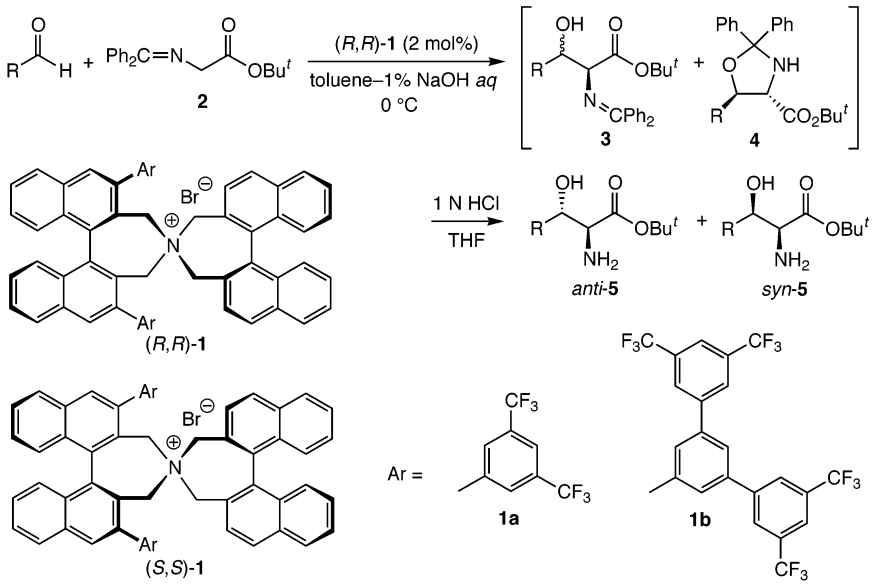
Scheme 1



silyl acetal is required. Recently, chiral aluminum Lewis acid-catalyzed aldolizations of oxazoles with aldehydes have been disclosed, offering facile access to optically active *anti*-β-aryl-β-hydroxy-α-amino esters.[12] In addition, the chemo-enzymatic process with glycine-dependent aldolases, particularly L-threonine aldolase, has been the subject of an intensive study led by Wong.[13] Although insufficient diastereoselectivity and the necessity of precisely controlled reaction conditions seem to be drawbacks, the salient features of this system, using glycine itself, are the perfect atom efficiency and absolute stereochemical control, both crucial elements for ideal synthesis of β-hydroxy-α-amino acids. A chemical approach to address this issue is the development of the direct asymmetric aldol reaction[14] between a glycine donor and aldehyde acceptors using small molecular chiral catalysts. Despite its potential synthetic importance, however, strictly limited contributions have appeared. The first catalytic asymmetric synthesis of β-hydroxy-α-amino acids by the direct aldol condensation was achieved by Miller's group under phase-transfer conditions.[15] The reaction of glycinate Schiff base **2** with aldehydes in the presence of *N*-benzylcinchoninium chloride as a catalyst afforded β-hydroxy-α-amino esters in moderate yields. Unfortunately, the diastereo- and enantioselectivities were not satisfactory. Recently, Shibasaki and co-worker developed a direct asymmetric aldol reaction of **2** catalyzed by heterobimetallic complexes.[16]

During our continuous research effort on the molecular design of new, *N*-spiro C_2-symmetric chiral phase-transfer catalysts and their application to practical asymmetric synthesis of α-amino acids,[17] we have been interested in exploring the ability of chiral quaternary ammonium salts, **1**, to efficiently catalyze direct aldol reactions of **2** with aldehydes under organic/aqueous biphasic conditions in a highly diastereo- and enantioselective manner (Scheme 1). In this article, we describe the details of this study, including the mechanistic investigation which revealed the intervention of an inexpedient retro aldol process, leading to the establishment of the reaction conditions for predictable yet rigorous stereochemical control. This approach harnesses the

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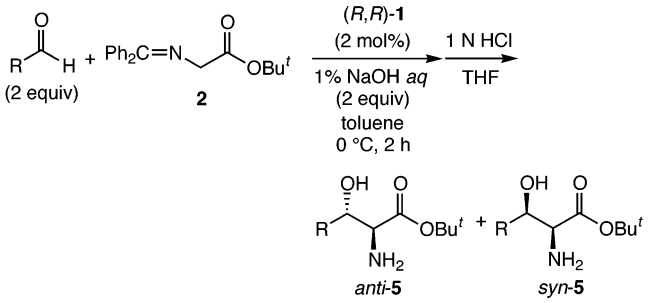
Table 1. Direct Asymmetric Aldol Reactions of **2** with Aldehydes by Chiral Phase-Transfer Catalysis of **1**[a]



entry	R	product	catalyst	% yield[b]	anti/syn[c]	% ee (anti)[d]
1	$PhCH_2CH_2$	**5a**	**1a**	78	73:27	90
2	$PhCH_2CH_2$	**5a**	**1b**	71	92:8	96
3	$CH_3(CH_2)_4CH_2$	**5b**	**1b**	65	91:9	91
4	$^iPr_3SiOCH_2$	**5c**	**1b**	72	>96:4	98
5	$BnOCH_2CH_2CH_2$	**5d**	**1b**	73	58:42	82
6	$(CH_3)_2CHCH_2$	**5e**	**1b**	81	37:63	15

[a] The direct aldol reaction of **2** (0.3 mmol) was carried out with 2 equiv of aldehyde in the presence of (*R,R*)-**1** (2 mol%) in toluene (3 mL)/1% NaOH aqueous solution (2.4 mL) at 0 °C for 2 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiomeric excess of *anti*-**5**, which was determined, after conversion to the corresponding oxazolidine-2-thione **6**, by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol as solvent.

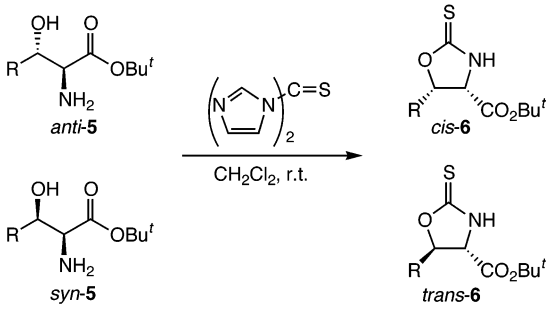
distinct advantage of chiral phase-transfer catalysis to provide a truly practical and environmentally benign chemical process for the synthesis of optically pure *anti*-β-hydroxy-α-amino acids.[18]

Results and Discussion

1. Initial Approach to Development of the Direct Asymmetric Aldol Reaction of Glycine Derivative with Aldehydes. We initiated our own examination of the direct asymmetric aldol reaction of *tert*-butyl glycinate benzophenone Schiff base (**2**) with 3-phenylpropanal as a representative acceptor under phase-transfer conditions. Treatment of **2** with 3-phenylpropanal (2 equiv) in toluene (0.1 M)/1% NaOH aqueous solution (volume ratio = 1.25:1; 2 equiv of base with respect to **2**) in the presence of chiral quaternary ammonium salt (*R,R*)-**1a** (2 mol%) at 0 °C for 2 h and subsequent hydrolysis with 1 N HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **5a** in 78% yield with an anti/syn ratio of 73:27 (entry 1, Table 1). The enantiomeric excess of the major anti isomer was determined to be 90% by HPLC analysis after transformation into the corresponding oxazolidine-2-thione derivatives, **6a**, using thiocarbonyl diimidazole (Scheme 2). Significantly, use of (*R,R*)-**1b**, which contains a 3,5-bis(3,5-bis-(trifluoromethyl)-phenyl)phenyl substituent, as a catalyst enhanced both diastereo- and enantioselectivities in this reaction system (anti/syn = 92:8; 96% ee for the anti isomer) (entry 2).

A variety of aldehydes were examined for this direct asymmetric aldol reaction with (*R,R*)-**1b**, and the representative results are listed in Table 1. Heptanal, an aliphatic aldehyde with a long hydrocarbon chain, was found to be a good candidate (entry 3), thus indicating the feasibility of direct asymmetric synthesis of lipophilic β-hydroxy-α-amino acid.[19] The reaction

Scheme 2



with α-triisopropylsiloxyacetaldehyde cleanly produced the desired β-hydroxy-α-amino ester **5c** in 72% yield with virtually complete stereochemical control (anti/syn = >96:4; 98% ee for the anti isomer) (entry 4), which parallels the L-threonine aldolase-catalyzed aldol reaction used for the synthesis of the monobactam antibiotic carunoman and its analogues.[13b] On the other hand, however, an inexplicably limited general applicability of this system was also revealed. The reaction of **2** with 4-benzyloxybutanal gave the aldol product **5d**, which is the key intermediate for the synthesis of mycestericin D,[13c] with low diastereoselectivity (anti/syn = 58:42; 82% ee for the anti isomer) (entry 5). Use of isovaleraldehyde as an acceptor afforded **5e** with a preference for the syn isomer (anti/syn = 37:63), and poor enantiomeric excess was observed for the anti isomer (15% ee) (entry 6).

2. Mechanistic Insights into the Direct Catalytic Asymmetric Aldol Reaction under Phase-Transfer Conditions. The uncertain outline of this direct catalytic asymmetric aldol reaction led us to inspect the reaction mechanism and the relationship between the reaction time and the chemical yield, as well as stereoselectivities of the aldol product **5**. As shown in Table 2, the direct aldol reaction of **2** with 3-phenylpropanal in the presence of (*R,R*)-**1a** (2 mol%) under the representative reaction conditions proceeded smoothly within 15 min to furnish **5a** with good diastereo- and enantioselectivities (entry 1). Interestingly, however, the diastereomeric ratio reversed, and the enantiomeric excess of the anti isomer gradually decreased as the reaction time was extended, while that of the syn isomer remained unchanged (entries 2−4). These unexpected results imply the involvement of the retro aldol process, since the epimerization at the α-stereogenic center of **3a** would not be likely under these conditions.[20] This interpretation prompted us to attempt an intentional retro aldol reaction of independently prepared racemic aldol adducts under the phase-transfer conditions. Thus, treatment of **2** with LDA in THF at −78 °C for 30 min followed by the addition of isobutyraldehyde gave a mixture of racemic, acyclic anti-aldol adducts (±)-*anti*-**3f** and trans-oxazolidine (±)-**4f**, the cyclized adduct of the syn-isomer, which were also detected by TLC analysis prior to the hydrolysis in the phase-transfer-catalyzed direct aldol reaction (Scheme 3).[21] Treatment of racemic (±)-*anti*-**3f** with isobutyraldehyde (1 equiv) in the presence of (*R,R*)-**1a** (2 mol%) under similar phase-transfer conditions and subsequent hydrolysis afforded **5f** in 57%

(18) Preliminary communication: Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542.

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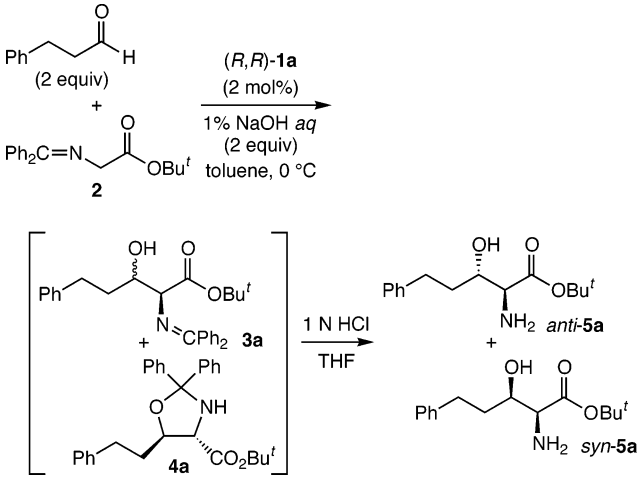
(21) To ease the purification of the aldol adducts, isobutyraldehyde was used as an acceptor. The syn-aldol adducts could not be isolated as an acyclic form in this reaction. See refs 8a, 10, and 15a.

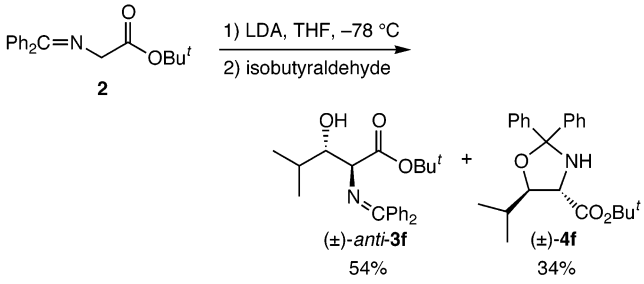
Table 2. Relationship between Reaction Time and Stereoselectivities of **5**[a]



entry	reaction time (h)	% yield[b]	anti/syn[c]	% ee[d] (anti/syn)
1	0.25	70	74:26	89/22
2	2	78	73:27	90/23
3	6	73	50:50	72/23
4	12	75	45:55	62/22

[a] The direct aldol reaction of **2** (0.3 mmol) was carried out with 2 equiv of aldehyde in the presence of (*R*,*R*)-**1a** (2 mol%) in toluene (3 mL)/1% NaOH aqueous solution (2.4 mL) at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiomeric excess was determined, after conversion to the corresponding oxazolidine-2-thione, by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol as solvent.

Scheme 3



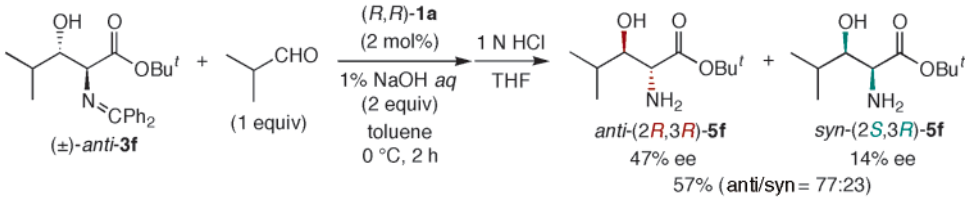
yield,[22] with an anti/syn ratio of 77:23, and the enantiomeric excess of the anti isomer was 47% ee (2*R*,3*R*) (Scheme 4). On the other hand, exposure of (±)-**4f** to the same conditions solely gave the racemic *syn*-β-hydroxy-α-amino ester (±)-*syn*-**5f** in 94% yield (Scheme 5). These results clearly indicate that the acyclic aldol adduct **3f** is highly susceptible to the retro aldol reaction and cyclized *trans*-oxazolidine **4f** is unaffected under the phase-transfer conditions. Particularly noteworthy is the fact that the direct asymmetric aldol reaction of **2** with isobutyraldehyde (2 equiv) in the presence of (*R*,*R*)-**1a** (2 mol%) under similar conditions gave rise to *anti*-**5f**, with 86% ee, and the configuration of the major enantiomer was determined to be (2*S*,3*S*) (Scheme 6), being opposite to that of *anti*-**5f**, obtained in Scheme 4; this strongly suggests the intervention of the chiral catalyst in the retro aldol process.

Under basic condition with 1% NaOH aqueous solution, sodium alkoxide **3**·Na could be formed in situ from aldol adduct **3** and converted into the corresponding chiral ammonium alkoxide by an ion-exchange process. This exchange would afford a mixture of diastereomeric intermediates and a kinetic resolution would operate in the subsequent retro aldol process. Thus, chiral phase-transfer catalyst (*R*,*R*)-**1a** would be able to predominantly recognize the alkoxide generated from the (2*S*,3*S*) isomer of *anti*-**3f**, the major enantiomer obtained in the original (*R*,*R*)-**1a**-catalyzed direct aldol reaction, and facilitate the stereoselective retro aldol reaction (Scheme 7). In addition, the selectivity of the kinetic resolution in this retro aldol process should be higher than the enantioselectivity of the original aldol reaction ($k_{-(S,S)}/k_{-(R,R)} > k_{(S,S)}/k_{(R,R)}$ in Scheme 7) to account for the enantiomeric imbalance toward *anti*-(2*R*,3*R*)-**5f**, the minor enantiomer of the original reaction catalyzed by (*R*,*R*)-**1a**, observed in Scheme 4. These unique observations offer reasonable explanations for the results in Table 2. Since the equilibrium of the present aldol reaction can only be established between the substrates (**2** and 3-phenylpropanal) and the acyclic aldol adducts **3a**, and since the *trans*-oxazolidine **4a** generated from *syn*-**3a** is isolated from this equilibrium, *syn*-**5a** is accumulated as the reaction time is extended and its enantiomeric excess is virtually unaffected (Table 2 and Scheme 7). Moreover, the decreased enantiomeric excess of *anti*-**5a** would be ascribed to the higher stereoselectivity of the retro aldol process than the enantioselectivity of the original aldol reaction.

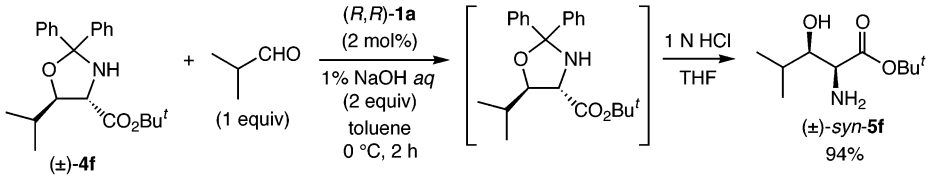
3. Improved Reaction Conditions for the Direct Catalytic Asymmetric Aldol Reaction under Phase-Transfer Conditions. This important mechanistic rationale suggests that the limited generality under the present reaction conditions would largely stem from the undesired, highly stereoselective retro aldol reaction. Although it would be inevitable under the basic conditions, suppressing the generation of metal alkoxide from the corresponding aldol adducts in the reaction system could minimize its intervention. This assumption led us to modify the reaction conditions by reducing the amount of aqueous base, as well as adding an inorganic salt to control the pH of the reaction system. Thorough optimization along this line revealed that the direct asymmetric aldol reaction of **2** with 3-phenylpropanal (2 equiv) in toluene (0.2 M) with a catalytic amount of 1% NaOH aqueous solution (15 mol% of base with respect to **2**) and ammonium chloride (10 mol%) under the influence of (*R*,*R*)-**1b** (2 mol%) at 0 °C for 1.5 h furnished, after hydrolysis, the corresponding aldol product **5a** in 82% yield, and the stereoselectivities were improved to anti/syn = 96:4 and 98% ee for the anti isomer (Table 3, entry 1). This modified procedure considerably expanded the scope of this method, as demonstrated by the results summarized in Table 3. While retardation of the reaction rate was generally observed, a variety of β-hydroxy-α-amino esters were obtained with excellent diastereo- and enantioselectivities. A key building block for the synthesis of the carbacephem antibiotic loracarbef, previously prepared by a chemo-enzymatic process with serine hydroxymethyltransferase (SHMT),[13e] was readily assembled with 4-pentenal as an acceptor (entry 7). L-*allo*-Threonine *tert*-butyl ester (**5i**) was found to be accessible by the reaction of **2** with acetaldehyde (entry 8), and the facile preparation of nonnatural D-*allo*-threonine appeared feasible because of ready availability of the enantiomerically pure catalyst (*S*,*S*)-**1b**. Furthermore, the α-branched aldehydes isobutyraldehyde and cyclohexanecarbaldehyde were also amenable to this reaction system, using

(22) Before the hydrolysis, generation of **2** (~25%) was confirmed by ^{1}H NMR analysis of the crude products.

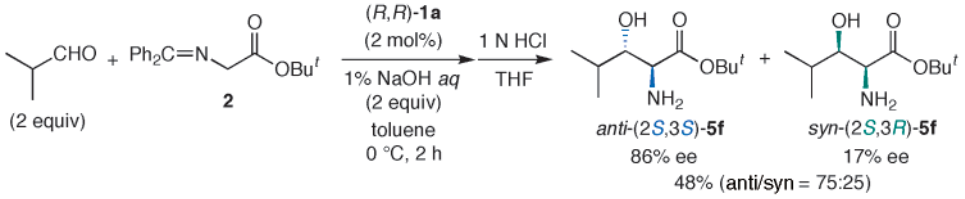
Scheme 4



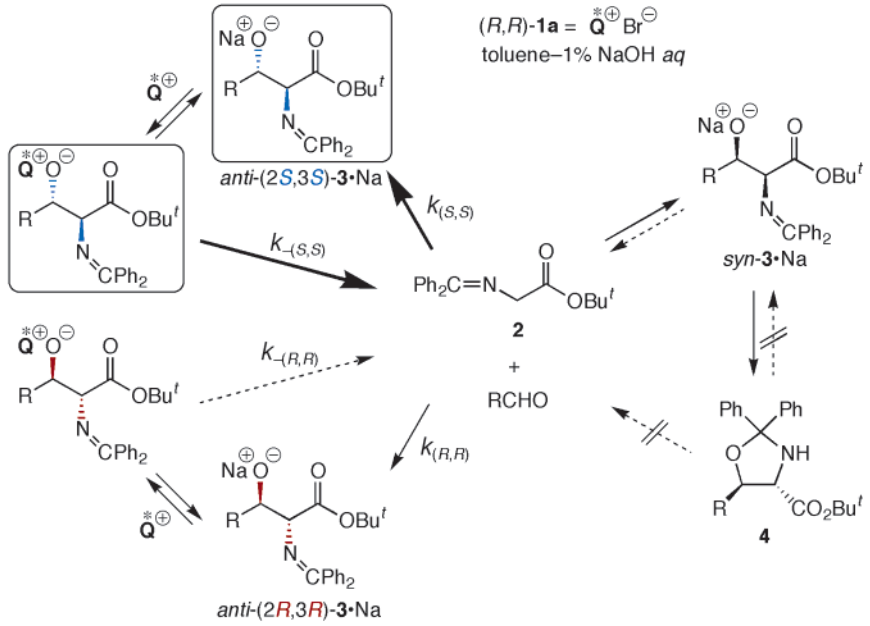
Scheme 5



Scheme 6



Scheme 7. Postulated Reaction Pathway of the Direct Catalytic Asymmetric Aldol Reaction under Phase-Transfer Conditions.[a]



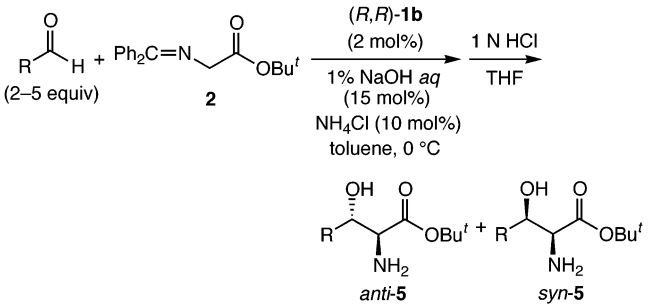
[a] R = $PhCH_2CH_2$, **a**; $(CH_3)_2CH$, **f**

cyclopentyl methyl ether (CPME) as solvent in the presence of 5 equiv of aldehydes to attain sufficient reactivity (entries 9−11). Unfortunately, aromatic aldehydes such as benzaldehyde were not a suitable substrate, and the corresponding *β*-arylserine derivative was obtained in moderate yield with poor stereoselectivity (entry 12), indicating the limitation of the present method.

4. Plausible Transition State. The observed excellent anti selectivity may be partially attributable to the selective formation of the E-enolate (Figure 1).[2] Although the nonchelate, acyclic extended transition state model has been proposed for fluoride-catalyzed reactions involving ammonium enolates,[24] the observed diastereoselectivity (anti-aldol adduct from E-enolate) contradicts that theory. This abnormal stereochemical consequence may be accounted for by the huge steric repulsion caused by the chiral quaternary ammonium cation, overwhelming the gauche interactions between the aldehyde substituent (R) and both the 2-imino moiety and the *tert*-butoxy group (Figure 1, **A** vs **B**). This proposed transition state model, **A**, is consistent with the significant improvement of diastereoselectivity when

(23) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. See also: ref 19.
(24) (a) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2016.

Table 3. Direct Asymmetric Aldol Reactions of **2** with a Wide Range of Aldehydes under the Improved Reaction Conditions[a]



entry	R	product	reaction time (h)	% yield[b]	anti/syn[c]	% ee (anti)[d]
1	$PhCH_2CH_2$	**5a**	1.5	82	96:4	98
2	$CH_3(CH_2)_4CH_2$	**5b**	10	80	94:6	97
3	$CH_3(CH_2)_3CH_2$	**5g**	10	79	>96:4	97
4	$^iPr_3SiOCH_2$	**5c**	4.5	73	>96:4	98
5	$BnOCH_2CH_2CH_2$	**5d**	2	83	96:4	96
6	$(CH_3)_2CHCH_2$	**5e**	10	64	>96:4	96
7	$CH_2{=}CHCH_2CH_2$	**5h**	3	82	96:4	98
8	CH_3	**5i**	8	54	>96:4	99
9	$(CH_3)_2CH$	**5f**	10	39	>96:4	98
10	$(CH_3)_2CH$[e,f]	**5f**	5	70	96:4	98
11	$c\text{-}C_6H_{11}$[e,f]	**5j**	3	83	>96:4	98
12	Ph	**5k**	10	58	47:53	25[g]

[a] Unless otherwise noted, the direct aldol reaction of **2** (0.3 mmol) was carried out with 2 equiv of aldehyde in the presence of (*R*,*R*)-**1b** (2 mol%) and ammonium chloride (10 mol%) in toluene (1.5 mL)/1% NaOH aqueous solution (15 mol%) at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiomeric excess of *anti*-**5**, which was determined, after conversion to the corresponding oxazolidine-2-thione **6**, by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol as solvent. [e] Use of cyclopentyl methyl ether (CPME) as solvent. [f] With 5 equiv of aldehyde. [g] Determined by HPLC analysis of its *N*-benzoate using a chiral column (DAICEL Chiralcel OJ).

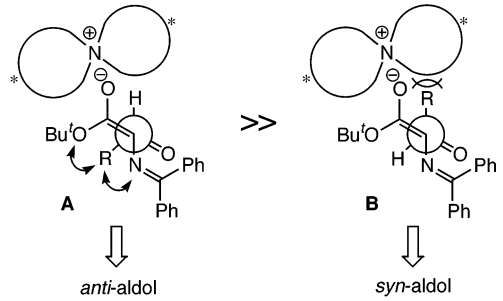


Figure 1. Plausible transition state model.

1b, possessing sterically hindered 3,3′-substituents, is used as a catalyst. On the basis of the product configuration, the *re*-face of the enolate should be shielded effectively by the chiral ammonium cation, and the aldehyde approaches only from the *si*-face.

Experimental Section

1. General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 (300 MHz) spectrometer, JEOL JNM-FX400 (400 MHz) spectrometer, and JMTC-400/54/SS (400 MHz) spectrometer. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using 4.6 mm × 25 cm DAICEL Chiralpak AD-H and Chiralcel OJ. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). High-resolution mass spectra (HRMS) were performed on an Applied Biosystems Mariner API-TOF workstation. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as "dehydrated". Toluene was dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4 Å molecular sieves. Triethylamine (Et_3N) was stored over potassium hydroxide (KOH) pellets. Other simple chemicals were purchased and used as received.

2. Characterization of C_2-Symmetric Chiral Quaternary Ammonium Salts, 1. 2.1. Chiral Ammonium Salt (*R*,*R*)-1a:[18] $[\alpha]_D^{27}$ −43.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (2 H, s, Ar−H), 8.24 (2 H, s, Ar−H), 8.15 (2 H, d, J = 8.4 Hz, Ar−H), 7.83 (2 H, d, J = 8.0 Hz, Ar−H), 7.68 (2 H, t, J = 8.0 Hz, Ar−H), 7.51 (2 H, t, J = 8.0 Hz, Ar−H), 7.40 (2 H, t, J = 8.0 Hz, Ar−H), 7.17−7.26 (4 H, m, Ar−H), 7.08 (2 H, d, J = 8.4 Hz, Ar−H), 8.00−8.60 (2 H, br, Ar−H), 6.80−8.00 (4 H, br, Ar−H), 6.25 (2 H, d, J = 8.4 Hz, Ar−H), 4.82 (2 H, d, J = 13.6 Hz, CH_2), 4.64 (2 H, d, J = 14.0 Hz, CH_2), 4.54 (2 H, d, J = 14.0 Hz, CH_2), 3.67 (2 H, d, J = 13.6 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.7, 136.5, 136.0, 133.9, 133.4 (q, J_{C-F} = 33 Hz), 131.9, 131.1, 130.8, 128.8, 128.7, 128.5, 128.4, 128.1, 127.7, 127.6, 127.3, 127.1, 125.9, 124.5, 123.2 (q, J_{C-F} = 275 Hz), 122.2, 122.1, 121.9, 63.0, 57.7; IR (KBr) 3649, 3379, 3057, 1618, 1470, 1377, 1311, 1281, 1177, 1134, 1030, 897, 847, 752, 681 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{60}H_{36}F_{12}N$, 998.2656 (M^+); found, 998.2645 (M^+).

2.2. Chiral Ammonium Salt (*R*,*R*)-1b:[18] $[\alpha]_D^{29}$ −10.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (2 H, br s, Ar−H), 8.52 (2 H, br s, Ar−H), 8.45 (2 H, s, Ar−H), 8.16 (2 H, d, J = 8.4 Hz, Ar−H), 8.10 (2 H, s, Ar−H), 7.90 (4 H, br s, Ar−H), 7.80 (4 H, d, J = 8.0 Hz, Ar−H), 7.67 (2 H, t, J = 7.2 Hz, Ar−H), 7.54 (2 H, br s, Ar−H), 7.49 (2 H, t, J = 7.2 Hz, Ar−H), 7.40 (2 H, t, J = 7.2 Hz, Ar−H), 7.29 (2 H, d, J = 8.4 Hz, Ar−H), 7.23 (2 H, s, Ar−H), 7.14−7.21 (6 H, m, Ar−H), 7.06 (2 H, d, J = 8.4 Hz, Ar−H), 6.59 (2 H, d, J = 8.4 Hz, Ar−H), 4.90 (2 H, d, J = 13.6 Hz, CH_2), 4.71 (2 H, d, J = 13.6 Hz, CH_2), 4.57 (2 H, d, J = 13.6 Hz, CH_2), 3.63 (2 H, d, J = 13.6 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.9, 141.6, 137.7, 136.8, 134.1, 133.8, 133.6, 132.7 (q, J_{C-F} = 32 Hz), 131.7, 131.1, 130.3, 128.7, 128.2, 128.0, 127.9, 127.6, 127.5, 127.1, 126.7, 126.6, 124.9, 122.1 (q, J_{C-F} = 273 Hz), 122.2, 122.1, 62.8, 57.7; IR (KBr) 3383, 3060, 1622, 1597, 1458, 1391, 1367, 1331, 1283, 1182, 1140, 901, 883, 845, 810, 750, 706, 685 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{88}H_{48}F_{24}N$, 1574.3398 (M^+); found, 1574.3402 (M^+).

3. Representative Procedure for Direct Catalytic Asymmetric Aldol Reaction of Glycinate Schiff Base 2 with Aldehydes under Phase-Transfer Conditions. To a solution of *tert*-butylglycinate benzophenone Schiff base (**2**, 88.6 mg, 0.3 mmol) and (*R*,*R*)-**1b** (9.9 mg, 2 mol%) in toluene (3.0 mL) was added 1% NaOH aqueous solution (2.4 mL, 0.6 mmol) at 0 °C under argon atmosphere, and then 3-phenylpropanal (79.0 μL, 0.6 mmol) was introduced dropwise. The whole mixture was stirred for 2 h at 0 °C and saturated NH_4Cl and ether were added sequentially. The ethereal phase was separated, washed with brine, and dried over Na_2SO_4. Evaporation of solvents gave the crude product, which was dissolved into THF (8.0 mL), and 1 N HCl (1.0 mL) was added at 0 °C. After the solution was stirred for 1 h, THF was removed in vacuo. The resulting aqueous solution was washed with ether three times and neutralized with $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15 as eluant) afforded *tert*-butyl 2-amino-3-hydroxy-5-phenylpentanoate (**5a**) as a mixture of diastereomers (56.8 mg, 0.214 mmol; 71%, anti/syn = 92:8). The diastereomeric ratio was determined by ^{1}H NMR analysis. The relative configuration and enantiomeric excess were determined, after conversion to the corresponding oxazoline-2-thione **6a** [thiocarbonyl diimidazole (1.0 equiv), CH_2Cl_2], by ^{1}H NOE analysis and HPLC analysis, respectively.

3.1. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxy-5-phenylpentanoate (*anti*-5a):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.29 (2 H, m, Ph), 7.16−7.20 (3 H, m, Ph), 3.77 (1 H, ddd, J = 7.6, 4.4, 3.2 Hz, C*H*OH), 3.47 (1 H, d, J = 4.4 Hz, C*H*NH_2), 2.84−2.91 (1 H, ddd, J = 14.0, 9.2, 4.8 Hz, PhCH), 2.65−2.73 (1 H, dt, J = 14.0, 8.0 Hz, PhCH), 1.85 (3 H, br, OH and NH_2), 1.65−1.75 (1 H, m, $PhCH_2CH$), 1.53−1.62 (1 H, m, $PhCH_2CH$), 1.41 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 141.8, 128.4, 128.3, 125.7, 81.7, 71.0, 59.0, 33.8, 32.0, 28.1; IR (neat) 3373, 2977, 2934, 1730, 1602, 1456, 1367, 1252, 1153, 1051, 849, 748, 700 cm^{-1}.

3.2. (4*S,5*S**)-5-(2′-Phenylethyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6a):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.32 (6 H, m, Ph and NH), 4.96 (1 H, ddd, J = 8.8, 8.0, 6.0 Hz, CHOC=S), 4.43 (1 H, dd, J = 8.8, 2.4 Hz, C*H*NH), 2.92−3.00 (1 H, m, PhCH), 2.76−2.84 (1 H, m, PhCH), 2.01−2.11 (2 H, m, $PhCH_2CH_2$), 1.48 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 166.4, 139.7, 128.5, 128.3, 126.3, 84.4, 83.4, 61.3, 31.6, 31.4, 28.0; IR (KBr) 3171, 2988, 2939, 1732, 1522, 1369, 1231, 1182, 1158, 1088, 852, 700 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 18.9 (major) and 28.7 min (minor).

3.3. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxy-5-phenylpentanoate (*syn*-5a):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.29 (2 H, m, Ph), 7.16−7.22 (3 H, m, Ph), 3.70 (1 H, ddd, J = 7.6, 5.2, 4.8 Hz, C*H*OH), 3.24 (1 H, d, J = 5.2 Hz, C*H*NH_2), 2.82−2.90 (1 H, ddd, J = 13.6, 9.0, 6.2 Hz, PhCH), 2.67−2.74 (1 H, ddd, J = 13.6, 8.8, 7.2 Hz, PhCH), 2.17 (3 H, br, OH and NH_2), 1.78−1.85 (2 H, m, $PhCCH_2$), 1.46 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 141.9, 128.3, 128.2, 125.7, 81.8, 71.4, 58.8, 36.0, 32.0, 28.1; IR (neat) 3377, 2977, 2934, 1730, 1603, 1456, 1393, 1369, 1250, 1155, 847, 750, 700 cm^{-1}.

3.4. (4*S,5*R**)-5-(2′-Phenylethyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6a):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.33 (6 H, m, Ph and NH), 4.87 (1 H, ddd, J = 8.0, 7.2, 4.8 Hz, CHOC=S), 4.10 (1 H, d, J = 7.2 Hz, C*H*NH), 2.88−2.95 (1 H, m, PhCH), 2.76−2.83 (1 H, m, PhCH), 2.10−2.27 (2 H, m, $PhCCH_2$), 1.45 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.7, 139.7, 128.5, 128.3, 126.3, 84.5, 84.4, 62.6, 36.6, 30.8, 27.9; IR (KBr) 3188, 2980, 2932, 1744, 1497, 1371, 1242, 1182, 1155, 1097, 1016, 840, 750, 700 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 19.9 and 32.9 min.

3.5. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxynonanoate (*anti*-5b):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75−3.79 (1 H, m, C*H*OH), 3.46 (1 H, d, J = 4.4 Hz, C*H*NH_2), 1.97 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.28−1.53 (10 H, m, $(CH_2)_5$), 0.88 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 81.6, 72.2, 59.0, 32.2, 31.8, 29.2, 28.1, 25.8, 22.7, 14.2; IR (neat) 3368, 2930, 2858, 1732, 1592, 1458, 1367, 1250, 1157, 851 cm^{-1}.

3.6. (4*S,5*S**)-5-Hexyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6b):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1 H, br, NH), 5.00 (1 H, ddd, J = 8.8, 8.0, 6.4 Hz, CHOC=S), 4.48 (1 H, d, J = 8.8 Hz, C*H*NH), 1.29−1.77 (10 H, m, $(CH_2)_5$), 1.50 (9 H, s, *t*-Bu), 0.88 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 166.5, 84.8, 84.2, 61.4, 31.6, 30.3, 28.9, 28.0, 25.5, 22.5, 14.1; IR (KBr) 3167, 2926, 2853, 1734, 1524, 1393, 1369, 1227, 1186, 1153, 1082, 856, 704 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 13.1 (major) and 19.8 min (minor).

3.7. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxynonanoate (*syn*-5b):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65−3.69 (1 H, m, C*H*OH), 3.23 (1 H, d, J = 4.8 Hz, C*H*NH_2), 2.09 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.29−1.52 (10 H, m, $(CH_2)_5$), 0.88 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 81.6, 72.2, 58.8, 34.1, 31.8, 29.4, 28.1, 25.7, 22.7, 14.2; IR (neat) 3373, 2930, 2858, 1732, 1593, 1458, 1367, 1251, 1157, 849 cm^{-1}.

3.8. (4*S,5*R**)-5-Hexyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6b):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1 H, br, NH), 4.89 (1 H, dd, J = 12.8, 6.8 Hz, CHOC=S), 4.13 (1 H, d, J = 6.8 Hz, C*H*NH), 1.77−1.94 (2 H, m, CH_2), 1.30−1.53 (8 H, m, $(CH_2)_4$), 1.50 (9 H, s, *t*-Bu), 0.89 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 167.0, 85.6, 84.2, 62.7, 34.9, 31.6, 28.7, 28.0, 24.3, 22.5, 14.1; IR (KBr) 3186, 2932, 2860, 1740, 1506, 1371, 1246, 1180, 1155, 914, 841, 733 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 14.0 and 23.4 min.

3.9. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxy-4-triisopropylsiloxybutanoate (*anti*-5c):** $[\alpha]_D^{28}$ 9.2° (*c* 0.46, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76−3.85 (3 H, m, $SiOCH_2$ and C*H*OH), 3.53 (1 H, br d, J = 4.4 Hz, C*H*NH_2), 1.83 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.06−1.16 (21 H, m, *i*-Pr_3SiO); IR (neat) 3369, 2943, 2868, 2360, 1734, 1464, 1393, 1367, 1250, 1157, 1121, 1067, 1015, 997, 920, 883, 849, 797, 683, 660 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{37}NO_4Si$, 348.2565 ($[M + H]^+$); found, 348.2565 ($[M + H]^+$).

3.10. (4*S,5*S**)-5-Triisopropylsiloxymethyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6c):** $[\alpha]_D^{29}$ −36.9° (*c* 0.31, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1 H, br, NH), 5.08 (1 H, ddd, J = 10.0, 4.0, 2.8 Hz, CHOC=S), 4.63 (1 H, d, J = 10.0 Hz, C*H*NH), 4.11 (1 H, dd, J = 12.0, 4.0 Hz, SiOCH), 4.06 (1 H, dd, J = 12.0, 2.8 Hz, SiOCH), 1.50 (9 H, s, *t*-Bu), 1.05−1.16 (21 H, m, *i*-Pr_3SiO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 165.6, 84.2, 84.1, 61.8, 59.0, 28.1, 18.0, 12.0; IR (KBr) 3184, 2945, 2868, 1738, 1520, 1464, 1369, 1244, 1178, 1155, 1111, 1067, 1032, 923, 883, 845, 683 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{35}NNaO_4SSi$, 412.1948 ($[M + Na]^+$); found, 412.1948 ($[M + Na]^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time = 12.0 (major) and 18.5 min (minor).

3.11. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxy-4-triisopropylsiloxybutanoate (*syn*-5c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (1 H, ddd, J = 6.0, 6.0, 2.8 Hz, C*H*OH), 3.78 (1 H, dd, J = 10.0, 6.0 Hz, $SiOCH_2$), 3.70 (1 H, dd, J = 10.0, 6.0 Hz, $SiOCH_2$), 3.56 (1 H, d, J = 2.8 Hz, C*H*NH_2), 1.64 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.05−1.17 (21 H, m, *i*-Pr_3SiO); IR (neat) 3385, 2943, 2893, 2866, 2370, 1734, 1464, 1393, 1369, 1279, 1250, 1157, 1121, 1067, 1013, 995, 918, 883, 847, 795, 681 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{37}NO_4Si$, 348.2565 ($[M + H]^+$); found, 348.2572 ($[M + H]^+$).

3.12. (4*S,5*R**)-5-Triisopropylsiloxymethyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1 H, br, NH), 4.98 (1 H, ddd, J = 6.0, 3.6, 3.2 Hz, CHOC=S), 4.54 (1 H, d, J = 6.0 Hz, C*H*NH), 4.09 (1 H, dd, J = 11.6, 3.6 Hz, SiOCH), 3.90 (1 H, dd, J = 11.6, 3.2 Hz, SiOCH), 1.50 (9 H, s, *t*-Bu), 1.05−1.17 (21 H, m, *i*-Pr_3SiO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 167.3, 85.1, 84.2, 62.8, 58.5, 28.0, 18.0, 12.0; IR (KBr) 3173, 2943, 2868, 1742, 1506, 1369, 1242, 1182, 1155, 883, 683 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{35}NNaO_4SSi$, 412.1948 ($[M + Na]^+$); found, 412.1948 ($[M + Na]^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time = 19.8 and 22.9 min.

3.13. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxy-6-benzyloxyhexanoate (*anti*-5d):** $[\alpha]_D^{29}$ 0.9° (*c* 0.50, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.35 (5 H, m, Ph), 4.50 (2H, s, $PhCH_2O$), 3.78 (1 H, m, C*H*OH), 3.51 (2 H, t, J = 6.0 Hz, $BnOCH_2$), 3.46 (1 H, d, J = 3.6 Hz, C*H*NH_2), 2.04 (3 H, br, OH and NH_2), 1.81−1.88 (1 H, m, C*H*COH), 1.71−1.76 (1 H, m, C*H*COH), 1.45−1.52 (2 H, m, $BnOCCH_2$), 1.45 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 138.2, 128.2, 127.5, 127.4, 81.6, 72.9, 72.2, 70.2, 59.1, 29.2, 28.1, 26.3; IR (KBr) 3369, 2934, 2858, 1730, 1587, 1454, 1367, 1252, 1153, 1101, 849, 737, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{28}NO_4$, 310.2013 ($[M + H]^+$); found, 310.2013 ($[M + H]^+$).

3.14. (4*S,5*S**)-5-(3′-Benzyloxypropyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6d):** $[\alpha]_D^{29}$ −2.9° (*c* 0.41, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, br, NH), 7.26−7.36 (5 H, m, Ph), 5.02 (1 H, ddd, J = 10.0, 9.2, 3.6 Hz, CHOC=S), 4.49 (2 H, s, $PhCH_2O$), 4.45 (1 H, d, J = 9.2 Hz, C*H*NH), 3.46−3.58 (2 H, m, $BnOCH_2$), 1.52−2.05 (4 H, m, $(CH_2)_2$), 1.48 (9 H, s, *t*-Bu);

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 166.4, 138.1, 128.2, 127.5, 127.5, 84.5, 84.2, 72.9, 69.0, 61.4, 28.0, 27.3, 25.8; IR (KBr) 3174, 2982, 2930, 2856, 1732, 1520, 1369, 1229, 1186, 1155, 1107, 1076, 928, 835, 739, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{25}NNaO_4S$, 374.1397 ([M + Na]$^+$); found, 374.1397 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 25.2 (major) and 40.5 min (minor).

3.15. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxy-6-benzyloxyhexanoate (*syn*-5d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.34 (5 H, m, Ph), 4.51 (2 H, s, $PhCH_2O$), 3.73 (1 H, m, C*H*OH), 3.52 (2 H, t, J = 6.4 Hz, $BnOCH_2$), 3.23 (1 H, d, J = 4.8 Hz, C*H*NH_2), 1.51−1.86 (7 H, m, $(CH_2)_2$, OH and NH_2), 1.46 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 138.2, 128.2, 127.5, 127.4, 81.6, 72.9, 72.1, 70.3, 59.0, 31.2, 28.1, 26.2; IR (KBr) 3379, 2934, 2860, 1728, 1587, 1454, 1367, 1250, 1157, 1101, 849, 739, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{28}NO_4$, 310.2013 ([M + H]$^+$); found, 310.2012 ([M + H]$^+$).

3.16. (4*S,5*R**)-5-(3′-Benzyloxypropyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1 H, br, NH), 7.27−7.37 (5 H, m, Ph), 4.93 (1 H, dt, J = 6.4, 6.4 Hz, CHOC=S), 4.51 (2 H, s, $PhCH_2O$), 4.10 (1 H, d, J = 6.4 Hz, C*H*NH), 3.47−3.58 (2 H, m, $BnOCH_2$), 1.95−2.01 (2 H, m, CH_2), 1.72−1.90 (2 H, m, CH_2), 1.48 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.9, 138.0, 128.3, 128.3, 127.5, 85.3, 84.2, 72.9, 69.1, 62.6, 31.8, 28.0, 24.7; IR (KBr) 3190, 2980, 2934, 2866, 1742, 1506, 1371, 1240, 1180, 1155, 1101, 912, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{25}NNaO_4S$, 374.1397 ([M + Na]$^+$); found, 374.1398 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 28.8 and 48.1 min.

3.17. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxy-5-methylhexanoate (*anti*-5e):** $[\alpha]_D^{29}$ −11.1° (*c* 0.43, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (1 H, ddd, J = 10.4, 4.4, 2.8 Hz, C*H*OH), 3.47 (1 H, d, J = 4.4 Hz, C*H*NH_2), 2.00 (3 H, br, OH and NH_2), 1.79−1.90 (1 H, m, $(CH_3)_2CH$), 1.47 (9 H, s, *t*-Bu), 1.35 (1 H, ddd, J = 14.0, 10.4, 4.4 Hz, *i*-PrCH), 0.99 (1 H, ddd, J = 14.0, 10.0, 2.8 Hz, *i*-PrCH), 0.93 (3 H, d, J = 6.4 Hz, CH_3), 0.91 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 81.6, 70.1, 59.3, 41.0, 28.1, 24.4, 23.9, 21.7; IR (KBr) 3375, 2957, 2870, 1732, 1592, 1470, 1367, 1252, 1153, 1069, 849 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{24}NO_3$, 218.1751 ([M + H]$^+$); found, 218.1751 ([M + H]$^+$).

3.18. (4*S,5*S**)-5-(2′-Methylpropyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6e):** $[\alpha]_D^{29}$ −22.1° (*c* 0.45, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1 H, br, NH), 5.10 (1 H, ddd, J = 10.8, 8.8, 3.6 Hz, CHOC=S), 4.48 (1 H, d, J = 8.8 Hz, C*H*NH), 1.90−2.00 (1 H, m, $(CH_3)_2CH$), 1.67−1.74 (1 H, m, *i*-PrCH), 1.50 (9 H, s, *t*-Bu), 1.46−1.53 (1 H, m, *i*-PrCH), 0.97 (3 H, d, J = 6.8 Hz, CH_3), 0.97 (3 H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 166.5, 84.2, 83.0, 61.6, 38.7, 28.0, 24.6, 23.3, 21.3; IR (KBr) 3177, 2964, 2876, 1730, 1520, 1391, 1380, 1354, 1248, 1227, 1188, 1151, 1084, 931, 866, 839, 756 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{21}NNaO_3S$, 282.1134 ([M + Na]$^+$); found, 282.1133 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 13.8 (major) and 20.2 min (minor).

3.19. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxy-5-methylhexanoate (*syn*-5e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (1 H, ddd, J = 8.8, 4.8, 4.0 Hz, C*H*OH), 3.18 (1 H, d, J = 4.8 Hz, C*H*NH_2), 1.77−2.18 (4 H, m, $(CH_3)_2CH$, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.42−1.48 (1 H, m, *i*-PrCH), 1.26 (1 H, ddd, J = 14.0, 8.8, 3.6 Hz, *i*-PrCH), 0.95 (3 H, d, J = 6.8 Hz, CH_3), 0.93 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 81.6, 70.3, 59.3, 43.2, 28.1, 24.8, 23.6, 22.0; IR (KBr) 3375, 2957, 2870, 1732, 1591, 1470, 1369, 1256, 1157, 849 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{24}NO_3$, 218.1751 ([M + H]$^+$); found, 218.1750 ([M + H]$^+$).

3.20. (4*S,5*R**)-5-(2′-Methylpropyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, br, NH), 4.95 (1 H, ddd, J = 8.8, 6.8, 5.2 Hz, CHOC=S), 4.10 (1 H, d, J = 6.8 Hz, C*H*NH), 1.83−1.98 (2 H, m, $(CH_3)_2CH$ and *i*-PrCH), 1.61 (1 H, ddd, J = 13.6, 8.0, 5.2 Hz, *i*-PrCH), 1.50 (9 H, s, *t*-Bu), 0.99 (6 H, d, J = 6.8 Hz, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.9, 84.3, 84.2, 63.1, 44.1, 28.0, 24.4, 22.9, 21.9; IR (KBr) 3188, 2961, 2874, 1740, 1504, 1371, 1254, 1232, 1184, 1157, 1078, 941, 840, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{21}NNaO_3S$, 282.1134 ([M + Na]$^+$); found, 282.1134 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 13.7 and 19.9 min.

4. Preparation of Racemic Aldol Adducts (±)-*anti*-3f and (±)-4f. To a solution of diisopropylamine (82.2 μL, 0.58 mmol) in THF (2.0 mL) was added a 1.54 M hexane solution of *n*-BuLi (357 μL, 0.55 mmol) at 0 °C. This mixture was stirred for 30 min and cooled to −78 °C. Then, a solution of **2** (148 mg, 0.5 mmol) in THF (1.0 mL) was added dropwise. After the mixture was stirred for 30 min at −78 °C, isobutyraldehyde (68.1 μL, 0.75 mmol) was added dropwise, and the mixture was stirred for 2 h at the same temperature. The reaction was quenched by addition of ice-cooled, saturated $NaHCO_3$ and extracted with ethyl acetate. The organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:15 then 1:6 as eluants).

4.1. *tert*-Butyl 2-[(Diphenylmethylene)amino]-3-hydroxy-4-methylpentanoate [(±)-*anti*-3f]:[8a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2 H, d, J = 8.4 Hz, Ph), 7.31−7.45 (6 H, m, Ph), 7.19−7.22 (2 H, m, Ph), 3.99 (1 H, dd, J = 6.8, 0.8 Hz, CHN), 3.88 (1 H, m, C*H*OH), 3.19 (1 H, d, J = 3.2 Hz, OH), 1.79−1.87 (1 H, m, $(CH_3)_2CH$), 1.49 (9 H, s, *t*-Bu), 0.94 (3 H, d, J = 6.8 Hz, CH_3), 0.75 (3 H, d, J = 6.8 Hz, CH_3).

4.2. *tert*-Butyl 5-Isopropyl-2,2-diphenyloxazolidine-4-carboxylate [(±)-4f]:[8a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2 H, d, J = 8.4 Hz, Ph), 7.49 (2 H, d, J = 8.4 Hz, Ph), 7.19−7.30 (6 H, m, Ph), 3.72 (1 H, dd, J = 7.2, 7.2 Hz, C*H*OH), 3.56 (1 H, d, J = 7.2 Hz, C*H*NH), 3.22 (1 H, br s, NH), 1.41−1.50 (1 H, m, $(CH_3)_2CH$), 1.44 (9 H, s, *t*-Bu), 0.98 (3 H, d, J = 6.8 Hz, CH_3), 0.87 (3 H, d, J = 6.8 Hz, CH_3).

5. Retro Aldol Reaction of Racemic Aldol Adducts (±)-*anti*-3f and (±)-4f. Retro aldol reactions of (±)-anti-**3f** and (±)-**4f** were performed in a manner similar to the representative procedure of direct catalytic asymmetric aldol reaction of **2**, respectively, except that 1.0 equiv of isobutyraldehyde and (*R*,*R*)-**1a** was used as a catalyst.

5.1. *tert*-Butyl (2*S*,3*S*)-2-Amino-3-hydroxy-4-methylpentanoate (*anti*-5f):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (1 H, br d, J = 4.8 Hz, C*H*NH_2), 3.39 (1 H, dd, J = 6.8, 4.8 Hz, C*H*OH), 2.10 (3 H, br, OH and NH_2), 1.79 (1 H, m, $(CH_3)_2CH$), 1.49 (9 H, s, *t*-Bu), 0.99 (3 H, d, J = 6.8 Hz, CH_3), 0.97 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 81.7, 78.6, 57.2, 30.9, 28.1, 19.6, 18.1; IR (KBr) 3167, 2977, 2874, 1732, 1593, 1477, 1369, 1248, 1157, 1045, 1008, 964, 916, 852 cm^{-1}. The absolute configuration was confirmed, after hydrolysis of the *tert*-butyl ester (6 N HCl), by comparison of the optical rotation of the amino acid hydrochloride with the literature value.[8h]

5.2. (4*S*,5*S*)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6f):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1 H, br, NH), 4.67 (1 H, dd, J = 8.8, 8.0 Hz, CHOC=S), 4.48 (1 H, d, J = 8.8 Hz, C*H*NH), 2.03−2.12 (1 H, m, $(CH_3)_2CH$), 1.51 (9 H, s, *t*-Bu), 1.09 (3 H, d, J = 6.8 Hz, CH_3), 1.07 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 166.7, 90.0, 84.2, 61.2, 29.1, 28.0, 19.3, 18.2; IR (KBr) 3188, 2984, 2934, 2878, 1746, 1728, 1524, 1371, 1263, 1227, 1190, 1142, 1070, 991, 937, 918, 860, 831, 754 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 16.0 (4*S*,5*S*) and 23.8 min (4*R*,5*R*).

5.3. *tert*-Butyl (2*S*,3*R*)-2-Amino-3-hydroxy-4-methylpentanoate (*syn*-5f):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40−3.41 (2 H, m, C*H*OH and C*H*NH_2), 1.99 (3 H, br, OH and NH_2), 1.70−1.78 (1 H, m, $(CH_3)_2CH$), 1.48 (9 H, s, *t*-Bu), 1.00 (3 H, d, J = 6.4 Hz, CH_3), 0.96 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 81.5, 77.3, 56.4, 30.9, 28.1, 19.6, 17.7; IR (KBr) 3381, 2976, 2874,

1732, 1593, 1474, 1369, 1254, 1159, 1008, 848 cm^{-1}. The absolute configuration was confirmed by comparison of the optical rotation of the amino acid hydrochloride with the literature value.[11]

5.4. (4*S*,5*R*)-5-Isopropyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6f):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1 H, br, NH), 4.73 (1 H, dd, J = 6.0, 6.0 Hz, CHOC=S), 4.17 (1 H, d, J = 6.0 Hz, C*H*NH), 2.03−2.11 (1 H, m, $(CH_3)_2CH$), 1.50 (9 H, s, *t*-Bu), 1.04 (3 H, d, J = 9.6 Hz, CH_3), 1.03 (3 H, d, J = 9.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 167.4, 90.0, 84.2, 60.2, 32.4, 28.0, 17.1, 16.9; IR (KBr) 3175, 2978, 2937, 2882, 1728, 1520, 1367, 1255, 1196, 1159, 985, 931, 907, 841 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 17.2 and 26.1 min.

6. Representative Improved Procedure for Highly Diastereo- and Enantioselective Direct Aldol Reaction of Glycinate Schiff Base 2 with Aldehydes Catalyzed by (*R*,*R*)-1b under Phase-Transfer Conditions. To a mixture of *tert*-butylglycinate benzophenone Schiff base (**2**, 88.6 mg, 0.3 mmol), (*R*,*R*)-**1b** (9.9 mg, 2 mol%), and NH_4Cl (1.6 mg, 0.03 mmol) in toluene (1.5 mL) was added 1% NaOH aqueous solution (180 μL, 0.045 mmol) at 0 °C under argon atmosphere, and then 3-phenylpropanal (79.0 μL, 0.6 mmol) was introduced dropwise. After the whole mixture was stirred at 0 °C for 1.5 h, saturated NH_4Cl and ether were added. The workup and acidic hydrolysis of the crude products were performed in a manner similar to the initial procedure, as described before.

6.1. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxyoctanoate (*anti*-5g):**[16a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74−3.79 (1 H, m, C*H*OH), 3.46 (1 H, d, J = 4.8 Hz, C*H*NH_2), 1.92 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.25−1.40 (8 H, m, $(CH_2)_4$), 0.89 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 81.6, 72.2, 59.0, 32.1, 31.8, 28.2, 25.6, 22.7, 14.2; IR (neat) 3371, 2932, 2860, 1732, 1593, 1458, 1393, 1367, 1250, 1157, 850 cm^{-1}.

6.2. (4*S,5*S**)-5-Pentyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6g):**[16a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1 H, br, NH), 5.00 (1 H, ddd, J = 9.2, 7.6, 6.4 Hz, CHOC=S), 4.48 (1 H, d, J = 9.2 Hz, C*H*NH), 1.71−1.76 (2 H, m, CH_2), 1.52−1.66 (2 H, m, CH_2), 1.50 (9 H, s, *t*-Bu), 1.40−1.50 (2 H, m, CH_2), 1.31−1.33 (4 H, m, $(CH_2)_2$), 0.90 (3 H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 166.4, 84.8, 84.2, 61.4, 31.4, 30.3, 28.1, 25.2, 22.5, 14.0; IR (KBr) 3159, 2934, 2870, 1736, 1524, 1366, 1230, 1186, 1153, 1088, 858 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 13.4 (major) and 19.9 min (minor).

6.3. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxyoctanoate (*syn*-5g):**[16a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65−3.69 (1 H, m, C*H*OH), 3.23 (1 H, d, J = 4.8 Hz, C*H*NH_2), 1.76 (3 H, br, OH and NH_2), 1.27−1.57 (8 H, m, $(CH_2)_4$), 1.48 (9 H, s, *t*-Bu), 0.90 (3 H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 81.6, 72.2, 58.9, 34.0, 31.9, 28.1, 25.4, 22.7, 14.1; IR (neat) 3373, 2931, 2860, 1732, 1593, 1458, 1393, 1369, 1252, 1157, 849 cm^{-1}.

6.4. (4*S,5*R**)-5-Pentyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6g):**[16a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1 H, br, NH), 4.89 (1 H, ddd, J = 7.2, 6.8, 5.6 Hz, CHOC=S), 4.10 (1 H, d, J = 6.8 Hz, C*H*NH), 1.77−1.93 (2 H, m, CH_2), 1.50 (9 H, s, *t*-Bu), 1.33−1.57 (6 H, m, $(CH_2)_3$), 0.91 (3 H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 167.0, 85.6, 84.3, 62.6, 34.9, 31.2, 28.0, 24.1, 22.5, 14.0; IR (KBr) 3182, 2934, 2862, 1742, 1506, 1371, 1252, 1180, 1157, 1082, 842 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 14.1 and 23.7 min.

6.5. *tert*-Butyl (2*S,3*S**)-2-Amino-3-hydroxy-6-heptenoate (*anti*-5h):** $[\alpha]_D^{29}$ 3.6° (*c* 0.68, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1 H, ddt, J = 16.8, 10.0, 6.8 Hz, CH_2=C*H*), 5.05 (1 H, d, J = 16.8 Hz, CH_2=CH), 4.98 (1 H, d, J = 10.0 Hz, CH_2=CH), 3.79 (1 H, ddd, J = 7.6, 5.2, 4.8 Hz, C*H*OH), 3.47 (1 H, d, J = 4.8 Hz, C*H*NH_2), 2.25−2.34 (1 H, m, CH_2=CHC*H*), 2.10−2.20 (1 H, m, CH_2=CHC*H*), 2.10 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.32−1.46 (2 H, m, CH_2CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.0, 114.8, 81.7, 71.5, 59.0, 31.4, 30.0, 28.1; IR (neat) 3369, 3078, 2978, 2934, 1732, 1641, 1593, 1456, 1394, 1369, 1252, 1157, 1074, 995, 912, 849, 775, 750 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{21}NO_3$, 216.1594 ([M + H]$^+$); found, 216.1603 ([M + H]$^+$).

6.6. (4*S,5*S**)-5-(3′-Butenyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6h):** $[\alpha]_D^{29}$ −35.6° (*c* 0.39, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1 H, br, NH), 5.79 (1 H, ddt, J = 17.2, 10.4, 6.4 Hz, CH_2=C*H*), 5.01−5.11 (3 H, m, CH_2=CH and CHOC=S), 4.49 (1 H, d, J = 9.2 Hz, C*H*NH), 2.33−2.42 (1 H, m, C*H*CHOC=S), 2.20−2.29 (1 H, m, C*H*CHOC=S), 1.82−1.88 (2 H, m, CH_2=CHCH_2), 1.51 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 166.4, 136.0, 116.2, 84.3, 83.8, 61.3, 29.3, 28.0, 28.0; IR (KBr) 3163, 2995, 2922, 1732, 1526, 1358, 1236, 1184, 1153, 1086, 918, 854 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{19}NNaO_3S$, 280.0978 ([M + Na]$^+$); found, 280.0977 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 16.5 (major) and 25.6 min (minor).

6.7. *tert*-Butyl (2*S,3*R**)-2-Amino-3-hydroxy-6-heptenoate (*syn*-5h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (1 H, ddt, J = 17.2, 10.0, 6.8 Hz, CH_2=C*H*), 5.05 (1 H, d, J = 17.2 Hz, CH_2=CH), 4.98 (1 H, d, J = 10.0 Hz, CH_2=CH), 3.69 (1 H, ddd, J = 7.6, 4.8, 4.8 Hz, C*H*OH), 3.23 (1 H, d, J = 4.8 Hz, C*H*NH_2), 2.95−2.99 (3 H, m, OH and NH_2) 2.24−2.33 (1 H, m, CH_2=CHC*H*), 2.12−2.22 (1 H, m, CH_2=CHC*H*), 1.55−1.63 (2 H, m, CH_2CHOH), 1.48 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 138.0, 114.7, 81.8, 71.5, 58.7, 33.3, 29.9, 28.1; IR (neat) 3371, 3078, 2978, 2934, 1732, 1641, 1593, 1479, 1456, 1394, 1369, 1285, 1252, 1157, 1080, 995, 912, 846, 754 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{21}NO_3$, 216.1594 ([M + H]$^+$); found, 216.1594 ([M + H]$^+$).

6.8. (4*S,5*R**)-5-(3′-Butenyl)-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1 H, br, NH), 5.81 (1 H, ddt, J = 16.8, 10.4, 6.8 Hz, CH_2=C*H*), 5.10 (1 H, dd, J = 16.8, 1.2 Hz, CH_2=CH), 5.06 (1 H, dd, J = 6.8, 1.2 Hz, CH_2=CH), 4.92 (1 H, ddd, J = 6.8, 6.4, 5.6 Hz, CHOC=S), 4.16 (1 H, d, J = 6.8 Hz, C*H*NH), 2.20−2.36 (2 H, m, CH_2CHOC=S) 1.85−2.05 (2 H, m, CH_2=CHCH_2), 1.50 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.8, 135.9, 116.1, 84.7, 84.3, 62.7, 34.0, 28.5, 28.0; IR (KBr) 3184, 2982, 2936, 1740, 1502, 1371, 1244, 1180, 1155, 914, 733 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{19}NNaO_3S$, 280.0978 ([M + Na]$^+$); found, 280.0977 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 17.1 and 25.9 min.

6.9. *tert*-Butyl (2*S*,3*S*)-2-Amino-3-hydroxybutanoate (*anti*-5i): $[\alpha]_D^{28}$ 8.7° (*c* 0.18, $CHCl_3$, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97−4.03 (1 H, m, C*H*OH), 3.46 (1 H, d, J = 4.8 Hz, C*H*NH_2), 2.16 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.08 (3 H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 81.7, 67.9, 59.3, 28.1, 17.8; IR (neat) 3369, 2978, 2934, 1732, 1589, 1458, 1369, 1252, 1157, 982, 914, 849 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_{18}NO_3$, 176.1281 ([M + H]$^+$); found, 176.1285 ([M + H]$^+$). The absolute configuration was determined, after cleavage of the *tert*-butyl ester (6 N HCl, MeOH), by comparison of the optical rotation value with that of the hydrochloride salt of commercially available L-*allo*-threonine.

6.10. (4*S*,5*S*)-5-Methyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6i): $[\alpha]_D^{27}$ 2.8° (*c* 0.40, $CHCl_3$, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1 H, br, NH), 5.20 (1 H, dq, J = 9.2, 6.8 Hz, CHOC=S), 4.51 (1 H, d, J = 9.2 Hz, C*H*NH), 1.51 (9 H, s, *t*-Bu), 1.49 (3 H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 166.3, 84.3, 80.8, 61.7, 28.1, 16.1; IR (KBr) 3198, 2986, 2939, 1736, 1495, 1369, 1261, 1229, 1173, 1157, 1072, 932, 850 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{15}NNaO_3S$, 240.0665 ([M + Na]$^+$); found, 240.0668 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 43.6 (4*R*,5*R*) and 48.0 min (4*S*,5*S*).

6.11. *tert*-Butyl (2*S*,3*R*)-2-Amino-3-hydroxybutanoate (*syn*-5i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76−3.82 (1 H, m, C*H*OH), 3.13 (1 H, d, J = 5.6 Hz, C*H*NH_2), 2.13 (3 H, br, OH and NH_2), 1.48 (9 H, s, *t*-Bu), 1.23 (3 H, d, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 81.7, 68.4, 60.6, 28.1, 19.8; IR (neat) 3369, 2978, 2934, 1730, 1593, 1458, 1369, 1252, 1159, 978, 849 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_{18}NO_3$, 176.1281 ([M + H]$^+$); found, 176.1285 ([M + H]$^+$).

6.12. (4*S*,5*R*)-5-Methyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1 H, br, NH), 5.20 (1 H, dq, J = 7.2, 6.4 Hz, CHOC═S), 4.09 (1 H, d, J = 7.2 Hz, C*H*NH), 1.61 (3 H, d, J = 6.4 Hz, CH_3), 1.50 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.6, 84.4, 82.0, 64.2, 28.0, 20.7; IR (KBr) 3190, 2982, 2934, 1738, 1506, 1371, 1252, 1184, 1155, 1053, 840, 731 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{15}NNaO_3S$, 240.0665 ([M + Na]$^+$); found, 240.0663 ([M + Na]$^+$); HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 21.4 and 38.5 min.

6.13. *tert*-Butyl (2*S,3*S**)-2-Amino-3-cyclohexyl-3-hydroxypropanoate (*anti*-5j):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (1 H, br d, J = 4.8 Hz, C*H*NH_2), 3.42 (1 H, dd, J = 7.2, 4.8 Hz, C*H*OH), 2.05 (3 H, br, OH and NH_2), 1.92−1.96 (1 H, m, *c*-Hex), 1.60−1.80 (4 H, m, *c*-Hex), 1.43−1.49 (1 H, m, *c*-Hex), 1.47 (9 H, s, *t*-Bu), 0.99−1.25 (5 H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 81.7, 78.0, 56.7, 40.8, 29.6, 28.6, 28.1, 26.4, 26.3, 26.1; IR (neat) 3145, 2924, 2851, 1741, 1605, 1448, 1369, 1256, 1155, 1005, 978, 939, 854 cm^{-1}.

6.14. (4*S,5*S**)-5-Cyclohexyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6j):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1 H, br, NH), 4.70 (1 H, dd, J = 8.8, 8.0 Hz, CHOC═S), 4.47 (1 H, d, J = 8.8 Hz, C*H*NH), 1.97−2.00 (2 H, m, *c*-Hex), 1.69−1.78 (5 H, m, *c*-Hex), 1.51 (9 H, s, *t*-Bu), 1.11−1.26 (5 H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 166.7, 89.0, 84.1, 61.1, 38.5, 29.4, 28.0, 28.0, 25.9, 25.6, 25.3; IR (KBr) 3205, 2922, 2853, 1736, 1508, 1367, 1259, 1178, 1155, 1069, 858 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 15.1 (major) and 23.5 min (minor).

6.15. *tert*-Butyl (2*S,3*R**)-2-Amino-3-cyclohexyl-3-hydroxypropanoate (*syn*-5j):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2 H, m, C*H*OH and C*H*NH_2), 1.97 (3 H, br, OH and NH_2), 1.93−1.97 (1 H, m, *c*-Hex), 1.75−1.80 (2 H, m, *c*-Hex), 1.62−1.68 (2 H, m, *c*-Hex), 1.48 (9 H, s, *t*-Bu), 1.39−1.47 (1 H, m, *c*-Hex), 1.03−1.31 (5 H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 81.5, 76.4, 55.9, 40.5, 29.7, 28.1, 28.1, 26.4, 26.4, 26.1; IR (neat) 3389, 2930, 2855, 1728, 1593, 1450, 1369, 1252, 1157, 910, 849, 783 cm^{-1}.

6.16. (4*S,5*R**)-5-Cyclohexyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6j):**[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1 H, br, NH), 4.70 (1 H, dd, J = 6.4, 6.0 Hz, CHOC═S), 4.22 (1 H, d, J = 6.0 Hz, C*H*NH), 1.65−1.89 (6 H, m, *c*-Hex), 1.50 (9 H, s, *t*-Bu), 1.09−1.33 (5 H, m, *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 167.5, 89.3, 84.1, 60.2, 41.9, 27.9, 27.5, 27.2, 26.0, 25.5, 25.4; IR (KBr) 3179, 2928, 2858, 1732, 1512, 1371, 1244, 1182, 1155, 952, 837 cm^{-1}; HPLC: DAICEL Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time = 20.7 and 29.2 min.

6.17. *tert*-Butyl (2*S,3*S**)-2-Amino-3-phenyl-3-hydroxypropanoate (*anti*-5k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.34 (5 H, m, Ph), 4.90 (1 H, d, J = 5.6 Hz, C*H*OH), 3.67 (1 H, d, J = 5.6 Hz, C*H*NH_2), 2.36 (3 H, br, OH and NH_2), 1.36 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 139.9, 127.9, 127.6, 126.4, 81.8, 74.3, 60.2, 27.9; IR (KBr) 3356, 3292, 2979, 2864, 1782, 1580, 1454, 1367, 1246, 1153, 1055, 1014, 848, 743, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{20}NO_3$, 238.1438 ([M + H]$^+$); found, 238.1443 ([M + H]$^+$). The enantiomeric excess was determined by HPLC analysis of its *N*-benzoate using a chiral column [DAICEL Chiralpak OJ, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time = 48.1 (major) and 64.9 min (minor)].

6.18. (4*S,5*S**)-5-Phenyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*cis*-6k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1 H, br, NH), 7.27−7.39 (5 H, m, Ph), 6.04 (1 H, d, J = 10.0 Hz, CHOC═S), 4.84 (1 H, d, J = 10.0 Hz, C*H*NH), 1.03 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 165.4, 133.6, 129.5, 128.5, 127.0, 85.2, 83.7, 62.9, 27.4; IR (KBr) 3152, 3009, 2934, 1732, 1545, 1369, 1348, 1244, 1192, 1157, 1105, 1024, 955, 839, 766, 704 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{17}NNaO_3S$, 302.0821 ([M + Na]$^+$); found, 302.0819 ([M + Na]$^+$).

6.19. *tert*-Butyl (2*S,3*R**)-2-Amino-3-phenyl-3-hydroxypropanoate (*syn*-5k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.37 (5 H, m, Ph), 4.73 (1 H, d, J = 5.6 Hz, C*H*OH), 3.52 (1 H, d, J = 5.6 Hz, C*H*NH_2), 1.81 (3 H, br, OH and NH_2), 1.34 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 140.8, 128.2, 127.7, 126.4, 81.7, 74.6, 61.0, 27.9; IR (KBr) 3371, 3300, 2978, 2934, 1728, 1454, 1367, 1252, 1155, 1051, 848, 702 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{20}NO_3$, 238.1438 ([M + H]$^+$); found, 238.1438 ([M + H]$^+$). The enantiomeric excess was determined by HPLC analysis of its *N*-benzoate using a chiral column [DAICEL Chiralpak OJ, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time = 77.1 (minor) and 91.9 min (major)].

6.20. (4*S,5*R**)-5-Phenyl-2-thiooxooxazoline-4-carboxylic Acid *tert*-Butyl Ester (*trans*-6k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1 H, br, NH), 7.38−7.45 (5 H, m, Ph), 5.91 (1 H, d, J = 6.8 Hz, CHOC═S), 4.39 (1 H, d, J = 6.8 Hz, C*H*NH), 1.53 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.6, 136.9, 129.3, 129.0, 125.6, 85.7, 84.7, 65.2, 28.1; IR (KBr) 3198, 2976, 1728, 1514, 1369, 1285, 1238, 1211, 1171, 981, 962, 844, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{17}NNaO_3S$, 302.0821 ([M + Na]$^+$); found, 302.0823 ([M + Na]$^+$).

Conclusions

We have developed the highly efficient direct aldol reaction of glycinate Schiff base **2** with aldehyde acceptors catalyzed by chiral quaternary ammonium salt **1b** under mild organic/aqueous biphasic conditions with excellent relative and absolute stereochemical control. Although the reaction condition using 2 equiv of aqueous base (1% NaOH (aq)) was initially developed, it exhibited limited general applicability in terms of aldehyde acceptors. Subsequent mechanistic studies revealed the unique reaction profile, involving an unfavorable yet inevitable retro aldol reaction. On the basis of this finding, a reliable reaction recipe was established using a catalytic amount of 1% NaOH (aq) and ammonium chloride, which tolerates a wide range of aldehydes to afford the corresponding *anti*-β-hydroxy-α-amino esters almost exclusively in an essentially optically pure form. This reaction offers a powerful chemical method for the synthesis of stereochemically homogeneous β-hydroxy-α-amino acids in a totally predictable manner and complements the aldolase-based chemo-enzymatic processes. Therefore, the present system can be regarded as an artificial glycine-dependent aldolase; its operational simplicity, environmentally friendly conditions, and suitability for large-scale reaction represent distinct advantages for practical industrial applications.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. M.K. is grateful to the Japan Society for the Promotion of Science for Young Scientists for a research fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA048865Q