Tetrahedron Vol. 47, No. 42, pp. 8869-8882, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Carbamate-Directed Stereoselective Hydrogenation and Kinetic Resolution of *N*-Protected α-(α-Aminoalkyl)acrylates

Masatoshi Takagi and Keiji Yamamoto*

Department of Chemical Engineering, Tokyo Institute of Technology,
Ookayama, Meguro, Tokyo 152, Japan

(*Received in Japan* 16 *August* 1991)

Key Words: homogeneous hydrogenation; diastereoselectivity; kinetic resolution; Ru(II) complex; Rh(I) complex

Abstract: *A series of racemic methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (**1a-e**) were hydrogenated using a variety of Rh(I) cationic complexes containing diphosphines and a chiral [Ru(OAc)$_2$(S)-BINAP] (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-dinaphthyl) as catalyst precursors to give preferentially the threo isomers (**2a-d**), the diastereoselectivity depending markedly on the alkyl group in **1**. In addition, the relative rate ratio, k_R/k_S, of a kinetic resolution during the Ru-catalyzed hydrogenation was found to be in a range 8-17, varying rather randomly as the alkyl group in **1** altered. The intercorrelation between the diastereoselectivity by virtue of the substrate-control and the kinetic discrimination of (±)-**1** arising from the chiral catalyst-control was discussed in one particular case.*

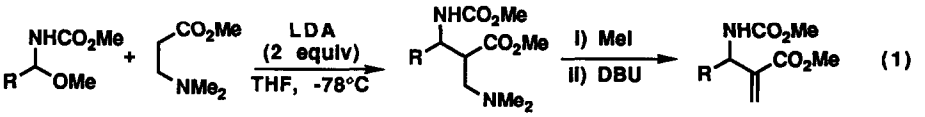
We have been concerned with (i) an efficient acyclic stereoselection in the hydrogenation of the title compounds, providing an asymmetric synthesis of β-amino acids and (ii) prospect of kinetic resolution in the homogeneous hydrogenation, which is one of recent topics in the functional group-directed hydrogenation.[1)]

In a previous paper,[2)] we have reported that methyl α-[α-(methoxycarbonylamino)benzyl]acrylate (**1a**) was hydrogenated by using either [Rh(cod)(dppb)]$^+$ClO$_4^-$ (cod = 1,5-cyclooctadiene; dppb = 1,4-bis(diphenylphosphino)butane) or [Ru(OAc)$_2$(PPh$_3$)$_2$] as a catalyst precursor with excellent threo selectivity (~99%) to afford methyl (2*R**, 3*S**)-α-[α-(methoxycarbonylamino)benzyl]propionate (**2a**). The result indicates that the carbamate group in **1a**, which is in coordination with the catalyst, directs hydrogenation of the chiral olefin **1a** to take place from one of the diastereotopic faces so as to avoid the site of steric congestion. Such a diastereoselectivity in hydrogenation must arise primarily from the chelation-control and thus is referred to as the substrate-controlled conditions, irrespective of the catalyst species employed. When the catalyst complex bears an optically active diphosphine, then a kinetic resolution should be observed during hydrogenation of this type of chiral substrate. We report here the investigation on the diastereoselective hydrogenation and kinetic resolution of a series of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates {alkyl = benzyl (**1a**), ethyl (**1b**), isobutyl (**1c**), isoamyl (**1d**) and neopentyl (**1e**)}. When our study was under way, Brown *et al.*[3)] reported the similar research to ours[4)] on the kinetic resolution during the Rh(I)-catalyzed hydrogenation of *N*-protected α-(α-aminoalkyl)acrylates.

RESULTS AND DISCUSSION

(a) Preparation of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (1a-e)

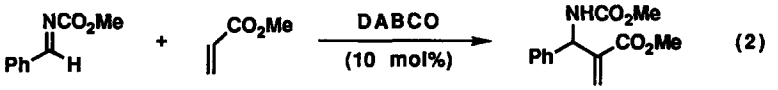
In order to extend the scope of the carbamate-directed diastereoselective hydrogenation of **1a** as mentioned above, we have prepared a series of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (**1b-e**) by a two-step procedure (Eq. 1). The procedure involves an *in-situ* generation of alkylidenecarbamates,[5] the requisite alkylidenecarbamate being known to exist only as an isomeric enamide at room temperature.[6] On the other hand, methyl *N*-benzylidenecarbamate[6] could be isolated and used for the preparation of **1a**[7] by the Baylis-Hillman reaction[8][9] (Eq. 2).



(1)

1

b, R = Me; c, R = ^{i}Pr; d, R = ^{i}Bu; e, R = ^{t}Bu

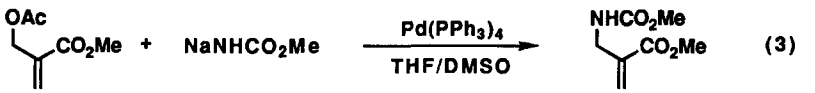


(2)

1a

In order to perform the kinetic resolution experiment (*vide infra*) using the present substrates, **1a-e**, it is indispensable to separate the hydrogenation product, e.g., **2a**, from unreacted, optically activated substrate **1a** both present in the reaction mixture. It is worthy of note here that the separation was very easily attained by the procedures which involved the conjugate addition of dimethylamine to **1a**, followed by separation of the hydrogenation component **2a** from the adduct, and the Hofmann elimination of the latter to regenerate **1a** just as formulated in the second step in Eq. 1 (see Experimental Section).

An analogous but prochiral substrate, methyl α-(methoxycarbonylaminomethyl)acrylate (**1f**), could not be obtained by the same procedure as that given in Eq. 1 (R = H), being prepared by a novel palladium(0)-catalyzed reaction of methyl α-(acetoxymethyl)acrylate with methyl sodiocarbamate (Eq. 3).[12]



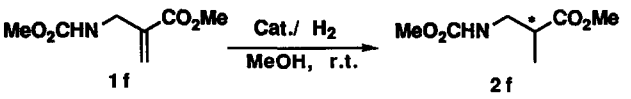
(3)

1f

(b) Enantioselective hydrogenation of methyl α-(methoxycarbonylaminomethyl)acrylate (1f) using chiral Rh(I)-diphosphine and Ru(II)-BINAP catalysts.

In order to examine the effectiveness of chiral catalysts which give rise to an enantioselective hydrogenation of **1f**, several Rh(I) cationic complexes containing conventional chiral diphosphines as well as a Ru(II)-BINAP complex were employed as catalysts. The results are given in Table I.

Table I Enantioselective Hydrogenation of Methyl α-(Methoxycarbonylaminomethyl)acrylate (**1f**) Using Chiral Rh(I)-diphosphine or Ru(II)-BINAP Catalyst



1f **2f**

Catalyst (1 mol%)	H_2 (atm)	Time (h)	E.e.[a] (%)	Isomn.[b] (%)
Rh-(*R*)-DIOP	30	40	0	15
Rh-(*S*)-CHIRAPHOS	30	40	0	7
Rh-(*S*)-NORPHOS	5	13	~0	11
	30	15	16 (*S*)	2
Rh-(*R*)-DEGUPHOS	30	13	0	11
Ru-(*S*)-BINAP	2	13	85 (*R*)	8
	5	14	83 (*R*)	5
	30	17	65 (*R*)	7
	90	13	~0	3

Conditions: Substrate (0.5 mmol), Catalyst (1 mol%), and MeOH (2.5 mL).

a) Conversion 100%, determined by Eu(DPPM)3 shifts.

b) Methyl β-(methoxycarbonylamino)methacrylate; (*E*)-olefin dominant (20 : 1).

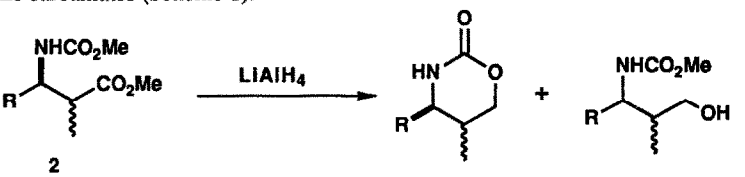
Although total conversion of **1f** in hydrogenation was secured under hydrogen pressure (2-90 atm) at room temperature, the hydrogenation was always accompanied by a significant amount of isomerization of **1f** into methyl β-(methoxycarbonylamino)methacrylate, the latter remaining intact under the conditions employed. Table I shows that the hydrogenation of **1f** using chiral Rh(I) cationic catalysts with conventional diphosphines proceeded mostly with no enantioselectivity. Only $Ru(OAc)_2$-(*S*)-BINAP[13] as a catalyst worked well to give methyl (*R*)-α-(methoxycarbonylaminomethyl)propionate (**2f**) in 85% e.e. under relatively low hydrogen pressure. It is not clear why the racemic **2f** resulted under high hydrogen pressure. Although the chiral Ru(II) complex employed here has been known to catalyze hydrogenation of a variety of substituted prochiral acrylic acids with extremely high enantioselectivities under selected conditions, their esters are generally found to be intact under the same hydrogenation conditions.[13b] Consequently, the highly enantioselective hydrogenation of **1f** observed here, most probably by virtue of an effective coordination of the carbamate group, reveals new aspects of this particular catalyst. The sense of enantioface-selection in the hydrogenation of **1f** by this Ru(II) catalyst was found to coincide with that of methyl α-(hydroxymethyl)acrylate using the same catalyst.[14] The fact reinforces that the similar face-matching of the olefin moiety in both substrates operates in chelation with this Ru(II) catalyst. It should be mentioned that the aptitude of (*S*)-BINAP in the Ru(II) catalyst for inducing (2*R*) of

the product **2f** in the hydrogenation of prochiral substrate **1f** must apply in the diastereoselective hydrogenation of related chiral substrates (**1a-d**, but **1e**), which will be the subject of the following discussion.

(c) Diastereoselective hydrogenation of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (1a-e) using an achiral Rh(I) cationic catalysts.

We have already found[2] that, under selected conditions, excellent diastereoselective hydrogenation of **1a** is achieved in methanol at room temperature to give methyl (2*R**,3*S**)-α-[α-(methoxycarbonylamino)benzyl]-propionate (**2a**) in up to 98% threo selectivity with the use of $[Rh(cod)(dppe)]^+ClO_4^-$ as a catalyst precursor.[15] Hydrogenation of a series of α-[α-(methoxycarbonylamino)alkyl]acrylates (**1b-e**) catalyzed by $[Rh(cod)(dppb)]^+ClO_4^-$ has also been carried out.[2] However, there were given significantly low or rather erroneous data for the threo selectivities. Thus, reexamination on the Rh(I) complex-catalyzed hydrogenation of **1a-e** was carried out in essentially the same procedure as that given previously (see Experimental Section also), the results being listed in Table II.

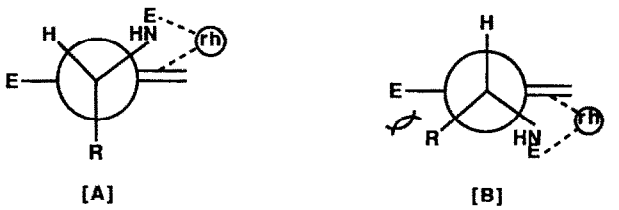
The relative configurations of the products were determined by converting the products into the corresponding cyclic carbamates (Scheme 1).



2

Scheme 1

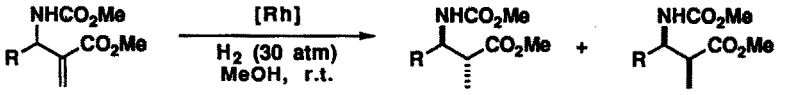
It is seen that the threo selectivity applies only for **1a**, **1b** and **1d**. A balkier isopropyl group in **1c** appears to interfere with the threo selectivity in hydrogenation, and with *t*-butyl group in **1e**, the selectivity even reversed to choose preferentially the erythro diastereomer. However, the uniform threo selectivities observed for **1a-d** are basically explained by a steric interaction of the substrate in chelation with this particular catalyst as depicted in Scheme 2.



Scheme 2 (E = CO_2Me)

Chelation [B] is disfavored because of the steric repulsion between R and E, the threo diastereomer should, consequently, result from the hydrogenation via chelation [A]. However, decrease in the threo selectivities in the case of bulkier R group and especially high threo selectivity in the hydrogenation of **1a** (R = Ph) does not seem to be adequately explained by a simple steric model just mentioned above. A stereoelectronic effect may account for these results. The interaction between a low-valent metal center and an electron-deficient olefin such as

Table II Diastereoselective Hydrogenation of Methyl α-[α-(Methoxycarbonylamino)alkyl]acrylates (**1a-e**) Using Rh[(cod)(dppb)]$^+ClO_4^-$ as a Catalyst



1 *threo*-**2** *erythro*-**2**

	R	Time (h)	Conversion[a] (%)	Threo : Erythro[a]
1a	Ph	17	100	97 : 3[b]
1b	Me	17	100	93 : 7[b,c]
1c	i-Pr	18	99.6	79 : 21[d]
1d	i-Bu	18	100	94 : 6[d]
1e	t-Bu	17	53	23 : 77[c]

Conditions: Substrate (1 mmol), [Rh(cod)(dppb)]$^+ClO_4^-$ (1 mol%) and MeOH (5 mL)
a) Determined by GLC.
b) Data taken from our previous work, Ref. 2.
c) Stereochemical assignment made by derivatization to six-membered ring carbamate (see Experimental).
d) By analogy to **1b-2b** with respect to the retention times of each diastereomers.

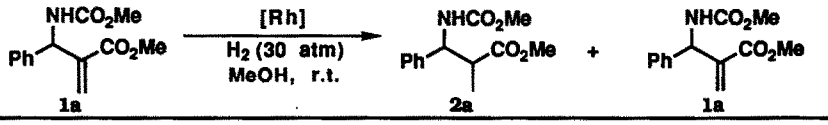
acrylate ester is usually governed by the back-donation (the interaction between the olefin π* orbital and the metal filled d orbital). Therefore, when R is an electron-withdrawing substituent (e.g., R = Ph) in the conformation of chelation [A], the energy level of the σ* orbital of the allylic carbon-R bond is lowered to interact with the olefin π* orbital, which enables the bond between the metal and the olefin strong. As a result, the threo selectivity in the hydrogenation of **1a** could especially be higher than other substrates. On the other hand, when R group is an electron releasing group (especially for α-branched alkyl groups with +I effect), the conformation of chelation [A] is stereoelectronically disfavored and even competes with the sterically disfavored conformer [B] to give rise to lower threo selectivity.

Such electronic effects of the allylic substituents on the transition states in chelation have been discussed by Burgess *et al.*[16] in rhodium(I)-catalyzed hydroboration of functionalized olefins.

(d) Kinetic resolution of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (1a-d) using chiral Rh(I)-diphosphine or Ru(II)-BINAP catalysts.

Once the catalyst complex bears certain optically active diphosphine, then the racemic substrate **1a** is expected to undergo hydrogenation with significantly different rates with respect to each enantiomer (*i.e.*, a kinetic resolution observable by interruption of the hydrogenation), while the chiral catalyst may not interfere with the diastereoselectivity which arises principally from the substrate chelation to the catalyst (substrate-control) in giving *threo*-**2a**. However, this is not the case as shown in Table III. All results given in Table III show there was little kinetic resolution by interrupting hydrogenation of (±)-**1a** by using chiral Rh(I) catalyst containing again several conventional diphosphines (including BINAP). The relative rate ratio k_{fast}/k_{slow} was in a range 1-1.3

Table III Diastereoselective Hydrogenation of (±)-**1a** Using Chiral Rh(I)-Diphosphine Catalysts



Diphosphine	Time (h)	Convn. (%)	Threo : Erythro	E.e.[a] (%)	k_f/k_s
(*R*)-BINAP	9	51	71 : 29	9 (*S*)	1.3
(*S*)-DIOP	6	87	97 : 3	14 (*R*)	1.1
(*S*)-CHIRAPHOS	10	59	96 : 4	11 (*S*)	1.3
(*S*)-SKEWPHOS	3	85	93 : 7	72 (*S*)	2.3
(*S*)-NORPHOS	0.5[b]	45	99 : 1	0	1.0

Conditions: Substrate (1 mmol), Chiral catalyst =$[Rh(cod)(P\text{-}P)]^+ClO_4^-$ (1 mol%), MeOH (5 mL), and H_2 (30 atm) at r.t.

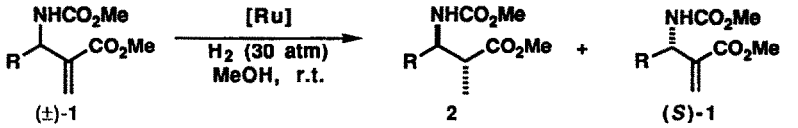
a) For recovered olefin and determined by $Eu(DPPM)_3$ shifts.

b) H_2 (5 atm).

except for Rh(I)-(S)-SKEWPHOS (k_f/k_s = 2.3). As far as the chiral Rh(I) cationic complexes employed as catalysts are concerned, that the very low level of enantiomer discrimination was observed for **1a** may well coincide with the results obtained for the attempted enantioselective hydrogenation of **1f** given in Table I. However, the diastereoselectivity for threo-**2a** was again excellent with respect to four chiral diphosphines, except (*R*)-BINAP, in a similar manner to the case with dppb (see Table II). Thus, we have observed the catalytic hydrogenation of (±)-**1a** to go with an excellent substrate-controlled diastereotopic face-selection, but little to do with the chiral catalyst-controlled enantiomer discrimination. Brown *et al.*[3] have reported the successful kinetic resolution in the highly diastereoselective hydrogenation of methyl α-[α-(*t*-butoxycarbonylamino)propyl]acrylate catalyzed by a Rh(I)-(*R,R*)-DIPAMP (DIPAMP = Bis{(*o*-methoxyphenyl)-phenylphosphino}ethane) cationic complex.

Then, hydrogenation of a series of methyl α-[α-(methoxycarbonylamino)alkyl]acrylates (**1a-d**) was carried out using [Ru(OAc)$_2$(*S*)-BINAP] as a catalyst which was effective for the enantioselective hydrogenation of **1f** (*vide supra*). The hydrogenation was also interrupted and examined the relative rate ratio, k_R/k_S of the each substrate enantiomer. All results are given in Table IV. It is seen that the threo selectivity in these hydrogenations decreased across the board as compared with that catalyzed by $[Rh(cod)(dppb)]^+ClO_4^-$ (see, Table II). On the other hand, the relative rate ratio k_R/k_S for each substrate (**1a-d**) was found to be significant in a range 8-17. Thus, **1a** gave rise to the highest values for both threo selectivity (94%) and enantiomer selectivity (i.e. the relative rate ratio, k_R/k_S = 17). The latter value is well compared with the relative rate ratio of twenty-two given by Brown *et al.*[3] Besides the mechanistic details, the stereochemical course would be (i) the carbamate group-directed (*via* the carbonyl oxygen atom) bidentate coordination of (±)-**1** to Ru-(*S*)-BINAP to form more or less mainly one pair of diastereomers which must be ready for the threo product upon hydrogenation, followed by (ii)

Table IV Diastereoselective Hydrogenation of Methyl α-[α-(Methoxycarbonylamino)alkyl]acrylates (**1a-d**). Kinetic Resolution



	R	Time (h)	Conv. (%)	Threo:Erythro	E.e.[a] (%)	k_R/k_S
1a	Ph	10	52	94 : 6	81	17[b]
1b	Me	5	68	77 : 23[c]	90	8
1c	*i*-Pr	17	48	62 : 38	60	8
1d	*i*-Bu	5	48	72 : 28	61	9

Conditions: Substrate (1 mmol), $Ru(OAc)_2$(*S*)-BINAP (1 mol%), and MeOH (5 mL).
a) For recovered (*S*)-**1**
b) For (*S*)-**1**; derived into (*R*)-(α-isopropylbenzyl)methylamine.
c) For *threo*-(2*R*,3*R*)-**2b** 74% ee; *erythro*-(2*R*,3*S*)-**2b** 18% ee.

the probably rate-determining hydrogenation step where the particular BINAP catalyst-control strongly favors a *si*-face of the diastereotopic faces in **1** to result in giving 2*R* and necessary 3*R* stereogenic centers for more or less preferred threo diastereomers.

In the case of hydrogenation of **1b-1d**, we have observed that both the threo selectivity and the relative rate ratio for kinetic resolution, k_R/k_S, were much lower compared with those of **1a**. Especially as to **1b**, we could isolate both product diastereomers, *threo*-**2b** and *erythro*-**2b**, in pure states and measure the optical purities of these compounds as well as recovered **1b** (Table IV, see also Experimental Section). On the basis of these optical and stoichiometric data by calculation, it was found that the fast-reacting enantiomer, (*R*)-**1b** (97% consumed) gave *threo*-(2*R*,3*R*)-**2b** and *erythro*-(2*S*,3*R*)-**2b** in a ratio 87 : 13, while the slow one, (*S*)-**1b** (39% consumed) gave *threo*-(2*S*,3*S*)-**2b** and *erythro*-(2*R*,3*S*)-**2b** in a ratio 53 : 47, the diastereoselectivity with respect to (*R*)-**1b** being much higher than the observed overall ratio (77 : 23) and much lower with (*S*)-**1b**. It appears of significance that the minor product *erythro*-**2b** was obtained in 18% ee of the (2*R*,3*S*)-isomer, while the major *threo*-**2b** in 74% ee of the (2*R*,3*R*)-isomer at 68% conversion of (±)-**1b**, the latter being recovered in 90% ee of the *S* isomer. Thus, relatively easy formation of the *erythro*-**2b** must arise from the fact that the chiral catalyst-control which strongly favors *si*-face of **1b** overrides threo-selectivity which is effected by the substrate (**1b**) chelation control. Having been obtained *erythro*-(2*R*,3*S*)-**2b**, it was concluded that the slow-reacting (*S*)-**1b** was consumed in forming *erythro*-**2b**, and in turn, diminished remarkably the relative rate ratio for the present kinetic resolution, k_R/k_S.

Acknowledgment. We are grateful to Dr. S. Akutagawa (Takasago Research Institute), Prof. H. Brunner (Regensburg University), and Drs. G. Prescher and J. Andrade (Degussa AG) for generous gifts of chiral phosphines and a rhodium complex. We deeply thank Dr. M. Miyazawa of this laboratory for a lot of HRMS measurements. The study was supported by a Grant-in-Aid for Special Project Research (No. 62215008) from the Ministry of Education, Japan, to which the authors' thanks are due.

Experimental Section

General

All melting points are uncorrected. ^1H NMR spectra were obtained on a JEOL FX-90Q (90 MHz) or Varian Gemini-200 (200 MHz) spectrometer with Me_4Si as an internal standard in $CDCl_3$. The former apparatus was used unless otherwise stated. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened). $^{13}C\{^1H\}$ NMR spectra were obtained on a JEOL FX-90Q spectrometer (22.5 MHz) with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a JEOL FX-90Q spectrometer (84 MHz) with trifluoroacetic acid as an external standard. $^{31}P\{^1H\}$ NMR spectra were obtained on a JEOL GSX-500 spectrometer with phosphoric acid as an external standard. IR spectra (neat or on a KBr disc) were recorded on a JASCO IRA-2 spectrometer. HRMS were obtained on a JEOL JSM-AX500 spectrometer. GLC was performed on a Shimazu GC-4CPT (analytical) or Varian 920 (preparative) gas chromatograph equipped with 15% silicone DC-550 or PEG-20M on 60/80 Uniport B column (3 mm x 3 m for analytical, 5 mm x 3 m for preparative), He or H_2 was used as a carrier gas. Column chromatography was performed by using Fuji Davison BW-820 or Daiso IR-60 silica gel. HPLC was performed on a Nihon Seimitsu Kagaku apparatus using a Si-60 column. Optical rotations were measured on a Yanako OR-50 polarimeter.

Materials

Substrates **1a-1e**[2], **1f**[12] and **1g**[11] were prepared according to the reported procedures. (*S*)-BINAP (2,2'-bis(diphenylphosphino)-1,1'-dinaphthyl), (*S*)-NORPHOS (2,3-bis(diphenylphosphino)-bicyclo[2.2.1]-hept-5-ene), [Rh(cod)(*R*)-DEGUPHOS]$^+BF_4^-$ (DEGUPHOS = *N*-benzyl-3,4-bis-(diphenylphosphino)-pyrrolidine) were donated by Takasago Research Institute, professor Henri Brunner and Degussa AG, respectively. (*S*)-SKEWPHOS (2,4-bis(diphenylphosphino)pentane) was prepared as reported.[17] (*R*)-DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) and (*S*)-CHIRAPHOS (2,3-bis(diphenylphosphino)butane) are commercially available. Catalyst precursor $[Rh(cod)L_2]^+ClO_4^-$[18] and $Ru(OAc)_2$-(*S*)-BINAP[13b] were prepared as reported previously. Freshly distilled methanol (from Mg) was used as the solvent.(+)-Eu(dppm)$_3$, (+)-tris[di(perfluoro-2-propoxypropionyl)methanato]europium(III), in Freon 113[19] was purchased from Dai-ichi Pure Chemicals Co.

Preparation of methyl α-[α-(diphenylphosphinylamino)benzyl]acrylate (1h)

To a mixture of *N*-benzylidene-diphenylphosphinamide[10] (3.28 g, 10.7 mmol) and methyl acrylate (7 mL, 78 mmol) was added DABCO (1,4-diazabicyclo[2.2.2]octane, 225 mg, 2 mmol), and the white suspension was stirred for 7 days at room temperature. The reaction to form **1h** proceeded very slowly in comparison to the preparation of **1a** or **1g**. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 *N* HCl, aq. $NaHCO_3$

and water. The organic phase was separated, dried ($MgSO_4$), and evaporated. The residue was then purified by silica gel column chromatography to give 2.20 g (5.6 mmol, 52%) of **1h** as a white powder. ^1H NMR δ 3.62 (s, 3H), 4.28 (dd, J = 8.4, 11 Hz, 1H), 5.09 (dd, J = 11, 11 Hz, 1H), 5.88 (s, 1H), 6.33 (s, 1H), 7.2-7.6 (m, 11H), 7.7-8.0 (m, 4H). ^{31}P NMR 22.8. IR (KBr) 3425, 1720, 1195 cm^{-1}. HRMS calcd for $C_{23}H_{22}O_3NP$ 391.1338, obsd 391.1342. mp 162.5-163.5 °C.

Enantioselective hydrogenation of methyl α-(methoxycarbonylaminomethyl)acrylate (1f)

The catalyst precursor ($5x10^{-3}$ mmol) was placed in a 50 mL-stainless autoclave under argon with a magnetic stirring bar. To this was added **1f** (0.5 mmol, 86.6 mg) dissolved in methanol (2.5 mL). The autoclave was purged 3-4 times with H_2, and appropriate pressure of H_2 was introduced, then the solution was stirred at room temperature. When the reaction finished (checked by GLC analysis), the solvent was evaporated and the metal complex was removed on a silica gel column (eluted with Et_2O) to give crude product in almost quantitative yield. The isomerized product, methyl β-(methoxycarbonylamino)methacrylate, was removed by preparative GLC to give pure methyl α-(methoxycarbonylaminomethyl)propionate **2f**. **2f**: ^1H NMR 1.18 (d, J = 7.2 Hz, 3H), 2.69 (ddq, J = 6.1, 6.1, 7.2 Hz, 1H), 3.22 (ddd, J = 2.6 Hz, 6.1 Hz, 14 Hz, 1H), 3.45 (ddd, J = 1.8, 6.1, 7.2 Hz, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 4.9-5.2 (br, 1H). ^{13}C NMR 14.7, 39.9, 43.5, 51.8, 52.1, 157.1, 175,6. IR (neat) 3300, 1710 cm^{-1}. HRMS calcd for $C_7H_{13}O_4N$ 175.0845, obsd 175.0847. (*E*)-methyl β-(methoxycarbonylamino)methacrylate: ^1H NMR 1.78 (d, J = 1.3 Hz, 3H), 3.74 (s, 3H), 3.82 (s, 3H), 6.53 (brd, J = 12 Hz, 1H), 7.80 (brd, J = 12 Hz, 1H). ^{13}C NMR 10.2, 51.6, 53.2, 106.1, 133.7, 153.3, 168.3. IR (KBr) 3300, 1750, 1650 cm^{-1}. HRMS calcd for $C_7H_{11}O_4N$ 173.0688, obsd 173.0682. (*Z*)-methyl β-(methoxycarbonylamino)methacrylate: ^1H NMR 1.82 (d, J = 1.2 Hz, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 7.14 (dq, J = 12, 1.2 Hz, 1H), 9.67 (br, 1H).

The enantiomeric excess of **2f** was determined by ^1H NMR (200 MHz) using (+)-Eu(dppm)$_3$ as an optishift reagent. At 20 mol% (+)-Eu(dppm)$_3$, the methoxy group (δ = 3.66) of (*R*) and (*S*)-**2f** shifted to 5.06 and 5.13 ppm, respectively.

The absolute configuration of **2f** was determined as follows. **2f** (65% ee) was treated with 6 equivalents of trimethylsilyl iodide in acetonitrile (reflux, 4 h). The reaction mixture was then passed through a silica gel column (with MeOH) to give α-methyl-β-alanine, $[\alpha]_D^{25}$ = -10.5° (c 0.82, MeOH). [*lit.*[20]: $[\alpha]_D^{25}$ = -32.4° (c 2.0, MeOH)].

Diastereoselective hydrogenation of methyl α-[α-(methoxycarbonylamino)alkyl]acrylate (1a-e)

The hydrogenation reaction was performed by the same procedure as for **1f**, using 1 mmol of substrate, 0.01 mmol of catalyst precursor and 5 mL of MeOH, stirring overnight at room temperature. After checking the conversion (by GLC analysis), the metal complex was removed on a silica gel column (eluted with Et_2O) to give a diastereomer mixture of methyl α-[α-(methoxycarbonylamino)alkyl]propionate **2**, whose ratio was determined by GLC analysis (the results were given in Table II). These two were separated by preparative GLC. Pd/C catalyzed hydrogenation [1 mol% in MeOH, 5 atm H_2, room temperature] gave, somewhat low, erythro selectivities (**2a**, 28 : 72; **2b**, 28 : 72; **2c**, 28 : 72; **2d**, 28 : 72; **2e**, 56 : 44). *threo*-**2a**: ^1H NMR 1.24 (d, J = 7.0 Hz, 3H), 2.93 (dq, J = 5.9, 7.0 Hz, 1H), 3.58 (s, 3H), 3.65 (s, 3H), 4.85 (dd, J = 5.9, 9.3 Hz, 1H), 5.98 (brd, J = 9.3 Hz, 1H), 7.27 (s, 5H). ^{13}C NMR 15.5, 45.1, 51.7, 52.2, 57.5, 126.2, 127.5, 128.5, 140.7,

156.6, 175.2. IR (neat) 3230, 1720, 1605 cm^{-1}. HRMS calcd for $C_{13}H_{17}O_4N$ 251.1157, obsd 251.1180. *erythro*-**2a**: ^1H NMR 1.16 (d, J = 7.0 Hz, 3H), 2.94 (dq, J = 7.0, 6.4 Hz, 1H), 3.59 (s, 3H), 3.65 (s, 3H), 4.99 (dd, J = 9.0, 6.4 Hz, 1H), 5.56 (brd, J = 9.0 Hz, 1H), 7.27 (s, 5H). ^{13}C NMR 13.3, 45.2, 51.7, 52.2, 57.3, 126.7, 127.6, 128.5, 139.9, 156.4, 174.0. IR (KBr) 3370, 1720 cm^{-1}. HRMS calcd for $C_{13}H_{17}O_4N$ 251.1157, obsd 251.1173. mp 88 - 89 °C. *threo*-**2b**: ^1H NMR 1.16 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 2.63 (dq, J = 4.3, 7.3 Hz, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.86 (ddq, J = 4.3, 16, 6.8 Hz, 1H), 5.28 (br, 1H). ^{13}C NMR 14.2, 19.3, 44.1, 49.0, 51.6, 52.0, 156.7, 175.4. IR (neat) 3350, 1710 cm^{-1}. HRMS calcd for $C_8H_{15}O_4N$ 189.1001, obsd 189.1051. *erythro*-**2b**: ^1H NMR 1.14 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 2.65 (dq, J = 5.1, 7.2 Hz, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 3.7-4.1 (m, 1H), 5.03 (d, J = 7.7 Hz, 1H). ^{13}C NMR 13.6, 17.4, 44.5, 49.1, 51.6, 52.0, 156.3, 174.5. IR (neat) 3350, 1710 cm^{-1}. HRMS calcd for $C_8H_{15}O_4N$ 189.1001, obsd 189.1023. *threo*-**2c**: ^1H NMR 0.92 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 7.3 Hz, 3H), 1.4-1.9 (m, 1H), 2.81 (dq, J = 4.3, 7.3 Hz, 1H), 3.45 (ddd, J = 4.3, 8.6, 10 Hz, 1H), 3.68 (s, 6H), 5.42 (brd, J = 10 Hz, 1H). ^{13}C NMR 15.8, 19.1, 19.9, 31.9, 40.4, 51.6, 52.1, 59.4, 159.8, 176.0. IR (neat) 3350, 1720 cm^{-1}. HRMS calcd for $C_{10}H_{19}O_4N$ 217.1314, obsd 217.1366. *erythro*-**2c**: ^1H NMR 0.88 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.6-2.0 (m, 1H), 2.77 (dq, J = 7.0, 7.0 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.9-4.1 (m, 1H), 4.70 (brd, J = 9.8 Hz, 1H). ^{13}C NMR 12.6, 17.3, 20.3, 30.4, 42.4, 51.7, 52.2, 58.2, 157.2, 175.1. IR (KBr) 3320, 1720, 1690 cm^{-1}. HRMS calcd for $C_{10}H_{19}O_4N$ 217.1314, obsd 217.1286. mp 87 - 88 °C. *threo*-**2d**: ^1H NMR 0.90 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.2-1.6 (m, 2H), 1.6-1.9 (m, 1H), 2.65 (dq, J = 3.9, 7.1 Hz, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.7-4.0 (m, 1H), 5.22 (brd, J = 9.9 Hz, 1H). ^{13}C NMR 14.5, 22.1, 23.1, 24.9, 43.2, 43.3, 51.5, 52.0, 157.1, 175.6. IR (KBr) 3320, 1730, 1685 cm^{-1}. HRMS calcd for $C_7H_{12}O_4N$ 174.0766, obsd 174.0762 (M-^{i}Bu); calcd for $C_7H_{14}O_2N$ 144.1024, obsd 144.1042 (M-MeCHCO$_2$Me). mp 47 - 48 °C. *erythro*-**2d**: ^1H NMR 0.91 (d, J = 6.4 Hz, 6H), 1.15 (d, J = 7.3 Hz, 3H), 1.1-1.3 (m, 2H), 2.62 (dq, J = 5.1, 7.3 Hz, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 3.6-4.1 (m, 1H), 4.80 (brd, J = 9.5 Hz, 1H). ^{13}C NMR 13.1, 21.7, 23.5, 25.0, 41.2, 44.4, 51.7, 52.1, 156.7, 174.8. IR (neat) 3330, 1720 cm^{-1}. HRMS calcd for $C_7H_{12}O_4N$ 174.0766, obsd 174.0835 (M-^{i}Bu); calcd for $C_7H_{14}O_2N$ 144.1024, obsd 144.1073 (M-MeCHCO$_2$Me). *threo*-**2e**: ^1H NMR 0.89 (s, 9H), 1.22 (d, J = 7.0 Hz, 3H), 2.87 (dq, J = 2.6, 7.0 Hz, 1H), 3.48 (dd, J = 2.6, 10 Hz, 1H), 3.67 (s, 3H), 3.69(s, 3H), 5.96 (brd, J = 10 Hz, 1H). ^{13}C NMR 17.6, 26.9, 35.9, 37.8, 51.7, 52.0, 62.5, 157.9, 177.0. IR (neat) 3420, 1725 cm^{-1}. HRMS calcd for $C_{10}H_{18}O_3N$ 200.1287, obsd 200.1290 (M-OMe); calcd for $C_7H_{12}O_4N$ 174.0766, obsd 174.0759 (M-^{t}Bu). *erythro*-**2e**: ^1H NMR 0.94 (s, 9H), 1.14 (d, J = 7.0 Hz, 3H), 2.69 (dq, J = 5.7, 7.0 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.98 (dd, J = 5.7, 11 Hz, 1H), 4.71 (brd, J = 11 Hz, 1H). ^{13}C NMR 13.8, 26.9, 35.6, 40.2, 51.8, 52.2, 59.8, 157.0, 175.9. IR (neat) 3340, 1715 cm^{-1}. HRMS calcd for $C_{10}H_{18}O_3N$ 200.1287, obsd 200.1290 (M-OMe); calcd for $C_7H_{12}O_4N$ 174.0766, obsd 174.0749 (M-^{t}Bu).

Diastereoselective hydrogenation of methyl α-[α-(phenylsulfonylamino)benzyl]acrylate (1g) and methyl α-[α-(diphenylphosphinylamino)benzyl]acrylate (1h)

The hydrogenation reaction was carried out by the same procedure as for **1f**, using 1 mmol of substrate, 0.02 mmol of catalyst precursor and 5 mL of MeOH. After stirring overnight under 30 atm H_2 at room temperature, the metal complex was removed on a silica gel column (elution: Et_2O for **1g**, AcOEt for **1h**) to give

a diastereomer mixture of **2** (see footnote 15), whose ratio was determined by the methoxy peak of ^{1}H NMR and HPLC analysis (elution: 1% IPA / hexane for **2g**, 10% IPA / hexane for **2h**). Pd/C catalyzed hydrogenation [1 mol% catalyst, 5 atm H_2, room temperature, overnight] gave rather low selectivities (**2g**, 40 : 60; **2h**, 53 : 47). *threo*-**2g**: ^{1}H NMR 1.15 (d, J = 7.0 Hz, 3H), 2.83 (dq, J = 6.0, 7.1 Hz, 1H), 3.56 (s, 3H), 4.53 (dd, J = 6.2, 9.0 Hz, 1H), 6.06 (d, J = 9.0 Hz, 1H), 7.0-7.4 (m, 8H), 7.6-7.7 (m, 2H). IR (neat) 3280, 1735, 1450 cm^{-1}. HRMS calcd for $C_{13}H_{12}O_2NS$ 246.0589, obsd 246.0550 (M-MeCHCO$_2$Me); calcd for $C_{11}H_{14}O_2N$ 192.1025, obsd 192.0978 (M-SO$_2$Ph). *erythro*-**2g**: ^{1}H NMR 1.16 (d, J = 7.0 Hz, 3H), 2.87 (dq, J = 6.6, 7.0 Hz, 1H), 3.47 (s, 3H), 4.57 (dd, J = 6.6, 9.0 Hz, 1H), 5.91 (d, J = 9.0 Hz, 1H), 7.0-7.4 (m, 8H), 7.6-7.7 (m, 2H). IR (neat) 3280, 1730, 1450 cm^{-1}. HRMS calcd for $C_{13}H_{12}O_2NS$ 246.0589, obsd 246.0561 (M-MeCHCO$_2$Me); calcd for $C_{11}H_{14}O_2N$ 192.1025, obsd 192.1052 (M-SO$_2$Ph). *threo*-**2h**: ^{1}H NMR (200 MHz) 1.26 (d, J = 7.1 Hz, 3H), 2.85 (dq, J = 6.0 Hz, 7.1 Hz, 1H), 3.62 (s, 3H), 4.27 (ddd, J = 6.0, 10.5, 10.5 Hz, 1H), 4.43 (dd, J = 10.5, 8.4 Hz, 1H), 7.1-7.5 (m, 11H), 7.6-7.9 (m, 4H). ^{31}P NMR 22.9. IR (KBr) 3445, 1730, 1190 cm^{-1}. HRMS calcd for $C_{19}H_{17}ONP$ 306.1048, obsd 306.0956 (M-MeCHCO$_2$Me); calcd for $C_{12}H_{10}OP$ 201.0470, obsd 201.0467 (Ph$_2$P=O). mp 194.0-194.5 °C. *erythro*-**2h**: ^{1}H NMR (200 MHz) 1.15 (d, J = 7.1 Hz, 3H), 3.08 (dq, J = 5.1, 7.1 Hz, 1H), 3.57 (s, 3H), 4.28 (dd, J = 8.4, 10.5 Hz, 1H), 4.39 (ddd, J = 5.1, 10.5, 10.5 Hz, 1H), 7.1-7.6 (m, 11H), 7.6-7.9 (m, 4H). ^{31}P NMR 23.7. IR (KBr) 3420, 1730, 1180 cm^{-1}. HRMS calcd for $C_{19}H_{17}ONP$ 306.1048, obsd 306.0976 (M-MeCHCO$_2$Me); calcd for $C_{12}H_{10}OP$ 201.0470, obsd 201.0420 (Ph$_2$P=O). mp 165-166 °C.

Determination of the relative configuration of 2a, 2b, and 2e

To a suspension of LiAlH$_4$ (91.1 mg, 2.4 mmol) in THF (5 mL) was added *threo*-**2a** (500 mg, 2 mmol) in THF (5 mL) at 0 °C and stirred for 3 h at 0 °C. After addition of drops of 2 *N* NaOH, obtained white solid was filtered off and washed successively with Et$_2$O to give 424 mg of crude product, which contains *trans*-3-phenyl-4-methyl-2-aza-δ-valerolactone and *trans*-2-methyl-3-(methoxycarbonylamino)propanol in a ratio 2 : 1. These two can be separated by preparative GLC. The relative configuration was determined by the vicinal coupling of the cyclic carbamate (J = 9.2 Hz). *trans*-3-phenyl-4-methyl-2-aza-δ-valerolactone: ^{1}H NMR 0.89 (d, J = 6.6 Hz, 3H), 1.8-2.3 (m, 1H), 4.04 (dd, J = 11, 10 Hz, 1H), 4.11 (d, J = 9.2 Hz, 1H) 4.27 (dd, J = 4.3, 11 Hz, 1H) 5.0-5.2 (br, 1H), 7.3-7.5 (m, 5H). ^{13}C NMR 12.9, 34.3, 62.5, 71.1, 126.9, 128.7, 129.0, 139.9, 153.7. IR (KBr) 3180, 1680 cm^{-1}. HRMS calcd for $C_{11}H_{13}O_2N$ 191.0946, obsd 191.0935.

Threo-**2b** was completely converted into *trans*-3,4-dimethyl-2-aza-δ-valerolactone with 2 equivalents of LiAlH$_4$ in Et$_2$O at 0 °C (88% yield). On the other hand, *erythro*-**2b** did not cyclize under the condition, yielding *cis*-2,3-dimethyl-3-(methoxycarbonylamino)propanol. The relative configuration was determined by the vicinal coupling constant of the *trans*-cyclic carbamate (J = 9.0 Hz). *trans*-3,4-dimethyl-2-aza-δ-valerolactone: ^{1}H NMR 0.97 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.5-1.9 (m, 1H), 3.15 (dq, J = 9.0, 6.3 Hz, 1H), 3.88 (dd, J = 10.7, 11 Hz, 1H), 4.16 (dd, J = 4.2, 11 Hz, 1H), 6.6-6.9 (br, 1H). ^{13}C NMR 12.9, 20.4, 33.4, 53.0, 71.3, 154.6. IR (KBr) 3230, 1685 cm^{-1}. *cis*-2,3-dimethyl-3-(methoxycarbonylamino)propanol: ^{1}H NMR 0.73 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.6-2.1 (m, 1H), 3.2-3.6 (m, 3H), 3.68 (s, 3H), 3.9-4.3 (m, 1H), 4.80 (brd, 1H).

Threo-**2e** was also cyclized (Et$_2$O, 0 °C, 5-6 h) completely to the corresponding cyclic carbamate. From *erythro*-**2e**, mixture of *cis*-cyclic carbamate and carbamate-alcohol (6 : 4) obtained under these conditions. The

relative configuration was determined from the comparison of chemical shifts of methyl group in the cyclic carbamate; the methyl doublet in *cis*-cyclic carbamate shifts to upfield because of the electronic effect of the carbonyl group. Furthermore, the vicinal coupling constant of *cis*-cyclic carbamate (J = 1.8 Hz) strongly suggests the configuration. *trans*-3-*t*-butyl-4-methyl-2-aza-δ-valerolactone (69% yield) ^{1}H NMR 0.98 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 1.9-2.1 (m, 1H), 3.5-3.9 (m, 3H), 6.4-6.5 (br, 1H). *cis*-3-*t*-butyl-4-methyl-2-aza-δ-valerolactone (33% yield) ^{1}H NMR 0.78 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H), 2.0-2.3 (m, 1H), 3.20 (dd, J = 8.7, 12 Hz, 1H), 3.40 (dd, J = 5.5, 12 Hz, 1H), 4.02 (dd, J = 1.8, 11 Hz, 1H), 5.8-5.9 (br, 1H). The relative configurations of **2** can also be determined by converting them to β-lactam[2].

Kinetic resolution of methyl α-[α-(methoxycarbonylamino)alkyl]acrylate (1a-d)

Hydrogenation was performed by the same procedure as the diastereoselective hydrogenation of **1a-e** using chiral catalyst precursor. At appropriate conversion (by GLC analysis), the solvent was removed *in vacuo*. The metal complex was removed through a silica gel column to give the mixture of **1**, *threo*-**2** and *erythro*-**2**, whose ratio (i.e., the conversion and the threo / erythro ratio) was determined by GLC. The mixture was treated with dimethylamine (3 mL of 2.1 N solution in Et_2O) at room temperature for 12 h and excess dimethylamine and Et_2O were evaporated. The residue was separated by silica gel column chromatography to give a diastereomer mixture of **2** (eluted with Et_2O) and dimethylamine adduct of **1** (with AcOEt / MeOH, ca. 1 : 1 mixture of diastereomers). The latter was treated with methyl iodide (0.2 mL in 1.2 mL MeOH, -30 °C – room temperature, 15 h), and evaporated to give the ammonium salt, which was then treated with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) [76.1 mg (0.5 mmol), in acetone (1 mL), room temperature, 8 h] to regenerate **1**. The yield of **1** + **2** was usually quantitative.

The enantiomeric excesses of **1a-d** recovered were determined by ^{1}H NMR of methoxy groups in the carbamate using Eu(dppm)$_3$ as a optishift reagent. **1a**: (*S*) 5.23 ppm, (*R*) 4.98 ppm (23 mol%); **1b**: (*S*) 5.08 ppm, (*R*) 4.85 ppm (25 mol%); **1c**: (*S*) 4.43 ppm, (*R*) 4.32 ppm (12 mol%); **1d**: (*S*) 4.80 ppm, (*R*) 4.45 ppm (33 mol%).

The relative rate ratios (k_R/k_S), given in Tables III and IV, were calculated according to the following equation:[21]

$$\text{relative rate ratio} = \ln(1 - C)(1 - ee)/\ln(1 - C)(1 + ee)$$

[C = conversion, ee = enantiomeric excess of the substrate recovered]

Determination of the absolute configuration of 1a

Separated **1a** (1 mmol, 260 mg, 60% ee) was hydrogenated ([Rh(cod)(dppb)]$^+$ClO$_4^-$ 1 mol%, 30 atm H_2, room temperature, 17 h) to give *threo*-**2a** quantitatively, $[\alpha]_D^{25}$ = +39.5° (c 5.2, EtOH). The latter was added to $LiAlH_4$ (1.2 mmol) suspended in Et_2O at 0 °C. After stirring for 2 h, drops of 2 N NaOH were added, and obtained white solid was filtered off. The solid was well washed with ether and the combined ether solution was evaporated to give 160 mg (0.7 mmol) of *trans*-2-methyl-3-phenyl-3-(methoxycarbonylamino)propanol. ^{1}H NMR 0.93 (d, J = 7.0 Hz, 3H), 1.7-2.2 (m, 1H), 2.7-2.9 (br, 1H), 3.3-3.9 (m, 2H), 4.60 (dd, J = 9.0, 9.0 Hz, 1H), 5.64 (brd, J = 9.0 Hz, 1H), 7.1-7.5 (m, 5H).

The alcohol was mixed with pyridine (0.17 mL, 2.1 mmol) in 1.5 mL of CH_2Cl_2, then *p*-toluenesulfonyl chloride (200 mg, 1.05 mmol) was added portionwise at 0 °C, and the solution was stirred at the temperature for

4 h. After usual workup, 254 mg (0.67 mmol) of corresponding tosylate was obtained. ^{1}H NMR 0.86 (d, J = 6.8 Hz, 3H), 1.9-2.5 (m, 1H), 2.46 (s, 3H), 3.61 (s, 3H), 3.90 (dd, J = 5.2, 9.7 Hz, 1H), 4.02 (dd, J = 5.0, 9.7 Hz, 1H), 4.54 (dd, J = 8.4, 8.8 Hz, 1H), 5.15 (brd, J = 8.8 Hz, 1H), 7.0-7.4 (m, 7H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR 14.3, 21.6, 38.3, 52.1, 57.6, 72.2, 126.7, 127.5, 128.0, 128.6, 129.9, 133.0, 140.3, 144.8, 156.4. IR (KBr) 1755, 1685 cm^{-1}.

The tosylate was added to $LiAlH_4$ (113.9 mg, 3 mmol) in THF (1 mL) at 0 °C and stirred overnight at room temperature. After workup as above and purification by silica gel column chromatography (eluent: Et_2O / hexane = 1 / 1), 58.2 mg (0.36 mmol) of (α-isopropylbenzyl)methylamine was obtained. ^{1}H NMR 0,75 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.3-1.6 (br, 1H), 1.6-2.1 (m, 1H), 2.23 (s, 3H), 3.19 (d, J = 7.0 Hz, 1H), 7.1-7.5 (m, 5H). ^{13}C NMR 19.5, 19.7, 34.3, 34.9, 72.0, 126.8, 128.0, 128.1, 142.8. IR (neat) 3300, 1600 cm^{-1}. $[\alpha]_D^{25}$ = +30.6° (c 1.16, C_6H_{12}) [*lit.*[22]) $[\alpha]_D^{25}$ = + 5.1° (*neat*)]

Determination of the optical purities of *threo*-2b and *erythro*-2b obtained from the kinetic resolution

Separated ***erythro*-2b** was reduced with $LiAlH_4$ (see above) and the alcohol obtained was converted to MTPA[23]) ester (3 equiv of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 7 equiv of pyridine in CH_2Cl_2). The diastereomer ratio of the latter was determined to be 59 : 41 from the measurement of ^{19}F NMR. *erythro*-2,3-dimethyl-3-(methoxycarbonylamino)propyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate [mixture of (2*S*,3*R*) and (2*R*, 3*S*)]: ^{1}H NMR 0.92 (d, J = 7.2 Hz, 3H), 1.06 and 1.09 (d, J = 6.8 Hz, 3H), 1.8-2.2 (m, 1H), 3.55 (q, J = 1.1 Hz, 3H), 3.63 and 3.64 (s, 3H), 3.6-4.0 (m, 1H), 4.0-4.4 (m, 2H), 4.56 (brd, 1H), 7.3-7.6 (m, 5H). ^{19}F NMR -4.29 for (2*S*, 3*R*), -4.36 for (2*R*, 3*S*).

A sample of ***threo*-2b** (69 mg, 0.37 mmol) was epimerized at C-2 position (0.5 mmol NaH in DMF, room temperature, 30 min) to give 43 : 57 mixture of ***threo*-2b** and ***erythro*-2b**, which were separated by HPLC (elution: 1.5% IPA / hexane) to give 11.2 mg of ***erythro*-2b**. The enantiomer ratio of the latter was determined to be 13 : 87 by the same procedure as described above.

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