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Catalytic Asymmetric Hydrogenation of α-(Acetamido)acrylates Using TRAP Trans-Chelating Chiral Bisphosphine Ligands: Remarkable Effects of Ligand *P*-Substituent and Hydrogen Pressure on Enantioselectivity

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The catalytic asymmetric hydrogenation of α-(acetamido)acrylates was carried out with the rhodium complexes prepared from $[Rh(cod)_2]BF_4$ and trans-chelating chiral bisphosphine ligands, (*S*,*S*)-2,2′-bis[(*R*)-1-(dialkylphosphino)ethyl]-1,1′-biferrocenes [(*R*,*R*)-(*S*,*S*)-TRAPs]. In the reaction of β-unsubstituted or β-monosubstituted α-(acetamido)acrylates [(*E*)-$RCH{=}C(NHAc)CO_2Me$], the selectivity for (*R*)-hydrogenation product increased with decreasing steric demand of the substrate β-substituent and the ligand *P*-substituent as well as decreasing hydrogen pressure. The selectivity for the (*R*)-product in the reaction with EtTRAP–rhodium catalyst at 60 °C and 0.5 $kg\,cm^{-2}$ of hydrogen pressure was as follows: R = H, 96% ee; R = Me, 92% ee; R = Ph, 77% ee; R = *i*-Pr, 57% ee. The remarkable steric and pressure effects caused a dramatic reversal of enantioselectivity in the reaction of methyl 2-(*N*-acetylamino)cinnamate (R = Ph). For example, the selectivity of 87% (*R*) with EtTRAP at 60 °C and 0.1 $kg\,cm^{-2}$ of hydrogen pressure has reversed to 92% (*S*) with *i*-BuTRAP at 15 °C and atmospheric hydrogen pressure. Hydrogenation of the β,β-disubstituted α-(acetamido)acrylates proceeded smoothly at 15 °C and atmospheric hydrogen pressure with high enantioselectivity in favor of the 2*S*-isomers when EtTRAP or BuTRAP was employed as the chiral ligand.

Asymmetric hydrogenation of α-(*N*-acylamino)acrylic acid derivatives catalyzed by a chiral rhodium complex has provided a useful method for preparation of optically active α-amino acids.[1] Various chiral ligands designed and synthesized for development of transition metal catalyzed asymmetric reactions have been often assessed with the historical and monumental asymmetric hydrogenation. Most of the efficient chiral ligands thus developed are chelate bisphosphines, which can be classified into the following three categories (Fig. 1): (i) Bisphosphines, in which the two phosphorus atoms, each bearing two achiral rigid and bulky substituents, are connected with a chiral backbone, as represented by BINAP[2] and DIOP[3,4] (Fig. 1a); (ii) Bisphosphines, in which two chiral phosphacycloalkanes are connected with an achiral tether, as represented by DuPHOS[5,6] (Fig. 1b); (iii) Bisphosphines, in which the two chiral phosphines with chiral center on the phosphorus are connected with an achiral tether, as represented by BisP*[7] and DIPAMP[8] (Fig. 1c). The common features of these ligands are that the two phosphorus atoms coordinate to a metal center to form a cis-chelating bisphosphine–metal complex and, upon the coordination, their rigid ligand *P*-substituents create a C_2 symmetrical chiral environment which shields two diagonal quadrants around the metal center.[9]

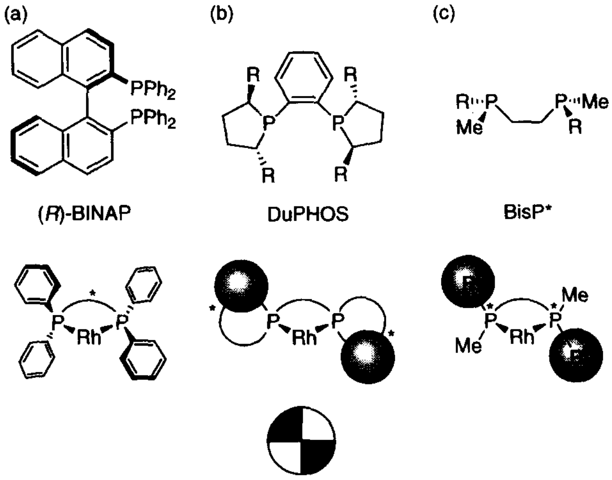
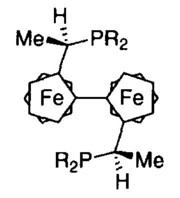


Fig. 1. Three categories of chiral bisphosphine ligands for asymmetric catalysis.

We have prepared a new class of chiral bisphosphine ligands, (*S*,*S*)-2,2′-bis[(*R*)-1-(dialkylphosphino)ethyl]-1,1′-biferrocenes [abbreviated to (*R*,*R*)-(*S*,*S*)-TRAPs,[10] Chart 1].[11,12] The TRAP ligands share a common feature with the ligands of category (i) in that they have a (C_2 symmetric) chiral backbone connecting two achiral diaryl- or dialkylphosphino groups, but differ from any other chiral bisphosphines so far prepared in that they can form *trans*-chelating metal com-



(*R,R*)-(*S,S*)-TRAP

R = Et: EtTRAP
R = Pr: PrTRAP
R = Bu: BuTRAP
R = *i*-Bu: *i*-BuTRAP
R = *i*-Pr: *i*-PrTRAP
R = Ph: PhTRAP
R = 2-Furyl: FurTRAP

Chart 1. Structure of TRAP ligands.

plexes, as shown by the X-ray crystal structure of *trans*-[RhCl(CO){(*R,R*)-(*S,S*)-BuTRAP}] (Fig. 2).[11c] By virtue of the trans-chelation, the chiral biferrocenyl backbone as well as the *P*-substituents contributes directly to the formation of the chiral surroundings around the metal center, unlike the conventional cis-chelating chiral bisphosphine ligands. Consequently, steric bulkiness and rigidity of the *P*-substituents are basically no longer requisite for stereocontrol in an asymmetric reaction, so that the trans-chelating chiral lignands bearing even primary alkyl substituents on the phosphorus may make a high enantioselection possible for some catalytic asymmetric reactions.[13] However, choice of the *P*-substituents will be essential for designing a highly enantioselective reaction. This report describes the rhodium-catalyzed asymmetric hydrogenation of α-(acetamido)acrylates using TRAPs, in which the structural tuning of the ligand *P*-substituents can remarkably influence enantioselectivity as well as catalytic activity.[14] Finally, highly enantioselective hydrogenation of unsymmetrically β,β-disubstituted α-(acetamido)acrylates was achieved by proper choice of TRAP ligands, providing optically active *erythro*- and *threo*-β-alkylated α-amino acids, diastereospecifically.[7,15]

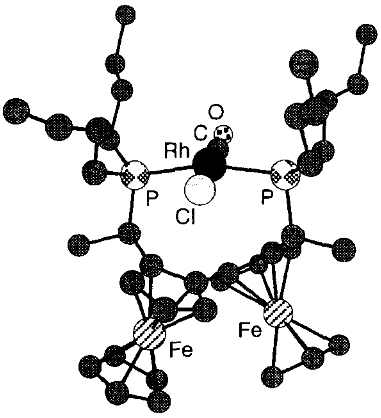
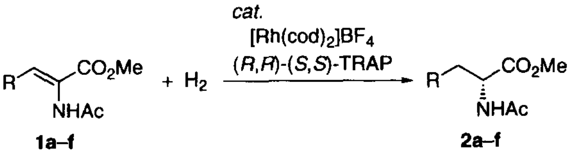


Fig. 2. X-ray crystal structure of *trans*-[RhCl(CO){(*R,R*)-(*S,S*)-BuTRAP)].

Results and Discussion

Asymmetric Hydrogenation of β-Unsubstituted and β-Monosubstituted α-(Acetamido)acrylates. Results of the asymmetric hydrogenations of methyl 2-(*N*-acetylamino)acrylate (**1a**) using 0.01 molar equivalent of $[Rh(cod)_2]BF_4$–(*R,R*)-(*S,S*)-TRAP catalysts (Eq. 1, R = H) are shown in Entries 1—9 in Table 1.



(1)

The highest enantioselectivity [96% ee (*R*)] for the reaction of **1a** was attained when EtTRAP was used in 1,2-dichloroethane at 60 °C and 0.5 $kg\,cm^{-2}$ of partial hydrogen pressure ($H_2 : N_2 = 1 : 1$) (Entry 1). It is important that the employment of hydrogen pressure of 1.0 $kg\,cm^{-2}$ and of 100 $kg\,cm^{-2}$ for the hydrogenation gave 70% ee and 2% ee, respectively (Entries 2 and 3). Besides the drastic hydrogen pressure effect, the ligand *P*-substituent also influenced the enantioselectivity to a great extent. The selectivity decreased significantly with increasing length of the ligand *P*-alkyl chain: Pr- and BuTRAPs afforded (*R*)-**2a** with 85% and 66% ee, respectively (Entries 4 and 5). The branch of the *P*-alkyl group at the β-position caused a drastic de-

Table 1. Catalytic Asymmetric Hydrogenation of **1**[a)]

Entry	R (**1**)	TRAP	$P(H_2)/kg\,cm^{-2}$	Product (**2**)	ee[b)]/%	Confign.
1	H (**1a**)	EtTRAP	0.5	**2a**	96	*R*
2	H (**1a**)	EtTRAP	1.0	**2a**	70	*R*
3	H (**1a**)	EtTRAP	100	**2a**	2	*R*
4	H (**1a**)	PrTRAP	0.5	**2a**	85	*R*
5	H (**1a**)	BuTRAP	0.5	**2a**	66	*R*
6	H (**1a**)	*i*-BuTRAP	0.5	**2a**	8	*S*
7	H (**1a**)	*i*-PrTRAP	0.5	**2a**	5	*S*
8	H (**1a**)	PhTRAP	0.5	**2a**	21	*S*
9	H (**1a**)	FurTRAP	0.5	**2a**	60	*S*
10	Me (**1b**)	EtTRAP	0.5	**2b**	92	*R*
11	Et (**1c**)	EtTRAP	0.5	**2c**	91	*R*
12	*i*-Bu (**1d**)	EtTRAP	0.5	**2d**	88	*R*
13	Ph (**1e**)	EtTRAP	0.5	**2e**	77	*R*
14	*i*-Pr (**1f**)	EtTRAP	0.5	**2f**	57	*R*

a) All reactions were carried out in 1,2-dichloroethane at 60 °C for 24 h. **1** : $[Rh(cod)_2]BF_4$: (*R,R*)-(*S,S*)-TRAP = 100 : 1 : 1.1. Complete conversion to **2** was observed in all cases.
b) Determined by chiral HPLC analysis.

crease in enantioselectivity, giving **2a** with 8% ee (*S*) (Entry 6). The hydrogenation using *i*-PrTRAP, which carries larger and rigid substituents on the phosphorus atoms, also gave nearly racemic **2a** (Entry 7). The TRAP ligands with *P*-aryl substituents (PhTRAP, FurTRAP) showed low to moderate selectivities for the (*S*)-product (Entries 8 and 9). The sense of enantioselection with the arylTRAPs is opposite to that with the ligand bearing linear alkyl *P*-substituents.

Next we examined the hydrogenation of β-monosubstituted α-(acetamido)acrylates (**1b**—**f**) with the chiral EtTRAP–rhodium catalyst. The hydrogenations of **1b**—**d**, which bear a primary alkyl group at the β-position, yielded (*R*)-**2b**—**d** with 92%, 91%, and 88% ee, respectively (Entries 10—12). The enantioselectivity decreased with increasing in bulkiness of the β-substituent of **1** under the identical conditions: **1e**, 77% ee; **1f**, 57% ee (Entries 13 and 14).

Further optimization of the conditions was carried out for the asymmetric hydrogenation of **1e** using TRAP ligands (Table 2). Unusual temperature effect on the enantioselectivity was observed in the reaction with EtTRAP–rhodium catalyst at 1.0 kg cm^{-2} of hydrogen pressure (Entries 1—4). The maximum enantioselectivity (70% ee) was observed at the reaction temperature of 60 °C. Lowering the temperature reduced the enantioselectivity significantly. These results may suggest that two or more reaction pathways compete with each other in the catalytic asymmetric hydrogenation using EtTRAP–rhodium complex. The change of the reaction solvent to THF or *i*-PrOH did not affect the enantioselectivity significantly, but the use of MeOH resulted in the formation of (*R*)-**2e** with only 18% ee (Entries 3 and 5—7).

The effect of the hydrogen pressure was dramatic. Decrease in the hydrogen pressure was favorable for the formation of **2e** with *R*-configuration (Entries 8 and 9). The reaction at 0.1 kg cm^{-2} of partial hydrogen pressure proceeded slowly, but gave (*R*)-**2e** with 87% ee (Entry 9). To our surprise, the opposite enantiomer with 69% ee was obtained from the hydrogenation at 100 kg cm^{-2} using the identical catalyst (Entry 10). In contrast to the hydrogenation at 1.0 kg cm^{-2}, lowering the reaction temperature and the use of MeOH under the high pressure conditions showed slight increases in the selectivity for (*S*)-product (Entries 11 and 12).

Effect of the ligand *P*-substituent in the hydrogenation of **1e** was also examined at 1.0 kg cm^{-2} of hydrogen pressure (Entries 3, 13, 14, and 17—19). (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP was found to be the most effective, giving (*S*)-**2e** with 84% ee at 30 °C (Entry 14) and with 92% ee at 15 °C (Entry 15). Note that use of this ligand gave a nearly racemic product in the reaction of **1a** (Table 1, Entry 6). It is also noteworthy that *i*-BuTRAP ligand presented the chiral sense of enantioselection opposite to that with EtTRAP under the same conditions. The hydrogen pressure hardly affected the enantioselectivity in the reaction with *i*-BuTRAP (Entries 14 and 16). The hydrogenation of **1e** using *i*-PrTRAP at 1.0 kg cm^{-2} was sluggish (Entry 17). The low activity of *i*-PrTRAP–rhodium catalyst seems to be due to steric repulsion between the *P*-isopropyl group and β-phenyl group of

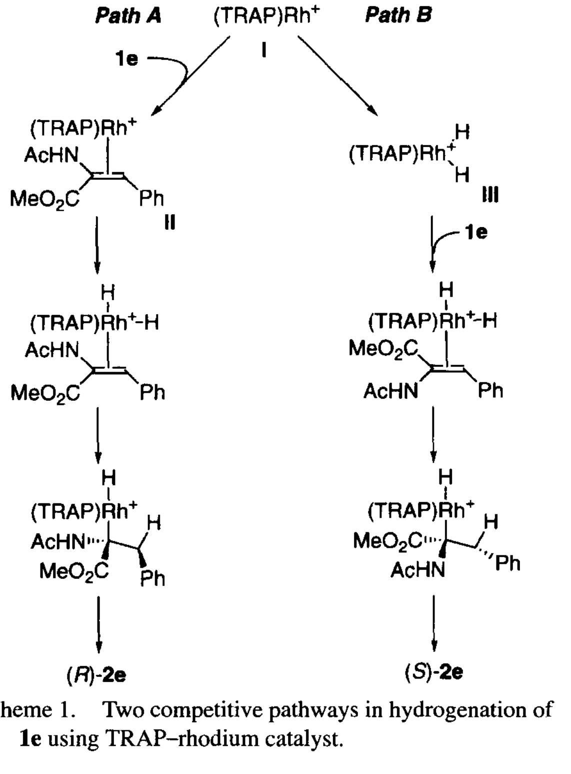
Table 2. Catalytic Asymmetric Hydrogenation of **1e**[a)]

Entry	TRAP	Solvent	$P(H_2)$/kg cm^{-2}	Temp/°C	Convn.[b)]/%	ee[c)]/%	Confign.
1	EtTRAP	$ClCH_2CH_2Cl$	1.0	80	100	68	*R*
2	EtTRAP	$ClCH_2CH_2Cl$	1.0	60	100	70	*R*
3	EtTRAP	CH_2Cl_2	1.0	30	100	64	*R*
4	EtTRAP	CH_2Cl_2	1.0	15	100	36	*R*
5	EtTRAP	THF	1.0	30	100	61	*R*
6	EtTRAP	*i*-PrOH	1.0	30	100	52	*R*
7	EtTRAP	MeOH	1.0	30	100	18	*R*
8	EtTRAP	$ClCH_2CH_2Cl$	0.5	60	100	77	*R*
9	EtTRAP	$ClCH_2CH_2Cl$	0.1	60	44	87	*R*
10	EtTRAP	CH_2Cl_2	100	30	100	69	*S*
11	EtTRAP	CH_2Cl_2	100	15	100	77	*S*
12	EtTRAP	MeOH	100	30	100	79	*S*
13	BuTRAP	CH_2Cl_2	1.0	30	100	42	*R*
14	*i*-BuTRAP	CH_2Cl_2	1.0	30	100	84	*S*
15	*i*-BuTRAP	CH_2Cl_2	1.0	15	100	92	*S*
16	*i*-BuTRAP	CH_2Cl_2	100	30	100	83	*S*
17	*i*-PrTRAP	CH_2Cl_2	1.0	30	22	46	*R*
18	PhTRAP	CH_2Cl_2	1.0	30	100	34	*R*
19	FurTRAP	CH_2Cl_2	1.0	30	100	80	*S*
20	BuTRAP	MeOH	100	30	100	78	*S*
21	*i*-BuTRAP	MeOH	100	30	100	71	*S*
22	*i*-PrTRAP	MeOH	100	30	100	7	*S*
23	PhTRAP	MeOH	100	30	77	6	*R*
24	FurTRAP	MeOH	100	30	100	3	*R*

a) All reactions were carried out for 24 h. **1e** : $[Rh(cod)_2]BF_4$: (*R*,*R*)-(*S*,*S*)-TRAP = 100 : 1 : 1.1. No by-products were detected by ^1H NMR analysis of the crude product in all cases. b) Determined by ^1H NMR analysis of the crude product. c) Determined by chiral HPLC analysis.

1e upon olefin coordination. (*R*,*R*)-(*S*,*S*)-FurTRAP–rhodium catalyst also produced (*S*)-**1e** with good selectivity (80% ee), while (*R*,*R*)-(*S*,*S*)-PhTRAP gave (*R*)-product with low enantiomeric excess (Entries 18 and 19). For the reaction at 100 kg cm^{-2} of hydrogen pressure in MeOH, the enantioselectivity decreased with increasing steric bulkiness of the ligand *P*-substituent (Entries 12 and 20—24).

Mechanistic Consideration. As mentioned above, the unusual temperature effect on enantioselectivity suggests that two or more competitive reaction pathways exist in the asymmetric hydrogenation of **1e** catalyzed by EtTRAP–rhodium complex. The remarkable effect of hydrogen pressure may be explained on the basis of the assumption that the hydrogenation of **1e** proceeds through the two competitive pathways, Path A and Path B, as shown in Scheme 1. Path A involves the coordination of olefin to (*R*,*R*)-(*S*,*S*)-EtTRAP–rhodium(I) complex **I** followed by the oxidative addition of hydrogen, giving (*R*)-**2e** preferentially. This pathway is similar to the mechanism of the rhodium-catalyzed hydrogenation of enamide using cis-chelating bisphosphine ligands.[16] Path B, which is generally accepted for the hydrogenation of olefins using Wilkinson's [RhCl(PPh$_3$)$_3$] catalyst,[17] involves the oxidative addition of hydrogen prior to the coordination of **1e**, favoring the formation of (*S*)-**2e**. Decrease in the hydrogen pressure suppresses Path B, because low hydrogen pressure is unfavorable for the oxidative addition of hydrogen forming **III**. Indeed, (*R*)-products were obtained with higher enantiomeric excesses in the hydrogenation at lower hydrogen pressure. On the other hand, the hydrogenation of **1e** at 100 kg cm^{-2} prefers Path B to Path A, because the dihydride complex **III** is easily formed under the high hydrogen pressure. Accordingly, the reactions in Entries 10—12 of Table 2 yielded the (*S*)-enantiomer with good enantiomeric excesses (up to 79% ee). Although the reverse of enantioselectivity in asymmetric hydrogenation of **1** under high hydrogen pressure has been reported previously by other groups,[18] the present results provide an unambiguous example.



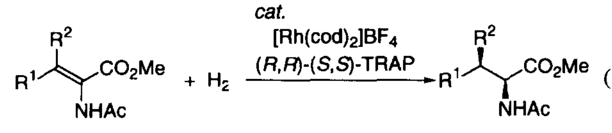
Scheme 1. Two competitive pathways in hydrogenation of **1e** using TRAP–rhodium catalyst.

The observed effect of the substrate *β*-substituent in the asymmetric hydrogenation of **1** using EtTRAP–rhodium complex may support the two competitive mechanisms. The Path A is not favored by sterically congested *β*-substituent on the substrate, because the steric repulsion between the chiral ligand and the substituent prevents the olefin coordination. Thus, in the reactions with substrates bearing a larger *β*-substituent, Path A is competitive with Path B. Consequently, the (*R*)-product is obtained in low enantioselectivity.

The hydrogenation catalyzed by *i*-BuTRAP–rhodium complex proceeds via Path B even at atmospheric pressure of hydrogen, because the large *P*-substituents of *i*-BuTRAP encumber the olefin coordination. The small effect of hydrogen pressure may explain why *i*-BuTRAP–rhodium catalyst prefers the oxidative addition of hydrogen prior to the olefin coordination (Path B).

Asymmetric Hydrogenation of *β*,*β*-Disubstituted *α*-(Acetamido)acrylates. On the basis of the aforementioned mechanistic considerations, we reasoned that the hydrogenation of more congested olefins, *β*,*β*-disubstituted *α*-(acetamido)acrylates (**3**), would proceed via Path B predominantly when the TRAP–rhodium complex is used as a catalyst, resulting in the preferential formation of *β*-branched *α*-(*N*-acetyl)amino acid ester **4** with 2*S*-configuration.

The catalytic asymmetric hydrogenations of **3** were carried out for 24 h at atmospheric pressure of hydrogen in the presence of 0.01 molar equivalent of TRAP–rhodium catalyst (Eq. 2, Table 3).



(2)

3a–g **4a–g**

3a: R^1 = R^2 = Me
3b: R^1, R^2 = -(CH$_2$)$_5$-
(*E*)-**3c**: R^1 = Me, R^2 = Ph
(*E*)-**3d**: R^1 = Me, R^2 = *p*-MeO-C$_6$H$_4$
(*E*)-**3e**: R^1 = Me, R^2 = *p*-F-C$_6$H$_4$
(*E*)-**3f**: R^1 = Et, R^2 = Ph
(*Z*)-**3c**: R^1 = Ph, R^2 = Me
(*Z*)-**3d**: R^1 = *p*-MeO-C$_6$H$_4$, R^2 = Me
(*Z*)-**3e**: R^1 = *p*-F-C$_6$H$_4$, R^2 = Me
(*Z*)-**3f**: R^1 = Ph, R^2 = Et
(*Z*)-**3g**: R^1 = *t*-Bu, R^2 = Me

Some TRAP–rhodium complexes provided good catalytic activity and high enantioselectivity for the hydrogenation of methyl 2-(*N*-acetylamino)-3-methyl-2-butenoate (**3a**) under the mild conditions. The chiral ligands bearing linear alkyl *P*-substituents, Et-, Pr-, and BuTRAPs, gave *N*-acetylvaline methyl ester (**4a**) with 83%, 88%, and 88% ee (Entries 1—3).

Table 3. Catalytic Asymmetric Hydrogenation of **3**[a]

Entry	Substrate (**3**)	TRAP	Solvent	Convn.[b]/%	Product (**4**)	ee[c]/%	Confign.
1[d]	**3a**	EtTRAP	*i*-PrOH	100	**4a**	83	*S*
2[d]	**3a**	PrTRAP	*i*-PrOH	100	**4a**	88	*S*
3[d]	**3a**	BuTRAP	*i*-PrOH	100	**4a**	88	*S*
4[d]	**3a**	*i*-BuTRAP	*i*-PrOH	0	**4a**	–	–
5[d]	**3b**	BuTRAP	*i*-PrOH	100	**4b**	78	*S*
6	(*E*)-**3c**	BuTRAP	*i*-PrOH	100	*erythro*-**4c**	80	(2*S*,3*S*)
7	(*E*)-**3c**	EtTRAP	*i*-PrOH	67	*erythro*-**4c**	56	(2*S*,3*S*)
8	(*E*)-**3d**	BuTRAP	*i*-PrOH	84	*erythro*-**4d**	80	(2*S*,3*S*)
9	(*E*)-**3e**	BuTRAP	*i*-PrOH	100	*erythro*-**4e**	79	(2*S*,3*S*)
10	(*E*)-**3f**	BuTRAP	*i*-PrOH	100	*erythro*-**4f**	77	(2*S*,3*S*)
11	(*Z*)-**3c**	BuTRAP	CH_2Cl_2	100	*threo*-**4c**	78	(2*S*,3*R*)
12	(*Z*)-**3c**	EtTRAP	CH_2Cl_2	100	*threo*-**4c**	85	(2*S*,3*R*)
13	(*Z*)-**3d**	EtTRAP	CH_2Cl_2	100	*threo*-**4d**	85	(2*S*,3*R*)
14	(*Z*)-**3e**	EtTRAP	CH_2Cl_2	100	*threo*-**4e**	83	(2*S*,3*R*)
15	(*Z*)-**3f**	EtTRAP	CH_2Cl_2	100	*threo*-**4f**	86	(2*S*,3*R*)
16	(*Z*)-**3g**	EtTRAP	CH_2Cl_2	100	*threo*-**4g**	86	(2*S*,3*R*)

a) Reactions were carried out at 15 °C and atmospheric pressure of hydrogen for 24 h unless otherwise noted. **3** : $[Rh(cod)_2]BF_4$: (*R*,*R*)-(*S*,*S*)-TRAP = 100 : 1 : 1.1. No by-products were detected by ^1H NMR analysis of the crude product in all cases. b) Determined by ^1H NMR analysis of the crude product. c) Determined by chiral HPLC analysis. d) At 0 °C.

As we expected, the product **4a** turned out to have *S*-configuration. The solvent effect was negligible (CH_2Cl_2, 85% ee; THF, 86% ee; *i*-PrOH, 87% ee; MeOH, 84% ee at 15 °C with BuTRAP). The hydrogen pressure did not have much effect on the enantioselectivity (0.5 kg cm^{-2} of partial pressure, 87% ee; 100 kg cm^{-2}, 75% ee at 15 °C). No reaction took place with *i*-BuTRAP–rhodium complex, whose β-branches of the *P*-substituents seemed to encumber the coordination of **3a** to the rhodium atom (Entry 4). β-Cyclic substrate **3b** was reduced to cyclohexylglycine derivative (*S*)-**4b** with 78% ee (Entry 5).

Finally, enantioselective hydrogenation of α-(acetamido)acrylate **3** bearing two different β-substituents provided an efficient method for the synthesis of optically active β-alkylated α-amino acids with vicinal stereogenic centers. The (*R*,*R*)-(*S*,*S*)-TRAP–rhodium catalysts were successfully applicable to the asymmetric hydrogenations of both (*E*)- and (*Z*)-2-(*N*-acetylamino)-3-phenyl-2-butenoate (**3c**). The hydrogenations of (*E*)- and (*Z*)-**3c** produced specifically *erythro*- and *threo*-*N*-acetyl-β-methylphenylalanine methyl ester (**4c**), respectively, as expected from cis hydrogen addition to olefin (Entries 6, 7, 11, and 12). The configurations at the 2-position of the both products were identical, indicating that the geometry of the two β-substituents does not influence the enantioface-selection of **3c**. The (*E*)-olefin was hydrogenated in higher enantioselectivity with BuTRAP than with EtTRAP (Entries 6 and 7), and *i*-PrOH was superior to CH_2Cl_2 (CH_2Cl_2, BuTRAP, 67% convn, 69% ee). In contrast, EtTRAP provided higher enantioselectivity for the hydrogenation of the (*Z*)-**3c** than BuTRAP (Entries 11 and 12), and CH_2Cl_2 is slightly better than *i*-PrOH (*i*-PrOH, BuTRAP, 94% convn, 76% ee). The *erythro*- and *threo*-products **4c** were readily hydrolyzed without epimerization with 1 M HCl aq (1 M = 1 mol dm^{-3}) under reflux for 5 h, giving *threo*- and *erythro*-L-β-methylphenylalanine in 96% and 88% yields, respectively.

The enantioselectivity was little affected by electronically different substituents on the β-aromatic group of **3** (Entries 8, 9, 13, and 14). The hydrogenation of (*Z*)-**3** was generally more selective than that of (*E*)-**3**. Similarly, β-ethylphenylalanine derivatives, *erythro*- and *threo*-**4f**, were obtained with 77% and 86% ee, respectively (Entries 10 and 15). Of particular importance is the result that the extremely bulky *t*-butyl substituted olefin (*Z*)-**1g** underwent the enantioselective hydrogenation smoothly to give (2*S*,3*R*)-**4g** with high enantiomeric excess (Entry 16).

Conclusion

Trans-chelating chiral bisphosphine ligands TRAPs were successfully applied to the rhodium-catalyzed enantioselective hydrogenation of α-(acetamido)acrylates. Only a small change in the ligand *P*-substituent influenced the catalytic activity and enantioselectivity dramatically, indicating that a unique and efficient asymmetric environment is created around the metal center of TRAP–rhodium complex. By choosing an appropriate ligand and conditions, high enantioselectivity was attained in the hydrogenation of a wide range of substrates including β,β-disubstituted α-(acetamido)acrylates. Only a few successful examples have been reported for the enantioselective hydrogenation of this type of substrate so far.[7,15] The TRAP–rhodium catalyst system is applicable for the β,β-disubstituted α-(acetamido)acrylates, irrespective of *E*/*Z* olefin stereochemistry, each giving *erythro*- and *threo*-β-alkylated α-amino acid esters.

Experimental

Materials. 1,2-Dichloroethane, CH_2Cl_2, and *i*-PrOH were distilled from CaH_2 under a nitrogen atmosphere. THF was distilled from sodium benzophenone ketyl. MeOH was distilled from $Mg(OMe)_2$. Methyl 2-(*N*-acetylamino)acrylate (**1a**) (Aldrich) and potassium *t*-butoxide (Nacalai tesque) were purchased and used without purification. Substrates **1b**—**d**, **1f**, **3a**, **3b** were prepared by Horner-Emmons reactions of methyl 2-(*N*-acetylamino)-2-(dimethoxyphosphoryl)acetate with the corresponding carbonyl compounds using 1,1,3,3-tetramethylguanidine as a base.[19] [Rh(cod)$_2$]BF$_4$[20] and **1e**[21] were prepared according to the literature procedures. Methyl isocyanoacetate was purchased from Janssen and purified by distillation before use. Flash column chromatography was performed with silica gel 60 (230—400 mesh, Merck).

General Procedure of the Preparation of 3c—g.[22] A solution of methyl isocyanoacetate (1.98 g, 20 mmol) in THF (20 ml) was added dropwise over 30 min at −78 °C to a solution of potassium *t*-butoxide (2.47 g, 22 mmol) in THF (30 ml). After 10 min, a solution of a ketone (20 mmol) in THF (20 ml) was added dropwise over 30 min to the solution at −78 °C. The mixture was allowed to warm to room temperature. After the completion of the aldol reaction was confirmed by TLC, a solution of acetyl chloride (1.42 ml, 20 mmol) in THF (20 ml) was added dropwise over 20 min to the mixture at 0 °C. The mixture was stirred for 1 h at room temperature and concentrated under a reduced pressure. The residue was treated with 3 M HCl in MeOH (30 ml, 90 mmol), and was stirred under reflux for 20 min. After concentration in vacuo, water was added to the residue. The mixture was extracted with EtOAc, and the organic layer was dried with $\mathrm{MgSO_4}$ and evaporated. Purification of the residue by flash column chromatography (EtOAc) on silica gel gave (*E*)- and (*Z*)-**3** separately. Each product was recrystallized from $\mathrm{CH_2Cl_2}$–hexane.

Methyl 2-(*N*-Acetylamino)-3-phenyl-2-butenoate (3c). (*E*)- and (*Z*)-**3c** were prepared from acetophenone in 9% and 24% yields, respectively. (*E*)-**3c**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 2.13$ (s, 3H), 2.16 (s, 3H), 3.44 (s, 3H), 7.03 (br s, 1H), 7.12—7.49 (m, 5H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 21.71$, 23.02, 51.77, 123.83, 127.12, 127.67, 128.05, 140.24, 140.78, 165.91, 168.60. (*Z*)-**3c**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 1.88$ (s, 3H), 2.27 (s, 3H), 3.83 (s, 3H), 6.57 (br s, 1H), 7.13—7.49 (m, 5H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 20.55$, 22.56, 52.11, 123.61, 127.31, 128.14, 128.78, 137.61, 139.85, 165.58, 168.66.

Methyl 2-(*N*-Acetylamino)-3-(4-methoxyphenyl)-2-butenoate (3d). (*E*)- and (*Z*)-**3d** were prepared from 4′-methoxyacetophenone in 7% and 22% yields, respectively. (*E*)-**3d**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 2.10$ (s, 3H), 2.14 (s, 3H), 3.48 (s, 3H), 3.81 (s, 3H), 6.80—6.90 (m, 2H), 7.01 (br s, 1H), 7.06—7.17 (m, 2H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 21.59$, 22.98, 51.82, 55.20, 113.47, 123.33, 128.52, 132.88, 139.80, 159.21, 166.21, 168.62. (*Z*)-**3d**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 1.92$ (s, 3H), 2.24 (s, 3H), 3.83 (s, 6H), 6.50 (br s, 1H), 6.87—6.97 (m, 2H), 7.11—7.22 (m, 2H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 20.60$, 22.66, 52.12, 55.29, 114.16, 123.31, 128.84, 131.86, 137.40, 159.41, 165.76, 168.65.

Methyl 2-(*N*-Acetylamino)-3-(4-fluorophenyl)-2-butenoate (3e). (*E*)- and (*Z*)-**3e** were prepared from 4′-fluoroacetophenone in 22% and 30% yields, respectively. (*E*)-**3e**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 2.10$ (s, 3H), 2.15 (s, 3H), 3.47 (s, 3H), 6.94—7.22 (m, 5H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 21.90$, 23.02, 51.86, 115.07 (d, $J = 22$ Hz), 126.64 (d, $J = 8$ Hz), 128.89 (d, $J = 8$ Hz), 136.68 (d, $J = 3$ Hz), 139.45, 162.25 (d, $J = 245$ Hz), 165.69, 168.60. (*Z*)-**3e**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 1.91$ (s, 3H), 2.26 (s, 3H), 3.84 (s, 3H), 6.47 (br s, 1H), 7.01—7.29 (m, 4H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 20.74$, 22.62, 52.21, 115.87 (d, $J = 21$ Hz), 123.84, 129.24 (d, $J = 8$ Hz), 135.83 (d, $J = 3$ Hz), 137.50, 162.33 (d, $J = 247$ Hz), 165.51, 168.73.

Methyl 2-(*N*-Acetylamino)-3-phenyl-2-pentenoate (3f). (*E*)- and (*Z*)-**3f** were prepared from propiophenone in 10% and 40% yields, respectively. (*E*)-**3f**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 0.94$ (t, $J = 7.6$ Hz, 3H), 2.15 (s, 3H), 2.51 (q, $J = 7.6$ Hz, 2H), 3.40 (s, 3H), 6.92 (br s, 1H), 7.09—7.41 (m, 5H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 11.69$, 22.96, 27.59, 51.74, 123.55, 127.57, 127.99, 139.09, 145.15, 166.07, 169.14. (*Z*)-**3f**: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 0.98$ (t, $J = 7.4$ Hz, 3H), 1.87 (s, 3H), 2.58 (q, $J = 7.4$ Hz, 2H), 3.84 (s, 3H), 6.44 (br s, 1H), 7.15—7.47 (m, 5H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 12.74$, 22.63, 27.19, 52.16, 123.50, 127.93, 128.15, 128.85, 138.11, 141.32, 165.56, 168.41.

Methyl (Z)-2-(*N*-Acetylamino)-3,3-dimethyl-2-pentenoate (3g). (*Z*)-**3g** was prepared from 3,3-dimethyl-2-butanone in 42% yield: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 1.21$ (s, 9H), 1.90 (s, 3H), 2.05 (s, 3H), 3.76 (s, 3H), 6.98 (br s, 1H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 17.60$, 22.67, 29.32, 36.62, 51.95, 122.99, 147.57, 167.48, 169.10.

General Procedure of Asymmetric Hydrogenation of *α*-(Acetamido)acrylates Using TRAP–Rhodium Catalyst. A solution of [Rh(cod)$_2$]BF$_4$ (2.0 mg, 5.0 μmol) and (*R*,*R*)-(*S*,*S*)-TRAP (5.5 μmol) in 1.0 ml of a solvent was stirred at room temperature for 10 min under an argon atmosphere, and *α*-(acetamido)acrylate (0.50 mmol) was added. Immediately, the flask was cooled at −78 °C, repeatedly evacuated and filled with hydrogen or hydrogen–nitrogen mixture. The reaction mixture was stirred for 24 h at the temperature indicated in Tables 1, 2, and 3. After the solvent was evaporated, the residue was passed through a short silica-gel column (hexane/EtOAc = 1/3).

General Procedure of Asymmetric Hydrogenation of *α*-(Acetamido)acrylates Using TRAP–Rhodium Catalyst at 100 kg cm^{-2} of Hydrogen Pressure. A solution of [Rh(cod)$_2$]BF$_4$ (2.0 mg, 5.0 μmol) and (*R*,*R*)-(*S*,*S*)-TRAP (5.5 μmol) in 1.0 ml of a solvent was stirred at room temperature for 10 min under an argon atmosphere in a test tube. Then, *α*-(acetamido)acrylate (0.50 mmol) was added. The test tube was placed into a stainless steel autoclave. The autoclave was charged with 100 kg cm^{-2} of hydrogen. The reaction mixture was stirred for 24 h at the temperature indicated in Tables 1, 2, and 3. After the hydrogen pressure was released, the solution was evaporated. The residue was passed through a short silica-gel column (hexane/EtOAc = 1/3).

Methyl (*R*)-2-(*N*-Acetylamino)propanoate (2a). $[\alpha]_{\mathrm{D}}^{25} -8.5$ (*c* 1.09, $\mathrm{CHCl_3}$), Ref. 5. $[\alpha]_{\mathrm{D}}^{25} -9.2$ (*c* 1, $\mathrm{CHCl_3}$) for (*R*). ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 1.41$ (d, $J = 7.1$ Hz, 3H), 2.02 (s, 3H), 3.76 (s, 3H), 4.61 (quintet, $J = 7.3$ Hz, 1H), 6.08 (br d, 1 H).

Methyl (*R*)-2-(*N*-Acetylamino)butanoate (2b). $[\alpha]_{\mathrm{D}}^{25} -24.0$ (*c* 1.04, $\mathrm{CHCl_3}$), Ref. 5. $[\alpha]_{\mathrm{D}}^{25} -25.2$ (*c* 1, $\mathrm{CHCl_3}$) for (*R*); ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 0.91$ (t, $J = 7.4$ Hz, 3H), 1.60—1.99 (m, 2H), 2.04 (s, 3H), 3.76 (s, 3H), 4.59 (q, $J = 6.7$ Hz, 1H), 6.12 (br d, 1H).

Methyl (*R*)-2-(*N*-Acetylamino)pentanoate (2c). $[\alpha]_{\mathrm{D}}^{25} -25.4$ (*c* 1.03, $\mathrm{CHCl_3}$), Ref. 5. $[\alpha]_{\mathrm{D}}^{25} -19.0$ (*c* 1, $\mathrm{CHCl_3}$) for (*R*); ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 0.93$ (t, $J = 7.1$ Hz, 3H), 1.17—1.49 (m, 2H), 1.49—1.91 (m, 2H), 2.03 (s, 3H), 3.75 (s, 3H), 4.62 (dt, $J = 5.6$, 7.6, 1H), 6.02 (br d, 1H).

Methyl (*R*)-2-(*N*-Acetylamino)-5-methylhexanoate (2d). $[\alpha]_{\mathrm{D}}^{25} -37.3$ (*c* 1.09, $\mathrm{CHCl_3}$); ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 0.87$ (d, $J = 6.5$ Hz, 6H), 0.97—1.32 (m, 2H), 1.40—1.93 (m, 3H), 2.03 (s, 3H), 3.75 (s, 3H), 4.60 (dt, $J = 5.4$, 7.4 Hz, 1H), 6.09 (br d, 1H); $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (50 MHz, $\mathrm{CDCl_3}$, TMS) $\delta = 22.28$, 22.44, 23.15, 27.72, 30.39, 34.03, 52.24, 169.73, 173.26. Anal. Found: C, 59.27; H, 9.74; N, 6.77%. Calcd for: $\mathrm{C_{10}H_{19}NO_3}$: C, 59.27; H, 9.52; N, 6.96%.

Methyl (*S*)-2-(*N*-Acetylamino)-3-phenylpropanoate (2e). $[\alpha]_{\mathrm{D}}^{25} +13.4$ (*c* 1.00, MeOH), Ref. 5. $[\alpha]_{\mathrm{D}}^{25} -15.8$ (*c* 1, MeOH) for (*R*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.99$ (s, 3H), 3.08 (dd, $J = 5.7$, 13.9 Hz, 1H), 3.18 (dd, $J = 5.7$, 13.9 Hz, 1H), 3.73 (s, 3H), 4.89 (dt, $J = 7.7$, 5.7 Hz, 1H), 5.93 (br d, 1H), 7.04—7.15 (m, 2H), 7.20—7.36 (m, 3H).

Methyl (*R*)-2-(*N*-Acetylamino)-4-methylpentanoate (2f). $[\alpha]_D^{25} -2.6$ (*c* 0.99, $CHCl_3$), $[\alpha]_D^{25} +26.1$ (*c* 1.00, MeOH), Ref. 5. $[\alpha]_D^{25} +41.8$ (*c* 1, MeOH) for (*R*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.95$ (d, $J = 5.0$ Hz, 6H), 1.41—1.74 (m, 3H), 2.02 (s, 3H), 3.74 (s, 3H), 4.65 (dt, $J = 5.2$, 8.6 Hz, 1H), 5.95 (br d, 1H).

Methyl (*S*)-2-(*N*-Acetylamino)-3-methylbutanoate (4a). $[\alpha]_D^{25} +27.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.91$ (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 2.05 (s, 3H), 2.15 (double septet, $J = 5.0$, 6.6 Hz, 1H), 3.75 (s, 3H), 4.57 (dd, $J = 5.0$, 8.9 Hz, 1H), 5.96 (br d, 1H). The absolute configuration was determined by comparison of the retention time on the chiral HPLC analysis (SUMICHIRAL OA-3000) with that of the authentic sample derived from L-valine.

Methyl (*S*)-2-(*N*-Acetylamino)-2-cyclohexylacetate (4b). $[\alpha]_D^{20} +46.7$ (*c* 1.01, $CHCl_3$), Ref. 15a. $[\alpha]_D^{20} +50.6$ (*c* 0.097, $CHCl_3$) for (*S*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.92$—1.36 (m, 5H), 1.53—1.88 (m, 6H), 2.03 (s, 3H), 3.74 (s, 3H), 4.55 (dd, $J = 5.3$, 8.7 Hz, 1H), 6.02 (br d, 1H).

Methyl (2*S*, 3*S*)-2-(*N*-Acetylamino)-3-phenylbutanoate (*erythro*-4c). $[\alpha]_D^{25} +45.8$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.35$ (d, $J = 7.2$ Hz, 3H), 1.96 (s, 3H), 3.38 (dq, $J = 5.6$, 7.2 Hz, 1H), 3.71 (s, 3H), 4.85 (dd, $J = 5.6$, 8.7 Hz, 1H), 5.66 (br d, 1H), 7.09—7.19 (m, 2H), 7.19—7.39 (m, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 17.65$, 23.14, 41.96, 52.14, 57.12, 127.35, 127.49, 128.66, 140.76, 169.95, 172.08. Anal. Found: C, 66.08; H, 7.26; N, 5.88%. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%.

***erythro*-(2*S*,3*S*)-2-Amino-3-phenylbutanoic acid.** A solution of *erythro*-4c (35.4 mg, 0.15 mmol) in 1 M HCl aq (0.6 ml) was refluxed for 5 h and then evaporated under a reduced pressure. Purification by ion-exchange chromatography (Amberlite IR-120B, H^+ form, elution with water followed by 10% aqueous ammonia) gave 25.7 mg (96%) of *erythro*-2-amino-3-phenylbutanoic acid: $[\alpha]_D^{21} -20.9$ (*c* 0.95, H_2O), Ref. 23. $[\alpha]_D^{23} -29$ (*c* 1.0, H_2O) for (2*S*,3*S*); ^{1}H NMR (200 MHz, D_2O, 1,4-dioxane as external std at $\delta = 3.55$) $\delta = 0.89$ (d, $J = 7.0$ Hz, 3H), 2.74 (dq, $J = 7.6$, 7.0 Hz, 1H), 3.21 (d, $J = 7.6$ Hz, 1H), 6.80—7.00 (m, 5H).

Methyl (2*S*, 3*S*)-2-(*N*-Acetylamino)-3-(4-methoxyphenyl)-butanoate (*erythro*-4d). $[\alpha]_D^{25} +41.5$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.32$ (d, $J = 7.2$ Hz, 3H), 1.97 (s, 3H), 3.33 (dq, $J = 5.5$, 7.2 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.80 (dd, $J = 5.5$, 8.7 Hz, 1H), 5.67 (br d, 1H), 6.80—6.92 (m, 2H), 7.01—7.13 (m, 2H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 17.85$, 23.13, 41.11, 52.11, 55.18, 57.21, 113.99, 128.42, 132.64, 158.72, 169.96, 172.17. Anal. Found: C, 63.27; H, 7.16; N, 5.24%. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28%.

Methyl (2*S*, 3*S*)-2-(*N*-Acetylamino)-3-(4-fluorophenyl)-butanoate (*erythro*-4e). $[\alpha]_D^{25} +39.3$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.32$ (d, $J = 7.1$ Hz, 3H), 1.97 (s, 3H), 3.36 (dq, $J = 5.6$, 7.1 Hz, 1H), 3.71 (s, 3H), 4.85 (dd, $J = 5.6$, 8.8 Hz, 1H), 5.69 (br d, 1 H), 6.94—7.18 (m, 4H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 17.65$, 23.15, 41.38, 52.19, 57.07, 115.45 (d, $J = 21$ Hz), 128.96 (d, $J = 8$ Hz), 136.54 (d, $J = 3$ Hz), 161.95 (d, $J = 244$ Hz), 169.90, 171.94. Anal. Found: C, 61.63; H, 6.42; N, 5.51%. Calcd for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53%.

Methyl (2*S*, 3*S*)-2-(*N*-Acetylamino)-3-phenylpentanoate (*erythro*-4f). $[\alpha]_D^{25} +64.5$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.86$ (t, $J = 7.3$ Hz, 3H), 1.61—1.92 (m, 2H), 1.96 (s, 3H), 3.10 (dt, $J = 9.0$, 5.8 Hz, 1H), 3.71 (s, 3H), 4.96 (dd, $J = 5.2$, 9.0 Hz, 1H), 5.64 (br d, 1H), 7.04—7.13 (m, 2H), 7.19—7.38 (m, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 11.95$, 23.14, 24.61, 49.66, 52.13, 55.68, 127.37, 128.11, 128.65, 139.05, 169.93, 172.21. Anal. Found: C, 67.30; H, 7.61; N, 5.64%. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62%.

Methyl (2*S*, 3*R*)-2-(*N*-Acetylamino)-3-phenylbutanoate (*threo*-4c). $[\alpha]_D^{25} +49.5$ (*c* 1.07, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.39$ (d, $J = 7.3$ Hz, 3H), 2.00 (s, 3H), 3.19 (dq, $J = 6.8$, 7.3 Hz, 1H), 3.55 (s, 3H), 4.81 (dd, $J = 6.8$, 8.8 Hz, 1H), 6.13 (br d, 1H), 7.11—7.37 (m, 5H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 16.95$, 23.09, 42.71, 51.92, 57.58, 127.15, 127.57, 128.37, 141.04, 169.64, 171.97. HRMS (EI) Found: *m/z* 235.1214. Calcd for $C_{13}H_{17}NO_3$: 235.1208.

***threo*-(2*S*,3*R*)-2-Amino-3-phenylbutanoic acid.** A solution of *threo*-4c (35.3 mg, 0.15 mmol) in 1 M HCl aq (0.6 ml) was refluxed for 5 h and then evaporated under a reduced pressure. Purification by ion-exchange chromatography (Amberlite IR-120B, H^+ form, elution with water followed by 10% aqueous ammonia) gave 23.6 mg (88%) of *threo*-2-amino-3-phenylbutanoic acid: $[\alpha]_D^{21} -5.8$ (*c* 0.97, H_2O), Ref. 23. $[\alpha]_D^{23} -5.8$ (*c* 1.0, H_2O) for (2*S*,3*R*); ^{1}H NMR (200 MHz, D_2O, 1,4-dioxane as external std at $\delta = 3.55$) $\delta = 0.88$ (d, $J = 7.3$ Hz, 3H), 3.01 (dq, $J = 5.0$, 7.3 Hz, 1H), 3.41 (d, $J = 5.0$ Hz, 1H), 6.78—7.00 (m, 5H).

Methyl (2*S*,3*R*)-2-(*N*-Acetylamino)-3-(4-methoxyphenyl)-butanoate (*threo*-4d). $[\alpha]_D^{25} +47.9$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.36$ (d, $J = 7.2$ Hz, 3H), 2.00 (s, 3H), 3.14 (dq, $J = 6.7$, 7.2 Hz, 1H), 3.58 (s, 3H), 3.79 (s, 3H), 4.76 (dd, $J = 6.7$, 8.8 Hz, 1H), 5.98 (br d, 1H), 6.78—6.91 (m, 2H), 7.02—7.16 (m, 2H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 17.24$, 23.18, 41.95, 51.97, 55.17, 57.68, 113.77, 128.56, 132.99, 158.62, 169.52, 172.00. Anal. Found: C, 63.17; H, 7.14; N, 5.28%. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28%.

Methyl (2*S*, 3*R*)-2-(*N*-Acetylamino)-3-(4-fluorophenyl)-butanoate (*threo*-4e). $[\alpha]_D^{25} +42.1$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 1.36$ (d, $J = 7.2$ Hz, 3H), 2.01 (s, 3H), 3.19 (dq, $J = 6.7$, 7.2 Hz, 1H), 3.58 (s, 3H), 4.79 (dd, $J = 6.7$, 8.9 Hz, 1H), 6.07 (br d, 1H), 6.91—7.06 (m, 2H), 7.06—7.20 (m, 2H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 17.09$, 23.13, 42.06, 52.03, 57.53, 115.21 (d, $J = 21$ Hz), 129.05 (d, $J = 8$ Hz), 136.81 (d, $J = 3$ Hz), 161.87 (d, $J = 244$ Hz), 169.59, 171.87. Anal. Found: C, 61.49; H, 6.34; N, 5.52%. Calcd for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53%.

Methyl (2*S*, 3*R*)-2-(*N*-Acetylamino)-3-phenylpentanoate (*threo*-4f). $[\alpha]_D^{25} +47.3$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.81$ (t, $J = 7.3$ Hz, 3H), 1.65—2.07 (m, 2H), 2.01 (s, 3H), 2.85 (ddd, $J = 5.0$, 7.0, 10.6 Hz, 1H), 3.53 (s, 3H), 4.83 (dd, $J = 7.0$, 8.8 Hz, 1H), 6.04 (br d, 1H), 7.03—7.18 (m, 2H), 7.18—7.36 (m, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 12.05$, 23.16, 24.41, 51.00, 51.85, 56.84, 127.21, 128.38, 139.15, 169.50, 171.91. Anal. Found: C, 67.44; H, 7.84; N, 5.41%. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62%.

Methyl (2*S*,3*R*)-2-(*N*-Acetylamino)-3,4,4-trimethylpentanoate (*threo*-4g). $[\alpha]_D^{25} +34.3$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) $\delta = 0.88$ (d, $J = 7.2$ Hz, 3H), 0.94 (s, 9H), 1.86 (dq, $J = 2.0$, 7.2 Hz, 1 H), 2.02 (s, 3H), 3.72 (s, 3H), 5.01 (dd, $J = 2.0$, 9.8 Hz, 1H), 5.81 (br d, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, TMS) $\delta = 9.56$, 23.47, 27.71, 33.34, 43.97, 52.34, 52.54, 169.78, 173.86. Anal. Found: C, 61.14; H, 9.70; N, 6.39%. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51%.

Determination of Enantiomeric Excesses of 2 and 4. The enantiomeric excesses of the hydrogenation products 2 and 4 were determined by HPLC analysis with a chiral stationary phase column, SUMICHIRAL OA-3000 (4.0 mm $\phi \times 250$ mm, 1.0 ml min^{-1}, at 35 °C). The racemic materials eluted as follows: **2a** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 20.0 min, (*S*) t_2 = 25.1 min; **2b** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 14.2 min, (*S*) t_2 = 19.4 min; **2c** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 11.5 min, (*S*) t_2 = 16.6 min; **2d** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 9.6 min, (*S*) t_2 = 15.8 min; **2e** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 254 nm) (*R*) t_1 = 14.1 min, (*S*) t_2 = 16.4 min; **2f** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 10.9 min, (*S*) t_2 = 17.1 min; **4a** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 11.2 min, (*S*) t_2 = 15.9 min; **4b** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (*R*) t_1 = 9.7 min, (*S*) t_2 = 15.2 min; *erythro*-**4c** (hexane/1,2-dichloroethane/ethanol = 115/20/1, UV 254 nm) (2*R*,3*R*) t_1 = 6.6 min, (2*S*,3*S*) t_2 = 8.5 min; *erythro*-**4d** (hexane/1,2-dichloroethane/ethanol = 115/20/1, UV 254 nm) (2*R*,3*R*) t_1 = 8.4 min, (2*S*,3*S*) t_2 = 11.1 min; *erythro*-**4e** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 254 nm) (2*R*,3*R*) t_1 = 7.9 min, (2*S*,3*S*) t_2 = 10.9 min; *erythro*-**4f** (hexane/1,2-dichloroethane/ethanol = 146/20/1, UV 254 nm) (2*R*,3*R*) t_1 = 8.5 min, (2*S*,3*S*) t_2 = 11.8 min; *threo*-**4c** (hexane/1,2-dichloroethane/ethanol = 115/20/1, UV 254 nm) (2*R*,3*S*) t_1 = 11.3 min, (2*S*,3*R*) t_2 = 18.2 min; *threo*-**4d** (hexane/1,2-dichloroethane/ethanol = 115/20/1, UV 254 nm) (2*R*,3*S*) t_1 = 13.2 min, (2*S*,3*R*) t_2 = 21.8 min; *threo*-**4e** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 254 nm) (2*R*,3*S*) t_1 = 12.3 min, (2*S*,3*R*) t_2 = 20.5 min; *threo*-**4f** (hexane/1,2-dichloroethane/ethanol = 124/20/1, UV 254 nm) (2*R*,3*S*) t_1 = 11.6 min, (2*S*,3*R*) t_2 = 20.5 min; *threo*-**4g** (hexane/1,2-dichloroethane/ethanol = 100/20/1, UV 230 nm) (2*R*, 3*S*) t_1 = 6.4 min, (2*S*,3*R*) t_2 = 11.6 min. The enantiomeric excesses of **2e** in Table 2 were determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OD-H (4.6 mm $\phi \times 250$ mm, hexane/2-propanol = 9/1, 0.5 ml min^{-1}, at 35 °C, UV 254 nm). The racemic **2e** eluted at (*R*) t_1 = 23.5 min, (*S*) t_2 = 28.4 min.

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