Tetrahedron: *Asymmetry* 19 (2008) 2816–2828

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Direct *anti*-selective asymmetric hydrogenation of α-amino-β-keto esters through dynamic kinetic resolution using Ru-axially chiral phosphine catalysts—stereoselective synthesis of *anti*-β-hydroxy-α-amino acids

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ARTICLE INFO

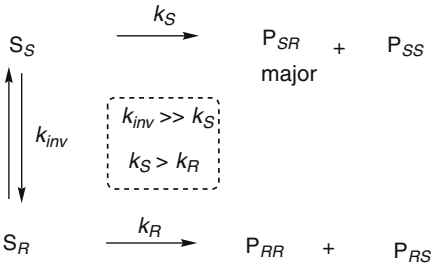
Article history:
Received 8 October 2008
Accepted 10 December 2008
Available online 23 January 2009

ABSTRACT

The asymmetric hydrogenation of α-amino-β-keto esters using ruthenium (Ru) *anti*-selectively proceeds via a dynamic kinetic resolution to afford *anti*-β-hydroxy-α-amino acids with high enantiomeric purities, which are important chiral building blocks for the synthesis of medicines and natural products. A mechanistic investigation has revealed that the Ru-catalyzed asymmetric hydrogenation takes place via the hydrogenation of the double bond in the enol tautomer of the substrate.

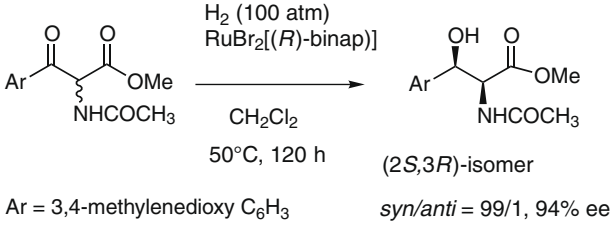
1. Introduction

Catalytic asymmetric hydrogenation is an important and fundamental process for the preparation of single enantiomers, which are useful chiral building blocks for the synthesis of medicines and natural products.[1] Asymmetric hydrogenation accompanied by dynamic kinetic resolution (DKR) has been established as one of the most effective methods for obtaining enantiomerically pure products from racemic starting materials.[2] As illustrated in Scheme 1, for the reaction accompanied by DKR, the stereogenic center, which exists in a substrate, can easily racemize under the reaction conditions; all the racemic substrate can convert into a single diastereomer. By using this method, optically active products with two or more contiguous stereogenic centers can be synthesized with theoretical yields of 100% from racemic substrates in a stereocontrolled fashion and in a single operation. Asymmetric hydrogenation using a ruthenium (Ru) catalyst via DKR was originally reported by Noyori et al. in 1989.[3] In their report, they achieved the highly stereoselective synthesis of *syn*-β-hydroxy-α-amino acids[4] from chirally labile α-acylamino-β-keto esters. A typical example is shown in Scheme 2. We have been working on the synthesis of biologically active cyclodepsipeptides from marine origins.[5] For this research, we required an efficient method for the preparation of *anti*-β-hydroxy-α-amino acids, which are common structural units widely found as components in biologically active natural products.[6] Typical examples are shown in Figure 1. There are many reports on the synthesis of these amino acids. Most of these methods often require careful and tedious handling. The Noyori method is highly efficient but is limited to the synthesis



Scheme 1. Dynamic kinetic resolution.

of only the *syn*-β-hydroxy-α-amino acids. Therefore, the development of a more expedient process for large-scale production is desirable. We envisaged that if the asymmetric hydrogenation of α-amino-β-keto esters can proceed *anti*-selectively through a DKR, it would become an attractive method for obtaining *anti*-β-hydroxy-α-amino acids. Herein, we report on the development of the Ru-catalyzed *anti*-selective asymmetric hydrogenation of α-



Scheme 2. Noyori *syn*-selective asymmetric hydrogenation.

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doi:10.1016/j.tetasy.2008.12.024

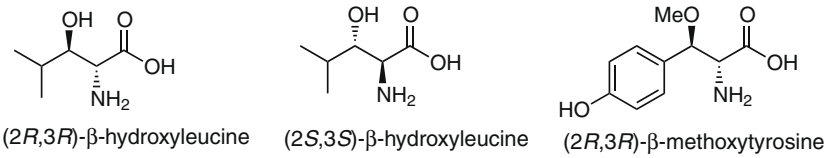
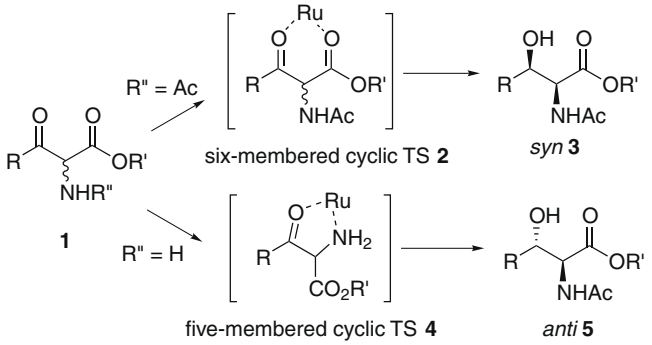


Figure 1. Naturally occurring β-hydroxy-α-amino acids.

amino-β-keto esters through a DKR in detail, which is capable of the diastereoselective and enantioselective synthesis of *anti*-β-hydroxy-α-amino acids.[7,8] Recent reports from other laboratories have also reported on the Ru-chiral phosphine-catalyzed *anti*-selective asymmetric hydrogenation.[9]

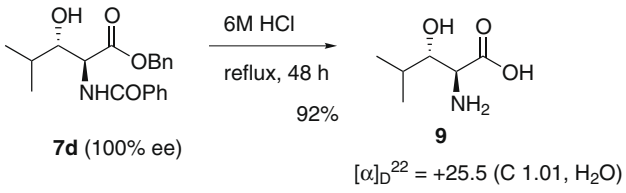
2. Results and discussion

We first examined the postulated reaction mechanism of the Noyori's *syn*-selective asymmetric hydrogenation of **1** as shown in Scheme 3. The Noyori reaction takes place through the six-membered cyclic transition state **2** by the chelation between two carbonyl groups of the keto and ester functions to provide the *syn*-β-hydroxy-α-amino acid **3**. We envisioned that, when the substrate with a free amino function is employed, the hydrogenation should take place *anti*-selectively through the five-membered cyclic transition state **4** by chelation between the amino group and the keto carbonyl function to afford the *anti*-β-hydroxy-α-amino acid **5**.



Scheme 3. Direct *anti*-selective asymmetric hydrogenation.

The required substrate **6a** was prepared by the acid cleavage of an oxazole with *p*-toluenesulfonic acid.[4i] The α-amino-β-keto ester toluenesulfonic acid salt obtained was then subjected to asymmetric hydrogenation by employing the reaction conditions for the Noyori's *syn*-selective asymmetric hydrogenation, Ru-(*S*)-BINAP in methanol at 50 °C for 48 h under 100 atm of hydrogen. Indeed, the hydrogenation took place (*anti*-selectively) to give the *anti*-β-hydroxy-α-amino acid ester **7a** in 72% yield with a diastereomeric ratio of 97:3 and 22% ee (Table 1, entry 1). The relative and absolute stereochemistry of **7a** was unambiguously confirmed after the N-benzoylation by comparison with an authentic sample using HPLC analysis.[4i] This result clearly shows that the reaction proceeds through DKR. With this encouraging result in hand, we studied extensively the optimized conditions for the *anti*-selective asymmetric hydrogenation. The acid salt, solvent, temperature, and solubility of the substrate were all found to be important factors for the yield and stereoselectivity of the product. The hydrochloride salt was superior to the toluenesulfonic acid for the enantio- and diastereoselectivities. The polarity of the solvent influenced the enantioselectivity. Methylene chloride was the solvent of choice for the enantioselectivity (entry 10). *i*-Propanol and *n*-propanol also gave satisfactory results, but they were inferior to methylene chloride (entries 6 and 7). However, the chemical yield in methylene chloride was poor. This may be due to the poor solubility of the substrate hydrochloride in this solvent. The enhancement of the lipophilicity by a change in the ester function positively affected the chemical yield (entries 10–13). Finally, benzyl ester **6d** produced a satisfactory chemical yield and stereoselectivity (entry 13). Using benzyl ester **6d**, the solvent effects were reexamined for confirmation (entries 13–17); it was seen that methylene chloride was the optimal choice. The effect of the reaction time was examined (entries 18–22). Although the reaction gave a 55% conversion after 3 h, 6 h was sufficient for the completion of the reaction. Based on these results, it can be seen that the *anti*-selective asymmetric hydrogenation can be completed in a shorter reaction time than that of the *syn*-selective counterpart. Raising the temperature to 100 °C caused a slight decrease in the stereoselectivity, although the rate of the reaction was improved (entry 22). The thus-obtained *anti*-β-hydroxy-α-amino acid ester **7d** was converted to enantiomerically pure (2*S*,3*S*)-3-hydroxyleucine **9**, the absolute stereochemistry of which was confirmed by comparison with an authentic sample (Scheme 4).

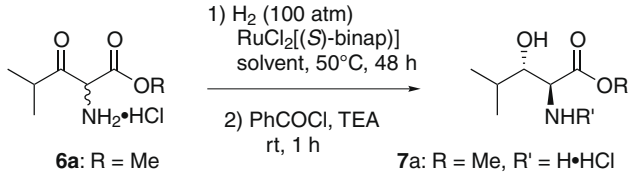


Scheme 4. Absolute stereochemistry.

The required α-amino-β-keto ester hydrochlorides **13** are readily available by the base-mediated N–C acyl migration of the *N*-*tert*-butoxycarbonyl-*N*-acylglycine ester followed by acid deprotection (Scheme 5). Thus, the *N*-*tert*-butoxycarbonylglycine benzyl ester **10** was allowed to react with the acyl chloride in the presence of potassium hexamethylsilazide (KHMDS) or lithium hexamethylsilazide (LHMDS) at −78 °C for 1 h. The resulting imide **11** was treated again with an excess amount of LHMDS in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) at −78 °C for 2 h, during which time the acyl group was migrated intramolecularly from the nitrogen to the carbon to afford the α-*N*-*tert*-butoxycarbonylamino-β-keto ester **12** in good yield. The deprotection of **12** furnished the α-amino-β-keto ester hydrochloride **13**.

The generality of the *anti*-selective asymmetric hydrogenation using the optimized conditions is shown in Table 2. The *anti*-selective asymmetric hydrogenation was affected by the bulkiness of the C4 substituent. Substrates **13b**–**e** with a secondary alkyl group, such as a cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl substituent, at the α-position of the ketone carbonyl group were hydrogenated in high diastereo- and enantioselectivities to afford the *anti*-β-hydroxy-α-amino acid esters in high yields (entries 1–8). The cyclohexyl substrate **17** in particular had a high reactivity for the present hydrogenation, and the reaction was completed in 6 h even with a substrate/catalyst ratio of 250 under 30 atm of

Table 1
Optimization of anti-selective asymmetric hydrogenation[a]



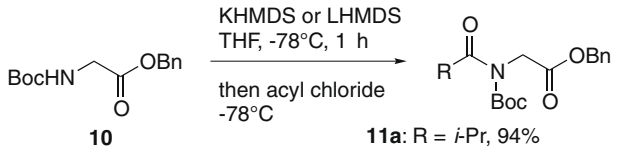
6a: R = Me
6b: R = Et
6c: R = *i*-Pr
6d: R = Bn

7a: R = Me, R' = H•HCl
7b: R = Et, R' = H•HCl
7c: R = *i*-Pr, R' = H•HCl
7d: R = Bn, R' = H•HCl

8a: R = Me, R' = COPh
8b: R = Et, R' = COPh
8c: R = *i*-Pr, R' = COPh
8d: R = Bn, R' = COPh

Entry	R	Solvent	Time	Yield[b] (%)	*anti*/*syn*[c]	% ee[d]
1[e]	Me	MeOH	48	72	97/3	22
2[f]	Me	MeOH	48	NR	—	—
3	Me	MeOH	48	71	99/1	56
4	Me	H_2O	48	NR	—	—
5	Me	$(CH_2OH)_2$	48	84	77/23	57
6	Me	*n*-PrOH	48	69	99/1	69
7	Me	*i*-PrOH	48	81	99/1	81
8	Me	*t*-BuOH	48	17	85/15	38
9	Me	CH_3CN	48	NR	–	—
10	Me	CH_2Cl_2	48	38	99/1	95
11	Et	CH_2Cl_2	48	73	96/4	93
12	*i*-Pr	CH_2Cl_2	48	96	98/2	92
13	Bn	CH_2Cl_2	48	87	>99/1	96
14	Bn	*n*-PrOH	48	83	97/3	79
15	Bn	*i*-PrOH	48	94	98/2	76
16	Bn	$PhCH_3$	48	87	66/34	76
17	Bn	PhCl	48	85	84/16	86
18	Bn	CH_2Cl_2	24	88	>99/1	96
19	Bn	CH_2Cl_2	13	81	>99/1	98
20	Bn	CH_2Cl_2	6	84	>99/1	98
21	Bn	CH_2Cl_2	3	55	95/5	98
22[g]	Bn	$(CH_2Cl)_2$	3	90	97/3	92

[a] The reaction was carried out using 3.8–4.6 mol % catalyst.
[b] Two-step yield after N-benzoylation.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC analysis after N-benzoylation.
[e] The *p*-toluenesulfonic acid salt was used instead of **6a**.
[f] The tetrafluoroboric acid salt was used instead of **6a**.
[g] The reaction was carried out at 100 °C.



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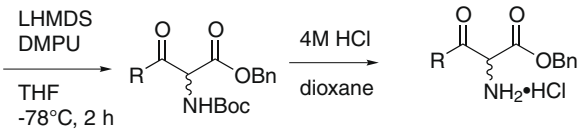
11a: R = *i*-Pr, 94%
11b: R = cyclobutyl, 70%
11c: R = cyclopentyl, 71%
11d: R = cyclohexyl, 94%
11e: R = cycloheptyl, 97%
11f: R = Et, 88%
11g: R = *n*-Pr, 88%
11h: R = *t*-Bu, 93%



12a: 85% **12b**: 80%
12c: 90% **12d**: 80%
12e: 99% **12f**: 80%
12g: 87% **12h**: 75%

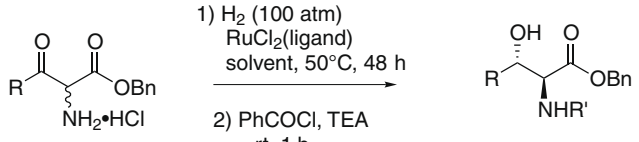
13a (**6d**): 97% **13b**: 85%
13c: quant. **13d**: quant.
13e: quant. **13f**: 92%
13g: 80% **13h**: 91%

Scheme 5. Preparation of substrates.

hydrogen (Scheme 6). The (2*R*,3*R*)-2-amino-3-cyclohexyl-3-hydroxy-propionic acid is a chiral core for the anti-HIV substance (GW873140/ONO-4128) with CCR5 antagonist activity.[10] The reaction of the primary alkyl substrate was inferior to the secondary one based on the enantioselectivity (entries 9–14). However, the use of MeO-BIPHEP instead of BINAP, together with lowering the temperature, improved its enantioselectivity (entry 14). The *tert*-butyl substrate was also inferior based on the diastereoselectivity and enantioselectivity under the standard conditions (entry 15). However, the hydrogenation in *n*-propanol improved the stereoselectivity, giving a product in 89% yield and 79% ee with a 96:4 diastereoselectivity (entry 16). In order to disclose the origin of the poor selectivity, we carried out kinetic experiments as shown in Scheme 7, and Tables 3 and 4. The k_{inv}/k_s value in *n*-propanol was 1.2, which was calculated according to the Noyori report. This result suggests that the racemization rate (k_{inv}) of the *tert*-butyl substrate is unsatisfactory and that the reaction proceeds through an incomplete dynamic kinetic resolution.

We next examined substrate **25** with a cyclic acetal, of which the product should serve as a building block for complex natural products with the skeleton of a β-hydroxy-α-amino acid or 2-amino-1,3-diol. Substrate **25** was synthesized starting from the commercially available ethyl diethoxyacetate **19** as shown in Scheme

Table 2
anti-Selective asymmetric hydrogenation



13b: R = cyclobutyl
13c: R = cyclopentyl
13d: R = cyclohexyl
13e: R = cycloheptyl
13f: R = Et
13g: R = *n*-Pr
13h: R = *t*-Bu

14b: R = cyclobutyl, R' = H•HCl
14c: R = cyclopentyl, R' = H•HCl
14d: R = cyclohexyl, R' = H•HCl
14e: R = cycloheptyl, R' = H•HCl
14f: R = Et, R' = H•HCl
14g: R = *n*-Pr, R' = H•HCl
14h: R = *t*-Bu, R' = H•HCl

15b: R = cyclobutyl, R' = COPh
15c: R = cyclopentyl, R' = COPh
15d: R = cyclohexyl, R' = COPh
15e: R = cycloheptyl, R' = COPh
15f: R = Et, R' = COPh
15g: R = *n*-Pr, R' = COPh
15h: R = *t*-Bu, R' = COPh

Entry	Substrate	Ligand	Solvent	Yield[a] (%)	*anti*/*syn*[b]	% ee[c]
1	**13b**	(*S*)-BINAP	*n*-PrOH	92	83/17	81
2	**13c**	(*S*)-BINAP	CH_2Cl_2	77	98/2	56
3	**13c**	(*S*)-BINAP	CH_2Cl_2/*n*-PrOH	82	99/1	94
4	**13c**	(*S*)-BINAP	*n*-PrOH	85	98/2	95
5	**13d**	(*S*)-BINAP	CH_2Cl_2	85	>99/1	97
6	**13d**	(*S*)-BINAP	*n*-PrOH	80	98/2	54
7	**13e**	(*S*)-BINAP	CH_2Cl_2	94	97/3	79
8	**13e**	(*S*)-BINAP	*n*-PrOH	86	97/3	97
9	**13f**	(*S*)-BINAP	CH_2Cl_2	89	89/11	76
10	**13g**	(*S*)-BINAP	CH_2Cl_2	88	94/6	74
11	**13g**	(*S*)-BINAP	CH_2Cl_2/*n*-PrOH	88	82/18	78
12	**13g**	(*S*)-BINAP	*n*-PrOH	53	91/9	58
13	**13g**	(*R*)-MeO-BIPHEP	CH_2Cl_2	92	98/2	85
14[d]	**13g**	(R)-MeO-BIPHEP	CH_2Cl_2	76	97/3	91
15	**13h**	(*S*)-BINAP	CH_2Cl_2	67	71/29	60
16	**13h**	(*S*)-BINAP	*n*-PrOH	89	96/4	79
17	**13h**	(*R*)-MeO-BIPHEP	*n*-PrOH	Quant	97/3	63
18[d]	**13h**	(*R*)-MeO-BIPHEP	*n*-PrOH	Quant	93/7	38

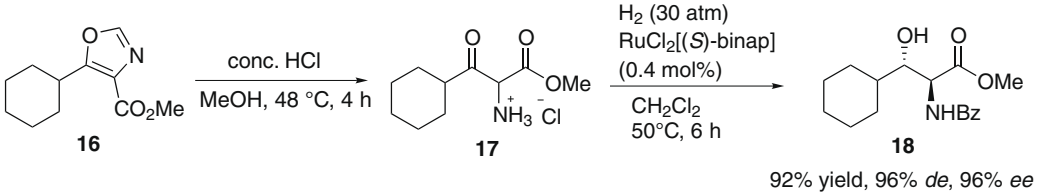
[a] Two-step yield after N-benzoylation.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis after N-benzoylation.
[d] The reaction was carried out at 23 °C.

8. After the transacetalization of **19** with 1,3-propanediol and the preparation of imide **23** from the resulting **20** by the usual procedure, the N–C acyl migration of **23** with LHMDS afforded the N-protected α-amino-β-keto ester **24**. The careful exposure of **24** to 4 M hydrogen chloride-dioxane provided the α-amino-β-keto ester hydrochloride **25**. Unfortunately, the present asymmetric hydrogenation of **25** after N-benzoylation produced product **27** with poor stereoselectivities, with the *anti*/*syn* ratio being 64:36 and 18% ee (Scheme 9). This result suggested that the reaction proceeded through two competitive transition states **28** and **29** to give the *anti*- and *syn*-products.

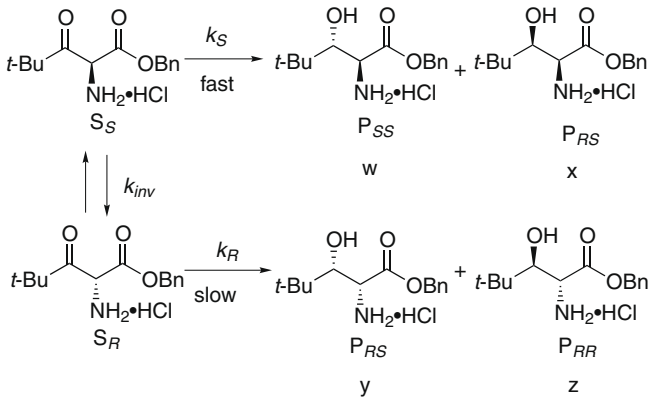
The asymmetric hydrogenation of the *N*-methyl substrate **30** was also investigated (Table 5). Although the standard conditions of the present asymmetric hydrogenation resulted in almost no reaction, product **32** could be obtained in low stereoselectively when sodium acetate was added or the solvent was changed. However, we were unable to find appropriate conditions to improve the stereoselectivity.

In contrast to aliphatic substrates, the present hydrogenation of an aromatic substrate **33** afforded racemic product **34** with an *anti*-stereochemistry in low yield (Scheme 10). For the *N*-methyl aromatic substrate **36**, the reaction proceeded stereo randomly to give a 1:1 mixture of *anti*- and *syn*-products with low enantioselectivities.

We briefly investigated the mechanism of this unique *anti*-selective asymmetric hydrogenation. In this hydrogenation, the α-amino-β-keto ester substrate exists as keto and enol tautomers through tautomerism. A simple question arose as to which tautomer is hydrogenated. For the *syn*-selective asymmetric hydrogenation, Noyori et al. have unambiguously elucidated the mechanism



Scheme 6. Methyl (2*S*,3*S*)-2-benzoylamino-3-cyclohexyl-3-hydroxy-propionate.



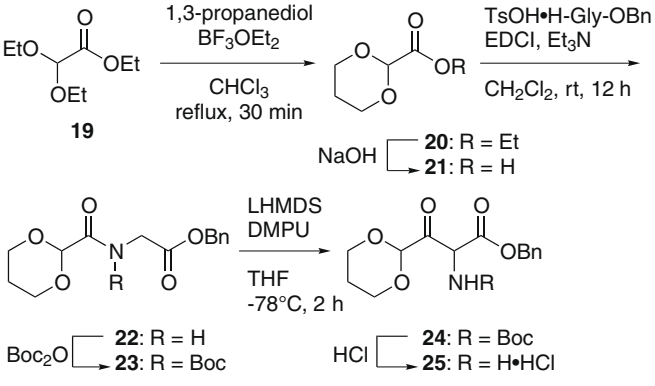
Scheme 7. Kinetic study of tertiary substrate.

Table 3
Hydrogenation of **13h**

Entry	Catalyst	Solvent	Product ratio			
			anti		*syn*	
			P_{SS}	P_{RR}	P_{RS}	P_{SR}
1	[$RuCl_2$(*S*)-binap]	*n*-PrOH	84.49	10.75	1.53	3.22
2	[$RuCl_2$(*rac*)-binap]	*n*-PrOH	95.9		4.07	
3	[$RuCl_2$(*S*)-binap]	CH_2Cl_2	59.68	14.81	7.82	17.69
4	[$RuCl_2$(*rac*)-binap]	CH_2Cl_2	57.57		42.43	

Table 4
Kinetic study of asymmetric hydrogenation

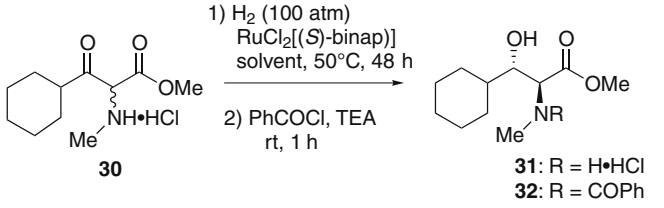
Solvent	*w*	*x*	*y*	*z*	k_S/k_R	k_{inv}/k_S
n-PrOH	0.87	0.016	0.025	0.083	8.3	1.2
CH_2Cl_2	0.25	0.032	0.32	0.34	—	—



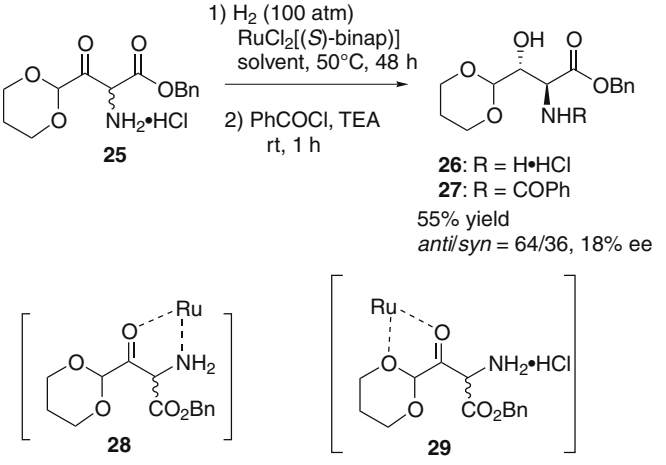
Scheme 8.

based on the deuterium experiments. Following their experiments, we performed the asymmetric hydrogenation of the deuterio substrate. As depicted in Scheme 11, when the reaction of **39** proceeds through the intermediate **41** of ketone reduction, the deuterium at the C2 position should remain in the product **42**. On the other hand, the hydrogenation of the enol tautomer **40** should give the deuterium-free amino acid **44** as the major product. The deuterio substrate **45** was first prepared from the cyclohexyl substrate **17** by exposure to an excess amount of deuteriomethanol as shown in Scheme 12. Avoiding any isotope exchange, the hydrogenation under standard conditions was subjected to work-up at 50 °C for 1 h. Products **46** and **47** were obtained in 46% yield and the H/D ra-

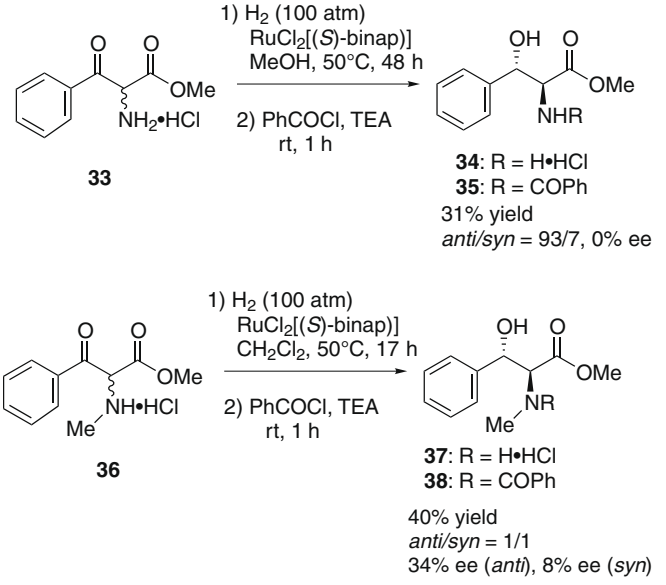
Table 5
Hydrogenation of the *N*-methyl substrate



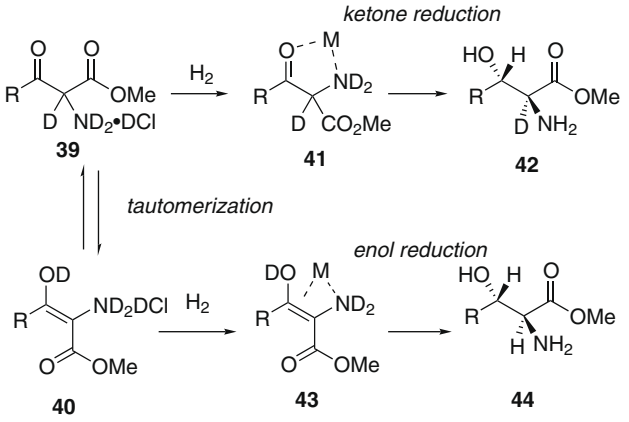
Entry	Solvent	Additive	Yield (%)	*anti*/*syn*	% ee
1	CH_2Cl_2	—	Trace	—	—
2	CH_2Cl_2	NaOAc	62	39/61	21
3	MeOH	—	12	94/6	19
4	MeOH	NaOAc	16	94/6	8
5	AcOH	NaOAc	13	72/28	19
6	[bdmin][PF_6]	—	9	80/20	31



Scheme 9. Asymmetric hydrogenation of the multi-functional substrate.



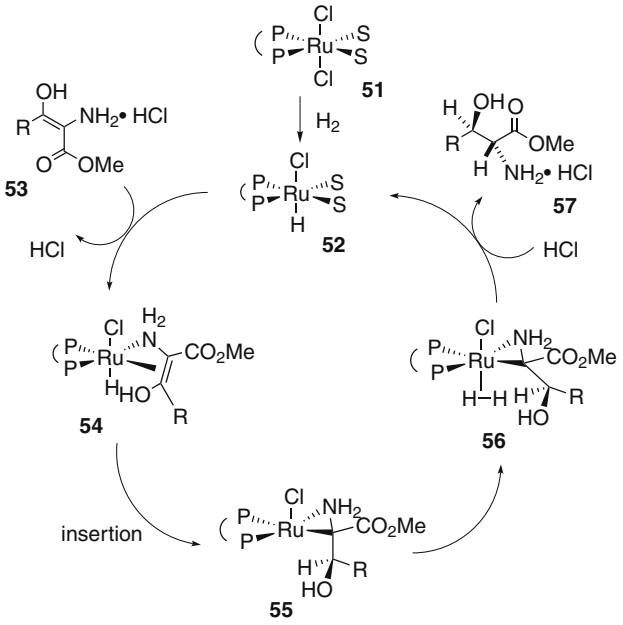
Scheme 10. Aromatic substrates.



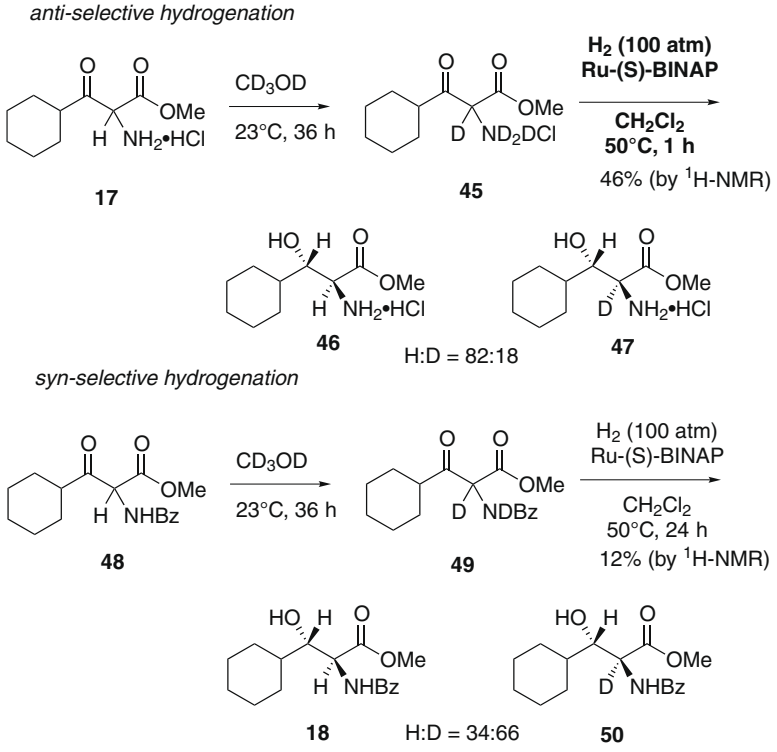
Scheme 11. Isotope labeling experiment.

tio was 82:18, which clearly supported the fact that the *anti*-selective asymmetric hydrogenation took place through the hydrogenation of the enol tautomer. As a control experiment, the *syn*-selective hydrogenation of the deuterio α-*N*-acylamino-β-keto ester **49** was carried out at 50 °C and 24 h. The H/D ratio of the obtained *syn*-amino acids **18** and **50** was 34:66, which is a result parallel to that of Noyori's experiments and supports the mechanism for reduction of the keto tautomer. Although *anti*- and *syn*-selective asymmetric hydrogenations are catalyzed by the same Ru-axially chiral phosphine complex, the above results clearly indicate that both reactions proceed through substantially different pathways, disclosing a new aspect of the Ru-chiral phosphine-catalyzed asymmetric hydrogenation. The shorter reaction time of the *anti*-selective asymmetric hydrogenation compared to that of the *syn*-selective counterpart also supports that described above.

Based on this information, the catalytic cycles of the *anti*-selective asymmetric hydrogenation using the Ru-catalyst can be illustrated as shown in Scheme 13. The [$RuCl_2$binap] complex **51** is hydrogenated to form the monohydride complex **52**, which undergoes the ligand-exchange reaction with the enol tautomer **53** of a substrate to produce the coordinated complex **54**. The insertion of the enol-double bond into the Ru–H bond affords complex **55**, which is subjected to σ-bond metathesis with hydrogen to generate the β-hydroxy-α-amino acid **57** and the real catalyst **52**. The alternative route, in which complex **55** is subjected to protonolysis with hydrogen chloride to produce **57** and the $RuCl_2$ complex **51**, is also possible.



Scheme 13. Catalytic cycle for Ru-catalyzed anti-selective hydrogenation.



Scheme 12. Deuterium experiment.

3. Conclusion

The *anti*-selective asymmetric hydrogenation of chirally labile α-amino-β-keto esters using the Ru-chiral phosphine catalysts provides a simple and straightforward access to important *anti*-β-hydroxy-α-amino acids. The Ru-catalyzed asymmetric hydrogenation of α-amino-β-keto esters via a DKR is the first example of producing *anti*-β-hydroxy-α-amino acids. The products, *anti*-β-hydroxy-α-amino acids, are useful building blocks for the synthesis of various pharmaceutical and natural products.

4. Experimental

4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus. Optical rotations were measured on a JASCO DIP-14-polarimeter and JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on a JASCO FT/IR-230 fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-GSX 400α (400 MHz) and JNM ECP400 spectrometers (400 MHz), unless otherwise indicated. Chemical shifts are recorded in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL HX-110A (LRFAB, LREI) spectrometer. HPLC analyses were carried out on a chiral column that was indicated in each experiment. Column chromatography was performed with silica gel BW-820MH (Fuji Davison Co.). All reactions were carried out in oven-dried glassware with magnetic stirring unless otherwise noted.

4.2. Benzyl *N*-*tert*-butoxycarbonyl glycinate 10

A mixture of glycine (35.0 g, 466 mmol), benzyl alcohol (231 mL, 2.23 mol), and *p*-toluenesulfonic acid monohydrate (106 g, 557 mmol) in benzene (469 mL) was stirred for 29 h at reflux using a Dean–Stark trap. The reaction mixture was cooled to 23 °C. The precipitates were filtered and washed with diethyl ether to afford benzyl glycinate toluenesulfonic acid salt (168 g) as colorless solids. Sodium hydrogen carbonate (47 g, 559 mmol) and di-*tert*-butyl dicarbonate (112 g, 513 mmol) were added to a stirred solution of the above-mentioned salt (168 g) in 1,4-dioxane (157 mL) and water (315 mL) at 23 °C. After stirring the mixture for 3 h, the reaction mixture was concentrated in vacuo. The residue was diluted with 1 M aqueous sodium hydrogen sulfate, and the whole was extracted with EtOAc. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was crystallized from ether–*n*-hexane to give **10** (113.4 g, 92%) as colorless solids: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.96 (d, J = 5.7 Hz, 2H), 5.00 (br, 1H), 5.18 (s, 2H), 7.34–7.38 (m, 5H).

4.3. Benzyl 2-(*tert*-butoxycarbonyl-isobutyryl-amino)-acetate 11a

To a stirred solution of **10** (1.06 g, 4.00 mmol) in THF (8.0 mL) at −78 °C was added dropwise KHMDS (0.5 M in toluene, 9.0 mL, 1.1 equiv) over 10 min under an argon atmosphere. After stirring for 2 h at −78 °C, isobutyryl chloride (0.46 mL, 4.39 mmol) was added to the mixture and the reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched with saturated aqueous ammonium chloride, and the resulting mixture was extracted with EtOAc/*n*-hexane (5/1). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to give **11a** (1.26 g, 94%) as a colorless oil: IR (neat) 2978, 1747, 1698, 1457, 1370, 1216, 1148, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 6H), 1.44 (s, 9H), 3.72–3.76 (m, 1H), 4.48 (s, 2H), 5.16 (s, 2H), 7.32–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 27.8, 34.6, 45.6, 66.9, 83.7, 128.4, 128.5, 135.4, 152.1, 168.9, 180.2; HRMS (FAB, NBA) calcd for $C_{18}H_{26}NO_5$ 336.1811 (M+H$^+$), found 336.1811.

4.4. General procedure for acylation using LHMDS

To a stirred solution of **10** in THF at −78 °C was added dropwise LHMDS (prepared from *n*-BuLi (1.56 M in *n*-hexane) and hexamethylsilazane, 1.1 equiv) under an argon atmosphere. After stirring for 1 h, acyl chloride (1.1 equiv) was added dropwise at −78 °C and the mixture was stirred for 3 h. The reaction was quenched with saturated aqueous ammonium chloride, and the resulting mixture was extracted with EtOAc/*n*-hexane (5/1). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.4.1. Benzyl (*tert*-butoxycarbonyl-cyclobutanecarbonyl-amino)-acetate 11b

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11b** (70%) as a colorless oil: IR (neat) 2979, 1746, 1694, 1369, 1214, 1192, 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.76–2.0 (m, 2H), 2.18–2.37 (m, 4H), 3.95–4.05 (m, 1H), 4.48 (s, 2H), 5.17 (s, 2H), 7.3–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 25.3, 27.6, 40.9, 45.3, 66.8, 83.4, 128.2, 128.3, 128.4, 135.5, 151.6, 168.8, 177.2. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.62; H, 7.38; N, 4.03.

4.4.2. Benzyl 2-(*tert*-butoxycarbonyl-cyclopentanecarbonyl-amino)-acetate 11c

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11c** (71%) as a colorless oil: IR (neat) 2971, 2871, 1746, 1695, 1455, 1370, 1148, 1048, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.53–1.94 (m, 8H), 3.80–3.85 (m, 1H), 4.49 (s, 2H), 5.16 (s, 2H), 7.31–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.8, 30.4, 45.2, 45.7, 66.9, 83.5, 128.4, 128.5, 135.4, 152.1, 169.0, 179.1; HRMS (FAB, NBA) calcd for $C_{20}H_{28}NO_5$ 362.1967 (M+H$^+$), found 362.1932.

4.4.3. Benzyl (*tert*-butoxycarbonyl-cyclohexanecarbonyl-amino)-acetate 11d

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5/1) to give **11d** (94%) as a white powder: mp 76–78 °C; IR (KBr) 2931, 2853, 1737, 1691, 1450, 1368, 1323, 1193, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.42 (m, 4H), 1.67–1.80 (m, 4H), 1.45 (s, 9H), 1.91–2.05 (m, 2H), 3.46 (tt, J = 3.3, 11.2 Hz), 4.47 (s, 2H), 5.15 (s, 2H), 7.32–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 25.9, 27.8, 29.7, 44.4, 45.7, 66.9, 83.6, 128.4, 128.5, 135.4, 152.1, 169.0, 179.1; HRMS (FAB, NBA) calcd for $C_{21}H_{30}NO_5$ 376.2124 (M+H$^+$), found 376.2148. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.32; H, 7.83; N, 3.75.

4.4.4. Benzyl 2-(*tert*-butoxycarbonyl-cycloheptanecarbonyl-amino)-acetate 11e

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11e** (97%) as a white powder: mp 49–50.5 °C; IR (KBr) 2929, 2857, 1741, 1698, 1457, 1339, 1149, 1043 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.44–1.66 (m, 17H), 1.72–1.78 (m, 2H), 1.90–1.97 (m, 2H), 3.64–3.71 (m, 1H), 4.47 (s, 2H), 5.16 (s, 2H), 7.30–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 27.8, 31.6, 45.2, 45.6, 66.9, 83.5, 128.4, 128.5, 135.4, 152.1, 169.0, 180.1; HRMS (FAB, NBA) calcd for $C_{22}H_{32}NO_5$ 390.2280 ($M+H^+$), found 390.2266. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 68.00; H, 8.07; N, 3.59.

4.4.5. Benzyl 2-(*tert*-butoxycarbonyl-propionyl-amino)-acetate 11f

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11f** (96%) as a colorless oil: IR (neat) 2979, 1743, 1702, 1368, 1337, 1193, 1150, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.6 Hz, 3H), 1.43 (s, 9H), 2.95 (q, J = 7.6 Hz, 2H), 4.51 (s, 2H), 5.17 (s, 2H), 7.3–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 27.6, 31.2, 45.1, 66.7, 83.4, 128.2, 128.4, 135.3, 151.0, 168.8, 176.3; HRMS (FAB, NBA) calcd for $C_{17}H_{23}NO_5$ 322.1654 ($M+H^+$), found 322.1634.

4.4.6. Benzyl 2-(*tert*-butoxycarbonyl-butyryl-amino)-acetate 11g

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11g** (88%) as a colorless oil: IR (neat) 2969, 1747, 1456, 1370, 1216, 1149, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.43 (s, 9H), 1.65–1.70 (m, 2H), 2.91 (t, J = 7.3 Hz, 2H), 4.50 (s, 2H), 5.17 (s, 2H), 7.32–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 18.4, 27.8, 39.8, 45.3, 66.9, 83.7, 128.4, 128.4, 128.6, 135.4, 152.2, 169.0, 175.6; HRMS (FAB, NBA) calcd for $C_{18}H_{26}NO_5$ 336.1811 ($M+H^+$), found 336.1804. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.52; H, 7.86; N, 4.15.

4.4.7. Benzyl 2-*tert*-butoxycarbonyl-(2,2-dimethyl-propionyl-amino)-acetate 11h

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **11h** (93%) as a colorless oil: IR (neat) 2974, 1747, 1694, 1456, 1336, 1148, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.44 (s, 9H), 4.33 (s, 2H), 5.16 (s, 2H), 7.33–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 27.8, 27.9, 43.1, 48.3, 66.0, 66.9, 83.2, 127.6, 127.9, 128.3, 128.3, 128.4, 128.5, 135.4, 152.7, 169.1, 184.6; HRMS (FAB, NBA) calcd for $C_{19}H_{28}NO_5$ 350.1967 ($M+H^+$), found 350.1976.

4.5. General procedure for N–C migration

To a stirred solution of **11** in THF at −78 °C were added dropwise *N*,*N*′-dimethylpropyleneurea (DMPU, 2.0 equiv) and LHMDS (prepared from *n*-BuLi (1.56 M in *n*-hexane) and hexamethylsilazane, 2.5 equiv) over 10 min under an argon atmosphere. After stirring for 3 h at −78 °C, the reaction was quenched with saturated aqueous ammonium chloride and the resulting mixture was extracted with EtOAc/*n*-hexane (5/1). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.5.1. Benzyl 2-*tert*-butoxycarbonylamino-4-methyl-3-oxo-pentanoate 12a

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1) to give **12a** (85%) as a colorless oil: IR (neat) 3431, 2977, 1759, 1715, 1496, 1367, 1251, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.44 (s, 9H), 2.94–2.99 (m, 1H), 5.15–5.29 (m, 3H), 5.73 (d, J = 7.0 Hz, 1H), 7.31–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.7, 28.2, 38.4, 62.1, 68.0, 80.5, 128.4, 128.6, 134.7, 154.8, 166.7, 205.1; HRMS (FAB, NBA) calcd for $C_{18}H_{26}NO_5$ 336.1811 ($M+H^+$), found 336.1816.

4.5.2. Benzyl 2-*tert*-butoxycarbonylamino-3-cyclobutyl-3-oxo-propionate 12b

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 8/1) to give **12b** (80%) as a colorless oil: IR (neat) 3426, 2979, 2948, 1754, 1713, 1496, 1368, 1250, 1162, 753, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.74–2.00 (m, 3H), 2.14–2.30 (m, 3H), 5.03 (d, J = 7.2 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.24 (d, J = 12.0 Hz, 1H), 5.74 (br d, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 24.3, 25.3, 28.4, 43.3, 62.4, 68.0, 80.6, 128.5, 128.7, 128.8, 134.9, 155.0, 166.8, 201.9; HRMS (FAB, NBA/PEG) calcd for $C_{19}H_{26}NO_5$ 348.1811 ($M+H^+$), found 348.1801.

4.5.3. Benzyl 2-*tert*-butoxycarbonylamino-3-cyclopentyl-3-oxo-propionate 12c

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1) to give **12c** (90%) as a colorless oil: IR (neat) 3430, 2967, 2871, 1759, 1714, 1489, 1367, 1254, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34–1.94 (m, 17H), 3.14–3.18 (m, 1H), 5.13–5.17 (m, 2H), 5.29 (d, J = 12.0 Hz, 1H), 5.76 (d, J = 6.8 Hz, 1H), 7.35–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.0, 28.2, 28.5, 30.3, 48.8, 63.5, 67.9, 80.5, 128.6, 134.8, 154.8, 166.8, 203.7; HRMS (FAB, NBA) calcd for $C_{20}H_{28}NO_5$ 362.1967 ($M+H^+$), found 362.1933.

4.5.4. Benzyl 2-*tert*-butoxycarbonylamino-3-cyclohexyl-3-oxo-propionate 12d

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 8/1) to give **12d** (80%) as a colorless oil: IR (neat) 3431, 2978, 2932, 2856, 1755, 1713, 1495, 1453, 1368, 1337, 1251, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05–1.92 (m, 19H), 2.64–2.68 (m, 1H), 5.14 (d, J = 12.1 Hz, 1H), 5.18 (d, J = 7.1 Hz, 1H), 5.31 (d, J = 12.1 Hz, 1H), 5.73 (d, J = 7.1 Hz, 1H), 7.31–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.5, 25.7, 27.6, 28.3, 29.1, 48.2, 62.3, 68.0, 80.5, 128.6, 128.7, 134.8, 154.9, 166.7, 204.0; HRMS (FAB, NBA) calcd for $C_{21}H_{30}NO_5$ 376.2124 ($M+H^+$), found 376.2118.

4.5.5. Benzyl 2-*tert*-butoxycarbonylamino-3-cycloheptyl-3-oxo-propionate 12e

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give **12e** (99%) as a colorless oil: IR (neat) 3429, 2978, 2928, 2858, 1754, 1713, 1492, 1367, 1338, 1254, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.93 (m, 21H), 2.88 (m, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.18 (d, J = 7.6 Hz, 1H), 5.30 (d, J = 12.0 Hz, 1H), 5.73 (d, J = 6.8 Hz, 1H), 7.35–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.5, 28.0, 28.1, 28.2, 29.1, 30.3, 49.4, 62.4, 67.9, 80.4, 128.5, 128.6, 134.8, 154.9, 166.7, 204.4; HRMS (FAB, NBA) calcd for $C_{22}H_{32}NO_5$ 390.2280 ($M+H^+$), found 390.2263.

4.5.6. Benzyl 2-*tert*-butoxycarbonylamino-3-oxo-pentanoate 12f

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1) to give **12f** (80%) as a colorless oil: IR (neat) 3432, 3377, 2979, 1754, 1714, 1496, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 2.50–2.75 (m, 2H), 5.07 (d, J = 7.2 Hz, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.27 (d, J = 12.0 Hz, 1H), 5.74 (br d, J = 6.4 Hz, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.26, 28.1, 33.9, 63.3, 67.8, 80.3, 128.2, 128.5, 134.6,

154.8, 166.5, 201.6; HRMS (FAB, NBA) calcd for $C_{17}H_{23}NO_5$ 322.1654 ($M+H^+$), found 322.1637.

4.5.7. Benzyl 2-*tert*-butoxycarbonylamino-3-oxo-hexanoate 12g

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1) to give **12g** (87%) as a colorless oil: IR (neat) 3432, 2970, 1759, 1715, 1496, 1368, 1253, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 3H), 1.44 (s, 9H), 1.52–1.62 (m, 2H), 2.52–2.60 (m, 2H), 5.05 (d, J = 7.1 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 5.29 (d, J = 12.3 Hz, 1H), 5.74 (d, J = 6.8 Hz, 1H), 7.31–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 16.8, 19.5, 27.8, 28.2, 42.4, 63.7, 68.0, 80.5, 128.4, 128.6, 134.7, 154.9, 166.6, 201.0; HRMS (FAB, NBA) calcd for $C_{18}H_{26}NO_5$ 336.1811 ($M+H^+$), found 336.1788.

4.5.8. Benzyl 2-*tert*-butoxycarbonylamino-4,4-dimethyl-3-oxo-pentanoate 12h

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1) to give **12h** (75%) as a colorless oil: IR (neat) 3376, 2977, 1758, 1713, 1504, 1368, 1326, 1252, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.43 (s, 9H), 5.15 (d, J = 12.3 Hz, 1H), 5.20 (d, J = 12.3 Hz, 1H), 5.52 (m, 2H), 7.29–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 28.2, 44.7, 57.0, 67.7, 80.6, 128.3, 128.5, 128.6, 154.8, 167.6, 208.0; HRMS (FAB, NBA) calcd for $C_{19}H_{28}NO_5$ 350.1967 ($M+H^+$), found 350.1913.

4.6. General procedure for α-amino-β-keto ester hydrochlorides

The protected compound **12** was dissolved in 4 M HCl–dioxane (0.3 M solution). After stirring for 24–72 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was triturated with diethyl ether to give **13** as a white powder. The crude material was used for the next hydrogenation without further purification.

4.6.1. Benzyl 2-amino-4-methyl-3-oxo-pentanoate hydrochloride salt 13a

Yield 97%; IR (KBr) 3403, 2972, 2936, 2654, 1762, 1736, 1523, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 3.03–3.09 (m, 1H), 5.24 (d, J = 11.6 Hz, 2H), 5.33 (d, J = 12.0 Hz, 2H), 5.47 (m, 1H), 7.32–7.38 (m, 5H), 9.00 (br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 18.9, 38.9, 60.4, 67.0, 69.2, 128.6, 128.7, 128.8, 134.1, 163.3, 202.1; HRMS (FAB, NBA) calcd for $C_{13}H_{18}NO_3$ 236.1287 (M^+-Cl), found 236.1272.

4.6.2. Benzyl 2-amino-3-cyclobutyl-3-oxo-propionate hydrochloride salt 13b

Yield 85%; IR (KBr) 3430, 2938, 2615, 1964, 1750, 1722, 1590, 1483, 1437, 1278, 1223, 1151, 1099, 1061, 984, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.7–2.0 (m, 3H), 2.1–2.3 (m, 2H), 2.35–2.45 (m, 1H), 3.63 (quint, J = 8.8 Hz, 1H), 5.23 (d, J = 8.8 Hz, 1H), 5.28 (d, J = 8.8 Hz, 1H), 5.34 (s, 1H), 7.3–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 24.0, 25.4, 43.4, 60.5, 69.3, 128.7, 128.8, 128.8, 134.1, 163.3, 198.8; HRMS (FAB, NBA) calcd for $C_{14}H_{18}NO_3Cl$ 248.1287 (M^+-Cl), found 248.1266. Anal. Calcd for $C_{14}H_{18}NO_3Cl$: C, 59.26; H, 6.39; 4.94. Found: C, 58.82; H, 6.46; N, 4.84.

4.6.3. Benzyl 2-amino-3-cyclopentyl-3-oxo-propionate hydrochloride salt 13c

Yield quant.; IR (KBr) 2951, 1746, 1720, 1508, 1458, 1269, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44–2.02 (m, 8H), 1.96–2.02 (m, 1H), 5.24 (d, J = 12.0 Hz, 1H), 5.33–5.36 (m, 2H), 7.26–7.39 (m, 5H), 9.00 (br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.0, 28.3, 30.6, 49.1, 61.6, 69.2, 128.6, 128.7, 128.8, 134.2, 163.3, 200.7; HRMS (FAB, NBA) calcd for $C_{15}H_{20}NO_3$ 262.1443 (M^+-Cl), found 262.1445. Anal. Calcd for $C_{15}H_{20}NO_3Cl{\cdot}1/2{\cdot}C_4H_8O_2$: C, 59.73; H, 7.08; 4.10. Found: C, 59.67; H, 7.01; N, 4.09.

4.6.4. Benzyl 2-amino-3-cyclohexyl-3-oxo-propionate hydrochloride salt 13d

Yield quant.; IR (KBr) 2931, 2854, 1747, 1719, 1509, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97–1.36 (m, 5H), 1.48–1.62 (m, 3H), 1.69–1.72 (m, 1H), 2.11–2.14 (m, 1H), 2.78 (tt, J = 3.2, 11.6 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.38 (d, J = 12.0 Hz, 1H), 5.53 (s, 1H), 7.30–7.39 (m, 5H, Ar–*H*), 8.93 (br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.5, 25.6, 27.2, 29.1, 48.3, 60.6, 69.2, 128.6, 128.8, 128.9, 134.2, 163,3, 200.8; HRMS (FAB, NBA) calcd for $C_{16}H_{22}NO_3$ 276.1600 (M^+-Cl), found 276.1602.

4.6.5. Benzyl 2-amino-3-cycloheptyl-3-oxo-propionate hydrochloride salt 13e

Yield quant.; IR (KBr) 2927, 2624, 1746, 1720, 1509, 1459, 1281, 1198, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15–1.18 (m, 1H), 1.45–1.57 (m, 11H), 2.93–2.97 (m, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.38 (d, J = 13.2 Hz, 1H), 5.40 (s, 1H), 7.31–7.39 (m, 5H), 9.01 (br); ^{13}C NMR (100 Hz, $CDCl_3$) δ 26.1, 26.5, 27.9, 28.1, 28.8, 30.3, 49.5, 60.7, 69.2, 128.6, 128.8, 128.9, 134.2, 163.3, 201,1; HRMS (FAB, NBA) cacld for $C_{17}H_{24}NO_3$ 290.1756 (M^+-Cl), found 290.1765.

4.6.6. Benzyl 2-amino-3-oxo-pentanoate hydrochloride salt 13f

Yield 92%; IR (KBr) 3432, 2932, 1751, 1725, 1471, 1287, 1227, 1148, 736 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.04–1.08 (m, 3H), 2.50–3.00 (m, 2H), 5.30–5.40 (m, 2H), 7.35–7.45 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 7.5, 35.0, 70.2, 129.8, 130.1, 135.9, 164.8, 199.9; HRMS (FAB, NBA) calcd for $C_{12}H_{16}NO_3Cl$ 222.1130 (M^+-Cl), found 222.1114.

4.6.7. Benzyl 2-amino-3-oxo-hexanoate hydrochloride salt 13g

Yield 80%; IR (KBr) 2968, 2935, 2599, 1750, 1725, 1459, 1280, 1226, 1147 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.84 (t, J = 7.6 Hz, 3H), 1.50–1.62 (m, 2H), 2.64–2.80 (m, 2H), 5.32 (d, J = 11.6 Hz, 1H), 5.41 (d, J = 12.0 Hz, 1H), 7.36–7.46 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 13.6, 17.6, 43.4, 70.2, 129.8, 130.1, 135.8, 164.7, 199.2; HRMS (FAB, NBA) calcd for $C_{13}H_{18}NO_5$ 236.1287 (M^+-Cl), found 236.1275. Anal. Calcd for $C_{13}H_{18}NO_3Cl$: C, 57.46; H, 6.68; N, 5.15. Found: C, 57.33; H, 6.59; N, 5.12.

4.6.8. Benzyl 2-amino-4,4-dimethyl-3-oxo-pentanoate hydrochloride salt 13h

Yield 91%; IR (KBr) 2971, 2900, 2867, 1747, 1718, 1543, 1508, 1265, 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 5.25 (s, 2H), 5.62 (s, 1H), 7.30–7.37 (m, 5H), 9.00 (br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 44.9, 56.7, 69.2, 128.6, 128.7, 128.9, 134.0, 163.6, 204.4; HRMS (FAB, NBA) calcd for $C_{14}H_{20}NO_3Cl$ 250.1443 (M^+-Cl), found 250.1438. Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; N, 4.90. Found: C, 58.62; H, 6.99; N, 4.90.

4.7. General procedure for the *anti*-selective asymmetric hydrogenation

To a mixture of $[RuCl_2(C_6H_6)]_2$ (10.3 mg, 0.0206 mmol) and (*S*)-BINAP (27.3 mg, 0.0438 mmol) in a flask under an argon atmosphere was added DMF (0.4 mL). After being degassed by freeze–thaw cycles, the mixture was stirred for 10 min at 100 °C. After cooling the mixture to 23 °C and removal of the solvent, the resulting red-brown catalyst was dried at 60 °C for 1 h under reduced pressure. A degassed solution of α-amino-β-keto ester hydrochloride **13** (1.00 mmol) in dichloromethane (1 × 2.5 mL, 1 × 0.5 mL) was added to the catalyst via cannula. The flask was transferred to a stainless autoclave. The mixture was stirred at 50 °C under

hydrogen pressure (100 atm) for 48 h. The solvent was removed in vacuo to afford **14**, which was used for the next step without any purification. Benzoyl chloride (0.13 mL, 1.12 mmol) and triethylamine (0.44 mL, 3.16 mmol) were added dropwise to a stirred solution of crude **14** in THF (2.0 mL) at 0 °C. After stirring the mixture for 1 h at 23 °C, the reaction was quenched with water and the resulting mixture was extracted with EtOAc/*n*-hexane (5/1). The organic layer was washed with 1 M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give **15**.

4.7.1. Methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-4-methylpentanoate (2*S*,3*S*)-8a

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **8a** (103 mg, 38%, 98% de, 95% ee) as a colorless oil: $[\alpha]_D^{25} = +35.4$ (*c* 0.99, $CHCl_3$); IR (neat) 3417, 2962, 1747, 1633, 1538, 1455, 1372, 1062, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.77 (sep, *J* = 6.6 Hz, 1H), 2.91 (d, *J* = 8.2 Hz, 1H), 3.62 (dt, *J* = 3.3, 8.6 Hz, 1H), 3.82 (s, 3H), 4.97 (dd, *J* = 3.3, 7.3 Hz, 1H), 7.14 (d, *J* = 6.6 Hz, 1H), 7.44–7.48 (m, 2H), 7.52–7.56 (m, 1H), 7.82–7.85 (m, 2H); HRMS (FAB, NBA) calcd for $C_{14}H_{20}NO_4$ 266.1392 ($M+H^+$), found 266.1408. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 85/15, 0.5 mL/min), t_R = 10.6 min ((2*R*,3*R*)-isomer, minor) and 15.6 min ((2*S*,3*S*)-isomer, major).

4.7.2. Benzyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-4-methylpentanoate (2*S*,3*S*)-8d

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **8d** (286 mg, 84%, >99% de, 98% ee) as a white powder: $[\alpha]_D^{24} = +33.9$ (*c* 1.00, $CHCl_3$); mp 95.5–96 °C; IR (KBr) 3414, 2961, 2935, 2858, 1749, 1647, 1519, 1192, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.71 (m, 1H), 2.92 (d, *J* = 8.4 Hz, 1H), 3.63 (dt, *J* = 3.1, 8.4 Hz, 1H), 4.99 (dd, *J* = 3.3, 7.3 Hz, 1H), 5.23 (d, *J* = 12 Hz, 1H), 5.29 (d, *J* = 12 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.34–7.39 (m, 5H), 7.43–7.47 (m, 2H), 7.52–7.56 (m, 1H), 7.81–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.0, 31.5, 56.2, 67.6, 78.9, 127.2, 128.4, 128.6, 128.7, 132.0, 133.4, 134.9, 167.5, 170.8; HRMS (FAB, NBA) calcd for $C_{20}H_{24}NO_4$ 342.1705 ($M+H^+$), found 342.1682. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.26; H, 6.82; N, 4.06. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 90/10, 0.5 mL/min), t_R = 21.6 min ((2*R*,3*R*)-isomer, minor) and 30.3 min ((2*S*,3*S*)-isomer, major).

4.7.3. Benzyl (2*S*,3*S*)-2-benzoylamino-3-cyclobutyl-3-hydroxypropionate (2*S*,3*S*)-15b

Prepared according to the general procedure using *n*-PrOH instead of dichloromethane, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **15b** (92%, *anti*/*syn* = 82/18, 81% ee (*anti*)) as a white powder, which was recrystallized from EtOAc–*n*-hexane to give pure **15b**: mp 94–95 °C; $[\alpha]_D^{23} = +22.3$ (*c* 1.00, $CHCl_3$); IR (KBr) 3407, 1745, 1727, 1639, 1527, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.6–2.1 (m, 6H), 2.3–2.5 (m, 1H), 3.15–3.35 (br s, 1H), 4.00 (dd, *J* = 2.8, 8.0 Hz, 1H), 4.87 (dd, *J* = 2.8, 6.8 Hz, 1H), 7.1–7.2 (br d, 1H), 7.3–7.6 (m, 8H), 7.82 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 24.6, 25.0, 37.9, 56.6, 67.6, 77.2, 127.2, 128.1, 128.4, 128.5, 128.6, 128.6, 128.7, 132.0, 133.3, 134.8, 167.9, 170.3. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.23; H, 6.50; N, 3.91. HPLC analysis: CHIRALPAK OD-H, (*n*-hexane/*i*-PrOH = 90/10, 0.5 mL/min), t_R = 26.1 min ((2*R*,3*R*)-isomer, minor) and 32.0 min ((2*S*,3*S*)-isomer, major).

4.7.4. Benzyl (2*S*,3*S*)-2-benzoylamino-3-cyclopentyl-3-hydroxypropionate (2*S*,3*S*)-15c

Prepared according to the general procedure using *n*-PrOH instead of dichloromethane, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **15c** (310 mg, 85%, 96% de, 95% ee) as a white powder: $[\alpha]_D^{24} = +20.5$ (*c* 1.00, $CHCl_3$); mp 109–111 °C; IR (KBr) 3414, 3342, 2938, 2867, 1746, 1644, 1521, 1488, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38–1.88 (m, 9H), 2.95 (d, *J* = 8.0 Hz, 1H), 3.78 (dt, *J* = 2.8, 8.8 Hz, 1H), 4.92 (dd, *J* = 2.8, 7.2 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.31 (d, *J* = 12.4 Hz, 1H), 7.19 (d, *J* = 6.4 Hz, 1H), 7.34–7.39 (m, 5H), 7.43–7.47 (m, 2H, 7.51–7.56 (m, 1H), 7.81–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.5, 29.0, 29.8, 43.5, 57.3, 67.5, 78.0, 127.2, 128.4, 128.6, 132.0, 133.4, 135.0, 167.6, 170.5; HRMS (FAB, NBA) calcd for $C_{22}H_{26}NO_4$ 368.1862 ($M+H^+$), found 368.1870. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.76. Found: C, 71.71; H, 6.74; N, 3.76. HPLC analysis: CHIRALPAK AD, (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R = 23.5 min ((2*R*,3*R*)-isomer, minor) and 28.4 min ((2*S*,3*S*)-isomer, major).

4.7.5. Benzyl (2*S*,3*S*)-2-benzoylamino-3-cyclohexyl-3-hydroxypropionate (2*S*,3*S*)-15d

Prepared according to the general procedure, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to give **15d** (325 mg, 85%, >99% de, 97% ee) as a white powder, which was recrystallized from *n*-hexane–EtOAc to give an analytical sample: $[\alpha]_D^{25} = +14.8$ (*c* 1.1, $CHCl_3$); mp 125–127 °C; IR (KBr) 3403, 2929, 2849, 1742, 1647, 1521, 1483, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95–1.78 (m, 10 H), 1.99 (m, 1H), 2.78 (d, *J* = 8.8 Hz, 1H), 3.66 (dt, *J* = 3.2, 8.8 Hz, 1H), 4.99 (dd, *J* = 2.9, 7.3 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.34 (d, *J* = 12.2 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 1H), 7.32–7.56 (m, 8H), 7.81–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 26.1, 29.0, 29.2, 40.9, 55.7, 67.5, 77.9, 127.2, 128.5, 128.6, 131.9, 133.5, 135.0, 167.4, 170.8; HRMS (FAB, NBA) calcd for $C_{23}H_{28}NO_4$ 382.2018 ($M+H^+$), found 382.1993. Anal Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.15; H, 7.16; N, 3.64. HPLC analysis for the crude sample: CHIRALPAK AD, (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R = 23.5 min ((2*R*,3*R*)-isomer, minor) and 28.4 min ((2*S*,3*S*)-isomer, major).

4.7.6. Benzyl (2*S*,3*S*)-2-benzoylamino-3-cycloheptyl-3-hydroxypropionate (2*S*,3*S*)-15e

Prepared according to the general procedure using *n*-PrOH instead of dichloromethane, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **15e** (341 mg, 86%, 94% de, 97% ee) as a white powder: $[\alpha]_D^{25} = +12.9$ (*c* 1.00, $CHCl_3$); IR (KBr) 3418, 3064, 3033, 2925, 2854, 1734, 1646, 1539, 1190, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.64 (m, 11H), 1.76–1.89 (m, 2H), 2.79 (m, 1H), 3.70 (dt, *J* = 3.2, 8.8 Hz, 1H), 5.01 (dd, *J* = 3.2, 7.2 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.32 (d, *J* = 12.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 7.32–7.40 (m, 5H), 7.42–7.46 (m, 2H), 7.51–7.55 (m, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.2, 28.2, 28.9, 30.6, 42.3, 55.8, 67.5, 77.6, 127.2, 128.5, 128.6, 131.9, 133.5, 135.0, 167.4, 170.9; HRMS (FAB, NBA) calcd for $C_{24}H_{30}NO_4$ 396.2175 ($M+H^+$), found: 396.2195. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.83; H, 7.34; N, 3.53. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 90/10, 0.5 mL/min), t_R = 30.5 min ((2*R*,3*R*)-isomer, minor) and 34.7 min ((2*S*,3*S*)-isomer, major).

4.7.7. Benzyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-pentanoate (2*S*,3*S*)-15f

Prepared according to the general procedure using (*R*)-MeO-BIPHEP at 23 °C instead of (*S*)-BINAP at 50 °C, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to

give **15f** (89%, *anti*/*syn* = 88/12, 76% ee (*anti*)) as a white powder, which was recrystallized from EtOAc–*n*-hexane to give an analytical sample **15f**: mp 116–117 °C; $[\alpha]_D^{22} = +36.2$ (>99% ee, *c* 1.00, $CHCl_3$); IR (KBr) 3384, 1734, 1640, 1531, 1242, 1207, 1119, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.4–1.6 (m, 2H), 3.23 (d, *J* = 7.6 Hz, 1H), 3.95–4.05 (m, 1H), 4.93 (dd, *J* = 3.2, 6.8 Hz, 2H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 7.18 (br d, *J* = 6.8 Hz, 1H), 7.30–7.60 (m, 8H), 7.80–7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 26.4, 57.9, 67.6, 74.8, 127.2, 128.3, 128.6, 128.6, 132.0, 133.3, 134.9, 167.9, 170.3. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.46; H, 6.42; 4.22. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 90/10, 0.5 mL/min), t_R = 18.8 min ((2*R*,3*R*)-isomer, minor) and 22.0 min ((2*S*,3*S*)-isomer, major).

4.7.8. Benzyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-hexanoate (2*S*,3*S*)-15g

Prepared according to the general procedure using (*R*)-MeO-BIPHEP at 23 °C instead of (*S*)-BINAP at 50 °C, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **15g** (129 mg, 76%, 94% de, 91% ee) as a white powder: $[\alpha]_D^{22} = -18.3$ (*c* 0.96, $CHCl_3$); mp 97–99 °C; IR (KBr) 3354, 2958, 2867, 1737, 1629, 1578, 1534, 1254, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, *J* = 7.2 Hz, 3H), 1.28–1.56 (m, 4H), 3.29 (d, *J* = 7.6 Hz, 1H), 4.05–4.10 (m, 1H), 4.93 (dd, *J* = 3.2, 6.8 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.31 (d, *J* = 12.4 Hz, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.26–7.56 (m, 8H), 7.82–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.9, 35.3, 58.3, 67.7, 73.1, 127.2, 128.2, 128.4, 128.7, 132.1, 133.3, 134.9, 168.0, 170.3; HRMS (FAB, NBA) calcd for $C_{20}H_{24}NO_4$ 342.1705 ($M+H^+$), found 342.1699. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.28; H, 6.86; 4.05. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 90/10, 0.5 mL/min), t_R = 26.6 min ((2*R*,3*R*)-isomer, minor) and 32.3 min ((2*S*,3*S*)-isomer, major).

4.7.9. Benzyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-4,4-dimethyl-pentanoate (2*S*,3*S*)-15h

Prepared according to the general procedure using *n*-PrOH instead of dichloromethane, and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **15h** (318 mg, 89%, 93% de, 79% ee) as a colorless oil: $[\alpha]_D^{22} = +23.9$ (*c* 1.00, $CHCl_3$); IR (neat) 3373, 3064, 3033, 2958, 2908, 2872, 1731, 1644, 1538, 1487, 1177, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 3.33 (d, *J* = 10 Hz, 1H), 3.67 (dd, *J* = 3.2, 9.6 Hz, 1H), 5.02 (dd, *J* = 3.2, 7.6 Hz, 1H), 5.20 (d, *J* = 12.4 Hz, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.34–7.40 (m, 5H), 7.43–7.47 (m, 2H), 7.51–7.55 (m, 1H), 7.78–7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 35.4, 54.5, 67.6, 81.1, 127.1, 128.5, 128.6, 132.0, 133.4, 134.6, 167.3, 171.1; HRMS (FAB, NBA) calcd for $C_{21}H_{26}NO_4$ 356.1862 ($M+H^+$), found 356.1827. HPLC analysis: CHIRALPAK AD, (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min), t_R = 17.8min ((2*S*,3*S*)-isomer, major) and 26.8 min ((2*R*,3*R*)-isomer, minor).

4.8. Methyl 5-cyclohexyl-oxazole-4-carboxylate 16

To a stirred mixture of methyl isocyanoacetate (3.11 g, 31.8 mmol) and cyclohexanecarboxylic anhydride (8.20 g, 34.4 mmol) in DMF (10.0 mL) at 0 °C was added dropwise DBU (4.7 mL, 31.8 mmol). After stirring for 11 h at room temperature, the reaction mixture was diluted with water and *n*-hexane/EtOAc (5/1) and washed with brine, 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was recrystallized from *n*-hexane/EtOAc to give oxazole **16** (5.00 g, 76%): mp 97.5–101 °C; IR (KBr) 2931, 2852, 1719, 1599, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.89 (m, 10H), 3.45–3.48 (m, 1H), 3.91 (s, 3H), 7.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 25.9, 30.6, 35.4, 51.9, 125.2, 148.6, 162.6, 164.1; HRMS (FAB, NBA) calcd for $C_{11}H_{16}NO_3$ 210.1130 ($M+H^+$), found 210.1119. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.05; H, 7.32; N, 6.71.

4.9. Methyl 2-amino-3-cyclohexyl-3-oxo-propioate hydrochloride salt 17

To a stirred solution **16** (1.05 g, 5.00 mmol) in MeOH (2.5 mL) at 23 °C was added 4 M hydrogen chloride in 1,4-dioxane (7.5 mL), and the mixture was heated to 50 °C for 4 h. After cooling the mixture to 23 °C, the mixture was concentrated in vacuo and the residue was triturated with ether to give the hydrochloride salt **17** (791 mg, 67%) as a white powder: IR (KBr) 2931, 2856, 1752, 1719, 1560, 1508, 1458, 1276, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19–1.50 (m, 5H), 1.66–1.82 (m, 4H), 2.18–2.20 (m, 1H), 2.90–2.95 (m, 1H), 3.91 (s, 3H), 5.50 (s, 1H), 8.92 (br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.6, 25.7, 27.4, 29.2, 48.4, 54.2, 60.3, 163.8, 201.0; HRMS (FAB, NBA) calcd for $C_{10}H_{18}NO_3$: 200.1287 (M^+-Cl), found: 200.1282.; Anal. Calcd for $C_{10}H_{18}ClNO_3$: C, 50.96; H, 7.70; N, 5.94. Found: C, 50.71; H, 7.71; N, 5.97.

4.10. Methyl (2*S*,3*S*)-2-benzoylamino-3-cyclohexyl-3-hydroxy-propionate (2*S*,3*S*)-18

Prepared according to the general procedure 4.7**,** and was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to give **18** (92%, 96% de, 96% ee) as a white powder: $[\alpha]_D^{26} = +35.5$ (*c* 1.07, $CHCl_3$); mp 94–97 °C; IR (KBr) 3545, 3493, 3281, 2927, 2854, 1739, 1630, 1542, 1363, 1230, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97–1.30 (m, 5H), 1.42–1.51 (m, 1H), 1.65–1.84 (m, 4H), 2.03–2.06 (m, 1H), 2.94 (d, *J* = 8.4 Hz, 1H), 3.68 (dt, *J* = 3.2, 8.8 Hz, 1H), 3.82 (s, 3H), 4.97 (dd, *J* = 3.2, 7.6 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.44–7.47 (m, 2H), 7.51–7.56 (m, 1H), 7.82–7.84 (m, 2H); HRMS (FAB, NBA) calcd for $C_{17}H_{24}NO_4$ 306.1705 ($M+H^+$), found 306.1724. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.68; H, 7.49; N, 4.55. HPLC analysis: CHIRALCEL OD-H, (*n*-hexane/*i*-PrOH = 85/15, 0.5 mL/min), t_R = 11.2 min ((2*R*,3*R*)-isomer, minor) and 15.3 min ((2*S*,3*S*)-isomer, major).

4.11. Benzyl [([1,3]dioxane-2-carbonyl)-amino]-acetate 22

To a refluxing solution of boron trifluoride etherate (7.7 mL, 60.8 mmol) in chloroform (18.0 mL) were added dropwise a solution of ethyl diethoxyacetate **12** (5.4 mL, 30.2 mmol) and 1,3-propanediol (2.2 mL, 30.4 mmol) in chloroform (6.0 mL) over 15 min under an argon atmosphere. After refluxing for 30 min, the reaction mixture was cooled to room temperature, washed with water, 10% aqueous potassium carbonate, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give ethyl 1,3-dioxane-2-carboxylate **20**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 1.43–1.48 (m, 1H), 2.14–2.26 (m, 1H), 3.85–3.92 (m, 2H), 4.23–4.28 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 5.03 (s, 1H). Aqueous sodium hydroxide (6.04 g, 151 mmol) in water (60 mL) was added dropwise to a stirred solution of the crude **20** (ca. 30.2 mmol) in ethanol (45 mL) at 0 °C. After stirring for 13 h at room temperature, the reaction mixture was cooled to 0 °C, acidified with 3 M hydrochloric acid, and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give 1,3-dioxane-2-carboxylic acid **21**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.45–1.51 (m, 1H), 2.16–2.27 (m, 1H), 3.88–3.95 (m, 2H), 4.24–4.29 (m, 2H), 5.07 (s, 1H). EDCI (6.95 g, 36.3 mmol) and triethylamine (5.1 mL, 36.6 mmol) were added to a stirred solution of the crude **21** (ca. 30.2 mmol) and glycine benzyl ester *p*-toluene sulfonate (10.2 g, 30.2 mmol) in

dichloromethane (100 mL) at 0 °C. After stirring for 12 h at 23 °C, the reaction was quenched with saturated aqueous ammonium chloride and the resulting mixture was extracted twice with dichloromethane. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/2) to give **22** (3.16 g, 38% (three steps)) as a yellow oil: IR (neat) 3411, 2964, 2862, 1750, 1694, 1535, 1192, 1132, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41–1.46 (m, 1H), 2.09–2.21 (m, 1H), 3.85–3.91 (m, 2H), 4.12 (d, J = 5.6 Hz, 2H), 4.21–4.25 (m, 2H), 4.94 (s, 1H), 5.20 (s, 2H), 7.13 (br, 1H), 7.34–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 40.0, 66.3, 96.0, 127.5, 127.6, 127.8, 134.4, 165.7, 168.4; HRMS (FAB, NBA) calcd for $C_{14}H_{18}NO_5$ 280.1185 ($M+H^+$), found 280.1161.

4.12. Benzyl [*tert*-butoxycarbonyl-([1,3]dioxane-2-carbonyl)-amino]-acetate 23

To a stirred solution of **22** (3.08 g, 11.0 mmol) in acetonitrile (24.0 mL) at 0 °C were added di-*tert*-butyl dicarbonate (2.88 g, 13.2 mmol), 4-dimethylaminopyridine (134 mg, 1.10 mmol), and *N*-ethyldiisopropylamine (2.3 mL, 13.2 mmol). After stirring for 2 h at rt, the reaction was quenched with saturated aqueous ammonium chloride and the resulting mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1) to give **23** (4.20 g, quant) as a yellow oil: IR (neat) 2978, 1748, 1704, 1337, 1222, 1149, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40–1.47 (m, 1H), 1.43 (s, 9H), 2.10–2.21 (m, 1H), 3.89–3.95 (m, 2H), 4.20–4.24 (m, 2H), 4.47 (s, 2H), 5.17 (s, 2H), 5.87 (s, 1H), 7.31–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 27.6, 45.8, 67.0, 67.1, 84.3, 96.6, 128.3, 128.5, 135.3, 151.3, 168.3, 168.4; HRMS (FAB, NBA) calcd for $C_{19}H_{26}NO_7$ 380.1709 ($M+H^+$), found 380.1690.

4.13. Benzyl 2-*tert*-butoxycarbonylamino-3-[1,3]dioxan-2-yl-3-oxo-propionate 24

To a stirred solution of amide **23** (2.00 g, 5.27 mmol) in THF (18.0 mL) at −78 °C were added dropwise DMPU (1.3 mL, 10.8 mmol) and LHMDS (prepared from *n*-BuLi (1.56 M in *n*-hexane, 8.4 mL, 13.1 mmol) and HMDS (2.8 mL, 13.3 mmol) under an argon atmosphere. After stirring for 2 h at −78 °C, the reaction was quenched with saturated aqueous ammonium chloride and the resulting mixture was extracted twice with EtOAc–*n*-hexane (5/1). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1) to give keto ester **24** (1.54 g, 77%): IR (neat) 3431, 2978, 2864, 1714, 1497, 1368, 1240, 1160, 1096, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.48 (m, 1H), 1.44 (s, 9H), 2.00–2.09 (m, 1H), 3.71 (dt, J = 2.4, 12 Hz, 2H), 4.07–4.17 (m, 2H), 5.00 (s, 1H), 5.16 (d, J = 12 Hz, 1H), 5.27 (d, J = 12 Hz, 1H), 5.50 (d, J = 8.4 Hz, 1H), 5.62 (d, J = 7.6 Hz, 1H), 7.32–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 28.2, 59.8, 67.0, 67.3, 67.8, 80.6, 98.4, 128.4, 128.6, 134.8, 154.7, 166.2, 194.4; HRMS (FAB, NBA + NaCl) calcd for $C_{19}H_{25}NO_7$ 402.1529 (M^++Na), found 402.1524.

4.14. Benzyl 2-amino-3-[1,3]dioxin-3-oxo-pentanoate hydrochloride salt 25

To the keto ester **24** (1.28 g, 3.38 mmol) at 0 °C was added 4 M HCl–dioxane (11.3 mL). After stirring for 30 min at 0 °C, the reaction mixture was concentrated in vacuo. The residue was triturated with diethyl ether to give **25** (963 mg, 91%). The crude material was used for the next step without further purification. **25**: IR (KBr) 2964, 1757, 1585, 1480, 1308, 1243, 1048 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.30–1.34 (m, 1H), 1.99–2.06 (m, 1H), 3.63–3.72 (m, 2H), 4.07–4.11 (m, 2H), 4.10 (s, 1H), 4.62 (s, 1H), 5.27 (d, J = 12 Hz, 1H), 5.30 (d, J = 12 Hz, 1H), 7.34–7.47 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 26.4, 26.6, 58.6, 67.9, 68.0, 68.9, 69.1, 93.6, 102.4, 128.0, 129.3, 129.6, 129.8, 129.9, 167.5; HRMS (FAB, NBA) calcd for $C_{14}H_{18}NO_5$ 280.1185 (M^+−Cl), found 280.1177.

4.15. Benzyl 2-benzoylamino-3-[1,3]dioxin-2-yl-3-hydroxy-propionate 27

To a mixture of $[RuCl_2(C_6H_6)]_2$ (5.0 mg, 0.010 mmol) and (*S*)-BINAP (13.5 mg, 0.0217 mmol) under an argon atmosphere was added DMF, (0.4 mL) and the mixture was degassed by three freeze–thaw cycles. Next, the mixture was heated to 100 °C and stirred for 10 min. After being cooled to room temperature and removal of the solvent, the resulting red-brown catalyst was dried in vacuo at 60 °C for 1 h. A degassed solution of α-amino-β-keto ester hydrochloride **25** (157.4 mg, 0.500 mmol) in dichloromethane (1 × 2.0 mL, 1 × 0.5 mL) was added to the catalyst via *cannula*. The mixture was stirred at 50 °C under a hydrogen pressure (100 atm) for 48 h. The solvent was removed in vacuo to afford **26,** which was used for the next step without any purification. Benzoyl chloride (0.07 mL, 0.603 mmol) and triethylamine (0.22 mL, 1.58 mmol) were added dropwise to a stirred solution of crude **26** in THF (1.0 mL) at 0 °C. After stirring for 1 h at rt, the reaction was quenched with water and the resulting mixture was extracted twice with EtOAc/*n*-hexane (5/1). The combined organic layers were washed with 1 M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1) to give **27** (106.9 mg, 55%, 28% de, 18% ee): IR (neat) 3410, 3062, 2961, 2860, 1745, 1660, 1524, 1487, 1143, 1092, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.36 (m, 1H × 2), 1.98–2.10 (m, 1H × 2), 2.74 (d, J = 4.0 Hz, 1H), 3.50 (d, J = 7.2 Hz, 1H), 3.61–3.78 (m, 2H × 2), 4.01–4.18 (m, 2H × 2), 4.55 (d, J = 6.4 Hz, 1H), 4.61 (d, J = 4.8 Hz, 1H), 5.08 (dd, J = 3.2, 7.2 Hz, 1H), 5.14 (dd, J = 2.4, 9.2 Hz, 1H), 5.20 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H), 5.25 (d, J = 12.4 Hz, 1H), 5.26 (d, J = 12.0 Hz, 1H), 6.99–7.01 (m, 1H × 2), 7.31–7.54 (m, 7H × 2), 7.81–7.84 (m, 3H × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 25.5, 53.1, 53.4, 54.9, 66.7, 66.8, 67.2, 67.3, 72.4, 72.5, 100.0, 100.7, 127.1, 127.3, 128.0, 128.2 (×2), 128.3, 128.4 (×3), 128.5, 131.6, 131.8, 133.5, 133.8, 135.2, 167.4, 167.9, 169.4, 170.4; HRMS (FAB, NBA) calcd for $C_{21}H_{24}NO_6$ 386.1604 ($M+H^+$), found 386.1623. The diastereomeric excess was determined by ^1H NMR. The enantiomeric excess was determined by HPLC analysis using CHIRALCEL OD-H and *n*-hexane/*i*-PrOH (50:50, 0.5 mL/min).

Acknowledgment

This work was financially supported in part by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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