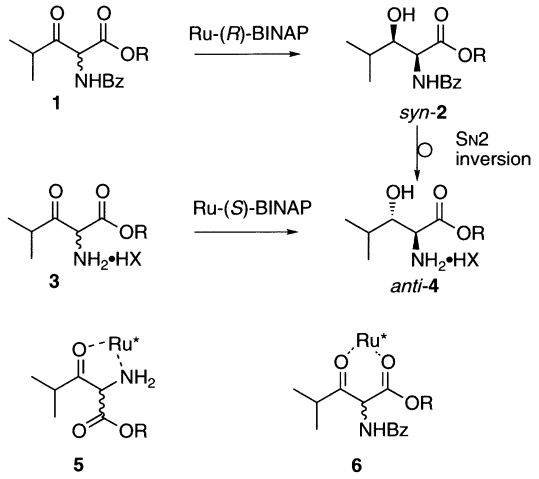
achieved stereoselective synthesis of all four stereoisomers of 3-hydroxyleucine.[3i] In this method, the *syn* isomer **2** of 3-hydroxyleucine was directly prepared by the asymmetric hydrogenation, but the *anti* isomer **4** needed to be constructed from **2** by two additional steps, oxazoline formation with internal SN2 inversion and acid hydrolysis (Scheme 1). To our knowledge, direct preparation of the *anti*-β-hydroxy-α-amino acids from the α-amino-β-keto esters by using an Ru–chiral-phosphane catalyst has not been reported. Herein, we describe the highly *anti*-selective hydrogenation of α-amino-β-keto esters through dynamic kinetic resolution with the Ru–BINAP catalyst. We envisioned hydrogenation through the five-membered transition state **5** (Scheme 1) with the 2-amino substituent of α-amino-β-keto ester **3** as a directing group; this reaction would directly produce *anti*-β-hydroxy-α-amino acid **4** in place of the *syn* product **2** that is produced through the six-membered transition state **6**.



Scheme 1. Synthesis of *syn*- and *anti*-β-hydroxy-α-amino acids through dynamic kinetic resolution with the Ru–BINAP catalyst. Bz = benzoyl.

anti-*Selective Hydrogenation*

Stereoselective Synthesis of *anti*-β-Hydroxy-α-amino Acids through Dynamic Kinetic Resolution

*Kazuishi Makino, Takayuki Goto, Yasuhiro Hiroki, and Yasumasa Hamada**

β-Hydroxy-α-amino acids are valuable constituents of a variety of biologically active natural products and medicinally important compounds, and many approaches for their enantioselective synthesis have been reported.[1–4] In connection with our ongoing research into the total synthesis of cyclodepsipeptides,[5] papuamides, and polyoxypeptins with biologically interesting activities, we needed a new method for the preparation of a large amount of (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucine bearing the skeleton of an *anti*-β-hydroxy-α-amino acid, with control of both relative and absolute configuration. It is reported that *syn*-β-hydroxy-α-amino acid derivatives have been efficiently synthesized with high diastereo- and enantioselectivities from chirally labile α-amino-β-keto esters through dynamic kinetic resolution with the Ru–BINAP catalyst (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), which was originally developed by Noyori and co-workers.[3,4,6] Using this methodology, we have

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Hydrogenation of methyl 2-amino-4-methyl-3-oxo-pentanoate (**3**, where R = Me), the substrate producing 3-hydroxyleucine, was examined in detail, and the results are shown in Table 1. Reactions were carried out with the Ru–(*S*)-BINAP catalyst (4.2 mol%) at 50 °C under 100 atm of hydrogen. The absolute and relative configurations of the hydrogenated product were established, after transformation into benzoylamide derivative **7**, by comparison with authentic samples.[3i] In the preliminary experiment with the TsOH salt in methanol we were pleased to find that excellent *anti* selectivity (97:3) was observed by ^{1}H NMR analysis, although the enantioselectivity needed to be improved (Table 1, entry 1). With this encouraging result in hand, we extensively surveyed the conditions for the *anti*-selective hydrogenation with high enantioselectivity. First, the effect of counter anions in ammonium salts was investigated. The hydrochloric acid salt showed high *anti* diastereoselectivity with modest enantioselectivity (Table 1, entry 3). Interestingly, the tetrafluoroboric acid salt inhibited the hydrogenation, and the starting material was recovered (entry 2). Next, the effect of solvents was screened. The use of a polar solvent such as water,

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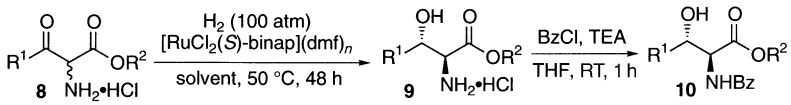
ethylene glycol, or *tert*-butyl alcohol was less or not effective for this hydrogenation. Methanol, *n*-propanol, 2-propanol, and dichloromethane were the solvents of choice for the diastereoselectivity. In particular, when the reaction was carried out in dichloromethane, the enantioselectivity of the desired *anti* product was increased to 95% *ee* but the yield was poor (entry 6). The decrease of the yield in dichloromethane may be due to very low solubility of the starting material. To improve the yield, the influences of the ester group and the solvent were next studied. Among the various ester derivatives examined in dichloromethane, the introduction of an isopropyl or a benzyl ester group led to the reaction being more effective in terms of yield (Table 1, entries 8 and 9). Especially in the case of a benzyl ester (Table 1, entry 9) the yield was increased to 87% with excellent diastereo- and enantioselectivity (>99% *de*, 96% *ee*). Although the reaction time was not optimized, the hydrogenation for 6 h under similar conditions was found to give almost the same result (Table 1, entry 11).

Table 2: The *anti*-selective asymmetric hydrogenation through dynamic kinetic resolution of other α-amino-β-keto esters.[a]

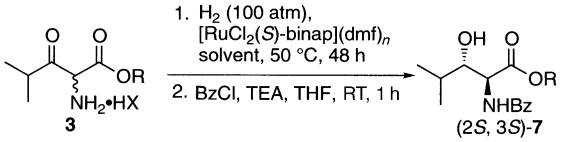


Entry	R^1	R^2	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	*i*Pr	Bn	CH_2Cl_2	87	>99:1	96
2	cyclobutyl	Bn	*n*PrOH	92	83:17	81
3	cyclopentyl	Bn	*n*PrOH	85	97.5:2.5	95
4	cyclohexyl	Bn	CH_2Cl_2	85	>99:1	97
5	cyclohexyl	Me	CH_2Cl_2	84	97.5:2.5	96
6	cycloheptyl	Bn	*n*PrOH	86	97:3	97
7	Et	Bn	CH_2Cl_2	89	89:11	76
8	*n*Pr	Bn	CH_2Cl_2	88	94:6	74
9	*n*Pr	Bn	*n*PrOH	53	91:1	58
10	*t*Bu	Bn	CH_2Cl_2	67	71:29	60
11	*t*Bu	Bn	*n*PrOH	89	96:4	79
12[e]	Ph	Bn	MeOH	93	>99:1	4
13[f]	cyclohexyl	Me	CH_2Cl_2	92	98:2	95

[a] Reaction conditions: Substrate (1 mmol), catalyst (3.8–4.6 mol%), and solvent (3 mL). [b] Yield over two steps. [c] *anti*:*syn* diastereomeric ratio. Determined by ^{1}H NMR analysis. [d] Value of the *anti*-3-hydroxyamino acid esters. Determined by HPLC analysis. [e] Reaction was carried out at 100°C. The product was analyzed after conversion into the corresponding acetamide. [f] The reaction was carried out by using 0.4 mol% of the catalyst under 30 atm of hydrogen for 6 h.

This method was then applied to various substrates to clarify the generality of the hydrogenation, and the results are shown in Table 2. The starting α-amino-β-keto ester hydrochlorides were easily prepared by the following three methods: 1) acid hydrolysis of 4-alkoxycarbonyloxazoles derived from carboxylic anhydrides and isocyanoacetic acid esters,[3i] 2) base-mediated N–C acyl migration of *N*-*tert*-butoxycarbonyl-*N*-acylglycine esters and then acid deprotection,[7] and 3) acylation of the benzophenone ketimine derived from a glycine ester in the presence of a strong base followed by acid hydrolysis.[8] Under our reaction conditions, the substrates with a secondary alkyl carbon, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl substituent at the α position of the ketone carbonyl group afforded the *anti* products with high diastereo- and enantioselectivities in excellent yields (Table 2, entries 2–6).[9] Furthermore, it was found that the hydrogenation of the cyclohexyl substrate was completed in 6 h even with a substrate/catalyst ratio of 250 under 30 atm of hydrogen (Table 2, entry 13). In the case of the *n*-alkyl substrate at the C4 position, the stereoselectivity was decreased to moderate (Table 2, entries 7–9). The hydrogenation of the α-amino-β-keto ester with the *tert*-butyl group was maximized in *n*-propanol to give the product in 89% yield and 79% *ee* with a diastereomeric ratio of 96:4 (Table 2, entry 11). In an aromatic substrate the hydrogenation in dichloromethane or *n*-propanol did not proceed under our reaction conditions. After some experiments we found that the hydrogenation of this substrate in MeOH at 100°C afforded exclusively the *anti* product in 93% yield. However, the enantioselectivity was poor. These results suggest that hydrogenation with the Ru–BINAP catalyst is affected by the structure at the C4 position of the α-amino-β-keto ester. Nonetheless, the results of the above asymmetric reaction with the Ru–BINAP catalyst are noteworthy not only because this represents the first example of *anti*-selective hydrogenation of α-amino-β-keto esters with high diastereo- and enantioselectivity through dynamic kinetic resolution but also because the amino group in the substrate is shown to serve as a stronger directing substituent than the ester function. Although the mechanism of the asymmetric induction with a high level of *anti* selectivity is not clear at present,

Table 1: The *anti*-selective asymmetric hydrogenation through dynamic kinetic resolution.[a]



Entry	R	HX	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	TsOH	MeOH	72	97:3	22
2[e]	Me	HBF_4	MeOH	–	–	–
3	Me	HCl	MeOH	71	99:1	56
4	Me	HCl	*n*PrOH	69	99:1	69
5	Me	HCl	*i*PrOH	81	99:1	81
6	Me	HCl	CH_2Cl_2	38	99:1	95
7	Et	HCl	CH_2Cl_2	73	96:4	93
8	*i*Pr	HCl	CH_2Cl_2	96	98:2	92
9	Bn	HCl	CH_2Cl_2	87	>99:1	96
10	Bn	HCl	*i*PrOH	94	98:2	76
11[f]	Bn	HCl	CH_2Cl_2	82	>99:1	98

[a] Reaction conditions: Substrate (1 mmol), catalyst (3.8–4.6 mol%), and solvent (3.0 mL). Abbreviations: TsOH = toluene-4-sulfonic acid, Bn = benzyl. [b] Yield over two steps. [c] *anti*:*syn* diastereomeric ratio. Determined by ^{1}H NMR analysis. [d] Value of the *anti*-3-hydroxyamino acid ester. Determined by HPLC analysis. [e] No reaction. [f] Reaction time for hydrogenation: 6 h.

we speculate that the reaction proceeds via a sterically constrained five-membered transition state.

In conclusion, we have succeeded in developing a new method for the preparation of *anti*-β-hydroxy-α-amino acids from α-amino-β-keto esters by using the Ru–BINAP catalyst in a dynamic kinetic resolution; this method provides the first example of the *anti*-selective hydrogenation and four-step access to the important (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxy-α-amino acids from readily available acid anhydrides or acid chlorides. Further studies to elucidate the reaction mechanism and extend the scope of the method's synthetic utility are in progress in our laboratory.

Experimental Section

Typical procedure: DMF (400 μL) was added to a mixture of $[\{RuCl_2(C_6H_6)\}_2]$ (9.8 mg, 19.6 μmol) and (*S*)-BINAP (26.4 mg, 42.4 μmol) in a Schlenk tube under an argon atmosphere. After being degassed, the mixture was stirred for 10 min at 100 °C. The resulting mixture was cooled and concentrated in vacuo at 50 °C for 2.5 h to give the reddish-brown catalyst. A degassed solution of α-amino-β-ketoester **8** ($R^1 = i$Pr, R^2 = Bn, 271.5 mg, 1.0 mmol) in CH_2Cl_2 (1 × 2.5 mL, 1 × 0.5 mL) was added dropwise to the catalyst through a canula under an argon atmosphere. The mixture was stirred at 50 °C under hydrogen (100 atm) for 6 h. The solvent was removed in vacuo to afford α-amino-β-hydroxy ester **9** which was used in the next step without further purification.

Benzoyl chloride (130 μL, 1.12 mmol) and triethylamine (440 μL, 0.316 mmol) were added dropwise to a solution of the crude **9** in THF (2.0 mL) at 0 °C. After stirring for 1 h at 23 °C, the reaction mixture was quenched with water and diluted with ethyl acetate/*n*-hexane (5:1). The mixture was washed with aqueous 1N HCl, water, saturated aqueous $NaHCO_3$, and brine, dried with Na_2SO_4, and filtered. The filtrate was then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane (1:2)) to give **10** (278.1 mg, 0.815 mmol, 82 % yield (2 steps), > 99 % *de*, 98 % *ee*): HPLC analysis with a Chiralcel OD-H chiral column (eluent = *n*-hexane/*i*PrOH (90:10, 0.5 mL min^{-1})): retention time for (2*R*,3*R*)-**10** = 21.6 min, for (2*S*,3*S*)-**10** = 30.3 min; $[\alpha]_D^{24} = +33.9$ (c = 1.00, $CHCl_3$); m.p. 95.5–96 °C; IR (KBr): $\tilde{\nu}$ = 3414, 2961, 2935, 2858, 1749, 1647, 1519, 1192, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.6 Hz, 3H; $(CH_3)_2CH$), 1.13 (d, J = 6.6 Hz, 3H; $(CH_3)_2CH$), 1.71 (m, 1H; $(CH_3)_2CH$), 2.92 (d, J = 8.4 Hz, 1H; CHO*H*), 3.63 (dt, J = 3.1, 8.4 Hz, 1H; C*H*OH), 4.99 (dd, J = 3.3, 7.3 Hz, 1H; C*H*NH), 5.23 (d, J = 12 Hz, 1H; CH_2Ph), 5.29 (d, J = 12 Hz, 1H; CH_2Ph), 7.14 (d, J = 7.3 Hz, 1H; CHN*H*), 7.34–7.39 (m, 5H; Ar*H*), 7.43–7.47 (m, 2H; Ar*H*), 7.52–7.56 (m, 1H; Ar*H*), 7.81–7.83 ppm (m, 2H; Ar*H*); ^{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 ppm; HRMS (FAB, NBA): calcd for $C_{20}H_{24}NO_4$: 342.1705 [M^+ + 1]; found: 342.1682; elemental analysis: 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.

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Keywords: amino acids · asymmetric synthesis · hydrogenation · kinetic resolution · ruthenium

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