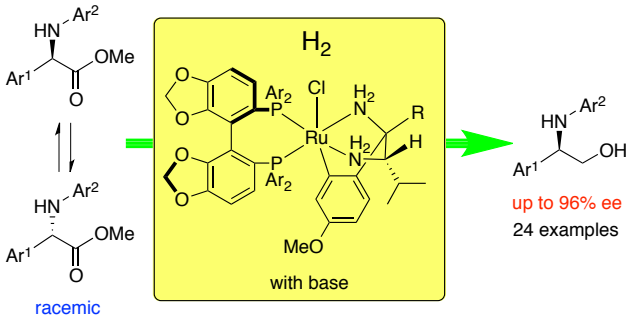
Asymmetric Hydrogenation of α-Amino Esters into Optically Active β-Amino Alcohols through Dynamic Kinetic Resolution Catalyzed by Ruthenabicyclic Complexes

Hiroki Ishikawa, Taiga Yurino, Ryo Komatsu, Ming-Yuan Gao, Noriyoshi Arai, Taichiro Touge, Kazuhiko Matsumura, and Takeshi Ohkuma*

Keywords: amino alcohols, amino esters, asymmetric catalysis, dynamic kinetic resolution, hydrogenation, ruthenium complexes



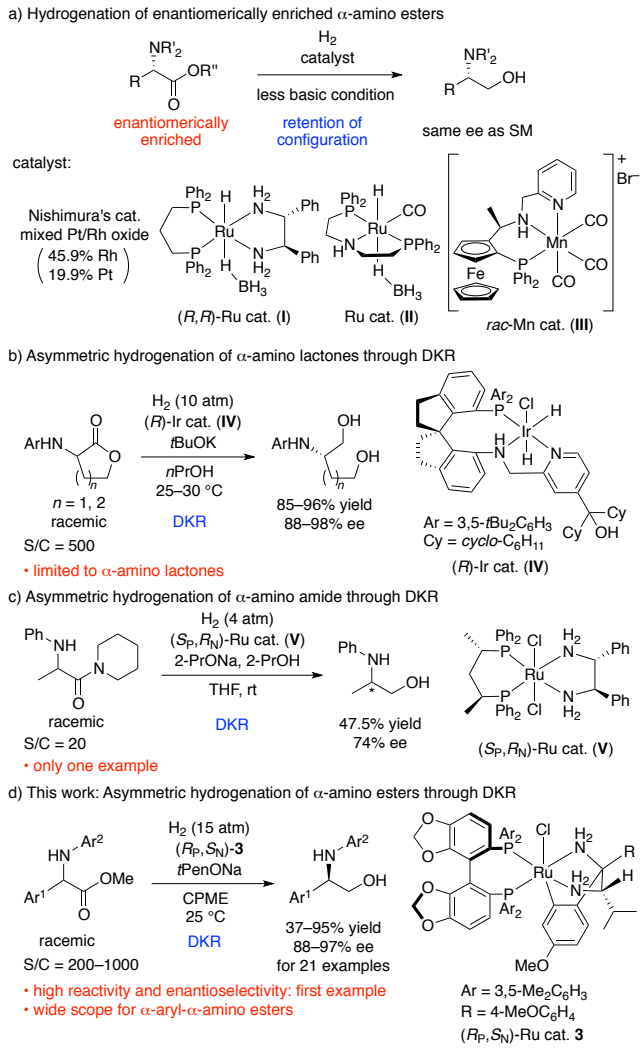
ABSTRACT: Racemic α-substituted α-amino esters were hydrogenated into enantio-enriched β-amino alcohols through dynamic kinetic resolution with chiral ruthenabicyclic complexes. The reaction was carried out with a substrate/catalyst molar ratio of 200–1000 under 15 atm of H_2 at 25 °C to afford a variety of β-substituted β-aminoethanols in up to 96% ee (24 examples). The mechanistic studies including deuteration experiments suggested that the reaction proceeds with 1,2-hydride migration of the α-amino acetalate intermediate into the α-hydroxy imine followed by the continuous reduction of the imino compound, affording the amino alcohol product.

Optically active β-substituted β-aminoethanols have been frequently utilized in the synthesis of a wide variety of bioactive compounds, including natural products, medicines, and agrochemicals.[1] These compounds also have made significant contribution to the advancement of asymmetric catalysis and synthesis as optically active ligands, auxiliaries, and their precursors.[2] Therefore, development of reliable and facile methods for the synthesis of the optically active β-amino alcohols is highly desirable.[3] Enantioselective aminohydroxylation of styrene derivatives is an elegant method to prepare the β-aryl-β-aminoethanols in high ee, although the products are obtained as a regioisomeric mixture.[1b,4] Regio- and setereoselective ring-opening reactions of enantio-enriched epoxides and aziridines are also applicable.[5,6]

Reduction of enantiomerically enriched α-amino esters into β-amino alcohols with maintenance of the enantiopurity is a well-known method.[2a] Stoichiometric metal hydride reduction is a representative rection using this approach. In recent years more efficient procedures with catalytic hydrogenation have been reported (Scheme 1a).[7] These reactions are carefully conducted under a less basic condition to avoid racemization through the reaction. A mixed Rh/Pt oxide (Nishimura's catalyst), RuH(η^1-BH_4)-type complexes, (**I**) and (**II**), and a cationic Mn complex (**III**) are typical catalysts.[8] However, these procedures require that the enantio-enriched α-amino esters be prepared in advance.

We expected that the desired optically active β-amino alcohols could be obtained by asymmetric hydrogenation of the racemic α-amino esters through dynamic kinetic resolution (DKR) under appropriate catalytic conditions. Stereoinversion at the α-position could occur with the assistance of a base, in contrast to the hydrogenation with retention of the α-configuration. Xie and coworkers reported the hydrogenation of racemic α-arylamino γ- and δ-lactones into the 2-amino 1,4-butanediols and 1,5-pentanediols in high ees with a chiral PNN ligand (SpiroPAP)–Ir catalyst (**IV**) in the presence of *t*BuOK (Scheme 1b).[9] However, less reactive (linear) α-amino esters were not applied to this reaction. Bergens and coworkers tried the reaction of a racemic α-phenylaminopropanamide with $RuCl_2$[(*S*,*S*)-skewphos][(*R*,*R*)-dpen] (**V**) and a base (substrate/catalyst molar ratio (S/C) 20, 4 atm H_2) to give the amino alcohol in 47.5% yield and 74% ee (Scheme 1c).[10] Only one example was given. The result is attractive, but a more reactive, enantioselective, and general hydrogenation procedure to synthesize enantio-enriched β-amino alcohols is highly desirable.

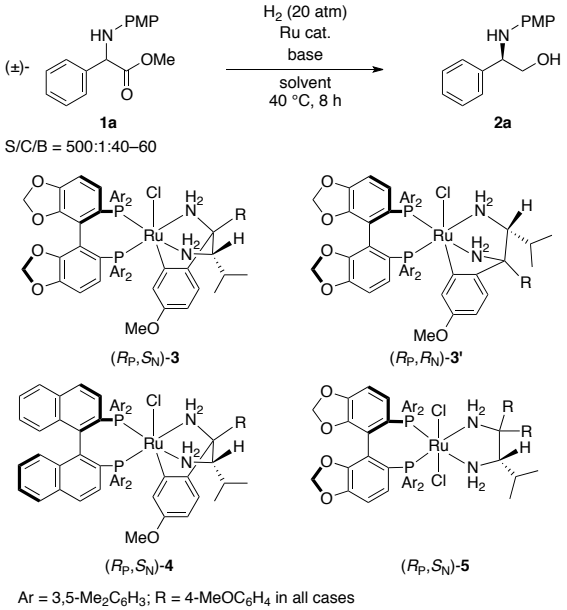
Scheme 1. Hydrogenation of α-Carboxylic Acid Derivatives



We previously studied asymmetric hydrogenation of a variety of ketones with optically active diphosphine/diamine–Ru catalysts.[11,12] Among them, ruthenabicyclic complex RuCl[(*S*)-daipena][(*S*)-xylbinap] (DAIPENA = anion of DAIPEN at the 2-position of an anisyl group) with a base showed excellent catalytic activity and enantioselectivity. The turnover frequency (TOF) of hydrogenation of acetophenone (S/C = 100 000, 50 atm H_2) reached about 35 000 min^{-1}, affording (*R*)-1-phenylethanol in >99% ee.[13,14] We herein report asymmetric hydrogenation of racemic α-amino esters through DKR catalyzed by a RuCl[(*S*)-daipena][(*R*)-dm-segphos] [(R_P,S_N)-**3**]/*t*PenONa system (Scheme 1d). The reaction was carried out with an S/C of 200–1000 under 15 atm of H_2 at 25 °C to afford a variety of β-aryl β-aminoethanols in up to 97% ee.

We selected *N*-PMP (PMP = *p*-methoxyphenyl) protected phenylglycine methyl ester **1a** as a substrate for optimization of catalyst structure and reaction conditions (Table 1). The racemic α-amino ester **1a** was hydrogenated in the presence of (R_P,S_N)-**3** and *t*BuONa with an S/C of 500 under 20 atm of H_2 in cyclopentyl methyl ether (CPME) at 40 °C in 8 h to afford the (*R*)-β-amino alcohol **2a** in 89% yield and 91% ee (entry 1). The reaction rate using *t*BuOK as a base was slowed (entry 2). Cs_2CO_3 and MeONa were not useful for this reaction (entries 3, 4). Sodium 2-methylbutoxide (*t*PenONa) gave an even better result (entry 5). CPME was the solvent of choice based on the

Table 1. Asymmetric Hydrogenation of α-Amino Ester 1a[a]

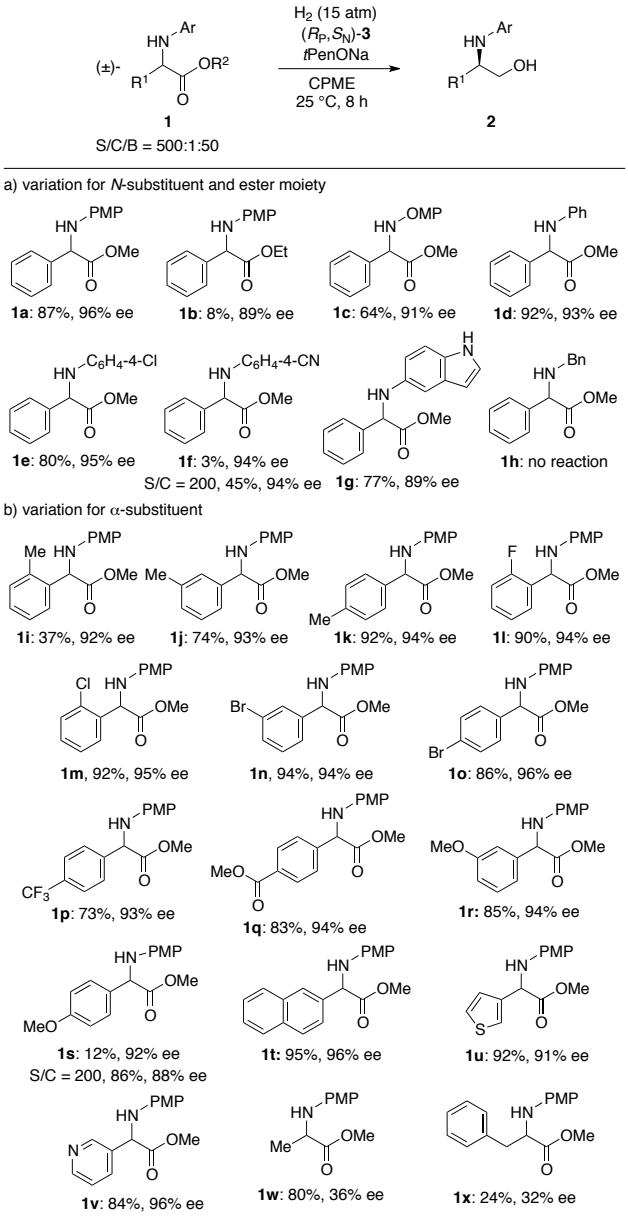


entry	Ru cat.	base	solvent	% yield[b]	% ee[c]
1	**3**	*t*BuONa	CPME	89	91
2[d]	**3**	*t*BuOK	CPME	32	91
3	**3**	Cs_2CO_3	CPME	trace	nd
4	**3**	MeONa	CPME	trace	nd
5	**3**	*t*PenONa	CPME	88	92
6	**3**	*t*PenONa	THF	32	93
7	**3**	*t*PenONa	dioxane[e]	trace	nd
8	**3**	*t*PenONa	toluene	70	91
9	**3**	*t*PenONa	MeOH	trace	nd
10	**3**	*t*PenONa	*i*PrOH	trace	nd
11[f]	**3**	*t*PenONa	CPME	87	92
12[f,g]	**3**	*t*PenONa	CPME	87	96
13[f,g]	**3'**	*t*PenONa	CPME	52	77
14[f,g]	**4**	*t*PenONa	CPME	47	95
15[f,g]	**5**	*t*PenONa	CPME	trace	nd
16[f,g,h]	**3**[i]	*t*PenONa	CPME	80	94

[a] S/C/B = substrate/catalyst/base molar ratio. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction for 11 h. [e] 1,4-dioxane. [f] Reaction under 15 atm of H_2. [g] Reaction at 25 °C. [h] Reaction for 24 h. [i] S/C/B = 1000:1:50.

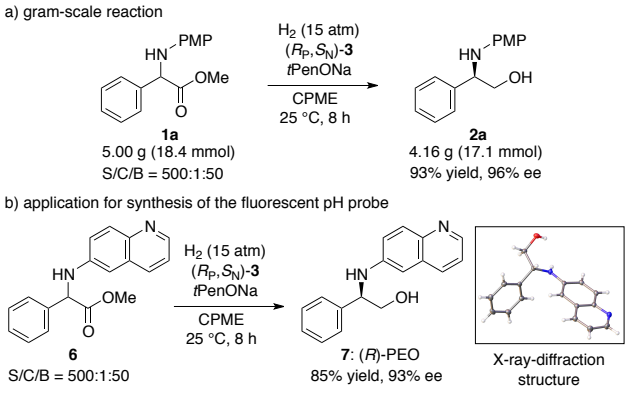
reactivity and enantioselectivity (entries 5–10). Notably, alcoholic solvents that were successfully used in the hydrogenation of ketones[13] gave almost no reaction (entries 9, 10). Hydrogen pressure could be reduced to 15 atm without loss of catalyst performance (entry 11). An ee value of 96% was achieved in the reaction at 25 °C with complete conversion of the substrate (entry 12). The diastereomeric complex (R_P,R_N)-**3'** showed somewhat lower activity and enantioselectivity (entry 13). The reaction with RuCl[(*S*)-daipena][(*R*)-xylbinap] [(R_P,S_N)-**4**] also afforded **2a** in high ee, but the reaction rate was slower (entry 14). The ruthenabicyclic structure of the complex is crucial to achieve high catalytic activity, so that almost no conversion was observed with $RuCl_2$[(*R*)-dm-segphos][(*S*)-daipen] [(R_P,S_N)-**5**] (entry 15). The hydrogenation catalyzed by the (R_P,S_N)-**3**/*t*PenONa system with an S/C of 1000 was completed within 24 h to give **2a** in 94% ee (entry 16). We decided to employ the conditions of entry 12 for further investigations.

Scheme 2. Asymmetric Hydrogenation of α-Amino Esters 1



We next examined the scope of the reaction (Scheme 2). The size of the ester moiety largely affected the reactivity. The reaction of ethyl ester **1b** gave the product in only 8% yield.

Scheme 3. Gram-scale Reaction and Synthetic Application



Several *N*-aryl groups could be introduced on the substrates. Bulky *o*-methoxyphenyl (OMP) (**1c**) slowed the reaction rate. Simple phenyl (**1d**) and electron-deficient *p*-chlorophenyl (**1e**) gave results comparable to the case with the electron-rich PMP (**1a**). Substitution of a strongly electron-attractive CN group at the *para* position (**1f**) significantly reduced the reactivity, although the high enantioselectivity was maintained. An indole structure could be employed without *N*-protection (**1g**). *N*-Aryl substitution was crucial for this reaction. In fact, no reaction was observed in the hydrogenation of *N*-benzyl ester (**1h**). The hydrogenation of *o*-, *m*-, and *p*-tolylglycine methylesters, **1i**–**1k**, under the typical conditions afforded the amino alcohols in high ee, although the rate for sterically hindered **1i** was slower. Halogen-substitution on the α-phenyl ring (**1l**–**1o**) even at the *ortho* position was suitable for this reaction, providing the products in 94%–96% ee. An amino ester with a strongly electron-withdrawing CF_3 at the *para* position (**1p**) was successfully hydrogenated. The methyl benzoate substructure was left intact through the amino ester hydrogenation with maintenance of the catalyst efficiency (**1q**). The high chemoselectivity was a benefit for this catalytic system. Introduction of a MeO group at the *para* position (**1s**) slowed the reaction rate, but the *meta*-substituted one (**1r**) reacted regularly. The hydrogenation of 2-naphthylglycine (**1t**) afforded a result comparable to that of **1a**. Heteroaryl rings were also left intact. Amino alcohols with a thienyl (**2u**) or pyridine (**2v**) ring were obtained in high yield with 91% ee and 96% ee, respectively. The reaction of alkyl-substituted amino esters, **1w** and **1x**, gave the products with only moderate enantioselectivity.

The reaction was readily applied to the gram-scale reaction (Scheme 3a). A 5.00 g aliquot of **1a** was hydrogenated under

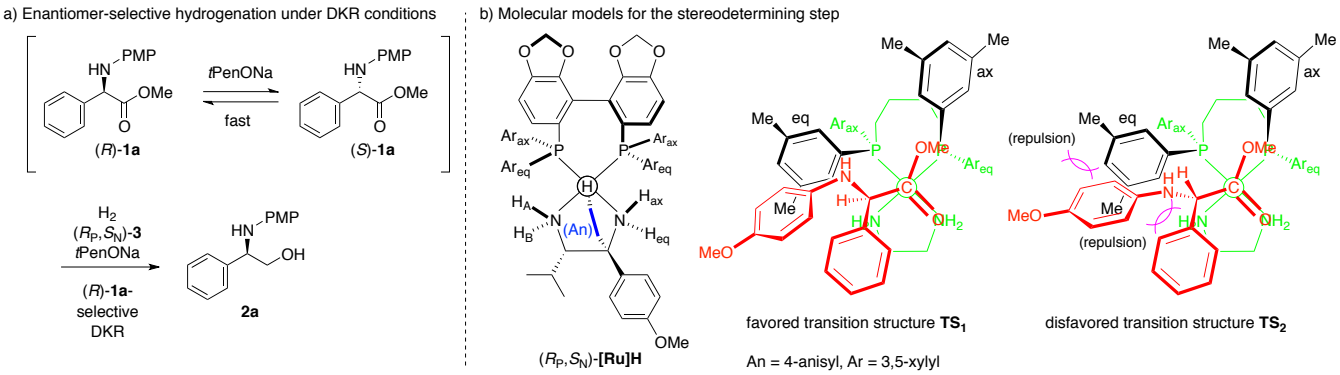
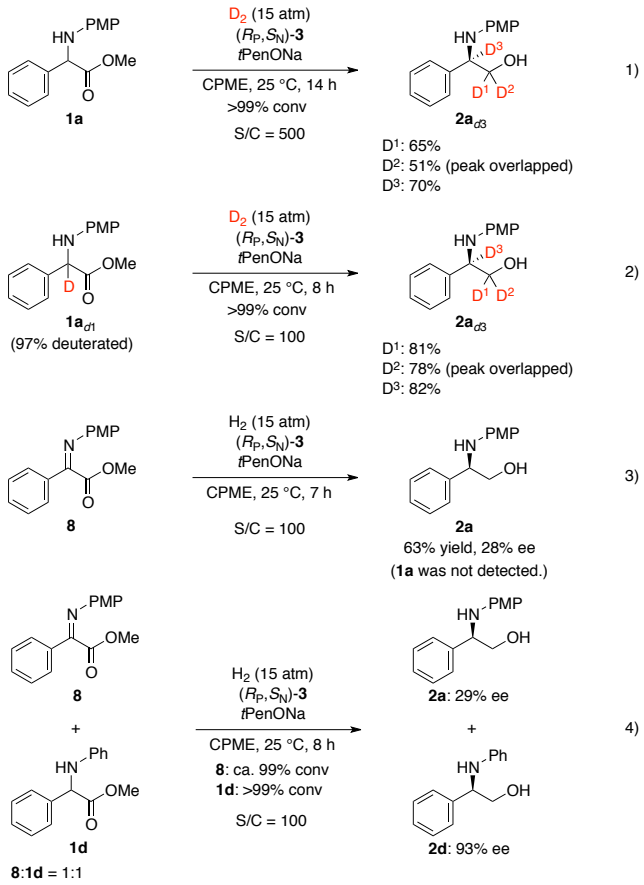


Figure 1. Proposed Reaction Scheme and Molecular Structures for the Stereodetermining Step

Scheme 4. Experiments for Mechanistic Considerations



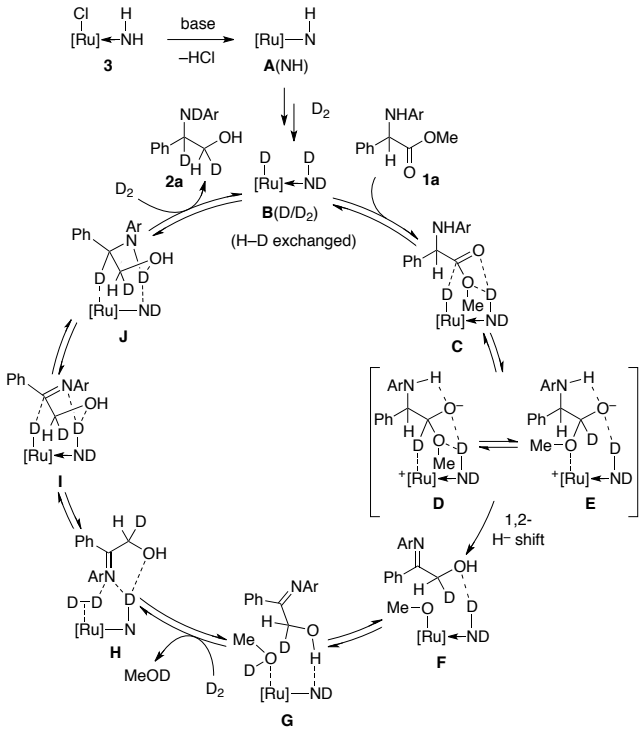
the regular conditions, affording **2a** (4.16 g, 93% yield) in 96% ee.

The (*R*)-*N*-(5-quinolyl)amino alcohol **7** [(*R*)-PEO] functions as a fluorescent pH probe,[15] and was prepared by hydrogenation with the (R_P,S_N)-**3**/*t*PenONa system from the corresponding amino ester **6** in 85% yield and 93% ee (Scheme 3b). The structure of **7** was determined by a single crystal X-ray analysis.

Asymmetric hydrogenation of **1a** through DKR is generally thought to proceed as shown in Figure 1a. The α-stereocenter of **1a** is reversibly invertible in the presence of a base. The (R_P,S_N)-**3**/*t*PenONa system selectively hydrogenates (*R*)-**1a** into **2a**, and then the leaving (*S*)-**1a** is reduced after epimerization to the *R* one under the DKR conditions. The (*R*)-**1a**-selective hydrogenation could occur as illustrated in Figure 1b. (*R*)-**1a** fits well with the chiral pocket of the active (R_P,S_N)-[Ru]H complex.[12a] The outer sphere [Ru]H$^{\delta-}$–C$^{\delta+}$=O$^{\delta-}$–H$_{ax}$$^{\delta+}$N interaction fixes the position and direction of the C=O group of **1a** (**TS$_1$** and **TS$_2$**). The smaller ester OMe group locates in close proximity to the axially oriented *P*-3,5-dimethylphenyl group of the catalyst. The bulkier α-PMP-NH moiety preferably locates at the far side of the catalyst to avoid steric repulsion (**TS$_1$** vs. **TS$_2$**). Therefore, (*R*)-**1a** is selectively reacted with the catalyst system through **TS$_1$**.

We then conducted some experiments to confirm our hypothesis (Scheme 4). The deuteration of **1a** under the regular conditions gave the deuterated amino alcohol **2a**$_{d3}$. The deuterium contents at the α position were only 65% (D^1) and 51% (D^2), whereas 70% deuterium content was observed at the β position (D^3) (eq 1). When the α-deuterated amino ester **1a**$_{d1}$[16] was

Scheme 5. Plausible Reaction Pathway under a D_2 Atmosphere



exposed to the deuteration conditions, the deuterium contents of D^1–D^3 were all increased compared to those in the reaction of **1a** (eq 2). These results suggest that the reaction is not a simple ester hydrogenation, but includes the dehydrogenative process of the amino group yielding the imino moiety. Interestingly, hydrogenation of the corresponding imino ester **8**, a candidate for the reaction intermediate, under the regular conditions was much slower than that of **1a**, affording **2a** in only 28% ee (eq 3). The hydrogenation of a 1:1 mixture of imino ester **8** and amino ester **1d** afforded the products **2a** (29% ee) and **2d** (93% ee), respectively (eq 4). The enantiomeric purity of each product was the same as that in the corresponding individual reaction. Both hydrogenations occurred separately with no crossover at all. We therefore surmised that the reaction includes 1,2-hydride migration from the α carbon (C$_\alpha$) of **1a** onto the carbonyl carbon (C$_{CO}$) with transformation of the amino group to the imino moiety. Then the resulting imine is hydrogenated into the amine. The deuterium contents of D^1–D^3 shown in equations 1 and 2 are consistent with this hypothesis. H–D exchange with the amino proton (NH) of **1a** exists during the reaction, and a part of H is incorporated in the product **2a**. The probable intermediates, α-hydroxy imine and α-amino aldehyde were so labile, therefore we could not prepare them as pure compounds.

Scheme 5 shows a plausible reaction pathway under a D_2 atmosphere based on the mechanistic experiments and reference studies.[17] The catalyst precursor **3** and a base give the amide complex **A**(NH) with removal of HCl. A [Ru]D complex **B**(D/D_2) formed by H–D exchange is employed among several hydride species **B**. Amino ester **1a** reversibly interacts with **B** in an outer sphere fashion (**C**), forming the [Ru]D$^{\delta-}$–C$^{\delta+}$=O$^{\delta-}$–D$^{\delta+}$N partial structure. The MeO$^{\delta-}$–D$^{\delta+}$N interaction may be incorporated in the intermediate. Migration of D$^-$ from the [Ru] center onto the C=O makes the acetal-oxide structure **D**, in which O$^-$ is stabilized by the hydrogen bonding with ArNH and

ND.[17b] The acetal OMe can coordinate to the Lewis acidic [Ru] center (**E**). The enantiomer selection of **1a** is performed at the step of ester reduction (**B** to **D**/**E** through **C**) through $\mathbf{TS_1}$ as depicted in Figure 1b. Species **D** or **E** is the possible resting site. The irreversible 1,2-hydride shift of amine α-H with a leaving OMe group forms the highly reactive α-hydroxy imine on the [Ru]-OMe species **F**. The [Ru]D complex interacted by the hydroxy imine with the outer sphere mode (**I**) is obtained through the Ru amide species coordinated by MeOD (**G**) or D_2 (**H**). The $HO^{\delta-}$–$D^{\delta+}N$ interaction may assist formation of the structure. Reduction of the imino group is performed on the Ru species **J**. The transformation from **D**/**E** to **J** is very rapid, and the series of hydrogenative/dehydrogenative processes occur at the same side of the substrate face. Therefore, the initially selected enantiomer of **1a** is reflected in the product configuration. The deuterated amino alcohol **2a** is replaced by D_2, followed by heterolytic cleavage of D_2, regenerating **B**(D/D_2). The deuterium contents in the product depend on the rate of the H–D exchange occurring through the reaction pathway.

In conclusion, asymmetric hydrogenation of racemic α-amino esters through DKR was achieved by using a RuCl[(*S*)-daipena][(*R*)-dm-segphos]/*t*PenONa catalyst system. A small amount of the catalyst (typical S/C = 500) promoted the reaction (15 atm H_2, 25 °C) even under a 5 g-scale condition. A variety of β-aryl- and β-heteroaryl-substituted β-aminoethanols was obtained in high ee (up to 96%). The *R* amino alcohol with an *N*-(5-quinolyl) moiety [(*R*)-PEO], a fluorescent pH probe, was obtained by the reaction. The mechanistic studies including deuteration experiments suggested that the reaction was not a simple ester hydrogenation, but contained a 1,2-hydride shift of the α-amino acetalate intermediate into the α-hydroxy imine. Then the reduction of the imino compound occurred continuously to afford the β-amino alcohol. The enantiomer-discrimination of the racemic amino ester was suggested to occur at the initial hydride migration from the [Ru]H species to the ester carbonyl group of the substrate.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Full experimental procedures and analytical data (^1H, ^{13}C and ^{19}F NMR spectral data; HPLC data; optical rotation data; HRMS and X-ray crystallographic data) (PDF and CIF)

Accession Codes

CCDC 2215616 and 2215626 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Takeshi Ohkuma – Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, 060-8628, Japan
orcid.org/0000-0002-5467-3169; Email: ohkuma@eng.hokudai.ac.jp

Authors

Hiroki Ishikawa – Takasago International Corporation, Corporate Research & Development Division, 1-4-11 Nishi-yawata, Hiratsuka City, Kanagawa 254-0073, Japan
orcid.org/0000-0002-6489-8644

Taiga Yurino – Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, 060-8628, Japan
orcid.org/0000-0002-4158-3463

Ryo Komatsu – Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan

Ming-Yuan Gao – Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan

Noriyoshi Arai – Division of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, 060-8628, Japan

Taichiro Touge – Takasago International Corporation, Corporate Research & Development Division, 1-4-11 Nishi-yawata, Hiratsuka City, Kanagawa 254-0073, Japan
orcid.org/0000-0002-8783-0335

Kazuhiko Matsumura – Takasago International Corporation, Corporate Research & Development Division, 1-4-11 Nishi-yawata, Hiratsuka City, Kanagawa 254-0073, Japan

Notes

The authors declare no competing financial interest.

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