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Rhodium-catalyzed asymmetric hydrogenation through dynamic kinetic resolution: asymmetric synthesis of *anti*-β-hydroxy-α-amino acid esters

Kazuishi Makino, Takefumi Fujii and Yasumasa Hamada*

Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

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This paper is dedicated to Dr. Jack Halpern on the occasion of his 80th birthday in recognition of his outstanding contributions to the areas of transition metal-catalyzed asymmetric hydrogenation

Abstract—Rhodium-catalyzed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides through dynamic kinetic resolution is described. The hydrogenation proceeds with the catalyst derived from a Rh complex and a chiral ferrocenylphosphine under hydrogen in the presence of sodium acetate in acetic acid to afford *anti*-β-hydroxy-α-amino acid esters with 58–83% ee in a diastereomeric ratio of 92:8–97:3.

1. Introduction

Rhodium (Rh) in combination with chiral phosphines has played a central role in the area of asymmetric hydrogenation[1] and the mechanism for Rh-catalyzed asymmetric hydrogenation of olefinic substrates has been elucidated by the pioneering work[2] of Halpern. We herein report that Rh-chiral phosphines catalyze asymmetric hydrogenation of ketonic substrates through dynamic kinetic resolution (DKR) in asymmetric synthesis of *anti*-β-hydroxy-α-amino acid esters. DKR is a powerful method for synthesizing one enantiomer from a racemic starting material with a labile stereocenter.[3] The ruthenium (Ru)-catalyzed DKR was originally developed by Noyori et al. in the asymmetric hydrogenation of α-substituted β-keto esters, in which they disclosed an efficient synthesis of *syn*-β-hydroxy-α-amino acid esters from α-acetoamido-β-keto esters.[4] As depicted in Figure 1, we have recently demonstrated for the first time that the Ru-BINAP catalyst catalyzes *anti*-selective asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides in the synthesis of *anti*-β-hydroxy-α-amino acid esters with high diastereoselectivities and enantiomeric excesses.[5] This hydrogenation, however, was limited to the substrates with alkyl groups

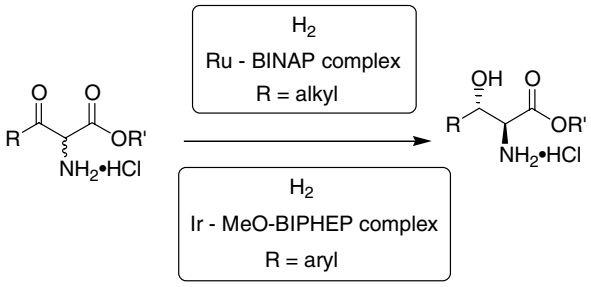

Figure 1. *anti*-Selective hydrogenation through DKR.

at the C4 position. From our efforts to overcome such a limitation, we found that iridium (Ir) in combination with axially chiral phosphines also catalyzes *anti*-selective asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides bearing an aromatic ring at the C4 position of the substrates with almost complete diastereoselectivity and high enantiomeric excess, which is the first example of DKR using the Ir axially chiral phosphine catalyst.[6] Over the course of the catalyst screening in our DKR study, we recognized that Rh, in combination with chiral phosphines, is a potential catalyst for this *anti*-selective asymmetric hydrogenation. Prior to our investigation, two groups have examined the Rh-catalyzed DKR approach, which remains at the stage of preliminary studies for low conversion and/or poor enantio- and diastereoselectivities.[7]

* Corresponding author. Tel./fax: +81 43 290 2987; e-mail: hamada@p.chiba-u.ac.jp

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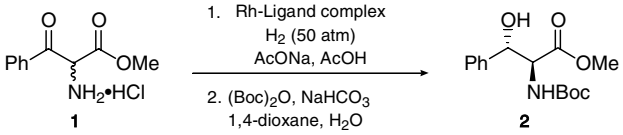
2. Results and discussion

We first investigated the effects of several catalyst precursors and chiral phosphines using methyl benzoylglycinate hydrochloride **1**[8] as shown in Table 1. The catalyst was prepared prior to the hydrogenation by mixing the catalyst precursor and chiral phosphine (1.3 equiv/Rh) in methylene chloride at 23 °C for 10 min and, after concentration in vacuo, was used without any purification. The hydrogenation of **1** was carried out using 3 mol % of the catalyst under 50 atm of hydrogen in the presence of sodium acetate (1 equiv) in acetic acid at 23 °C for 12 h. The solvent and additive were chosen according to the case of the iridium-catalyzed DKR developed.[6] The enantiomeric purity and diastereomeric ratio of the product were determined after conversion to the *N*-*tert*-butoxycarbonyl derivative **2**. The use of the neutral and cationic Rh-catalyst from (*S*)-MeO-BIPHEP **3** proved disappointing in both yields and enantiomeric excesses (entries 1 and 2). Chiral ferrocenylphosphines **4** and **5** developed by Togni[9] were superior to axially chiral phosphines in this asymmetric hydrogenation (entries 3–5). There was a slight improvement in the chemical yield when the cationic rhodium complex, $[Rh(nbd)_2]BF_4$, was used as the catalyst precursor (entries 3 and 4). In particular, the cationic Rh-catalyst from $[Rh(nbd)_2]BF_4$ and (*R*,*S*)-PPF-P^{t}Bu$_2$ **4** afforded *anti*-β-hydroxy-α-amino acid ester **2** in 70% yield with 75% ee and diastereomeric ratio of 94:6 (entry 4). The bulkier substituent at the phosphorus of the ligand affected the enantioselectivity (entries 4 and 5). Next, using the catalyst from $[Rh(nbd)_2]BF_4$ and **4**, we carried out further optimization as shown in Table 2. The substrate concentration tended to vary the chemical yield but not the enantioselectivity (entries 1–3). When the hydrogenation was performed using the toluenesulfonic acid salt as the substrate instead of **1**, the chemical yield, and the enantiomeric excess decreased remarkably (entry 4). Interestingly, the presence of a chloride ion proved to be essential for a satisfactory enantiomeric excess (entry 5). After some trial and error, we found that, surprisingly, the chemical yield is time dependent. A reaction time of 30 min was found to be enough for this hydrogenation and the chemical yield and enantiomeric excess were maximized to 82% yield and 83% ee (entry 7).[10] These results indicate that the hydrogenation is extremely rapid and that the product might decompose under the hydrogenation conditions. The pressure of hydrogen had no effect on the enantiomeric excess but affected the chemical yield (entries 9 and 10). Longer reaction times under moderate hydrogen pressure (5 atm) caused decomposition of the substrates and no effect on the chemical yield (entry 10). The low loading (0.3 mol %) of the catalyst was fruitless and gave only 24% yield of the product (entry 11). Using the optimized conditions, we carried out the asymmetric hydrogenation of several aromatic substrates as shown in Table 3. As can be seen from the results in Table 3, the reaction time for giving the maximized yield proved to vary for each substrate. Although the yields are moderate, the enantiomeric excess and diastereoselectivities are satisfactory. It should be noted that this asymmetric hydrogenation using the Rh-ferrocenylphosphine is not only the first practically successful example of rhodium-catalyzed dynamic kinetic resolution but also demonstrates new potential of rhodium-catalyzed asymmetric synthesis.

We next investigated the reaction mechanism of this unique rhodium-catalyzed hydrogenation. Generally, rhodium-catalyzed hydrogenation proceeds through a dihydride mechanism, which differs from a monohydride mechanism of ruthenium-catalyzed hydrogenation. Therefore, it was anticipated that the mechanism

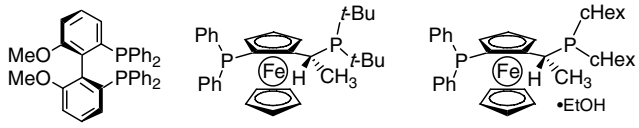
Table 1. *anti*-Selective asymmetric hydrogenation catalyzed by Rh-chiral phosphines[a]



1 **2**

Entry	Rh precursor	Ligand	*anti*:*syn*[b]	Yield[c] (%)	ee[d] (%)
1	$[Rh(cod)Cl]_2$	(*S*)-MeO-BIPHEP	>90:10	26	5
2	$[Rh(cod)_2]BF_4$	(*S*)-MeO-BIPHEP	>90:10	8	48
3	$[Rh(nbd)Cl]_2$	(*R*,*S*)-PPF-P^{t}Bu$_2$	>90:10	58	74
4	$[Rh(nbd)_2]BF_4$	(*R*,*S*)-PPF-P^{t}Bu$_2$	>90:10	70	75
5	$[Rh(nbd)_2]BF_4$	(*R*,*S*)-PPF-PCy$_2$·EtOH	>90:10	70	5

[a] The hydrogenation was carried out by using Rh-phosphine (prepared from Rh precursor (3 mol %) and ligand (4 mol %) prior to the hydrogenation) and sodium acetate (1 equiv) in acetic acid at 23 °C for 12 h.
[b] Determined by ^{1}H NMR spectra of the reaction mixture.
[c] Isolated yield in two steps.
[d] Determined by HPLC analysis.

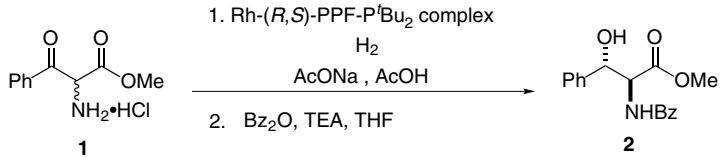


3 (*S*)-MeO-BIPHEP

4 (*R*,*S*)-PPF-P^{t}Bu$_2$

5 (*R*,*S*)-PPF-PCy$_2$•EtOH

Table 2. Effects of hydrogen pressure and reaction time[a]

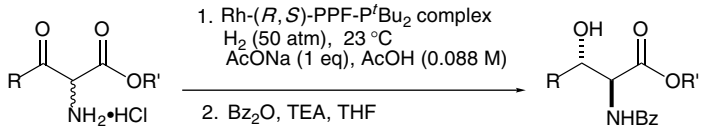


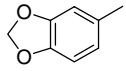
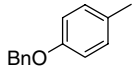
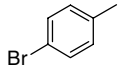
1 2

Entry	Concentration (M)	Time	H_2 (atm)	*anti*:*syn*[b]	Yield[c] (%)	ee[d] (%)
1	0.088	48 h	50	94:6	71	73
2	0.044	48 h	50	93:7	55	83
3	0.022	48 h	50	91:9	49	79
4[e]	0.088	48 h	50	96:4	15	36
5[f]	0.088	48 h	50	94:6	44	73
6	0.088	1 h	50	94:6	75	84
7	0.088	30 min	50	94:6	82	83
8	0.088	10 min	50	96:4	26	77
9	0.088	10 min	100	93:7	62	80
10	0.088	1 h	5	93:7	34 (37)[g]	80
11[h]	0.088	12 h	50	94:6	24	82

[a] The hydrogenation was carried out by using Rh-catalyst (prepared from $[Rh(nbd)_2]BF_4$ (3 mol %) and (*R*,*S*)-PPF-P^{t}Bu$_2$ (4 mol %) prior to the hydrogenation) and sodium acetate (1 equiv) in acetic acid at 23 °C.
[b] Determined by ^{1}H NMR spectra of the reaction mixture.
[c] Isolated yield in two steps.
[d] Value of the *anti*-3-hydroxyamino acid ester. Determined by HPLC analysis.
[e] The toluenesulfonic acid salt as the substrate instead of **1** was used.
[f] To the conditions in entry 4, tetrabutylammonium chloride was added.
[g] Isolated yield after 48 h.
[h] The hydrogenation was carried out by using 0.3 mol % of the Rh-catalyst.

Table 3. *anti*-Selective asymmetric hydrogenation catalyzed by Rh-(*R*,*S*)-PPF-P^{t}Bu$_2$ complex[a]



Entry	R	R′	Time (h)	*anti*:*syn*[b]	Yield[c] (%)	ee[d] (%)
1		Et	5	97:3	61	80
2		Me	3	92:8	53	84
3		Me	2.5	96:4	73	77
4		Et	1.5	97:3	66	79
5		Me	1.5	93:7	63	58

[a] The hydrogenation was carried out by using Rh-catalyst (prepared from $[Rh(nbd)_2]BF_4$ (3 mol %) and (*R*,*S*)-PPF-P^{t}Bu$_2$ (4 mol %) prior to the hydrogenation) and sodium acetate (1 equiv) in acetic acid at 23 °C.
[b] Determined by ^{1}H NMR analysis.
[c] Isolated yield for two steps.
[d] Determined by HPLC analysis.

of the Rh-catalyzed hydrogenation might differ from that of the Ru-catalyzed hydrogenation. In addition, the *anti*-product should also be obtained by hydrogenation of the enol form **7** of the substrates as shown in Figure 2. In order to elucidate the origin of the extremely high *anti*-selectivity, we carried out hydrogenation of a substrate with a quaternary carbon at the C2 position, which should disclose whether the reaction proceeds by hydrogenation of keto form **6** or enol form **7**. Thus, racemic 2-amino-2-methyl-3-oxo-3-phenylpropionic

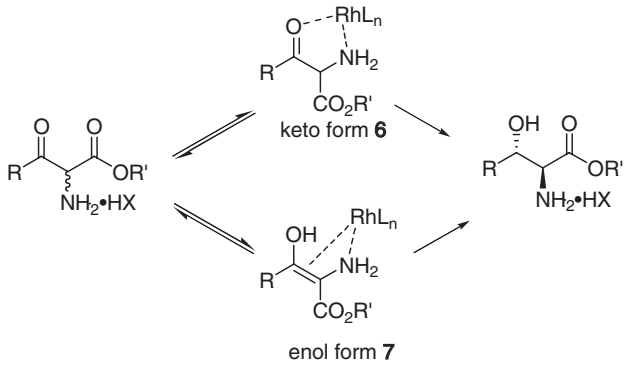
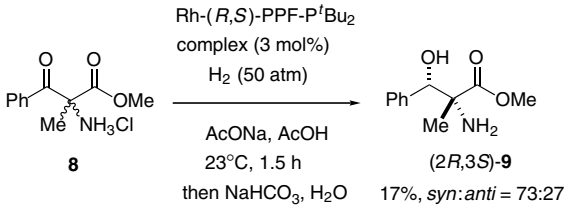


Figure 2.



Scheme 1.

acid methyl ester **8**,[11] a non-enolizable substrate, was subjected to asymmetric hydrogenation as shown in Scheme 1. The reaction also proceeded under the conditions described above to afford after 1.5 h, a mixture of two corresponding β-hydroxy-α-amino acid esters in 17% yield with a ratio of 73:27 (judged by the ^{1}H NMR spectrum). The major isomer was found to be 96% ee by HPLC analysis and confirmed as (2*R*,3*S*)-*syn* by comparison to the literature value,[12] although the absolute stereochemistry of the minor *anti*-isomer remains to be determined. Nevertheless, this result clearly indicates that the Rh-catalyzed asymmetric hydrogenation of the α-amino-β-keto esters takes place through reduction of the C=O double bond to produce the β-hydroxy-α-amino acid esters with *anti*-stereochemistry.

3. Conclusion

In conclusion, we have succeeded in the development of a rhodium-catalyzed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides through dynamic kinetic resolution in the synthesis of *anti*-aromatic β-hydroxy-α-amino acid esters. Further investigations on the mechanism and optimization of this unique rhodium-catalyzed dynamic kinetic resolution are under way in this laboratory.

Acknowledgments

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10. General procedure: A mixture of $[Rh(nbd)_2]BF_4$ (2.5 mg, 0.0066 mmol) and (*R*,*S*)-PPF-P^{t}Bu$_2$ (4.8 mg, 0.0088 mmol) in CH_2Cl_2 (1.0 mL) was degassed by three freeze–thaw cycles. The mixture was stirred for 10 min at 23 °C under an argon atmosphere. The resulting yellow solution was dried over in vacuo. Methyl benzoylglycinate (50 mg, 0.22 mmol), sodium acetate (18 mg, 0.22 mmol), and acetic acid (2.5 mL) were added to the freshly prepared yellow Rh-catalyst and the mixture stirred at 23 °C under hydrogen pressure (50 atm) for 30 min. The reaction mixture was added to 1 M HCl (3.0 mL) and concentrated in vacuo to dryness below 40 °C. The resulting residue was dissolved in methanol and the mixture concentrated in vacuo. This cycle was repeated five times. The residue was used in the next step without any purification. Benzoic anhydride (55 mg, 0.24 mmol) followed by a solution of triethylamine (92 μL, 0.66 mmol) in THF (3 mL) was added dropwise to a solution of the above residue in THF (3 mL) at 0 °C. After stirring the mixture at 23 °C overnight, the mixture was quenched with water and diluted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated aqueous sodium hydrogen carbonate, and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/*n*-hexane = 1:2) to give methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-3-phenylpropionate.[6] The diastereomeric ratio was determined by the ^{1}H NMR spectrum and the enantiomeric excess was determined by HPLC.
11. Compound **8** was prepared from (*S*)-alanine methyl ester hydrochloride in four steps: (1) formation of alanine methyl ester benzophenone imine by exchange reaction with benzophenone imine, (2) C-benzoylation of the benzophenone imine with benzoyl chloride in the presence of potassium *tert*-butoxide at 23 °C in THF and subsequent treatment with 3 M hydrochloric acid, (3) N-

protection of the resulting 2-methyl-alanine methyl ester for purification with di-*tert*-butyldicarbonate in the presence of triethylamine in THF, (4) N-deprotection with 4 M HCl-dioxane.

12. (2*R*,3*S*)-**9**: $[\alpha]_D^{23} = -15$ (*c* 0.25, $CHCl_3$) {lit. $[\alpha]_D^{25} = -10.9$ (*c* 0.44, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, $J = 6.0$ Hz, 3H), 3.77 (s, 3H), 4.90 (s, 3H), 7.30–7.35 (m, 5H), see (a) Schöllkopf, U.; Groth, U.; Hartwig, W. *Liebigs Ann. Chem.* **1981**, 2407–2418; (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204. The enantiomeric excess of **9** was determined to be 96% ee by HPLC analysis of the *N*-Bz derivative using Daicel Chiralcel AD (0.46 ∅ × 25 cm, *n*-hexane/2-PrOH = 85:15, flow 0.5 mL/min): (2*S*,3*R*)-isomer, 28.3 min (minor), (2*R*,3*S*)-isomer, 31.9 min (major).