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Enantio- and Diastereoselective Hydrogenation via Dynamic Kinetic Resolution by a Cationic Iridium Complex in the Synthesis of β-Hydroxy-α-amino Acid Esters

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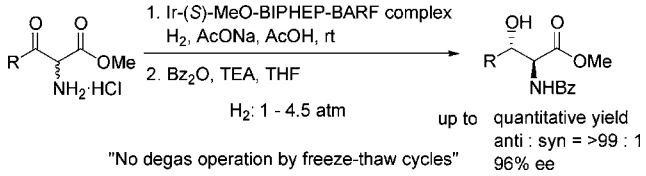
ABSTRACT

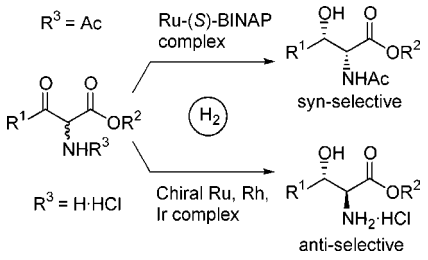


Anti-selective asymmetric hydrogenation of α-amino-β-keto esters via dynamic kinetic resolution under low hydrogen pressure has been achieved by an easily-handled cationic iridium complex with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) as a counterion.

Catalytic asymmetric hydrogenation of α-amino-β-keto esters through dynamic kinetic resolution (DKR) is a powerful methodology for the synthesis of chiral β-hydroxy-α-amino acids, which are an important class of amino acids broadly found in nature as components of complex natural products. It was reported by Noyori and Genêt for the first time that a chiral Ru−BINAP complex catalyzed asymmetric hydrogenation of α-acylamino-β-keto esters via DKR to gives *syn*-β-hydroxy-α-acylamino acid derivatives with high diastereo- and enantioselectivities (Scheme 1).[1,2]

In the context of our ongoing studies on total synthesis of cyclodepsipeptides, papuamides, polyoxypeptins, and GE3,[3] we have developed for the first time a direct anti-selective asymmetric hydrogenation of α-amino-β-keto ester hydrochloride salts via DKR catalyzed by the Ru, Ir, or Rh complex.[4a,5,6] In particular, DKR in the presence of the Ir catalyst is a first example, and this hydrogenation can be carried out in an environmentally benign solvent using commercially available chiral phosphines. This method is effective for the synthesis of anti-aromatic β-hydroxy-α-amino acids. However, high hydrogen pressure (100 atm) and tedious degas operation by freeze−thaw cycles in the preparation of the catalyst and the stage prior to hydrogena-

Scheme 1. Asymmetric Hydrogenation via Dynamic Kinetic Resolution



(1) For reviews on dynamic kinetic resolution, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490. (c) Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: 2000; pp 1−110. (d) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327. (e) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001.

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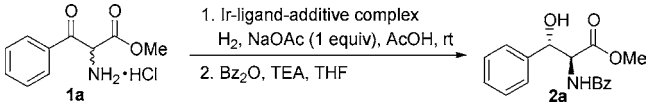
Table 1. Asymmetric Anti-Selective Hydrogenation Using the Ir Catalyst[a]



entry	Ir catalyst (mol %)	ligand	additive	H_2 (atm)	time (h)	yield[b] (%)	anti/syn[c]	ee[d] (%)
1	3	(*S*)-MeO-BIPHEP		100	3	71	>99:1	78
2	3	(*S*)-MeO-BIPHEP	NaI	100	24	82	>99:1	90
3	3	(*S*)-MeO-BIPHEP	NaBARF	100	3	quant	>99:1	74
4	3	(*S*)-MeO-BIPHEP	NaBARF	60	12	quant	>99:1	80
5	3	(*S*)-MeO-BIPHEP	NaBARF	30	24	quant	>99:1	84
6	3	(*S*)-MeO-BIPHEP	NaBARF	4.5	24	quant	>99:1	93
7	3	(*S*)-MeO-BIPHEP	NaBARF	1	96	91	>99:1	92
8[e]	3	(*S*)-MeO-BIPHEP	NaBARF	1	96	90	>99:1	92
9	1	(*S*)-MeO-BIPHEP	NaBARF	4.5	96	quant	>99:1	92
10	0.5	(*S*)-MeO-BIPHEP	NaBARF	4.5	96	98	>99:1	92
11	0.5	(*S*)-BINAP	NaBARF	4.5	96	87	>99:1	83
12	0.5	(*S*)-Tol-BINAP	NaBARF	4.5	96	82	>99:1	84
13	3	(*S*)-SEGPHOS	NaBARF	4.5	24	87	>99:1	91
14	1	(*S*)-MOP	NaBARF	4.5	24	n.r.		

[a] The reaction was carried out by using the Ir−ligand−NaBARF complex (Ir/ligand/NaBARF = 1:1.3:1) and NaOAc (1 equiv) in AcOH under hydrogen atmosphere. [b] Yield in two steps. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] No freeze−thaw operation.

tion are essential for smooth reaction and make it difficult to run this hydrogenation in a practical sense. Herein, we report an anti-selective asymmetric hydrogenation of α-amino-β-keto esters via DKR under low hydrogen pressure catalyzed by an easy-handled cationic iridium complex with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) as a counterion.

In our effort to expand the utility of the first-generation Ir catalyst into hydrogenation via DKR under mild reaction conditions, we examined various additive effects in the preparation of the catalyst (Table 1). The first-generation iridium complex prepared from $[IrCl(cod)]_2$, (*S*)-MeO-BIPHEP, and sodium iodide previously reported by us[5] afforded the *anti*-β-hydroxy-α-amino ester with 90% ee in 82% yield under high hydrogen pressure (100 atm) (entries 1 and 2). The enantioselectivity could be improved by the addition of sodium iodide,[7] which, however, was found to retard the reaction. Therefore, we chose the condition whereby sodium iodide was removed from the first-generation catalyst as the starting point for reoptimization. So we examined again various additives, such as phthalimide,[8] tetrabutylammonium bromide, potassium fluoride, or silver trifluoroacetate instead of sodium iodide, but no improvement was observed in the stereoselectivity, yield, and efficiency of the catalyst. Recently, Pfaltz's group[9] reported highly enantioselective hydrogenation of alkenes using the Ir−PHOX catalyst in combination with the BARF counterion,[10] which is known to stabilize the Ir complex and accelerate

(2) For syn-selective asymmetric hydrogenation via DKR using Ru catalyst, see: (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc*. **1989**, *111*, 9134−9135. (b) Genêt, J.-P.; Mallart, S.; Juge, S. French Patent 8911159, 1989. (c) Mashima, K.; Matsumura, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Chem. Commun*. **1991**, 609−610. (d) Genêt, J.-P.; Pinel, C.; Mallart, S.; Juge, S. Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555−567. (e) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc*. **1993**, *115*, 144−152. (f) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem*. **1994**, *59*, 3064−3076. (g) Genêt, J.-P.; de Andrade, M. C. C.; Ratovelomanana-Vidal, V. *Tetrahedron Lett*. **1995**, *36*, 2063−2066. (h) Coulon, E.; de Andrade, M. C. C.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron Lett*. **1998**, *39*, 6467−6470. (i) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757−1762. (j) Mohar, B.; Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun*. **2001**, 2572−2573.

(3) (a) Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1353−1358. (b) Reference 2i. (c) Makino, K.; Henmi, Y.; Hamada, Y. *Synlett* **2002**, 613−615. (d) Makino, K.; Kondoh, A.; Hamada, Y. *Tetrahedron Lett*. **2002**, *43*, 4695−4698. (e) Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. *J. Org. Chem*. **2002**, *67*, 9210−9215. (f) Makino, K.; Suzuki, T.; Awane, S.; Hara, O.; Hamada, Y. *Tetrahedron Lett*. **2002**, *43*, 9391−9395. (g) Henmi, Y.; Makino, K.; Yoshitomi, Y.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3477−3481. (h) Suzuki, T.; Makino, K.; Hamada, Y. *Peptide Sci. 2003*, **2004**, 57−60. (i) Makino, K.; Henmi, Y.; Terasawa, M.; Hara, O.; Hamada, Y. *Tetrahedron Lett*. **2005**, *46*, 555−558. (j) Makino, K.; Nagata, E.; Hamada, Y. *Tetrahedron Lett*. **2005**, *46*, 6827−6830.

(4) For anti-selective asymmetric hydrogenation via DKR using Ru catalyst, see: (a) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed*. **2004**, *43*, 882−884. (b). Lei, A.; Wu, S.; He, M.;. Zhang, X. *J. Am. Chem. Soc*. **2004**, *12*6, 1626−1627. (c) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J. P. *Chem. Commun*. **2004**, 1296−1297. (d) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem*. **2004**, 3017−3026.

(5) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc*. **2005**, *127*, 5784−5785.

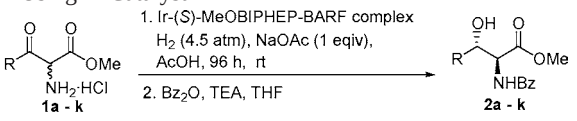
(6) Makino, K.; Fujii, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 481−485.

(7) Additive effect of I^-: (a) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed*. **1990**, *29*, 558−559. (b) Morimoto, T.; Nakajima, N.; Achiwa, K. *Chem. Pharm. Bull*. **1994**, *42*, 1951−1953. (c) Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748−750.

(8) Additive effect of phthalimide: (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Heterocycles* **1996**, *43*, 2557−2560. (b) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661−2664.

(9) (a) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 2897−2899. (b) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal*. **2003**, *345*, 33−43.

Table 2. Asymmetric Anti-Selective Hydrogenation through DKR Using Ir Catalyst[a]



entry	R	yield (%)[b]	anti : syn[c]	ee (%)[d]
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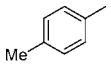
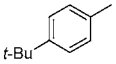
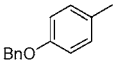
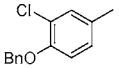
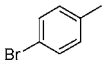
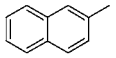
2		92	>99 : 1	92
3		quant	>99 : 1	90
4		97	99 : 1	91
5		quant	>99 : 1	93
6		97	>99 : 1	90
7		96	>99 : 1	82
8		94	>99 : 1	90
9		94	>99 : 1	96
10		61	>99 : 1	84
11[e]	*t*-Bu	quant	>99 : 1	91

[a] The reaction was carried out by using Ir−(*S*)-MeOBIPHEP−BARF complex (prepared from $[IrCl(cod)]_2$ (0.005 equiv), (*S*)-MeOBIPHEP (0.013 equiv), and NaBARF (0.01 equiv) in CH_2Cl_2 prior to the hydrogenation) and NaOAc (1 equiv) in AcOH. [b] Yield over two steps. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Ir−(*S*)-MeOBIPHEP−BARF complex prepared from $[IrCl(cod)]_2$ (0.015 equiv), (*S*)-MeOBIPHEP (0.04 equiv), and NaBARF (0.03 equiv).

the reaction rate. Interestingly, when the Ir−PHOX catalyst was applied to the asymmetric hydrogenation of α-amino-*β*-keto ester hydrochloride salts via DKR, no reaction was observed. However, the addition of NaBARF to the iridium catalyst prepared from $[IrCl(cod)]_2$ and (*S*)-MeO-BIPHEP effected increase of the isolated yield to 100%, but the diastereo- and enantioselectivity remained at a similar level with the case of the reaction under high hydrogen pressure (100 atm) (entry 3). After some trial and error, we were pleased to find an unusual relationship between hydrogen pressure and enantioselectivity.[11] Thus, lowering hydrogen pressure enhanced enantioselectivity (entries 4−7). Under 4.5 atm of hydrogen, the enantioselectivity was improved to 93% ee. Furthermore, the reaction progressed even under 1 atm of hydrogen with similar stereoselectivity in excellent yield. This cationic Ir−(*S*)-MeO-BIPHEP−BARF complex can be readily prepared by mixing $[IrCl(cod)]_2$, (*S*)-MeO-BIPHEP, and NaBARF in methylene chloride at 23 °C for 1 h under air atmosphere and can be easily handled without a strictly degassed anhydrous condition (entry 8). The catalyst loading can be lowered from 3 mol % to 0.5 mol % without loss of the yield and diastereo- and enantioselectivities (entries 9 and 10). A survey of several chiral phosphines revealed that (*S*)-MeO-BIPHEP was the most efficient in terms of yield and enantioselectivity (entries 11−14). (*S*)-SEGPHOS was somewhat inferior to (*S*)-MeO-BIPHEP in terms of the chemical yield and enantioselectivity (entries 6 and 13). Under the optimized reaction conditions, the present catalytic direct *anti*-selective asymmetric hydrogenation under low hydrogen pressure was applied to various aromatic substrates (Table 2). The hydrogenation was carried out by using the second-generation Ir−(*S*)-MeO-BIPHEP−BARF catalyst prepared from $[IrCl(cod)]_2$ (0.005 equiv), (*S*)-MeO-BIPHEP (0.013 equiv), and NaBARF (0.01 equiv) in the presence of sodium acetate (1 equiv) in acetic acid under 4.5 atm of hydrogen at 23 °C for 96 h. From a practical point of view, we employed 4.5 atmospheric pressure of hydrogen. The yields and enantioselectivities were improved in comparison with our previous data by using the first-generation Ir catalyst.[5] The introduction of an electron-withdrawing group at the para position on the phenyl ring resulted in a slight decrease of the enantionselectivity (82% ee), but the anti selectivity and yield were excellent (entry 7). The cationic Ir complex was also applicable to heteroaromatic substrates containing a sulfur or on oxygen atom. In the case of aliphatic substrates, such as R = *n*-Pr and cyclohexyl substrates, at the C4 position, no or low conversion was observed. Surprisingly, hydrogenation of the highly hindered substrate with a *tert*-butyl group stereoselectively proceeded to provide *β*-hydroxy-α-amino acid ester with the anti/syn ratio of >99:1 in quantitative yield and 91% ee (entry

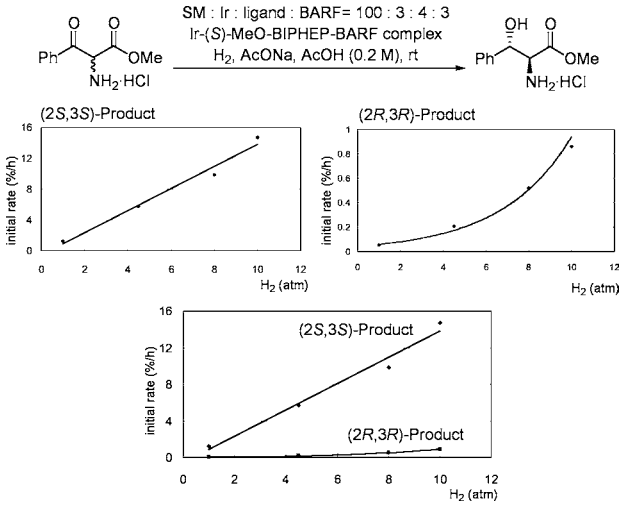


Figure 1. Dependence of the initial rate on the H_2 pressure.

(10) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600−2604.

(11) Hydrogen pressure effects on enantioselectivity using Ir complex: Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113−123.

11). It is noted that this result is the highest value for the *tert*-butyl substrate and is superior to that of the Ru−BINAP-catalyzed anti-selective hydrogenation developed by us.

To obtain further insight into the relationship between the enantioselectivity and the hydrogen pressure, the initial rate kinetics of the (2*S*,3*S*)-product and its enantiomer using the Ir−(*S*)-Me-OBIPHEP−BARF catalyst were investigated. The results are summarized in Figure 1. Interestingly, the relationship between the initial rate of the major (2*S*,3*S*)-product and the increase of hydrogen pressure showed a linear fashion. On the other hand, in the case of the (2*R*,3*R*)-product, a nonlinear increase of the product with the increase in the hydrogen pressure was observed. This result indicates that the hydrogenation of the α-amino-*β*-keto esters using the Ir−(*S*)-Me-OBIPHEP−BARF catalyst proceeds through two different mechanisms at least.

In conclusion, we have developed an efficient synthesis of anti-aromatic *β*-hydroxy-α-amino acid esters through direct anti-selective asymmetric hydrogenation via DKR under very low hydrogen pressure catalyzed by the Ir−(*S*)-MeO−BIPHEP−BARF complex, which is readily prepared from commercially available chiral phosphine and iridium complex and the resulting catalyst can be easily handled without care. This hydrogenation can be also used for efficient asymmetric synthesis of anti-hindered aliphatic *β*-hydroxy-α-amino acid esters. It is noted that this method does not require special instruments and techniques and can be carried out even by use of the hydrogen-balloon technique. In addition, this hydrogenation using the Ir−(*S*)-MeO−BIPHEP−BARF catalyst can be applied to the synthesis of various pharmaceutical and natural products. Further investigation on the scope and mechanism of this unique hydrogenation is currently in progress.

Supporting Information Available: Experimental procedures, characterization of the products, and the data for mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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