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Dynamic Kinetic Resolution Catalyzed by Ir Axially Chiral Phosphine Catalyst: Asymmetric Synthesis of anti Aromatic β-Hydroxy-α-amino Acid Esters

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Dynamic kinetic resolution (DKR) is one of several powerful tools for efficient synthesis of one enantiomer from racemic starting materials without any loss.[1] The ruthenium-catalyzed DKR in combination with axially chiral phosphines was originally developed by Noyori et al.[2] for asymmetric synthesis of 2-substituted β-hydroxyesters including *syn*-β-hydroxy-α-amino esters from chirally labile 2-substituted β-keto esters.[3] This epoch-making methodology has attracted considerable attention in the organic chemistry community and has been successfully applied to production of β-lactam antibiotic intermediate.[3a] Recently, we have demonstrated[4] for the first time that α-amino-β-keto ester hydrochlorides have been directly hydrogenated in an anti selective manner through DKR with the Ru−BINAP catalyst to produce *anti*-β-hydroxy-α-amino esters with high diastereo- and enantioselectivities.[5] This method has revealed that alkyl substrates are the most suitable for the hydrogenation; however, aromatic substrates are poor for the enantioselectivity (Scheme 1). The anti aromatic β-hydroxy-α-amino acids are of importance and are incorporated into the backbone of a wide range of antibiotics and cyclopeptides such as vancomycins and papuamides. Therefore, stereoselective synthesis of the anti aromatic β-hydroxy-α-amino acids still remains a formidable challenge.[6] Herein we describe the first successful dynamic kinetic resolution catalyzed by in situ generated Ir axially chiral phosphine catalyst in asymmetric synthesis of anti aromatic β-hydroxy-α-amino esters from the corresponding α-amino-β-keto esters.

Initially, we briefly surveyed transition metals for the hydrogenation of the α-amino-β-keto ester, as shown in Table 1. Interestingly, in addition to the known ruthenium catalyst, the rhodium and iridium catalysts also underwent highly anti selective hydrogenation but with low enantioselectivities (entries 1−3). However, we were pleased to find for the first time that the iridium complex derived from $[Ir(cod)Cl]_2$ and BINAP is a promising catalyst for DKR in asymmetric hydrogenation of α-amino-β-keto ester (entry 3). The procedure for preparation of the catalyst was critical for its catalytic activities. The most active catalyst was made prior to hydrogenation by mixing the iridium complex with BINAP in methylene chloride at 23 °C for 10 min (entries 3 and 4). Acetic acid was the solvent of choice for the diastereoselectivity (entry 5). The presence of sodium acetate affected the enantioselectivity dramatically (entry 6). Next, we examined the ability of several chiral phosphines. Among them, MeOBIPHEP was most efficient for the enantioselectivity (entry 7). Moreover, the addition of an iodide anion source,[7] especially sodium iodide, led to maximized enantioselectivity (entries 8 and 9). The absolute stereochemistry of the thus-obtained amino acid was unambiguously determined as the known *N*-acetyl derivative.[8]

This method was then applied to various aromatic 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

Scheme 1. Ru−BINAP-Catalyzed anti Selective Hydrogenation

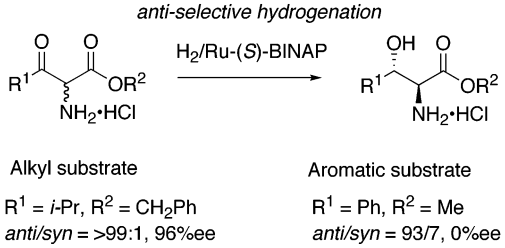
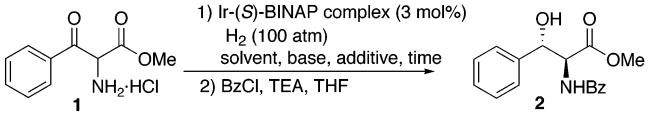


Table 1. Optimization of Asymmetric Hydrogenation Using Ir Catalyst[a]



entry	solvent	additives (eq)	time (h)	yield (%)	dr anti:syn	ee (%)
1[b]	MeOH	-	48	31	93:7	0
2[c]	PhH	-	48	44	98:2	8
3[d]	MeOH	-	48	83	93:7	32
4[d,e]	MeOH	-	48	18	-[f]	19
5	AcOH	-	48	81	99:1	27
6	AcOH	AcONa (1)	3	90	>99:1	69
7[g]	AcOH	AcONa (1)	3	79	>99:1	77
8[g]	AcOH	AcONa (1), NaI (0.06)	24	82	>99:1	90
9[g]	AcOH	AcONa (1), I_2 (0.03)	24	55	>99:1	87

[a] The reaction was carried out by using Ir−(*S*)-BINAP (prepared from $[IrCl(cod)]_2$ and BINAP prior to the hydrogenation) additive(s) in solvent. [b] $RuCl_2[(S)\text{-binap}](dmf)_n$ was used instead of Ir−(*S*)-BINAP. [c] The catalyst derived from $[Rh(cod)Cl]_2$ and (*S*)-BINAP and 50 atm of hydrogen was used instead of Ir−(*S*)-BINAP and 100 atm of hydrogen. [d] 50 atm of hydrogen was used. [e] The in situ generated catalyst from $[IrCl(cod)]_2$ and (*S*)-BINAP in the hydrogenation was used. [f] Not determined. [g] (*S*)-MeO-BIPHEP was used as a chiral ligand instead of (*S*)-BINAP.

easily prepared by the known methods.[4,9,10] The anti selective hydrogenation via dynamic kinetic resolution using 3 mol % of the Ir−(*S*)-MeOBIPHEP catalyst proceeded with almost complete diastereoselectivities under 100 atm of hydrogen in the presence of sodium acetate (1 equiv) and sodium iodide (0.06 equiv) in acetic acid at 27−30 °C to afford the anti aromatic β-hydroxy-α-amino esters with high enantioselectivities in excellent yields. The products were protected without purification as the *N*-benzolyl derivatives for their isolation and HPLC analysis. The diastereoselection in this reaction was surprisingly high despite the substituent on the aromatic nucleus, and the ^1H NMR analysis of the crude products revealed almost no presence of the *syn*-β-hydroxy-α-amino esters. The halogeno substrates are compatible under the hydrogenation

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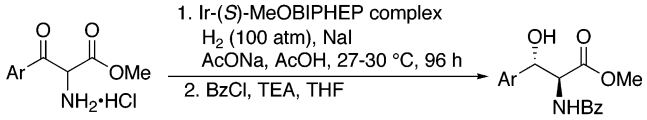
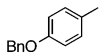
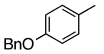
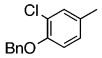
Table 2. Asymmetric anti Selective Hydrogenation[a]



entry	R	yield (%)	dr anti : syn	ee (%)
1		82	>99 : 1	90
2		80	>99 : 1	94
3[b]		88[c]	>99 : 1	95[d]
4		80	98 : 2	93
5		81	>99 : 1	94
6		93	>99 : 1	87
7		95	98 : 2	86
8		87	>99 : 1	75
9		75	>99 : 1	92
10		74[c]	>99 : 1	88
11		72	>99 : 1	88

[a] The reaction was carried out by using Ir−(*S*)-MeOBIPHEP (prepared from $[IrCl(cod)]_2$ (0.015 equiv), (*S*)-MeOBIPHEP (0.04 equiv), and NaI (0.06 equiv) prior to the hydrogenation) and NaOAc (1 equiv) in AcOH. [b] (*R*)-MeOBIPHEP was used instead of (*S*)-MeOBIPHEP. [c] As the *N*-Boc protected derivative. [d] (2*R*,3*R*)-Isomer was obtained.

conditions (entries 8 and 11). The heteroaromatic substrates are also suitable for the hydrogenation (entries 9 and 10).

The method opens up a new efficient access to 3-methoxytyrosine with anti stereochemistry, a stereochemically undefined component of papuamides.[11] For instance, O-methylation of the obtained benzyloxyphenyl derivative (entry 3) using trimethyloxonium tetrafluoroborate in the presence of Proton Sponge and subsequent hydrolysis furnished (2*R*,3*R*)-3-methoxytyrosine, a building block for papuamides, in good overall yield and excellent stereoselection.

As part of our study on the potential of the Ir−MeOBIPHEP catalyst, we carried out asymmetric hydrogenation of β-keto ester, α-amino acetophenone, and *N*-benzoyl α-amino-β-keto ester, which, surprisingly, gave apparently different results, namely, no or low conversion, no diastereoselectivity, and poor enantioselectivity, compared to those of the Ru-catalyzed hydrogenation.[12] This failure suggests that the Ir-catalyzed hydrogenation might proceed with a different mechanism from that of the Ru-catalyzed hydrogenation.

In conclusion, we have developed an efficient asymmetric synthesis of anti aromatic β-hydroxy-α-amino acid esters from the readily available α-amino-β-keto esters using the Ir−MeOBIPHEP catalyst for the first time. Our hydrogenation is the first example of dynamic kinetic resolution using the Ir axially chiral phosphine catalyst and can be carried out in an environmentally friendly solvent using commercially available chiral phosphines. The product anti aromatic β-hydroxy-α-amino acids are useful as building blocks for the synthesis of various pharmaceuticals and natural products. Further studies on the mechanism and the expansion of the scope and applicability are now in progress.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information.

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