Iridium–SYNPHOS-Catalyzed Hydrogenation through Dynamic Kinetic Resolution of α-Amino β-Keto Ester Hydrochlorides

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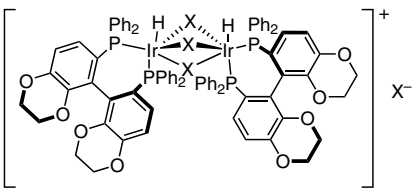
Abstract: The stereoselective synthesis of *anti* β-hydroxy α-amino esters by iridium–SYNPHOS-catalyzed asymmetric hydrogenation of α-amino β-keto ester hydrochlorides is reported. The reaction proceeded through dynamic kinetic resolution to afford a variety of β-hydroxy α-amino ester derivatives with good yields and high level of diastereo- and enantioselectivities (de up to 99%, ee up to 92%).

Key words: iridium, hydrogenation, asymmetric catalysis, enantioselectivity, amino alcohols

Dynamic kinetic resolution (DKR)[1] is a useful and highly efficient tool to access enantiomerically enriched compounds starting from racemic substrates bearing a labile stereocenter. Catalytic asymmetric hydrogenation of α-substituted β-keto esters via DKR in particular, provides a broad range of functionalized molecules in a high diastereo- and enantioselective fashion. In this field, the use of chiral ruthenium complexes for the hydrogenation of β-keto-α-amino esters via DKR was first reported by Noyori[2] and one of our laboratories[3] for the *syn*-selective formation of β-hydroxy-α-amino esters. The *anti*-selective Ru-mediated asymmetric hydrogenation of α-amino-β-keto esters via DKR was later described by Hamada,[4] Zhang[5] and one of our groups.[6] As part of our ongoing studies toward the development of practical and efficient catalysts for asymmetric hydrogenation of unsaturated compounds, we have previously reported a convenient one-pot synthesis of cationic triply halogen-bridged dinuclear iridium(III) complexes of general formula [{Ir(H)[(*S*)-diphosphine]}$_2$(μ-X)$_3$]X (X = Cl, Br and I).[7] These complexes were successfully used for the asymmetric hydrogenation of quinolines[8a,b] and quinoxalines derivatives,[8c,d] and allowed for the synthesis of the corresponding tetrahydroquinolines and tetrahydroquinoxalines with a high level of enantioselectivity. As an extension of our previous work on the dynamic kinetic resolution[9] of α-amino-β-keto ester hydrochlorides through asymmetric hydrogenation, and in an effort to expand the scope of the [{Ir(H)[(*S*)-diphosphine]}$_2$(μ-X)$_3$]X complexes, we report herein an application of these Ir(III) complexes bearing SYNPHOS,[10] an atropisomeric ligand developed by one of us, for the synthesis of *anti* β-hydroxy-α-amino esters.

The first example of DKR of α-amino-β-keto ester catalyzed by an in situ generated Ir axially chiral phosphine complex was reported by Hamada et al.[11] who showed that the method was effective for the preparation of aromatic *anti*-β-hydroxy-α-amino acids. The authors used either an Ir-(*S*)-MeOBIPHEP complex (prepared from [IrCl(cod)]$_2$, (*S*)-MeOBIPHEP, and NaI prior to the hydrogenation) with NaOAc in AcOH under high hydrogen pressure,[11a] or the Ir-(*S*)-MeO-BIPHEP-BARF complex prepared from [IrCl(cod)]$_2$, (*S*)-MeOBIPHEP, and NaBARF in the presence of sodium acetate in acetic acid under low hydrogen pressure.[11b] In both cases, the chiral iridium complex was prepared in situ and the hydrogenation proceeded in good yields and with high levels of diastereo- and enantioselectivities. In connection with the work disclosed by the group of Hamada, we describe herein the results obtained for the hydrogenation of α-amino β-keto ester hydrochlorides using the cationic dinuclear iridium(III) catalysts [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-X)$_3$]X[7] **1a–c** (Figure 1). These complexes are conveniently prepared from [IrCl(coe)$_2$]$_2$ by adding (*S*)-SYNPHOS[10] and an excess of aqueous HX in toluene at room temperature, and the isolated catalysts are easy to handle and can be stored.



1a: X = Cl
1b: X = Br
1c: X = I

Figure 1 Structures of cationic dinuclear triply halogen-bridged iridium complexes **1a–c**

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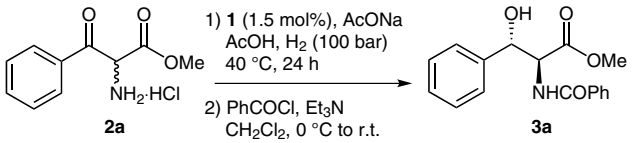
The DKR was first performed with **2a** as the standard substrate using 1.5 mol% of [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-Cl)$_3$]Cl (**1a**) and NaOAc in acetic acid at 40 °C under 100 bar of hydrogen pressure (Table 1). After 24 hours of reaction time, complete conversion of **2a** was observed and the resulting substituted β-hydroxy-α-amino ester **3a** (prepared by protection of the corresponding ammonium with benzoyl chloride) was obtained in good yield with an excellent *anti* diastereoselectivity (dr >99:1) and with a high er (90:10; Table 1, entry 1). Similar results were observed under these reaction conditions with [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-Br)$_3$]Br (**1b**; Table 1, entry 2).

Table 1 Optimization of the Reaction Conditions[a]



2a **3a**

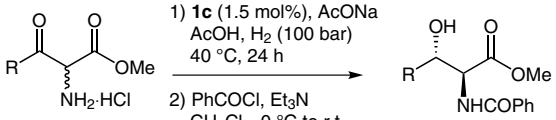
Entry	Ir complex	Conv[b] (%)	Yield (%)	dr[c] *anti*/*syn*	er[d]
1	**1a**	100	80	>99:1	90:10
2	**1b**	100	79	>99:1	90:10
3	**1c**	100	72	>99:1	–4:6
4[e]	**1c**	0	–	–	–
5[f]	**1c**	76	67	99:1	84:16
6[g]	**1c**	13	–[h]	–[h]	–[h]
7[i]	**1c**	100	72	>99:1	92:8
8[j]	**1c**	100	68	93:7	94:6

[a] Reaction conditions: **2** (0.44 mmol), catalyst (1.5 mol%), NaOAc (0.44 mmol) in AcOH (2 mL) at 40 °C for 24 h under 100 bar of hydrogen pressure.
[b] Conversions were determined after the hydrogenation reaction by ^{1}H NMR spectroscopy of the crude product.
[c] The dr value was determined by ^{1}H NMR spectroscopy of the crude product **3a**.
[d] The er value was determined by SFC or HPLC analysis of **3a**.
[e] The reaction was run in the absence of NaOAc.
[f] (*S*)-DIFLUORPHOS ligand was used instead of (*S*)-SYNPHOS.
[g] CF_3CO_2H was used as a solvent instead of AcOH.
[h] Not determined.
[i] The reaction was carried out with 1 mol% of the Ir complex.
[j] The reaction was conducted under 70 bar of H_2.

Pleasingly, the use of [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-I)$_3$]I complex **1c** allowed a higher enantiomeric ratio (94:6) whereas the dr remained excellent (Table 1, entry 3). In contrast with the result reported by Hamada et al. with a mononuclear Ir-(*S*)-MeOBIPHEP complex, in our case, no reaction was observed in the absence of sodium acetate (Table 1, entry 4). Replacing (*S*)-SYNPHOS by the electron-deficient (*S*)-DIFLUORPHOS[12] ligand resulted in incomplete conversion after 24 hours with a slightly lower er (Table 1, entry 5). When the hydrogenation was carried out in trifluoroacetic acid instead of acetic acid, poor conversion was observed (Table 1, entry 6). Lowering the catalyst loading to 1 mol% had no influence on either the conversion or the diastereo- and enantioselectivities (Table 1, entry 7). Finally, when the reduction was performed under 70 bar of hydrogen pressure instead of 100 bar, a decrease of the diastereomeric ratio was observed (93:7 vs >99:1, Table 1, entries 8 and 3).

In an attempt to establish the scope of the Ir–(*S*)-SYNPHOS-promoted hydrogenation, a series of α-amino-β-keto ester hydrochlorides **2a**–**k**[13] bearing various substitution patterns were subjected to catalytic asymmetric hydrogenation under the optimized reaction conditions (Table 2).

Table 2 DKR of Various α-Amino-β-Keto Ester Hydrochlorides through Ir-SYNPHOS-Czatalyzed Hydrogenation[a]



2 **3**

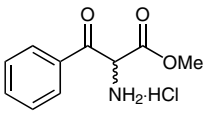
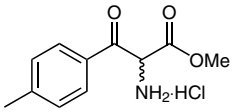
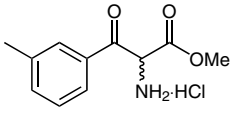
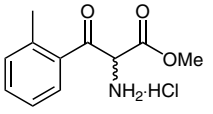
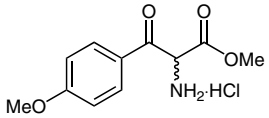
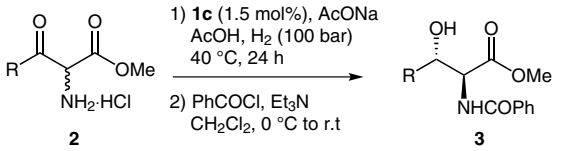
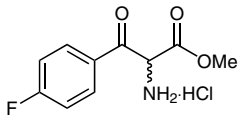
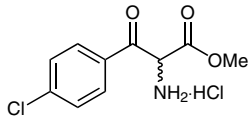
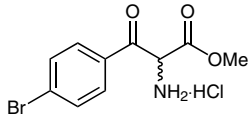
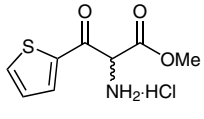
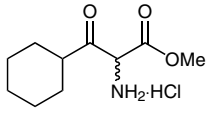
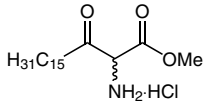
Entry	Substrate	Yield (%)	dr[b] *anti*/*syn*	er[c]
1	 **2a**	72	>99:1	94:6
2	 **2b**	73	>99:1	94:6
3	 **2c**	72	>99:1	93:7
4	 **2d**	58	>99:1	92:8
5	 **2e**	87	>99:1	95:5

Table 2 DKR of Various α-Amino-β-Keto Ester Hydrochlorides through Ir-SYNPHOS-Czatalyzed Hydrogenation[a] (continued)



2 **3**

Entry	Substrate	Yield (%)	dr[b] *anti*/*syn*	er[c]
6	 **2f**	63	>99:1	92:8
7	 **2g**	72	>99:1	89:11
8	 **2h**	68	> 99:1	86:14
9	 **2i**	85	>99:1	96:4
10	 **2j**	60	95:5	91:9
11	 **2k**	60	83:17	81:19

[a] Reaction conditions:[14] **2** (0.44 mmol), catalyst (1.5 mol%), NaOAc (0.44 mmol) in AcOH (2 mL) at 40 °C for 24 h under 100 bar of hydrogen pressure. Complete conversions were obtained for all compounds.
[b] Determined by ^{1}H NMR spectroscopy of the crude product **3**.
[c] Determined by SFC or HPLC analysis of **3**.

Thus, the hydrogenation of **2a**–**k** was carried out by using 1.5 mol% of [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-I)$_3$]I **1c** and NaOAc in acetic acid at 40 °C under 100 bar of hydrogen pressure for 24 hours, affording mainly excellent diastereomeric ratios as high as >99:1 with er ranging from 81:19 to 96:4. The introduction of a methyl group at the *para*, *meta* or *ortho* positions on the phenyl ring of the corresponding α-amino-β-keto ester hydrochlorides **2b**, **2c** and **2d** had no influence on either the yield or the diastereo- and enantioselectivities (Table 2, entries 1–4). Substrate **2e** bearing a methoxy group at the 4-position of the phenyl ring provided high diastereo- and enantioselectivities (Table 2, entry 5). The introduction at the *para* position on the phenyl ring of electron-withdrawing substituents such as fluorine, as in **2f**, a chlorine as in **2g** or a bromine as in **2h**, resulted in a slight decrease of the enantioselectivity, from 92:8 er for the fluorinated compound **3f** to 86:14 for the brominated compound **3h** (Table 2, entries 6–8). The DKR of **2i** bearing a thiophenyl substituent afforded the *anti*-substituted β-hydroxy-α-amino ester **3i** with high enantiomeric ratio and excellent diastereoselectivity as high as >99:1 (Table 2, entry 9). α-Amino β-keto ester hydrochlorides **2j** and **2k** having alkyl substituents were also investigated. In the case of compound **2j** bearing a sterically demanding cyclohexyl group, the corresponding *anti* product **3j** was obtained with high diastereoselectivity (dr 95:5, Table 2, entry 10) whereas a lower dr of 83:17 was obtained for the hydrogenation reaction of α-amino-β-keto ester hydrochloride **2k** having a linear alkyl chain (Table 2, entry 11).

In summary, we have shown that a cationic dinuclear iridium(III) iodide complex bearing the in-house developed SYNPHOS ligand is efficient for the hydrogenation reactions of a variety of α-amino-β-keto ester hydrochlorides via a dynamic kinetic resolution process. The efficiency of our catalyst system was demonstrated through the substrate scope of the reaction. Indeed, a series of *anti*-β-hydroxy-α-amino ester derivatives was synthesized in good chemical yields and with high levels of asymmetric induction. In addition, these compounds are key intermediates for the synthesis of targets of medicinal interest.

Acknowledgment

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(14) **Typical Procedure for the Ir-SYNPHOS-Catalyzed Asymmetric Hydrogenation of α-Amino-β-Ketoester Hydrochlorides**: To a Teflon tube charged with α-substituted β-keto ester **2** (0.44 mmol), NaOAc (36 mg, 0.44 mmol, 1 equiv) and AcOH (2 mL), was added solid catalyst [{Ir(H)[(*S*)-SYNPHOS]}$_2$(μ-I)$_3$]I (15 mg, 7 μmol, 1.5 mol%) in one portion and the reaction mixture was subjected to three vacuum/argon cycles. Under a flow of argon, the reaction vessel was placed in a stainless steel parallel hydrogenation system equipped with a central mechanical stirrer. The atmosphere of the autoclave was purged three times with argon and twice with H_2. The temperature was adjusted to 40 °C and the autoclave was filled with H_2 (100 bar). After 24 h of reaction, the autoclave was adjusted to r.t. and atmospheric pressure and finally purged three times with argon. The resulting mixture was concentrated under reduced pressure. The conversion was determined by ^{1}H NMR analysis of the crude product. To a solution of the previous β-hydroxyester hydrochloride (0.44 mmol, 1 equiv) in anhyd CH_2Cl_2 (2 mL) were added benzoyl chloride (67 mg, 55 μL, 1.1 equiv) and Et_3N (134 mg, 190 μL, 3 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and for 1 h at r.t., then diluted with CH_2Cl_2, quenched with sat. aq NH_4Cl, extracted with CH_2Cl_2 and dried over $MgSO_4$. The crude protected product was purified by flash chromatography to afford compound **3**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product, and the enantiomeric ratio was determined by chiral SFC analysis of the purified product using a Chiralcel OD-H, Chiralpak IA, IC or AD-H column.

