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Diastereo- and Enantioselective Hydrogenation of α-Amino-β-Keto Ester Hydrochlorides Catalyzed by an Iridium Complex with MeO-BIPHEP and $NaBAr_F$: Catalytic Cycle and Five-Membered Chelation Mechanism of Asymmetric Hydrogenation

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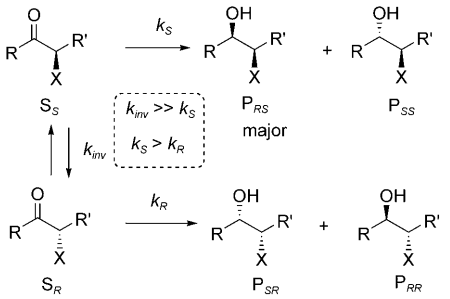
Abstract: The development of Ir-catalyzed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides is described. This reaction proceeds through a dynamic kinetic resolution to produce *anti*-β-hydroxy-α-amino acid esters in a high diastereo- and enantioselective manner. Mechanistic studies have revealed that this unique asymmetric hydrogenation proceeds through reduction of the ketone moiety via the five-membered transition state involving the chelation between the oxygen of the ketone and the nitrogen of the amine function. The relationship studies between the hydrogen pressure and the stereoselectivity have disclosed two mechanisms dependent on hydrogen pressure. Under low hydrogen pressure (<15 atm), the reaction rate proportionally increased with the hydrogen pressure. However, under the high hydrogen conditions, the reaction rate exponentially accelerated along with the increasing hydrogen pressure, which suggests the participation of two or more of hydrogen atoms.

Keywords: amino acids · asymmetric hydrogenation · dynamic kinetic resolution · iridium · reaction mechanisms

Introduction

Catalytic asymmetric hydrogenation through dynamic kinetic resolution (DKR) is one of the most efficient methods for the preparation of optically active compounds.[1] As illustrated in Scheme 1, the reaction of a rapidly racemizing substrate under the stated reaction conditions with a highly enantioselective catalyst, when the racemization rate is high enough compared to the reaction rate, can proceed through DKR and finally, all of the substrate can be converted into a single diastereomer in a, theoretically, 100% yield in a stereocontrolled fashion through a single operation.

In 1989, Noyori's group reported for the first time that a chiral Ru–BINAP complex catalyzes the *syn*-selective asymmetric hydrogenation[2] of α-acylamino-β-keto esters via DKR to produce the *syn*-β-hydroxy-α-acylamino acid derivatives,[3] which are useful chiral building blocks for the synthesis of natural products and medicines[4] with high diastereo- and enantioselectivity. Recently, as a complementary method for Noyori's asymmetric hydrogenation, we have succeeded in the development of the direct *anti*-selective asymmetric hydrogenation of α-amino-β-keto ester hydrochloride salts by DKR, catalyzed by an Ru,[5] Rh,[6] Ir,[7] or Ni[8] complex with a bisphosphine ligand (Scheme 2),[9] which provides *anti*-β-hydroxy-α-amino acid esters—important building blocks needed for our synthetic studies of cyclodepsipeptides.[10]



Scheme 1. Asymmetric hydrogenation of racemic ketones through dynamic kinetic resolution.

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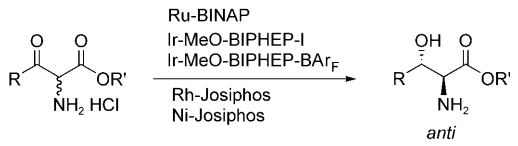
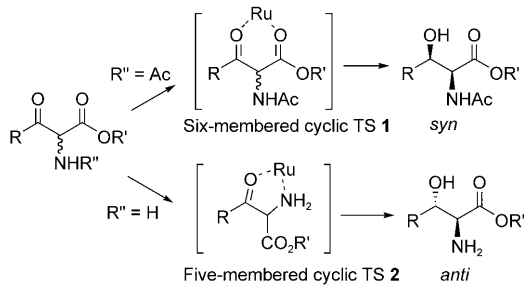


Scheme 2. Direct *anti*-selective asymmetric hydrogenation.

The reversal of diastereoselectivity from *syn* to *anti* was achieved based on our working hypothesis that the use of a protection-group free α-amino-β-keto ester as a substrate should induce a change in the transition state from the six-membered cyclic transition state (TS) **1** to the five-membered cyclic TS **2** to yield an *anti*-β-hydroxy-α-amino acid ester as shown in Scheme 3.



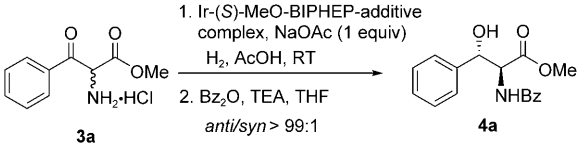
Scheme 3. Direct stereodivergent asymmetric hydrogenation.

The Ru-axially chiral bisphosphine-catalyzed asymmetric hydrogenation of an α-amino-β-keto ester hydrochloride with an alkyl group at the γ-position exclusively gave an *anti* product with an excellent enantioselectivity in high yield. This method has a serious problem in that substrates with an aromatic ring at the γ-position have a poor reactivity and enantioselectivity. In our efforts to address this problem, we developed new efficient Ir catalysts for the *anti*-selective asymmetric hydrogenation of the aromatic substrates.[7] We now report the details of the Ir-catalyzed direct *anti*-selective asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides by DKR as well as mechanistic studies using isotope labeling experiments, NMR spectroscopy analysis, and kinetics. Although mechanistic studies for the Ir-catalyzed hydrogenation of alkenes, ketones, and imines have been reported by several groups,[11] the mechanism for the Ir-catalyzed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides through DKR has never been reported.

Results and Discussion

Development of catalytic asymmetric hydrogenation of α-amino-β-keto esters by DKR: The Ru-axially chiral phosphine-catalyzed asymmetric hydrogenation of methyl *C*-benzoylglycinate hydrochloride (**3a**), an aromatic substrate, resulted in the formation of the racemic amino acid **4a** in a diastereomeric ratio of 93:7 and 31% yield. This disappointingly low level of asymmetric induction prompted us to examine other transition metals for the *anti*-selective asymmetric hydrogenation of **3a**. Interestingly, in addition to the known ruthenium catalyst Rh and Ir proved to be potential catalysts for the highly *anti*-selective asymmetric hydrogenation through DKR. Therefore, we first carried out the optimization of the Ir-catalyzed *anti*-selective asymmetric hydrogenation. The selected conditions for the optimization are summarized in Table 1.[12]

Table 1. Optimization of the Ir-catalyzed asymmetric hydrogenation.[a]



Entry	Additive (3 mol%)	H_2 [atm]	Time[b]	Yield [%][b]	*ee* [%][c]
1[d]	–	100	3	90	69
2	–	100	3	77	77
3	NaI	100	24	82	90
4	KI	100	24	57	87
5	I_2	100	24	55	87
6	$NaBAr_F$	100	3	100	74
7	$NaBAr_F$	4.5	24	100	93
8	$NaBAr_F$	1	96	91	92
9[e]	$NaBAr_F$	1	96	90	92
10[f]	$NaBAr_F$	4.5	96	100	92
11[g]	$NaBAr_F$	4.5	96	98	92

[a] The Ir catalyst was prepared from $[Ir(cod)Cl]_2$, ligand, and additive in CH_2Cl_2 prior to hydrogenation. [b] Yield in two steps. [c] Determined by HPLC analysis. [d] (*S*)-BINAP was used. [e] No freeze–thaw operation. [f] 1 mol% catalyst was used. [g] 0.5 mol% catalyst was used.

The hydrogenated product was isolated as the *N*-benzoyl derivative for HPLC analysis. Reactions in polar solvents, such as alcohols and acetic acid rather than dichloromethane, tended to proceed smoothly, exclusively giving an *anti* product in a high yield with a moderate enantiomeric excess. The presence of triethylamine or sodium acetate as a base in an alcoholic solvent caused a decreased yield due to the significant decomposition of the substrate, while the addition of sodium acetate in acetic acid improved the enantioselectivity from 27 to 69% *ee* with a strongly enhanced reactivity (90% yield after 3 h; entry 1). The other bases with a different counter cation, such as lithium or ammonium acetate, were inferior to sodium acetate in yield. The choice of the chiral phosphine ligand was critical for promoting the *anti*-selective asymmetric hydrogenation through DKR. The axially chiral bidentate phosphines formed an efficient catalyst with $[Ir(cod)Cl]_2$, but the use of other phosphines, such as a DIOP or NORPHOS, resulted in no reaction.

Among several axially chiral phosphines, MeO-BIPHEP with an electron-donating group and a large bite angle, was very effective, and the enantioselectivity reached 77% *ee* (entry 2). To further improve the enantioselectivity, various

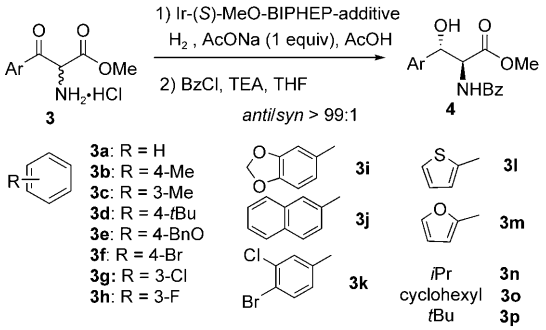
additives used in the preparation of the Ir complex were examined. The addition of phthalimide,[13] potassium fluoride, tetrabutylammonium bromide or silver trifluoroacetate was either not or less effective in yield and stereoselectivity, but iodine or iodide salts were found to be effective additives that improved the enantioselectivity (entries 3–5).[14,15] Especially, the use of the Ir complex prepared from $[Ir(cod)Cl]_2$ (0.015 equiv), (*S*)-MeO-BIPHEP (0.04 equiv), and sodium iodide (0.06 equiv) led to a remarkable improvement in the enantiomeric excess from 77 to 90% (entry 3).

The first-generation iridium catalyst, that is, the Ir-(*S*)-MeO-BIPHEP-I complex, has a number of problems. For instance, the reaction required a high hydrogen pressure (100 atm) and tedious degassing operation with freeze-thaw cycles for the preparation of the catalyst and during assembling an apparatus prior to hydrogenation for a smooth reaction. In addition, longer reaction times were required for completion. Therefore, we sought an additive(s), other than iodine or the iodide ion, for a more efficient catalyst than the first-generation Ir catalyst. Recently, Pfaltz's group reported the effect of a tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) counterion, which serves to stabilize the Ir-PHOX catalyst and enhances its catalytic activity.[16,17] Inspired by this report, we applied the Ir-PHOX catalyst to the asymmetric hydrogenation of **3a** by DKR, but no reaction was observed. The addition of $NaBAr_F$ during the preparation of the Ir catalyst from $[Ir(cod)Cl]_2$ and (*S*)-MeO-BIPHEP resulted in the completion of the reaction with the quantitative isolated yield of **4a**, but the enantioselectivity remained at a similar level to that under a high hydrogen pressure (100 atm, entry 6). After several preliminary experiments, a key discovery was made when the effect of the hydrogen pressure was examined. We found that the enantioselectivity increased when the hydrogen pressure was reduced. The change in the hydrogen pressure from 100 to 4.5 atm enhanced the enantiomeric excess of **4a** from 74 to 93% (entry 7).

To our surprise, the hydrogenation proceeded even below 1 atm hydrogen with a similar stereoselectivity and excellent isolated yield (entry 8). The addition of sodium acetate was essential for this asymmetric hydrogenation. This cationic Ir-(*S*)-MeO-BIPHEP-BAr_F complex, the second-generation iridium catalyst, can be readily prepared by mixing $[Ir(cod)Cl]_2$ (0.5 equiv), (*S*)-MeO-BIPHEP (1.3 equiv), and $NaBAr_F$ (1 equiv) in methylene chloride at 23°C, and can be easily handled without a strict degassing operation and anhydrous conditions (entry 9). The catalyst loading can be reduced from 3 to 0.5 mol% without any loss in stereoselectivities and yield (entry 11).

Under the optimized reaction conditions, we investigated the scope and limitation of these Ir catalysts. The results are summarized in Table 2. For the second-generation Ir catalyst the hydrogenation reactions were carried out in the presence of the catalyst (1 mol%) and sodium acetate (1 equiv) in acetic acid under 4.5 atm of hydrogen at 23°C for 96 h. For practical reasons, 4.5 atm hydrogen was employed. The Ir-catalyzed asymmetric hydrogenation through DKR was

Table 2. Ir-catalyzed *anti*-selective asymmetric hydrogenation.



Entry	Substrate	1st Ir catalyst[a]		2nd Ir catalyst[b]	
		Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1	**3a**	82	90	100	92
2	**3b**	81	94	92	92
3	**3c**	83	87	100	90
4	**3d**	–	–	97	91
5	**3e**	80	94	100	93
6	**3f**	87	75	96	82
7	**3g**	–	–	76	74
8	**3h**	–	–	67	67
9	**3i**	80	93	–	–
10	**3j**	95	86	94	90
11	**3k**	72	88	97	90
12	**3l**	75	92	94	96
13	**3m**	74	88	61	84
14	**3n**	47	82	33	85
15	**3o**	45	81	9	87
16	**3p**	–	–	100	91

[a] Hydrogenation was carried out by using the Ir-(*S*)-MeO-BIPHEP-I catalyst (3 mol%) under hydrogen pressure (100 atm) at 27–30°C for 96 h. [b] The hydrogenation was carried out by using the Ir-(*S*)-MeO-BIPHEP-BAr_F catalyst (1 mol%) under hydrogen pressure (4.5 atm) at 23°C for 96 h.

generally applicable to γ-aromatic α-amino-β-keto esters, which exclusively produced the corresponding *anti* products.

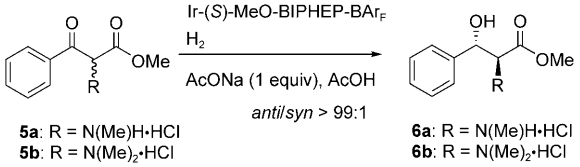
Compared to the first-generation Ir catalyst, the second-generation Ir catalyst showed higher yields and enantioselectivities under moderate hydrogen pressures. Halogen atoms in the substrates were compatible under the hydrogenation conditions, but the presence of an electron-withdrawing substituent on the γ-aromatic ring resulted in a slight decrease in the enantioselectivities (entries 6–8). These results showed that the stereoselectivity of the Ir-catalyzed *anti*-selective asymmetric hydrogenation is seriously influenced by the electronic environment of the substrates. α-Amino-β-keto esters with a heteroaromatic ring containing a sulfur or an oxygen atom were good substrates for this hydrogenation (entries 12 and 13).

In the case of γ-alkyl substrates, such as those in which R is *n*-propyl, isopropyl, or cyclohexyl, either no or low conversion was observed (entries 14 and 15). Interestingly, hydrogenation of the highly hindered substrate **3p** with a *tert*-butyl group proceeded stereoselectively to provide the β-hydroxy-α-amino acid ester **4p** with a diastereomeric ratio of >99:1 in a quantitative yield and 91% *ee* (entry 16).

In order to investigate the potential of this second-generation Ir catalyst, the hydrogenation of *N*-methyl- and *N,N*-di-

methyl α-amino-β-keto esters **5a** and **5b** were attempted as shown in Table 3.

Table 3. Asymmetric hydrogenation of *N*-methyl- and *N*,*N*-dimethyl α-amino-β-keto esters.



Entry	Substrate	Catalyst [mol%]	H_2 [atm]	Time [h]	Conversion yield [%][a]	*ee* [%]
1	**5a**	1	4.5	96	99	7
2	**5b**	3	100	120	64	60

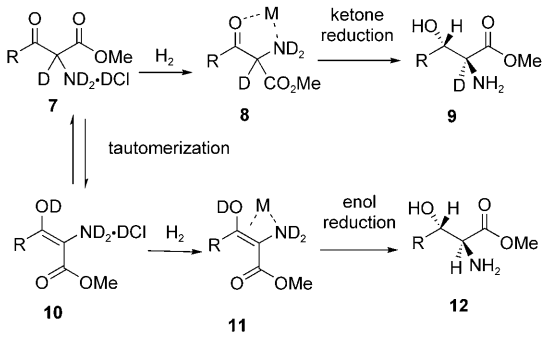
[a] Determined by ^{1}H NMR spectroscopy analysis.

In stark contrast to the *N*-nonsubstituted **3a**, the hydrogenation of **5a** proceeded diastereoselectively, but afforded almost only the racemic amino acid ester **6a**, while **5b** needed extreme reaction conditions, that is, 100 atm hydrogen and 120 h, to yield the amino acid ester **6b** with a moderate enantioselectivity. These results indicated that the presence of a nonsubstituted amino group in a substrate is essential for efficient Ir-catalyzed *anti*-selective asymmetric hydrogenation through DKR.

Nonetheless, the results of the above asymmetric hydrogenation are noteworthy, not only because the Ir-catalyzed *anti*-selective hydrogenations produced results complementary to those of a Ru-axially chiral phosphine catalyst, but also because the Ir-catalyzed asymmetric hydrogenation through DKR has never been reported so far.[18]

Isotope labeling experiments: To elucidate the reaction mechanism of this unique *anti*-selective asymmetric hydrogenation, we carried out isotope labeling experiments. For this hydrogenation, the substrate α-amino-β-keto ester is as an equilibrating mixture of keto and enol tautomers through tautomerism. One simple question to pose is: which tautomer is hydrogenated? As for the Ru-catalyzed asymmetric hydrogenation by DKR, Noyori and co-workers have unambiguously elucidated by isotope labeling experiments that the *syn*-selective asymmetric hydrogenation proceeds through the reduction of a keto tautomer.[3a] We have also disclosed that the Ru-catalyzed *anti*-selective asymmetric hydrogenation can be ascribed to the hydrogenation of an enol tautomer.[5f] As in Noyori's experiments, we performed the Ir-catalyzed asymmetric hydrogenation of the deuterio substrate **7**.

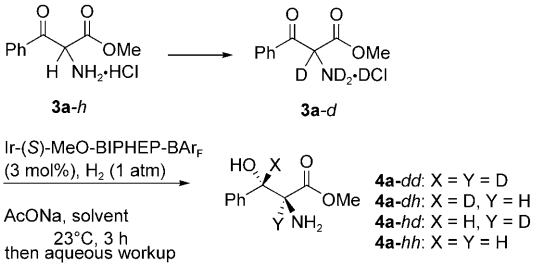
As depicted in Scheme 4, when the reaction of **7** proceeds through intermediate **8** of the ketone reduction, the deuterium at the C2 position should remain in product **9**. On the other hand, hydrogenation of enol tautomer **10** should give the deuterium-free amino acid **12** as the major product. All reactions were stopped after a low conversion to minimize



Scheme 4. Possible reaction pathway through ketone and/or enol reduction.

any complication caused by the deuterium-exchange reaction between the gas and solvent (Table 4).

Table 4. Isotope experiment with the second-generation Ir catalyst.

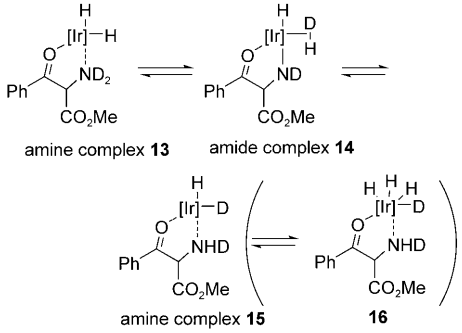


Entry	Substrate	Conditions	Yield [%]	Ratio of deuterio isomers[a]			
				4a-*dd*	**4a**-*dh*	**4a**-*hd*	**4a**-*hh*
1	**3a**-*d*	H_2 CD_3CO_2D	17	47	0	53	0
2	**3a**-*h*	HD CH_3CO_2H	8	0	26	0	74
3	**3a**-*h*	D_2 CH_3CO_2H	3	0	41	0	59

[a] Determined by ^{1}H NMR spectroscopy.

The reaction of the deuterio compound **3a**-*d* with H_2 (1 atm) in the presence of sodium acetate in CD_3COOD for 3 h at 23 °C by using the Ir-(*S*)-MeOBIPHEP-BAr$_F$ complex (3 mol%) afforded a 47:53 mixture of **4a**-*dd* and **4a**-*hd* (17% conversion). Under the same conditions, except for the use of HD and CH_3COOH, compound **3a**-*h* was converted to a 26:74 mixture of **4a**-*dh* and **4a**-*hh* (8% conversion). The hydrogenation of compound **3a**-*h* with D_2 in CH_3CO_2H gave **4a**-*dh* and **4a**-*hh* in a ratio of 41:59 (3% conversion). All these results suggested that this cationic Ir-catalyzed asymmetric hydrogenation by DKR proceeded through the keto and not the enol form. The unexpected mixing, that is, the incorporation of a deuterium at the C3 position, could be explained by the H/D exchange process between a dihydride amino tautomer and a dihydrogen-monohydride amido tautomer proposed by Dahlenburg and Götz.[11e] The dihydride–amino complex **13** with an acidic N–D bond, a possible intermediate in the Ir-catalyzed hydrogenation reaction, equilibrates with the η^2-HD–monohy-

dride amido complex **14**, which can be converted to the deuteride-hydride-amino complex **15**. Complex **13** gives the hydrogenated product with a hydrogen, but complex **15** gives one with a deuterium at the C3 position (Scheme 5).



Scheme 5. Deuterium-exchange mechanism.

To obtain further insight into the unusual relationship between the enantioselectivity and hydrogen pressure, the initial rates were investigated under various pressures (Figure 1). Up to 10 atm of hydrogen, the initial rate linearly

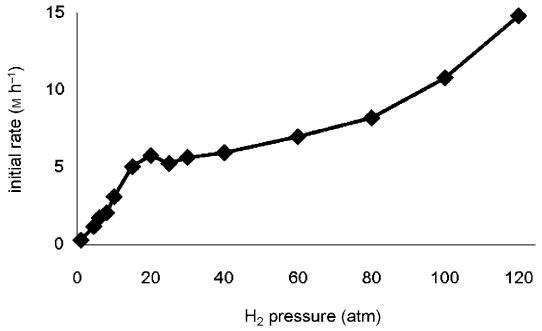


Figure 1. Plot of hydrogen pressure against initial rate.

We also performed deuterium-incorporation studies under various hydrogen pressures. As shown in Table 5, elevation of H_2 pressure up to 30 atm increased H/D incorporation

Table 5. H/D incorporation ratio at C3 position under various hydrogen pressures.

Entry[a]	H_2 [atm]	**4a**-*dd*/**4a**-*hd*[a]
1	1	47:53
2	10	64:36
3	20	21:79
4	30	20:80
5	100	19:81

[a] Determined by ^{1}H NMR spectroscopy analysis.

ratios at the C3 position. Above 30 atm H/D incorporation ratios at the C3 position were almost constant; this implies the presence of another reaction pathway, such as via complex **16**, derived from the reaction of **15** with a hydrogen molecule under high hydrogen pressure.[11f]

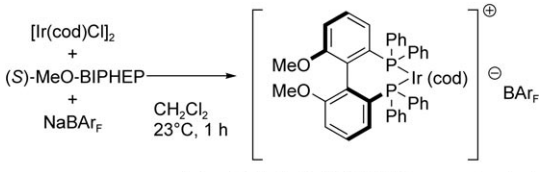
Kinetics of hydrogenation: To gain insight into the actual species formed during the Ir-catalyzed asymmetric hydrogenation, we initially investigated a nonlinear effect. During hydrogenation of the α-amino-β-keto ester **3a**, the correlation between the *ee* of (*S*)-MeO-BIPHEP and that of the product was carefully examined, and it was concluded that no nonlinear effects were evident at 1 and 120 atm of hydrogen pressure. These results indicate that the obtained enantiomeric excess from this asymmetric hydrogenation through DKR was not influenced by the aggregation of the chiral Ir complex.[12]

Next, we performed the initial kinetic studies of the Ir-catalyzed asymmetric hydrogenation at 1 atm hydrogen. The reaction was first order with respect to the concentration of the Ir catalyst and sodium acetate, and independent of the concentration of substrate.[12]

depended on the hydrogen pressure. At hydrogen pressures higher than 20 atm, the initial rate remained constant and a pseudo-zero-order dependency on the hydrogen pressure was observed. Above 40 atm the initial rate again increased nonlinearly. These kinetic studies lead us to conclude that the rate of the Ir-catalyzed hydrogenation at low hydrogen pressure conditions (<15 atm) is proportional to the concentrations of the catalyst, sodium acetate, and hydrogen, which are involved in the rate-determining step.

NMR spectroscopy experiments: The cationic Ir complex **17**, Ir-cod-(*S*)-MeO-BIPHEP-BAr_F, was prepared by mixing $[Ir(cod)Cl]_2$, (*S*)-MeO-BIPHEP, and $NaBAr_F$ in CH_2Cl_2 at 23 °C for 1 h, and then purified by silica gel column chromatography. The precatalyst structure composed of iridium, cyclooctadiene, (*S*)-MeO-BIPHEP, and BAr_F was confirmed by high resolution mass spectroscopy and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy as shown in Scheme 6.

To elucidate the intermediates in the catalytic cycle of the second-generation Ir catalyst, we conducted ^{31}P NMR spectroscopic experiments on the Ir complexes (Figure 2). The chemical shift (14.5 ppm) of the prepared Ir-cod-(*S*)-MeO-BIPHEP-BAr_F complex (**17**) was uninfluenced by the addition of substrate **3a** (100 equiv to the Ir catalyst) and



Ir (cod)-(*S*)-MeO-BIPHEP-BAr_F complex (**17**)
HRMS (FAB, NBA)
Calcd for $C_{46}H_4O_2P_2Ir$: 883.2446 [M^+-BAr_F^-]
Found: 883.2449
^{31}P NMR (CD_3CO_2D): δ=14.5 ppm

Scheme 6. Preparation of complex **17**.

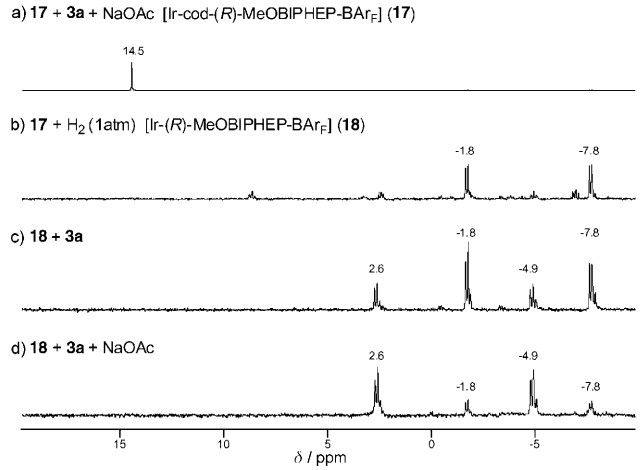
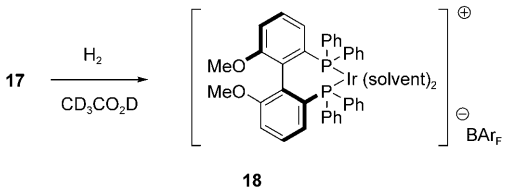


Figure 2. ^{31}P NMR spectra of Ir complexes.

sodium acetate (100 equiv) in CD_3COOD under an argon atmosphere. However, when the resulting mixture was stirred under hydrogen (1 atm) at 23 °C for 0.5 h, the release of cyclooctane was detected by ^{1}H NMR spectroscopy analysis and two new peaks appeared at 2.7 and −4.7 ppm in the ^{31}P NMR spectrum. These results showed that the complexation of the Ir complex with **3a** occurred after the hydrogenative removal of 1,5-cyclooctadiene as a cyclooctane. The appearance of new peaks in the ^{31}P NMR spectrum suggested the formation of an Ir-(*S*)-MeO-BIPHEP-substrate-BAr_F complex.

On the other hand, exposure of the Ir-cod-(*S*)-MeO-BIPHEP-BAr_F complex (**17**) to hydrogen (1 atm) for 0.5 h in CD_3COOD without the addition of substrate **3a** and sodium acetate produced a species with two peaks at −1.8 and −7.8 ppm in the ^{31}P NMR spectrum. This suggested that the 1,5-cyclooctadiene on the Ir-cod-(*S*)-MeO-BIPHEP-BAr_F complex was hydrogenated to afford the Ir-(*S*)-MeO-BIPHEP-BAr_F complex (**18**) as the solvated form (Scheme 7).

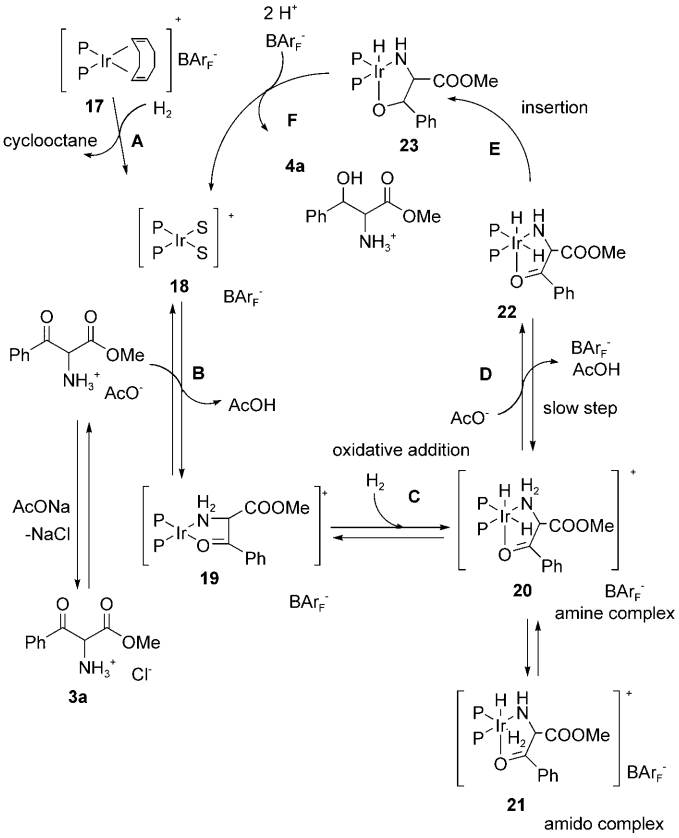


Scheme 7. Hydrogenation of complex **17**.

To obtain further information about the observed NMR signals, substrate **3a** and sodium acetate were added to Ir complex **18**. The addition of only substrate **3a** (50 equiv for the Ir complex) produced the appearance of two signals at 2.6 and −4.9 ppm along with the original signals (−1.8 and −7.8 ppm; Figure 2c). The intensities of these new signals were enhanced by the presence of both **3a** and sodium acetate (Figure 2d). This means that the presence of sodium acetate promoted the coordination of substrate **3a** to the Ir-(*S*)-MeO-BIPHEP-BAr_F complex.

Our proposed five-membered cyclic structure of the Ir-(*S*)-MeO-BIPHEP-substrate-BAr_F complex was supported by comparing the chemical shifts in the ^{31}P NMR spectra of the analogous Ir complexes with other substrates. The complexation of an α-amino ketone with the Ir complex **18** gave new peaks at −7.4 and −12.3 ppm along with the original peaks of the Ir complex (−1.8 and −7.8 ppm). When the Ir-(*S*)-MeO-BIPHEP-BAr_F complex (**18**) was treated with a β-keto ester, no change was observed with the −1.8 and −7.8 ppm peaks of the ^{31}P NMR spectrum. These results support the fact that the amino group in the α-amino-β-keto ester **3a** plays an important role in coordination to the Ir complex.

Proposed catalytic cycle: Based on the kinetics, NMR spectroscopy, and isotope labeling experiments, the plausible catalytic cycles of the asymmetric hydrogenation by using the second-generation Ir catalyst under low-pressure conditions are illustrated in Scheme 8. The cationic Ir catalyst **17** is formed during the preparation step of the catalyst. The hydrogenation of **17** then produces the unsaturated Ir catalyst **18** with the reductive elimination of cyclooctadiene, which coordinates with the substrate through chelation between the oxygen of the ketone and the nitrogen of the amine



Scheme 8. Plausible catalytic cycle for the *anti*-selective asymmetric hydrogenation by using the second-generation Ir catalyst

function, to produce the five-membered intermediate **19**. The oxidative addition of hydrogen to the intermediate generates the dihydride complex **20**, which can easily equilibrate with the amide complex **21**. This equilibration has no effect on the yield and enantioselectivity. The deprotonation of **21** with sodium acetate then produces the amide complex **22**. This process would be a slow step during this hydrogenation, based on the fact that the reaction has a first-order dependence on sodium acetate. The insertion reaction of the carbonyl group in **22**, the reductive elimination of the amide complex **23**, followed by the ligand-exchange reaction together with protonation then furnishes the β-hydroxy-α-amino acid ester **24** and the regeneration of the real catalyst **18**.

For asymmetric hydrogenation under high pressure conditions, the participation of two molecules of hydrogen is suggested, because the reaction rate increases remarkably in response to increasing hydrogen pressure. It is known that an iridium complex is oxidatively added with two molecules of hydrogen to generate the more reactive trivalent iridium complex.[11f]

Conclusion

We have succeeded in the development of the Ir-catalyzed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides; this proceeds through DKR to produce *anti*-β-hydroxy-α-amino acid esters in a high diastereo- and enantioselective manner. Mechanistic studies have revealed that this unique asymmetric hydrogenation proceeds through reduction of the ketone moiety via the five-membered complex involving the chelation between the oxygen of the ketone and the nitrogen of the amine function. The relationship studies between the hydrogen pressure and stereoselectivity have disclosed two mechanisms dependent on hydrogen pressure. Under low hydrogen pressure condition (< 15 atm), the reaction rate proportionally increases with the hydrogen pressure. However, under high hydrogen pressure, the reaction rate exponentially accelerates along with the increasing hydrogen pressure, which suggests the participation of two or more molecules of hydrogen.

Experimental Section

General: Melting points were measured with a SIBATA NEL-270 melting point apparatus. Optical rotations were measured on a JASCO DIP-14-polarimeter and JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on a JASCO FT/IR-230 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-GSX 400α (400 MHz) and JNM ECP400 spectrometers (400 MHz), unless otherwise indicated. Chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL HX-110A (LRFAB, LREI) spectrometer. HPLC analyses were carried out on a chiral column indicated in each experiment. Column chromatography was performed with silica gel BW-820MH (Fuji Davison, Co.). All reactions were carried out in oven-dried glassware and stirred magnetically unless otherwise noted.

Preparation of the cationic Ir catalyst, Ir-cod-(*R*)-MeO-BIPHEP-BAr$_F$ (17): A mixture of $[Ir(cod)Cl]_2$ (13.2 mg, 0.0197 mmol), (*R*)-MeO-BIPHEP (25.2 mg, 0.0433 mmol) and $NaBAr_F$ (37.0 mg, 0.0394 mmol) in dry CH_2Cl_2 (2.0 mL) was stirred for 1 h at room temperature under argon atmosphere and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2/Et_2O, 3:1) to give **17** as a green oil (68.9 mg, 0.0394 mmol, quant). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.05 (m, 2H), 1.35 (m, 2H), 1.71 (m, 2H), 1.91 (m, 2H), 2.76 (s, 6H), 3.75 (m, 2H), 4.11 (m, 2H), 5.84 (d, J = 8,4 Hz, 2H), 6.62 (t, J = 8.4 Hz, 1H), 6.63 (t, J = 8.4 Hz, 1H), 6.77 (t, J = 6.8 Hz, 4H), 6.87 ~ 6.99 (m, 8H), 7.13 ~ 7.18 (m, 6H), 7.28 ~ 7.32 (m, 4H), 7.62 (s, 4H), 8.40 ppm (s, 8H); ^{13}C NMR (100 MHz, C_6D_6): δ = 26.6, 33.2, 53.7, 86.0, 89.3, 111.7, 117.4, 120.5, 122.4, 123.2, 125.9, 127.9, 128.5, 128.6, 129.1, 129.4, 130.5, 130.8, 133.7, 134.7, 157.5, 161.4, 161.9, 162.4, 162.8 ppm; HRMS (FAB, NBA) calcd for $C_{46}H_{44}O_2P_2Ir$: 883.2446 $[M-BAr_F]^+$, found: 883.2449.

General procedure for *anti*-selective asymmetric hydrogenation through DKR by using the second-generation Ir-catalyst (Ir-(*S*)-MeO-BIPHEP-BAr$_F$ complex: The reaction was carried out in autoclaved glassware. A mixture of $[Ir(cod)Cl]_2$ (1.5 mg, 0.0022 mmol), (*S*)-MeO-BIPHEP (3.3 mg, 0.0057 mmol) and $NaBAr_F \cdot 3H_2O$ (4.1 mg, 0.0044 mmol) in CH_2Cl_2 (1.0 mL) was stirred for 1 h at 23 °C under air atmosphere. The resulting yellow solution was concentrated and dried in vacuo. α-Amino-β-keto ester hydrochloride (0.435 mmol), sodium acetate (35.7 mg, 0.435 mmol) and acetic acid (2.2 mL) were added to the prepared Ir catalyst. The mixture was stirred at 23 °C under 4.5 atm of hydrogen for 96 h. Aqueous HCl (1 M in H_2O, 3.0 mL) was added and the resulting mixture was concentrated in vacuo to dryness below 40 °C. The obtained residue was dissolved in MeOH and the mixture was concentrated in vacuo. This cycle was repeated five times. The residue was used for the next step without any purification.

A solution of Et_3N (0.18 mL, 1.29 mmol) in THF (2 mL) was added dropwise to a stirred mixture of the above residue and benzoic anhydride (108 mg, 0.477 mmol) in THF (6 mL) at 0 °C. After being stirred at 23 °C, overnight, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with aqueous hydrochloric acid (1 M in H_2O), saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give α-benzoylamino-β-hydroxy ester.

Methyl (2*S*,3*S*)-2-benzoylamino-3-(3-chlorophenyl)-3-hydroxypropionate (2*S*,3*S*) (4g): Prepared according to the general procedure: 76% yield, *anti*/*syn*, 99:1, 74% *ee*; HPLC analysis by using CHIRALCEL OD-H and *n*-hexane/*i*PrOH (85:15, 0.4 mL min^{-1}); t_R for (2*R*,3*R*): 17.6 min, for (2*S*,3*S*): 27.4 min; m.p.: 115–118 °C; $[\alpha]_D^{22}$ = +97.0 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 4.81 (d, J = 5.6 Hz, 1H), 5.19 (dd, J = 3.2, 6.8 Hz, 1H), 5.36 (br, 1H), 6.95 (d, J = 6.4 Hz, 1H), 7.14–7.16 (m, 1H), 7.23–7.29 (m, 3H), 7.44 (t, J = 8 Hz), 7.52–7.56 (m, 1H), 7.74–7.76 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 59.5, 74.8, 124.1, 126.2, 127.2, 128.2, 128.7, 129.6, 132.3, 132.8, 134.3, 141.3 ppm; IR (KBr) $\tilde{\nu}$ = 3905, 3306, 1742, 1645, 1578, 1534, 1438, 1272, 1025, 790, 691 cm^{-1}; HR-FABMS (NBA) calcd for $C_{17}H_{17}ClNO_4$: 334.0846 $[M+H]^+$; found: 334.0817.

Methyl (2*S*,3*S*)-2-benzoylamino-3-(3-fluorophenyl)-3-hydroxypropionate (2*S*,3*S*) (4h): Prepared according to the general procedure: 67% yield, *anti*/*syn*, 99:1, 67% *ee*; HPLC analysis by using CHIRALCEL OD-H and *n*-hexane/*i*PrOH (85:15, 0.4 mL min^{-1}), t_R for (2*R*,3*R*): 17.5 min, for (2*S*,3*S*): 28.9 min; m.p.: 132–133 °C; $[\alpha]_D^{21}$ = +106.7 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 4.85 (d, J = 5.6 Hz, 1H), 5.21 (dd, J = 3.2, 6.8 Hz, 1H), 5.38 (dd, J = 3.2, 5.2 Hz, 1H), 6.95–7.04 (m, 4H), 7.26–7.31 (m, 1H), 7.42–7.46 (m, 2H), 7.52–7.56 (m, 1H), 7.74–7.76 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 59.5, 74.6, 113.0 (d, J = 22.3 Hz), 114.9 (d, J = 20.6 Hz), 121.5 (d, J = 3.2 Hz), 127.1, 128.7, 129.8 (d, J = 8.2 Hz), 132.3, 132.8, 141.9 (d, J = 6.6 Hz), 162.8 (d, J = 245 Hz), 168.7, 169.7 ppm; IR (KBr) $\tilde{\nu}$ = 3420, 3328, 1720, 1646, 1531, 1270, 1023, 792, 693 cm^{-1}; HR-FABMS (NBA) calcd for $C_{17}H_{17}FNO_4$: 318.1142 $[M+H]^+$; found: 318.1163.

Methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-3-(naphthalen-2-yl)-propionate (2*S*,3*S*) (4j): Prepared according to the general procedure: 94% yield, *anti*/*syn*, 99:1, 90% *ee*; HPLC analysis by using CHIRALCEL OD-H and *n*-hexane/*i*PrOH (75:25, 0.5 mL min^{-1}), t_R for (2*R*,3*R*): 15.5 min, for (2*S*,3*S*): 19.4 min; m.p.: 134–136 °C (ethyl acetate-*n*-hexane); $[\alpha]_D^{23} = +107$ ($c = 1.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.77$ (s, 3H), 4.68 (br d, $J = 6.0$ Hz, 1H), 5.32 (dd, $J = 3.2$, 6.8 Hz, 1H), 5.50–5.58 (m, 1H), 6.92 (br d, $J = 6.8$ Hz, 1H), 7.37–7.55 (m, 6H), 7.73–7.84 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.7$, 59.6, 75.4, 123.7, 125.1, 126.1, 126.2, 127.2, 128.0, 128.1, 128.7, 132.2, 133.0, 133.1, 133.2, 136.6, 168.7, 169.9 ppm; IR (KBr) $\tilde{\nu} = 3333$, 1741, 1646, 1523, 1488, 1437, 1363, 1217, 712, 479 cm^{-1}; elemental analysis calcd for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 3.94; found: C 72.08, H 5.28, N 3.95.

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[1] For reviews of dynamic kinetic resolution, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; c) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; d) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040–4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; e) H. Pellissier, *Tetrahedron* **2008**, *64*, 1563–1601; f) E. Fogassy, M. Nógrádi, D. Kozma, G. Egri, E. Pálovics, V. Kiss, *Org. Biomol. Chem.* **2006**, *4*, 3011–3030; g) B. Martín-Matute, J. E. Bäckvall, *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232.

[2] For reviews of asymmetric hydrogenation, see: a) T. Ohkuma, M. Kitamura, R. Noyori in *Catalytic Asymmetric Synthesis* 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, pp. 1–110; b) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; c) J. G. de Vries, C. J. Elsevier in *Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**.

[3] For the *syn*-selective asymmetric hydrogenation of α-acylamino-β-keto esters through DKR, see: a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135; b) J.-P. Genêt, S. Mallart, S. Juge, French Patent 8911159, **1989**; c) J.-P. Genêt, C. Pinel, S. Mallart, S. Juge, S. Thorimbert, J. A. Laffitte, *Tetrahedron: Asymmetry* **1991**, *2*, 555–567; d) E. Coulon, M. C. C. de Andrade, V. Ratovelomanana-Vidal, J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 6467–6470; e) P. Phansavath, S. D. de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, *Eur. J. Org. Chem.* **2000**, 3903–3907; f) K. Makino, N. Okamoto, O. Hara, Y. Hamada, *Tetrahedron: Asymmetry* **2001**, *12*, 1757–1762; g) K. Makino, T. Goto, J. Ohtaka, Y. Hamada, *Heterocycles* **2009**, *77*, 629–634.

[4] For a review of the synthesis of β-hydroxy-α-amino acids, see: K. Makino, Y. Hamada, *J. Synth. Org. Chem.* **2005**, *63*, 1198–1208.

[5] For the *anti*-selective asymmetric hydrogenation of α-amino-β-keto ester derivatives by DKR with Ru catalysts, see: a) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Angew. Chem.* **2004**, *116*, 900–902; *Angew. Chem. Int. Ed.* **2004**, *43*, 882–884; b) C. Mordant, P. Dunkelmann, V. Ratovelomanana-Vidal, J.-P. Genêt, *Chem. Commun.* **2004**, 1296–1297; c) C. Mordant, P. Dunkelmann, V. Ratovelomanana-Vidal, J.-P. Genêt, *Eur. J. Org. Chem.* **2004**, 3017–3026; d) O. Labeeuw, P. Phansavath, J.-P. Genêt, *Tetrahedron: Asymmetry* **2004**, *15*, 1899–1908; e) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Tetrahedron: Asymmetry* **2008**, *19*, 2816–2828. f) For the *anti*-selective asymmetric hydrogenation of an *N*-protected α-amino-β-keto ester derivative, see: A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 1626–1627.

[6] K. Makino, T. Fujii, Y. Hamada, *Tetrahedron: Asymmetry* **2006**, *17*, 481–485.

[7] a) K. Makino, Y. Hiroki, Y. Hamada, *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785; b) Y. Hamada, K. Makino, World Patent WO2005/005371A1, **2005**; c) K. Makino, M. Iwasaki, Y. Hamada, *Org. Lett.* **2006**, *8*, 4573–4576.

[8] Y. Hamada, Y. Koseki, T. Fujii, T. Maeda, T. Hibino, K. Makino, *Chem. Commun.* **2008**, 6206–6208. For a related process, see: T. Hibino, K. Makino, T. Sugiyama, Y. Hamada, *ChemCatChem* **2009**, *1*, 237–240.

[9] a) Y. Hamada, K. Makino, *J. Synth. Org. Chem.* **2008**, *66*, 1057–1065; b) Y. Hamada, K. Makino in *Asymmetric Synthesis and Application of α-Amino Acids* (Eds.: V. A. Soloshonok, K. Izawa), ACS, Washington, **2009**, pp. 227–238.

[10] For recent reports, see: a) K. Makino, E. Nagata, Y. Hamada, *Tetrahedron Lett.* **2005**, *46*, 6827–6830; b) S. Hara, K. Makino, Y. Hamada, *Pept. Sci.* **2006**, 39–42; c) S. Hara, K. Makino, Y. Hamada, *Tetrahedron Lett.* **2006**, *47*, 1081–1085; d) K. Makino, H. Jiang, T. Suzuki, Y. Hamada, *Tetrahedron: Asymmetry* **2006**, *17*, 1644–1649; e) Y. Yoshitomi, K. Makino, Y. Hamada, *Org. Lett.* **2007**, *9*, 2457–2460; f) S. Hara, E. Nagata, K. Makino, Y. Hamada, *Pept. Sci.* **2008**, 27–30.

[11] For the mechanistic studies of Ir-catalyzed hydrogenations, see: a) R. H. Crabtree, H. Felkin, G. E. Morris, *J. Chem. Soc. Chem. Commun.* **1976**, 716–717; b) W. J. Hälg, L. R. Öhrström, H. Rüegger, L. M. Venanzi, *Magn. Reson. Chem.* **1993**, *31*, 677–684; c) T. W. Brauch, C. R. Landis, *Inorg. Chim. Acta* **1998**, *270*, 285–297; d) B. F. M. Kimmich, E. Somsook, C. R. Landis, *J. Am. Chem. Soc.* **1998**, *120*, 10115–10125; e) L. Dahlenburg, R. Gotz, *Eur. J. Inorg. Chem.* **2004**, 888–905; f) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113–123; g) P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339–347; h) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194–3200; i) X. Cui, Y. Fan, M. B. Hall, K. Burgess, *Chem. Eur. J.* **2005**, *11*, 6859–6868; j) Z. M. Heiden, T. B. Rauchfuss, *J. Am. Chem. Soc.* **2009**, *131*, 3593–3600; k) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, *J. Org. Chem.* **2009**, *74*, 2780–2787; l) Z. E. Clarke, P. T. Maragh, T. P. Dasgupta, D. G. Gusev, A. J. Lough, K. Abdur-Rashid, *Organometallics* **2006**, *25*, 4113–4117; m) S. Bi, Q. Xie, X. Zhao, Y. Zhao, X. Kong, *J. Organomet. Chem.* **2008**, *693*, 633–638; n) V. R. Landaeta, B. K. Munoz, M. Peruzzini, V. Herrera, C. Bianchini, R. A. Sanchez-Delgado, *Organometallics* **2006**, *25*, 403–409; o) V. Herrera, B. Munoz, V. Landaeta, N. Canudas, *J. Mol. Catal. A* **2001**, *174*, 141–149; p) V. Herrera, A. Fuentes, M. Rosales, R. A. Sánchez–Delgado, C. Bianchini, A. Meli, F. Vizza, *Organometallics* **1997**, *16*, 2465–2471; q) M. J. Hostetler, M. D. Butts, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 2743–2752; r) M. A. Esteruelas, J. Herrero, A. M. Lopez, L. A. Oro, M. Shulz, H. Werner, *Inorg. Chem.* **1992**, *31*, 4013–4014; s) A. S. Goldman, J. Halpern, *J. Organomet. Chem.* **1990**, *382*, 237–253; t) A. S. Goldman, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 7537–7539; u) M. M. T. Khan, B. T. Khan, S. M. Ali, *J. Mol. Catal.* **1989**, *57*, 29–45; v) M. M. T. Khan, B. Taqui Khan, M. Safia, *React. Kinet. Catal. Lett.* **1985**, *31*, 63–70; w) M. M. T. Khan, B. T. Khan, Safia, K. Nazeeruddin, *J. Mol. Catal.* **1984**, *26*, 207–217; x) R. H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelcic, C. A. Parnell, J. M. Quirk, G. E. Morris, *J. Am. Chem. Soc.* **1982**, *104*, 6994–7001.

[12] For the data of the optimization, see the Supporting Information.

[13] For the additive effect of phthalimide on the Ir-catalyzed hydrogenation of imines, see: a) T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 2661–2664; b) T. Morimoto, N. Suzuki, K. Achiwa, *Heterocycles* **1996**, *43*, 2557–2560.

[14] For the additive effect of the iodide source or iodine on the Ir-catalyzed hydrogenation of imines, see: a) F. Spindler, B. Pugin, H.-U. Blaser, *Angew. Chem.* **1990**, *102*, 561–562; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558–559; b) Y. N.-C. Chan, D. Meyer, J. A. Osborn, *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401; c) Y. N.-C. Chan, D. Meyer, J. A. Osborn, *J. Chem. Soc. Chem. Commun.* **1990**, 869–871; d) T. Morimoto, N. Nakajima, K. Achiwa, *Chem. Pharm. Bull.* **1994**,

42, 1951–1953; e) T. Morimoto, N. Nakajima, K. Achiwa, *Synlett* **1995**, 748–750; f) F. Spindler, B. Pugin, H.-P. Jalett, H.-P. Buser, H.-U. Pittelkow, H.-U. Blaser, *Chem. Ind.* **1996**, *68*, 153–166; g) K. Satoh, M. Inenaga, K. Kanai, *Tetrahedron: Asymmetry* **1998**, *9*, 2657–2662; h) H.-U. Blaser, H.-P. Buser, K. Coers, R. Hanreich, H.-P. Jalett, E. Jelsch, B. Pugin, H.-D. Schneider, F. Spindler, A. Wegmann, *Chimica* **1999**, *53*, 275–280; i) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533–3536; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; j) R. Dorta, D. Broggini, R. Stoop, H. Ruegger, F. Spindler, A. Togni, *Chem. Eur. J.* **2004**, *10*, 267–278; For reviews on halide effects in transition metal catalysis, see: K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26–49; *Angew. Chem. Int. Ed.* **2002**, *41*, 26–47.

[15] For the additive effect of iodine on Ir-catalyzed hydrogenation of quinolines, see: a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; b) see reference [11k], and references therein.

[16] A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 3047–3050; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897–2899.

[17] H. Nishida, N. Takada, M. Yoshimura, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600–2604.

[18] For the Ir-catalyzed asymmetric hydrogenation of ketones, see: a) K. Mashima, T. Akutagawa, X. Zhang, H. Takaya, *J. Organomet. Chem.* **1992**, *428*, 213–222; b) X. Zhang, H. Kumobayashi, H. Takaya, *Tetrahedron: Asymmetry* **1994**, *5*, 1179–1182; c) see reference [11e].

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