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Enantioselective Hydrogenation of α-Aryloxy and α-Alkoxy α,β-Unsaturated Carboxylic Acids Catalyzed by Chiral Spiro Iridium/Phosphino-Oxazoline Complexes

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Abstract: The iridium-catalyzed highly enantioselective hydrogenation of α-aryloxy and α-alkoxy-substituted α,β-unsaturated carboxylic acids was developed. By using chiral spiro phosphino-oxazoline ligands, the hydrogenation proceeded smoothly to produce various α-aryloxy- and α-alkoxy-substituted carboxylic acids with extremely high enantioselectivities (ee up to 99.8%) and reactivities (TON up to 10 000) under mild conditions. The hydrogenation of α-benzyloxy-substituted α,β-unsaturated acids provided an efficient alternative for the synthesis of chiral α-hydroxy acids after an easy deprotection. A mechanism involving a catalytic cycle between Ir^{I} and Ir^{III} was proposed on the basis of the coordination model of the unsaturated acids with the iridium metal center. The rationality of the catalytic cycle, with an olefin dihydride complex as the key intermediate, was supported by the deuterium-labeling studies. The X-ray diffraction analysis of the single crystal of catalyst revealed that the rigid and sterically hindered chiral environment created by the spiro phosphino-oxazoline ligands is the essential factor that permits the catalyst to obtain excellent chiral discrimination. A chiral induction model was suggested on the basis of the catalyst structure and the product configuration.

Introduction

Optically active α-oxy-functionalized carboxylic acids are an important class of building blocks for asymmetric synthesis in pharmaceutical and agrochemical industries and for total synthesis of natural products.[1] For example, the α-aryloxy propionic acids exhibit significant biological properties as crop protection reagents.[2] (*R*)-α-(*p*-Chlorophenoxy)butyric acids possess antiplatelet activities.[3] Many α-aryloxy and α-alkoxy dihydrocinnamic acid derivatives, including Ertiprotafib, Tesaglitazar, and Aleglitazar, have attracted considerable attention as potential agonists against peroxisome proliferator-activated receptors (PPARs) in the treatment of type 2 diabetes and dyslipidemia,[4] and several compounds of this class are now in various stages of development. The chiral β-phenyllactic acid derivatives, such as Aeruginosins,[5] are important parts of bioactive peptides, which have been shown to be potent protease inhibitors. Figure 1 shows selected examples of bioactive compounds containing chiral α-oxy-functionalized carboxylic acids.

Transition metal-catalyzed asymmetric hydrogenation of α-aryloxy- or α-alkoxy-substituted α,β-unsaturated acids, which are easily prepared from readily available starting materials, represents one of the most atom-economic and efficient methods for the synthesis of chiral α-oxy-functionalized carboxylic acids. Over the past decades, significant progress has been achieved in the catalytic asymmetric hydrogenation of a wide range of unsaturated substrates.[6] A variety of efficient chiral rhodium and ruthenium complexes have been developed for the hydrogenation of α-aryl- or α-alkyl-substituted α,β-unsaturated acids with excellent activities and enantioselectivities.[7] However, highly efficient catalysts for the asymmetric hydrogenation of α-aryloxy- or α-alkoxy-substituted α,β-unsaturated acids, a

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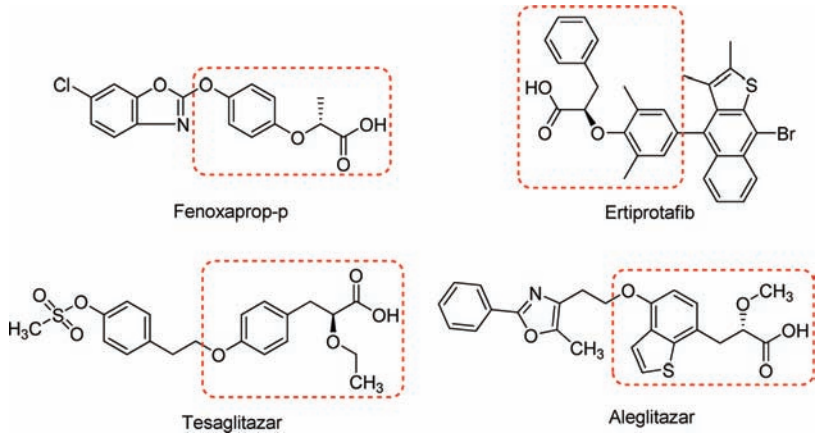
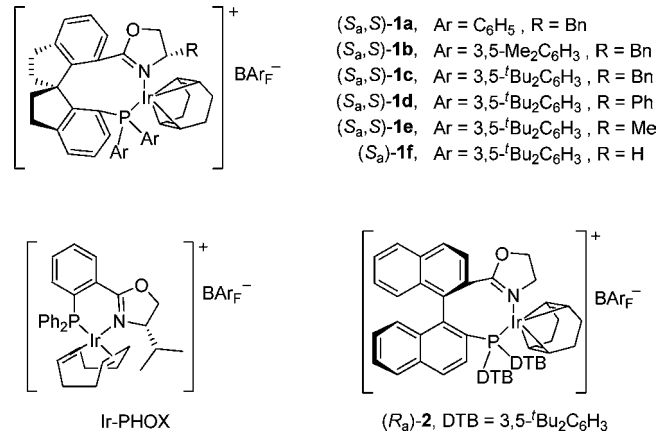


Figure 1. Selected bioactive compounds derived from chiral α-aryloxy or alkoxy carboxylic acids.

reaction which has great potential for wide application in organic synthesis, are limited. In 2004, Maligres and Krska[8] reported the first highly enantioselective hydrogenation of α-aryloxy crotonic acids using ruthenium−BINAP complexes as catalysts. However, this reaction required high catalyst loading for some substrates. Shortly thereafter, we demonstrated that the ruthenium diacetate complexes ligated by chiral spiro diphosphine ligands SFDP were highly efficient catalysts for the hydrogenation of α-aryloxy crotonic acid derivatives.[9] The α-aryloxy saturated acids were obtained in up to 95% ee at a mole ratio of substrate to catalyst (*S*/*C*) of 200. However, when this procedure was extended to the hydrogenation of α-methoxy cinnamic acids, this catalyst only afforded a moderate enantioselectivity. Houpis and co-workers[10] screened more than 250 catalysts and conditions in the asymmetric hydrogenation of α-ethoxy cinnamic acid, and finally obtained 92% ee by using Rh-Walphos catalyst. Puentener et al.[11] reported that the chiral ruthenium/diphosphine complex ((*S*)-TMBTP)Ru(OAc)$_2$ was an efficient catalyst for the hydrogenation of α-methoxy cinnamic acid with high enantioselectivities (up to 94% ee). Chen and McCormack and colleagues[12] used a new ferrocene-based diphosphine ligand Trifer and obtained up to 98% ee in the Rh-catalyzed hydrogenation of α-ethoxy cinnamic acids. Woltering et al.[13] also investigated the asymmetric hydrogenation of α-alkoxy cinnamic acids by using rhodium, ruthenium, and iridium complexes of diphosphine ligands as catalysts; however, the catalyst activity and enantioselectivity (≤90% ee) were unsatisfactory. Although tremendous efforts have been devoted in this field, none of the present chiral catalysts gave acceptable results for the asymmetric hydrogenations of both α-aryloxy- and α-alkyloxy-substituted α,β-unsaturated acids. Moreover, the catalytic asymmetric hydrogenation of α-aryloxy-substituted cinnamic acids has not been documented yet.

Scheme 1



Since Pfaltz and co-workers[14] developed chiral analogues of Crabtree's catalyst (abbreviated as Ir-PHOX, Scheme 1), such cationic iridium catalysts have been extensively studied in the asymmetric hydrogenations of unfunctionalized olefins, imines, and heteroaromatic compounds,[15] although they were long neglected in the hydrogenation of functionalized olefins.[16] Very recently, we reported a highly enantioselective hydrogenation of α-alkyl α,β-unsaturated carboxylic acids catalyzed by Ir/chiral spiro phosphino-oxazoline (abbreviated as Ir−SIPHOX, Scheme 1, **1a**−**f**) cationic complexes.[17] The extremely high activities,

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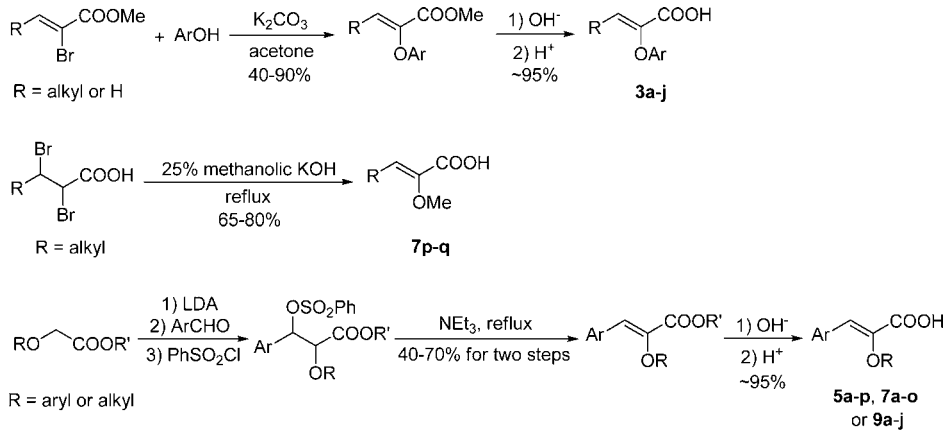
Scheme 2



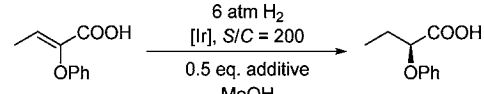
enantioselectivities, broad substrate scope, and mild reaction conditions demonstrated that Ir−SIPHOXs were excellent catalysts for the hydrogenations of α,β-unsaturated carboxylic acids. Therefore, we envisioned that the introduction of various α-aryloxy and α-alkoxy substituents into α,β-unsaturated acids would extend the scope of this practically useful hydrogenation. In this article, we report a detailed investigation on the asymmetric hydrogenation of α-aryloxy- and α-alkoxy-substituted α,β-unsaturated acids using Ir−SIPHOX catalysts. Under very mild conditions, a broad range of α-aryloxy- and α-alkoxy-substituted α,β-unsaturated acids were hydrogenated with unprecedented enantioselectivities (up to 99.8% ee) at high reactivities (TON up to 10 000). This procedure provided a facile access to a variety of optically active α-oxy-functionalized carboxylic acids.

Results and Discussion

Synthesis of the α,β-Unsaturated Carboxylic Acids. The α-aryloxy- or α-alkoxy-substituted crotonic acid derivatives **3a**−**j**[8,9] and **7p**−**q**[18] were prepared in good yields according to the literature procedures. The α-oxy-functionalized cinnamic acids **5a**−**p**, **7a**−**o**, and **9a**−**j** were prepared by using the aldol reaction of 2-aryloxy or 2-alkoxy acetates with appropriate aldehydes, followed by dehydroxylation with benzenesulfonyl chloride and triethylamine. The hydrolysis of the resulting unsaturated esters afforded unsaturated acids as (*Z*)-isomers in moderate to good yields (Scheme 2). So as not to introduce impurity to the catalytic hydrogenation reaction, the unsaturated acids were further purified by recrystallization from petroleum ether/ethyl acetate (unoptimized solvent) until 99% pure.

Asymmetric Hydrogenation of α-Aryloxy Crotonic Acid Derivatives. To examine the catalytic capability of Ir−SIPHOX complexes (**1**) in the hydrogenation of α-oxy-functionalized unsaturated acids, we chose α-phenoxy crotonic acid (**3a**) as the model substrate. The hydrogenation was initially performed at a substrate to catalyst mole ratio (*S*/*C*) of 200 in MeOH under 6 atm of H_2 at room temperature for 24 h, with 0.5 equiv of Cs_2CO_3 as an additive. By using catalyst (S_a,*S*)-**1a**, the reaction proceeded with 25% conversion, afforded the hydrogenation product in 79% ee (Table 1, entry 1). The inefficiency of catalyst (R_a,*S*)-**1a** (entry 2) revealed that it has mismatched configurations. Next, we studied the catalysts with various substituent groups on the *P*-phenyl rings of the catalysts and found that only the catalysts with 3,5-di-*tert*-butyl substituents afforded both high activity and high enantioselectivity (Table 1, entries 4−7). This result implied that the sterically hindered *P*-aryl group is a necessary factor for achieving good results. Further comparison of the substituents on the oxazoline ring of the catalyst showed that the (S_a,*S*)-**1c** was the most efficient catalyst, providing the hydrogenation product **4a** in 98% ee (Table 1, entry 4). In contrast, other types of *P*,*N*-ligated chiral Ir complexes, such as Ir−PHOX and (R_a)-**2**, were incapable of this hydrogenation reaction (conversion ≤15%). Interestingly, increasing the reaction temperature from room temperature to 40 °C significantly accelerated the hydrogenation rate, leading

Table 1. Asymmetric Hydrogenation of α-Phenoxy Crotonic Acid with Iridium Complexes[a]



entry	[Ir]	additive	time (h)	conv (%)[b]	ee (%)[c]
1	(S_a,*S*)-**1a**	Cs_2CO_3	24	25	79
2	(R_a,*S*)-**1a**	Cs_2CO_3	24	0	
3	(S_a,*S*)-**1b**	Cs_2CO_3	24	30	64
4	(S_a,*S*)-**1c**	Cs_2CO_3	24	95	98
5	(S_a,*S*)-**1d**	Cs_2CO_3	24	100	89
6	(S_a,*S*)-**1e**	Cs_2CO_3	24	90	98
7	(S_a)-**1f**	Cs_2CO_3	24	75	95
8	Ir-PHOX	Cs_2CO_3	24	0	
9	(R_a)-**2**	Cs_2CO_3	24	15	79
10[d]	(S_a,*S*)-**1c**	Cs_2CO_3	10	100	99.2 (*S*)
11[d]	(S_a,*S*)-**1c**		24	<5	
12[d]	(S_a,*S*)-**1c**	NEt_3	24	15	95
13[d]	(S_a,*S*)-**1c**	Na_2CO_3	24	65	97
14[d]	(S_a,*S*)-**1c**	K_2CO_3	24	60	96

[a] Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol L^{-1} in MeOH, *S*/*C* = 200, 0.5 equiv of Cs_2CO_3 as additive, P_{H2} = 6 atm, room temperature. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis of the respective anilide with a chiral column (see the Supporting Information); absolute configuration was determined by comparison of optical rotation with literature date.[8] [d] Carried out at 40 °C.

(16) The asymmetric hydrogenation of 2-phenethylacrylic acid catalyzed by Ir−PHOX has been tried with moderate enantioselectivity. See: Scrivanti, A.; Bovo, S.; Ciappa, A.; Matteoli, U. *Tetrahedron Lett.* **2006**, *47*, 9261–9265. The iridium-catalyzed asymmetric hydrogenation of tiglic acid was also reported with modest enantioselectivity. See: Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.-Eur. J.* **2007**, *13*, 7162–7170.

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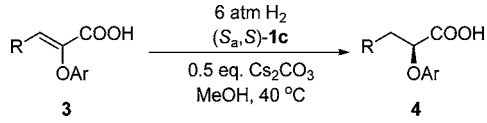
Table 2. Asymmetric Hydrogenation of α-Aryloxy Crotonic Acids[a]



entry	substrate	R	Ar	*S/C*	time (h)	yield (%)	ee (%)
1	**3a**	Me	C_6H_5	200	10	95	99.2 (*S*)
2	**3b**	Me	3-$CH_3C_6H_4$	200	18	93	98 (*S*)
3	**3c**	Me	3-BrC_6H_4	100	24	91	96 (*S*)
4	**3d**	Me	3,5-$F_2C_6H_3$	100	24	88	89 (*S*)
5	**3e**	Me	4-$CH_3C_6H_4$	200	10	92	99.5 (*S*)
6	**3f**	Me	4-*tert*-BuC_6H_4	200	18	94	97 (*S*)
7	**3g**	Me	4-$MeOC_6H_4$	200	4	93	99.7
8	**3h**	Me	4-ClC_6H_4	100	18	92	98 (*S*)
9	**3i**	Me	2-naphthyl	200	18	94	97 (*S*)
10[b]	**3j**	H	C_6H_5	200	24	95	83 (*S*)

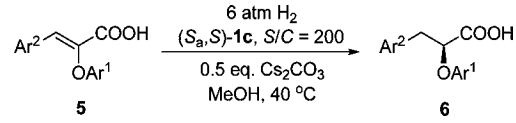
[a] Reaction conditions and analysis are the same as those in Table 1, entry 10. Full conversions were obtained for all reactions. [b] By using catalyst (S_a)-**1f**.

to a complete reaction within 10 h and a higher enantioselectivity using catalyst (S_a,*S*)-**1c** (99.2% ee, Table 1, entry 10). Because no racemization of the hydrogenation product was observed under the reaction conditions, we believe that the relative high temperature shorted the reaction time, and thus reduced the chance of the catalyst decomposition, which may enhance enantioselectivity of reaction. It is worth mentioning that without adding basic additives the hydrogenation could hardly occur (Table 1, entry 11). A comparison of different basic additives under the optimal conditions established that Cs_2CO_3 was the most suitable base for achieving high conversion and high enantioselectivity.

Under the optimal reaction conditions, the hydrogenations of different α-aryloxy crotonic acids **3a**−**i** were examined, and good to excellent enantioselectivities were obtained. Both steric and electronic properties of the aryl groups of the substrates have a great impact on the reactivity (Table 2). When a substituent existed at the ortho position of the phenyl ring, the substrate could not be completely hydrogenated, even using 2 mol % catalyst (*S/C* = 50, data not shown). Conversely, all of the substrates having meta or para substituents on the phenyl rings gave full conversions within 24 h. A higher catalyst loading (1 mol %) was needed when an electron-withdrawing group was introduced into the phenyl ring, but it did not have an obvious influence on enantioselectivity (Table 2, entries 3 and 8). An exceptional example was the substrate **3d** having two *meta*-fluoro groups on the phenyl ring, which provided a lower enantioselectivity (89% ee, Table 2, entry 4). The hydrogenation of α-aryloxy acrylic acid (**3j**) was also investigated by using catalyst (S_a)-**1f**; the corresponding product was obtained in 83% ee. Increasing the size of β-substituent to ethyl (R = Et) seriously inhibited the reaction and led to only a trace amount of hydrogenation product (data not shown).

Asymmetric Hydrogenation of α-Aryloxy Cinnamic Acids. Encouraged by the successful hydrogenation of α-aryloxy crotonic acids **3**, we then applied catalyst (S_a,*S*)-**1c** to the hydrogenation of α-aryloxy cinnamic acid derivatives. Although chiral α-aryloxy dihydrocinnamic acid derivatives are important chiral building blocks in organic synthesis, the asymmetric hydrogenation of related prochiral α,β-unsaturated acids remains undeveloped. We observed that the hydrogenation of α-aryloxy cinnamic acid derivatives **5** proceeded smoothly under the standard conditions. Full conversions were achieved at *S/C* ratio of 200 with extremely high enantioselectivities (99−99.8% ee)

Table 3. Asymmetric Hydrogenation of α-Aryloxy Cinnamic Acids[a]



entry	substrate	Ar^1	Ar^2	time (h)	yield (%)	ee (%)
1	**5a**	C_6H_5	C_6H_5	8	95	99.6
2	**5b**	2-$CH_3C_6H_4$	C_6H_5	18	89	99.5
3	**5c**	3-$CH_3C_6H_4$	C_6H_5	15	92	99.5
4	**5d**	4-$CH_3C_6H_4$	C_6H_5	8	91	99.5
5	**5e**	4-$CH_3OC_6H_4$	C_6H_5	8	94	99.8 (*S*)
6	**5f**	4-ClC_6H_4	C_6H_5	18	93	99.1 (*S*)
7	**5g**	C_6H_5	2-$CH_3C_6H_4$	24	93	99.8
8	**5h**	C_6H_5	3-$CH_3C_6H_4$	8	91	99.7
9	**5i**	C_6H_5	4-$CH_3C_6H_4$	10	94	99.8
10	**5j**	C_6H_5	3-$CH_3OC_6H_4$	14	96	99.6
11	**5k**	C_6H_5	4-$CH_3OC_6H_4$	16	91	99.4
12	**5l**	C_6H_5	3-$CF_3C_6H_4$	1	92	99.7
13	**5m**	C_6H_5	4-$CF_3C_6H_4$	1	93	99
14	**5n**	C_6H_5	naphthalen-1-yl	18	98	99.4
15	**5o**	C_6H_5	naphthalen-2-yl	2	92	99.2
16	**5p**	C_6H_5	furan-2-yl	10	94	99

[a] Reaction conditions and analysis are the same as those in Table 1, entry 10. Full conversions were obtained for all reactions.

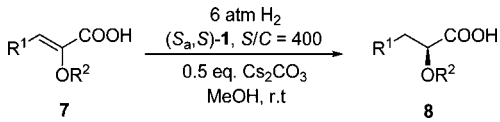
(Table 3). Similarly, the substrates with ortho substituents on Ar^1 or Ar^2 needed a longer reaction time in the hydrogenation of α-aryloxy cinnamic acid derivatives (Table 3, entries 2 and 7). It is interesting that the electronic effects of substituents were opposite for Ar^1 and Ar^2. When an electron-withdrawing group was introduced into Ar^1, the hydrogenation became slower (Table 3, entry 6), while an electron-withdrawing group on Ar^2 accelerated the reaction (Table 3, entries 12 and 13). The unsaturated acids with a naphthyl or furanyl at the β-position (**5n**−**5p**) were also suitable substrates for the hydrogenation, affording the corresponding saturated carboxylic acids in high yields and excellent enantioselectivities (Table 3, entries 14−16).

Asymmetric Hydrogenation of α-Alkoxy α,β-Unsaturated Carboxylic Acids. Chiral α-alkoxy carboxylic acid derivatives have received increasing attention due to their successful utility as starting materials for the asymmetric synthesis of a series of PPARs agonists.[4] Mild and practical methods for the preparation of these compounds are still highly sought after.[19] When we applied our Ir−SIPHOXs catalysts in the hydrogenation of α-alkoxy cinnamic acid derivatives, we found all of the catalysts (S_a,*S*)-**1c**−**1f** bearing 3,5-di-*tert*-butylphenyl groups on the *P* atom, but with different substituents on the oxazoline rings, showed essentially the same catalytic capabilities. Under the optimal reaction conditions, all of these catalysts afforded excellent enantioselectivities (97−99.3% ee) at 0.25 mol % catalyst loading (*S/C* = 400) (Table 4). Among the tested catalysts, (S_a,*S*)-**1e** containing a methyl group on the oxazoline ring gave the best results in terms of activity and enantioselectivity (Table 4, entry 5).

A variety of α-methoxy cinnamic acid derivatives **7a**−**o** can be hydrogenated by catalyst (S_a,*S*)-**1e** with full conversions and excellent enantioselectivities (>99% ee) regardless of the steric and electronic properties of the substituents on the phenyl ring

(19) (a) Deussen, H.-J.; Zundel, M.; Valdois, M.; Lehmann, S. V.; Weil, W.; Hjort, C. M.; Østergaard, P. R.; Marcussen, E.; Ebdrup, S. *Org. Process Res. Dev.* **2003**, *7*, 82–88. (b) Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev.* **2004**, *8*, 838–845. (c) Aikins, J. A.; Haurez, M.; Rizzo, J. R.; Van Hoeck, J.-P.; Brione, W.; Kestemont, J.-P.; Stevens, C.; Lemair, X.; Stephenson, G. A.; Marlot, E.; Forst, M.; Houpis, I. N. *J. Org. Chem.* **2005**, *70*, 4695–4705.

Table 4. Asymmetric Hydrogenation of α-Alkoxy Cinnamic Acids[a,b]



entry	subst	R^1	R^2	[Ir]	time (h)	yield (%)	ee (%)
1	**7a**	C_6H_5	CH_3	(S_a,S)-**1a**	24	27[c]	33 (*S*)
2	**7a**	C_6H_5	CH_3	(S_a,S)-**1b**	24	27[c]	13 (*S*)
3	**7a**	C_6H_5	CH_3	(S_a,S)-**1c**	6	95	99.1 (*S*)
4	**7a**	C_6H_5	CH_3	(S_a,S)-**1d**	10	96	99 (*S*)
5	**7a**	C_6H_5	CH_3	(S_a,S)-**1e**	6	95	99.3 (*S*)
6	**7a**	C_6H_5	CH_3	(S_a)-**1f**	12	93	97 (*S*)
7	**7b**	2-$CH_3C_6H_4$	CH_3	(S_a,S)-**1e**	10	93	99.7
8	**7c**	4-$CH_3C_6H_4$	CH_3	(S_a,S)-**1e**	6	94	99.6
9	**7d**	2-$CH_3OC_6H_4$	CH_3	(S_a,S)-**1e**	24	97	99.2
10	**7e**	3-$CH_3OC_6H_4$	CH_3	(S_a,S)-**1e**	10	91	99.6
11	**7f**	4-$CH_3OC_6H_4$	CH_3	(S_a,S)-**1e**	10	92	99.7
12	**7g**	2-ClC_6H_4	CH_3	(S_a,S)-**1e**	24	95	99.4
13	**7h**	4-ClC_6H_4	CH_3	(S_a,S)-**1e**	8	91	99.8
14	**7i**	2-BrC_6H_4	CH_3	(S_a,S)-**1e**	24	91	99.5
15	**7j**	3-BrC_6H_4	CH_3	(S_a,S)-**1e**	6	94	99.6
16	**7k**	4-$CF_3C_6H_4$	CH_3	(S_a,S)-**1e**	6	95	99.2
17	**7l**	4-$NO_2C_6H_4$	CH_3	(S_a,S)-**1e**	4	96	99.7
18	**7m**	2-naphthyl	CH_3	(S_a,S)-**1e**	10	93	99.8
19	**7n**	C_6H_5	C_2H_5	(S_a,S)-**1e**	10	92	99.7
20	**7o**	4-$BnOC_6H_4$	C_2H_5	(S_a,S)-**1e**	16	93	99.5 (*S*)
21[d]	**7o**	4-$BnOC_6H_4$	C_2H_5	(S_a)-**1f**	18	94	99.2 (*S*)
22	**7p**	CH_3	CH_3	(S_a,S)-**1e**	6	91	99
23[e]	**7q**	C_2H_5	CH_3	(S_a,S)-**1e**	20	97	95

[a] Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol L^{-1} in MeOH, *S*/*C* = 400, 0.5 equiv of Cs_2CO_3 as additive, P_{H2} = 6 atm, room temperature. [b] Analysis is the same as that in Table 1, entry 10. Full conversions were obtained for all cases except entries 1 and 2. [c] Conversion. [d] *S*/*C* = 6000, 2 equiv of NEt_3 as additive, 90 °C. [e] *S*/*C* = 50.

of the substrates (Table 4, entries 7−20). The catalyst (S_a,S)-**1e** was also sensitive to the *ortho*-substituent on the phenyl rings of substrates **7**, as indicated by the lowered reaction rate (Table 4, entries 7, 9, 12, and 14). Changing the alkoxy group from methoxy to ethoxy did not affect the activity and enantioselectivity (Table 4, entry 19 vs entry 5). Encouraged by this promising result, we investigated the enantioselective hydrogenation of α-ethoxy cinnamic acid derivative **7o**. The product of this reaction is a key intermediate in the synthesis of potential PPARs agonist for the treatment of type 2 diabetes and dyslipidemia.[10] Gratifyingly, (S_a,S)-**1e** showed a good catalytic efficiency in the asymmetric hydrogenation of **7o** and gave the desired product **8o** in 93% yield with an unprecedented 99.5% ee (Table 4, entry 20). Further investigation indicated that the catalysts Ir−SIPHOX allowed the reaction to be performed at a very low catalyst loading (*S*/*C* = 6000) without compromising the enantioselectivity.[20] This result represents the highest levels of enantioselectivity and efficiency in the asymmetric hydrogenation of α-alkoxy cinnamic acid derivatives so far reported (Table 4, entry 21).[10−13] Catalyst (S_a,S)-**1e** was also found to be the suitable catalyst for asymmetric hydrogenation of α-methoxy crotonic acid **7p** and its homologue **7q**. In both cases, the corresponding saturated acids were obtained in high enantioselectivities (Table 4, entries 22 and 23), although a much higher catalyst loading was needed when a bulkier ethyl group was introduced into the β-position of substrate.

Asymmetric Hydrogenation of α-Benzyloxy Cinnamic Acid Derivatives: An Alternative Route for Chiral α-Hydroxy Dihydrocinnamic Acids. Optically pure α-hydroxy dihydrocinnamic acid derivatives are important intermediates in medicinal, biological, and synthetic chemistry, and thus effective methods for their synthesis are highly desired. On the basis of the success in the hydrogenation of α-alkoxyl cinnamic acids, we envisioned that the asymmetric hydrogenation of α-benzyloxy cinnamic acids, followed by readily deprotection of the benzyl group, would afford an efficient approach to the synthesis of chiral α-hydroxy dihydrocinnamic acids. This strategy should be an important complement to the asymmetric hydrogenation of 3-aryl-2-oxapropionic acids or esters[21] and 2-acyloxy-3-arylacrylate esters,[22] which met the challenges of the substrate availability, hydrogenation reactivity, as well as enantioselectivity from the practical point of view. Thus, we performed the hydrogenation of α-benzyloxy cinnamic acids under the optimal conditions determined above. Fortunately, **9a** was smoothly hydrogenated to **10a** with 99.7% ee in the presence of 0.25 mol % of catalyst (S_a,S)-**1e** and 0.5 equiv of Cs_2CO_3 in methanol under 6 atm H_2 pressure at room temperature (Table 5, entry 1). The product **10a** was easily deprotected by Pd/C under a hydrogen atmosphere to generate α-hydroxy dihydrocinnamic acid quantitatively without diminishing the optically purity (see the Supporting Information for details). This methodology is rather flexible and worked well with a broad scope of substrates (Table 5, entries 1−10). Excellent enantioselectivities of higher than 98% ee were achieved for all substrates, indicating a high tolerance of the current reaction toward the pattern and electronic properties of the substituents on the phenyl ring of the substrates. As compared to other methods that led to α-hydroxy dihydrocinnamates such as asymmetric hydrogenation of α-ketoesters,[21,23] this method has the advantages of substrate accessibility, high activity and enantioselectivity, and mild reaction conditions.

(*R*)-3-(4-Fluorophenyl)-2-hydroxy propionic acid **11** is one of the fragments of rupintrivir, a rhinovirus protease inhibitor currently in human clinical trials to treat the common cold, and is a basis for the design of anticoronaviral drugs.[24] However, only a few methods have been described for the synthesis of this compound, and most of them are not suitable for a large-scale preparation.[23] To demonstrate the practical potential of our strategy for the enantioselective synthesis of α-hydroxy dihydrocinnamic acid derivatives, the asymmetric synthesis of **11** was studied with catalytic hydrogenation (Scheme 3). In the hydrogenation of compound **9k**, the catalyst (R_a)-**1f** was employed to fit the configuration of the product. Impressively, the saturated acid **10k** was attained in 97% yield with over 99% ee at a catalyst loading of 0.01 mol % (*S*/*C* = 10 000).[20] After deprotection, (*R*)-3-(4-fluorophenyl)-2-hydroxy propionic acid (**11**) was obtained in quantitative yield with no defluorination.

Mechanism Consideration. The mechanism of hydrogenation of unfunctionalized olefins by Crabtree's catalyst and chiral

(20) In this reaction with high substrate concentration, the addition of 2 equiv of NEt_3 can increase the solubility of unsaturated carboxylic acids, besides act as a basic additive, while Cs_2CO_3 has no such effect.

(21) (a) Boaz, N. W.; Debenham, S. D. WO0226750, 2002. (b) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, J. A. *J. Org. Chem.* **2005**, *70*, 1872–1880. (c) Fujiwara, T.; Yokozawa, T. US20070073065, 2007. (d) Amano, S.; Fujii, A.; Yamamoto, S.; Mitsuda, M. WO 2008018520, 2008.

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(23) Tao, J.; McGee, K. *Org. Process Res. Dev.* **2002**, *6*, 520–524, and references therein.

(24) (a) Dragovich, P. S.; et al. *J. Med. Chem.* **1999**, *42*, 1213–1224. (b) Zalman, L. S.; Brothers, M. A.; Dragovich, P. S.; Zhou, R.; Prins, T. J.; Worland, S. T.; Patick, A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1236–1241. (c) Anand, K.; Ziebuhr, J.; Wadhwani, P.; Mesters, J. R.; Hilgenfeld, R. *Science* **2003**, *300*, 1763–1767.

Scheme 3

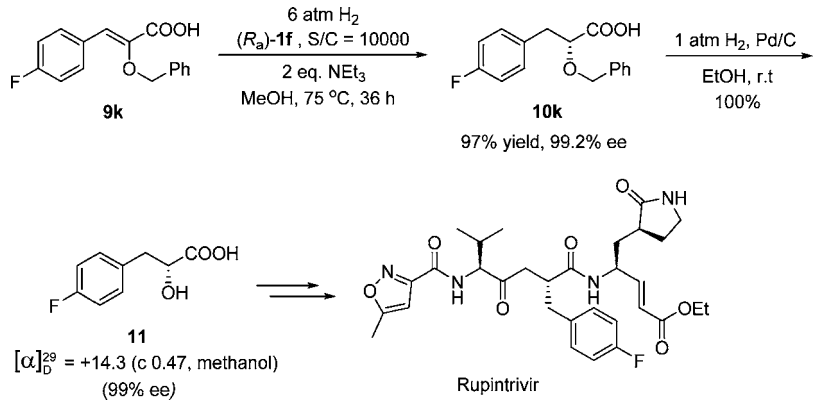
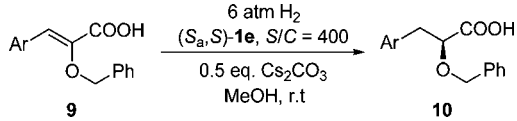


Table 5. Asymmetric Hydrogenation of α-Benzyloxy Cinnamic Acids[a]

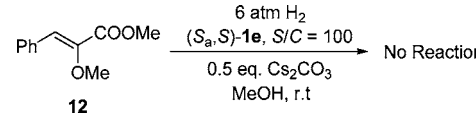


entry	substrate	Ar	time (h)	yield (%)	ee (%)
1	**9a**	C_6H_5	4	96	99.7 (*S*)
2	**9b**	2-$CH_3C_6H_4$	10	93	99.7
3	**9c**	3-$CH_3C_6H_4$	6	90	99.6
4	**9d**	4-$CH_3C_6H_4$	6	93	99.8
5	**9e**	2-$CH_3OC_6H_4$	12	91	99.2
6	**9f**	3-$CH_3OC_6H_4$	3	96	99.5
7	**9g**	4-$CH_3OC_6H_4$	5	95	99.4
8	**9h**	3-$CF_3C_6H_4$	2	95	98
9	**9i**	4-$CF_3C_6H_4$	2	93	99.5
10	**9j**	2-naphthyl	6	92	99.8

[a] Reaction conditions are the same as those for Table 4, entry 5. Full conversions were obtained for all reactions.

analogues has been investigated for many years.[25] Two different catalytic cycles, $Ir^{I}-Ir^{III}$ [26] and $Ir^{III}-Ir^{V}$,[27] have been proposed on the basis of experimental and computational results. Both cycles involved a key olefin dihydride complex, containing *P*,*N*-ligands, two hydrides, and an olefin. The vacant site of the complex can be coordinated with solvent or molecular H_2, thus generating two different catalytic cycles. If the prochiral olefin contains an additional coordination group, six orbitals of the iridium will be fully occupied, and thus the hydrogenation most likely passes through the $Ir^{I}-Ir^{III}$ catalytic cycle. To learn more details about the hydrogenation of unsaturated acids, we needed to clarify whether the acid group, the part which is essentially different from the unfunctionalized olefins, coordinates with iridium during the catalytic cycle. As shown in Scheme 4, (*Z*)-methyl 2-methoxy-3-phenylacrylate (**12**), a structural analogue of **7a**, was not able to undergo the hydrogenation under the standard reaction conditions. This outcome implied that the acid group plays a crucial role in the catalytic cycle and the coordination of the acid group to the metal center of the catalyst triggered the subsequent hydrogenation steps.

Scheme 4



On the basis of the results presented above, a mechanism involving a catalytic cycling between Ir^{I} and Ir^{III} was proposed for Ir−SIPHOX-catalyzed hydrogenation of α,β-unsaturated acids (Figure 2). Because the reactions cannot be completed without basic additives (see Table 1, entry 11 and ref 17), we speculated that the addition of base formed the carboxy anion, which chelates to the iridium center of catalyst more easily than the acid itself. The active catalyst is generated with the oxidative addition of hydrogen to the catalyst precursor **1** to generate the Ir^{III} intermediate **A**, which undergoes the coordination by the olefinic carboxy anion to form the complex **B**. The intramolecular rearrangement of **B** gives the key olefin dihydride intermediate **C**, which is the chiral discriminating step. Next, the migratory insertion of hydride from the metal of the catalyst to the double bond of the substrate leads to an alkyl hydride **D**. Subsequently, the reductive elimination of the alkyl and the hydride releases the product and yields the Ir^{I} complex **E**, which then undergoes the oxidative addition with hydrogen to regenerate the Ir^{III} intermediate **A** and accomplishes the catalytic cycle. However, the Ir(III)/Ir(V) mechanism, although less likely, cannot be completely excluded at this stage.

We also conducted a deuterium-labeling study to obtain further information about the reaction mechanism. When substrate **7a** was treated with D_2 in methanol catalyzed by (S_a,*S*)-**1e**, deuterium atoms were detected at both α and β positions of product in a similar ratio (54% and 58% respectively, Scheme 5, equation a). This trend was also observed in the reaction using H_2 in CD_3OD (Scheme 5, equation b), indicating the existence of H/D exchange between Ir−H and methanol.[28] The similar distribution of deuterium atoms at both α and β positions in product clearly showed that an olefin dihydride intermediate must be involved in the catalytic cycle. This distribution of deuterium atoms also strongly supports a hydrogenolysis mechanism, instead of a protonolysis mechanism in the product-yielding step (Figure 2, from **D** to **E**). An analogous experiment

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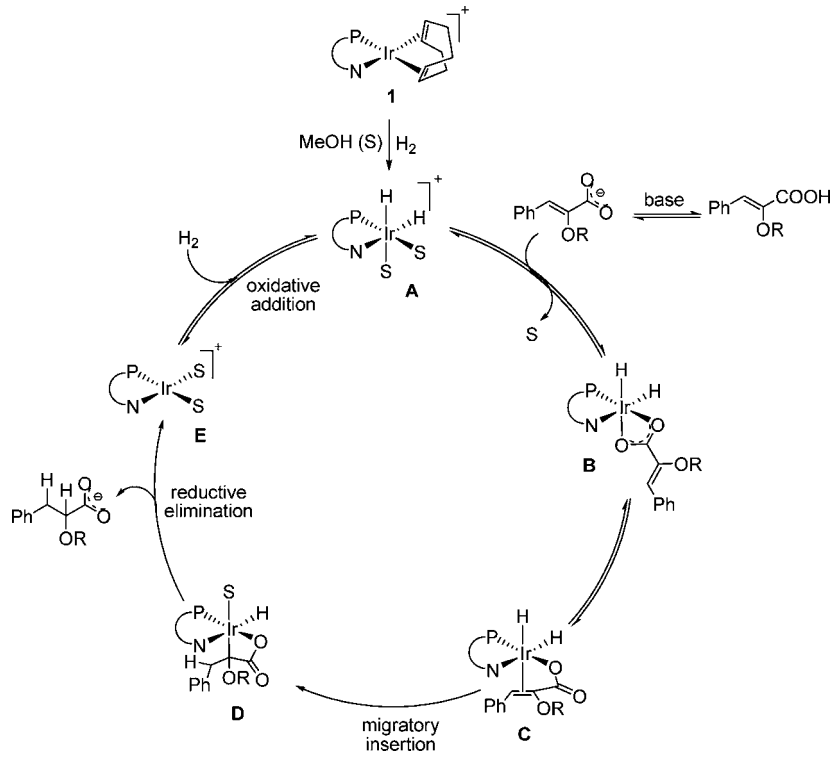


Figure 2. Plausible mechanism for the Ir−SIPHOXs-catalyzed hydrogenation of α,β-unsaturated acids.

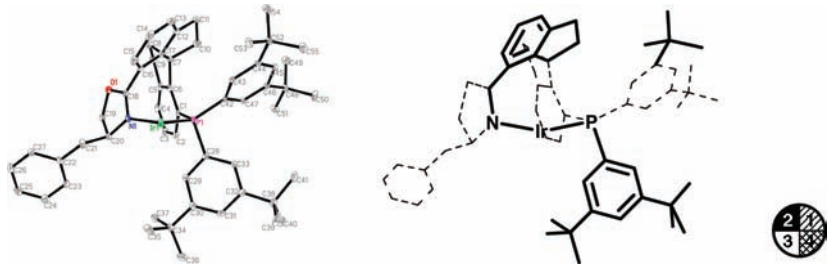
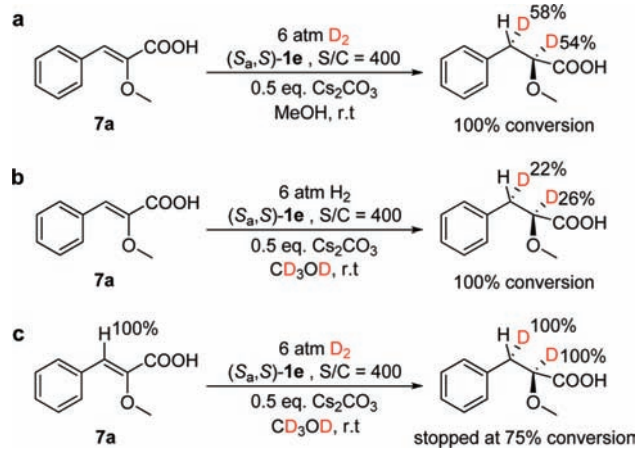


Figure 3. The crystal structure and model of catalyst (S_a,*S*)-**1c** (the hydrogen atoms, anion BAr_F^-, and COD have been omitted for clarity).

with D_2 in CD_3OD was performed and stopped at 75% conversion (Scheme 5, equation c). The product was quantitatively deuterium-labeled in the positions where double bonds localized, and no deuterium was detected in the recovered starting material. This result suggests that the migratory insertion step in the catalytic cycle is irreversible (Figure 2, from **C** to **D**).

Enantiocontrol Model. To understand the chiral induction model and stereochemistry in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids catalyzed by Ir−SIPHOX complexes **1**, we grew a single crystal of (S_a,*S*)-**1c** and performed X-ray diffraction analysis.[29] As shown in Figure 3, spiro phosphino-oxazoline ligand created a rigid and sterically hindered chiral environment ("chiral pocket") around the iridium center. The crowded "chiral pocket" efficiently minimized the number of possible transition states in the reaction and facilitated chiral discrimination. For easy understanding, the space in the front of iridium center was modeled into four quadrants. A part of spirobiindane backbone of SIPHOX ligand, which is strongly rigid and sterically hindered, occupied the quadrant 2. One *P*-phenyl and one of the *tert*-butyl groups on another *P*-phenyl hindered the quadrants 1 and 4, respectively. Only the quadrant 3 is relatively open, which could be accessed by the most sterically demanding part of the substrate.

Scheme 5. Deuterium-Labeling Studies



According to this model, the olefin double bond of α,β-unsaturated acid will prefer to coordinate to catalyst (S_a,*S*)-**1c** by its *Re* face, leading to the saturated carboxylic acid product with *S* configuration, which is consistent with the experimental results (Figure 4).

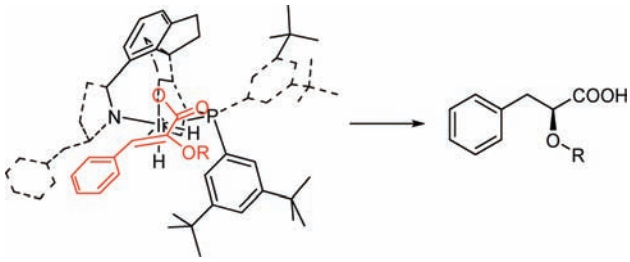
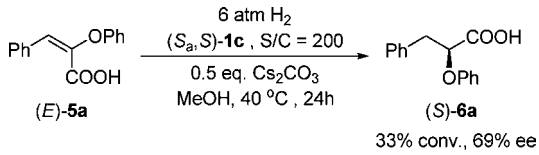


Figure 4. Coordination model of unsaturated acid with catalyst (S_a,*S*)-**1c**.

With this model, we can readily understand why the catalyst favors the *Z*-isomer of unsaturated acids over its *E* counterpart. For example, the hydrogenation of (*E*)-**5a** gave a very low conversion, as well as a low enantioselectivity (Scheme 6).

Scheme 6. Asymmetric Hydrogenation of (*E*)-2-Phenoxy-3-phenylacrylic Acid



Conclusions

In conclusion, we have demonstrated that the Ir/chiral spiro phosphino-oxazoline (Ir−SIPHOX) cationic complexes are highly efficient catalysts for the enantioselective hydrogenation of α-aryloxy- and α-alkoxy-substituted α,β-unsaturated carboxylic acids, producing a variety of optically active α-oxy-functionalized carboxylic acids in extremely high enantioselectivities under mild reaction conditions. Among them, the hydrogenation of α-benzyloxy-substituted α,β-unsaturated acids provided a convenient methodology for the synthesis of chiral α-hydroxy acids. A mechanism involving a catalytic cycle between Ir^{I} and Ir^{III} was proposed on the basis of the experimental results. The rationality of the catalytic cycle, with an olefin dihydride complex as the key intermediate, was supported by the deuterium-labeling studies. The X-ray diffraction analysis of the single crystal structure of the iridium catalyst revealed that the rigid and sterically hindered spiro phosphino-oxazoline ligands created an efficient chiral environment around the metal of the catalyst, which accounts for the high level of enantioselectivity of the reaction.

Experimental Section

General Procedure for the Synthesis of Unsaturated Carboxylic Acids 5a−p, 7a−o, and 9a−j. At −78 °C, 24 mL (48 mmol) of ^{n}BuLi (2.0 M in hexane) was added to a solution of 7 mL (50 mmol) of diisopropylamine in 60 mL of dry THF. After being stirred for 30 min at the same temperature, a solution of 40 mmol of 2-aryloxy or 2-alkoxy acetate in 20 mL of THF was added dropwise. The mixture was stirred for 20 min at −78 °C, allowed to warm to −30 °C, and then a solution of 35 mmol of aromatic aldehyde in 20 mL of THF was added dropwise at this temperature. Next, 45 mmol of benzenesulfonyl chloride was added, and the resulting mixture was allowed to warm to room temperature and was stirred overnight.

The reaction was quenched with brine and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was mixed with 20 mL of triethylamine and heated under reflux in an oil bath for 3 h. After being cooled to room temperature, the mixture was concentrated, and 3 M HCl was added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography to yield the unsaturated carboxylic ester.

To a stirred solution of carboxylic ester in 25 mL of EtOH was added 25 mL of 3 M NaOH. The mixture was stirred for 2 h under reflux. The reaction mixture was cooled and concentrated, and ether (100 mL) and 3 M HCl (50 mL) were added at 0 °C. The organic phase was separated, and the aqueous phase was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by recrystallization from petroleum ether/ethyl acetate.

General Procedure for the Asymmetric Hydrogenation. To a hydrogenation tube equipped with a stir bar were added α,β-unsaturated carboxylic acids, catalyst, Cs_2CO_3, and MeOH at ambient atmosphere. The hydrogenation tube was then put into an autoclave. The air in the autoclave was replaced with hydrogen five times. The autoclave was then charged with hydrogen to 6 atm, and the reaction mixture was stirred at the appropriate temperature for a certain time. After releasing the hydrogen, the reaction mixture was acidified with 3 M HCl and extracted with ether. The extract was dried over Na_2SO_4 and concentrated on a rotary evaporator. The conversion of substrate was determined by ^{1}H NMR analysis. The crude product was purified by flash chromatography on silica gel column to give the pure product. The product was reacted with aniline (1.1 equiv) in the presence of DMAP and DCC in THF for 30 min to afford the corresponding amide. After flash chromatography on a neutral Al_2O_3 column, the desired amide was obtained and analyzed on SFC with a chiral column to determine the ee value.

Acknowledgment. We thank the National Natural Science Foundation of China, the Major Basic Research Development Program (Grant No. 2006CB806106), and the "111" project (B06005) of the Ministry of Education of China.

Supporting Information Available: Details of experimental procedures, the synthesis and analysis data of substrates, and the analysis data of ee values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA909810K

(29) For original data of the crystal structure of the iridium complex (S_a,*S*)-**1c**, see the Supporting Information.