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Chiral Iridium Spiro Aminophosphine Complexes: Asymmetric Hydrogenation of Simple Ketones, Structure, and Plausible Mechanism

Jian-Bo Xie, Jian-Hua Xie,* Xiao-Yan Liu, Qian-Qian Zhang, and Qi-Lin Zhou*[a]

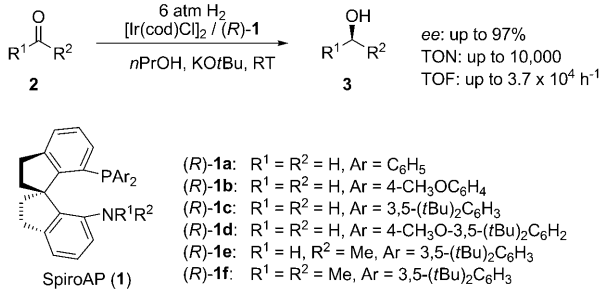
Abstract: The iridium complexes of chiral spiro aminophophine ligands, especially the ligand with 3,5-di-*tert*-butylphenyl groups on the P atom (**1c**) were demonstrated to be highly efficient catalysts for the asymmetric hydrogenation of alkyl aryl ketones. In the presence of KO*t*Bu as a base and under mild reaction conditions, a series of chiral alcohols were synthesized in up to 97% *ee* with high turnover number (TON up to 10000) and high turnover frequency (TOF up to $3.7\times10^4\ h^{-1}$). Investigation on the structures of the iridium complexes of ligands (*R*)-**1a** and **1c** by X-ray analyses disclosed that the 3,5-di-*tert*-butyl groups on the *P*-phenyl rings of the ligand are the key factor for achieving high activity and enantioselectivity of the catalyst. Study of the catalysts generated from the Ir-(*R*)-**1c** complex and H_2 by means of ESI-MS and NMR spectroscopy indicated that the early formed iridium dihydride complex with one (*R*)-**1c** ligand was the active species, which was slowly transformed into an inactive iridium dihydride complex with two (*R*)-**1c** ligands. A plausible mechanism for the reaction was also suggested to explain the observations of the hydrogenation reactions.

Keywords: aminophosphines · asymmetric catalysis · hydrogenation · iridium · ketones

Introduction

Catalytic asymmetric hydrogenation is an efficient and economically feasible protocol for the synthesis of optically active organic compounds in both academia and industry. Iridium complexes derived from chiral P,N ligands are among the most prominent catalysts used in asymmetric hydrogenation.[1] For instance, iridium complexes based on chiral phosphine-oxazolines that contain an sp^2 nitrogen atom have shown high enantioselectivity in the catalytic asymmetric hydrogenation of olefins and imines.[2] Recently, the design and synthesis of chiral aminophosphine ligands, another type of chiral P,N ligand with an sp^3 nitrogen atom, has attracted increasing attention in the development of new efficient transition-metal catalysts for asymmetric hydrogenations.[3] Several ruthenium complexes of aminophosphine ligands have been reported to be highly efficient catalysts for asymmetric hydrogenation of carbonyl compounds such as ketones[3d–f,h] and imides.[3j,k] However, iridium catalysts containing chiral aminophosphine ligands has been less explored. The only example was a chiral iridium catalyst containing β-aminophosphine ligands with an aliphatic amino group (alkyl-NH_2), which gave a moderate level of enantioselectivity (20–75% *ee*) in the asymmetric hydrogenation of ketones.[4]

With the goal of developing highly efficient chiral iridium catalysts for asymmetric hydrogenations, we recently prepared a new type of chiral spiro aminophosphine ligands (**1**) with an aromatic amino group (aryl-NH_2), named as SpiroAP (Scheme 1).[5] In the presence of the base KO*t*Bu, the



Scheme 1. Asymmetric hydrogenation of simple ketones with Ir-SpiroAP.

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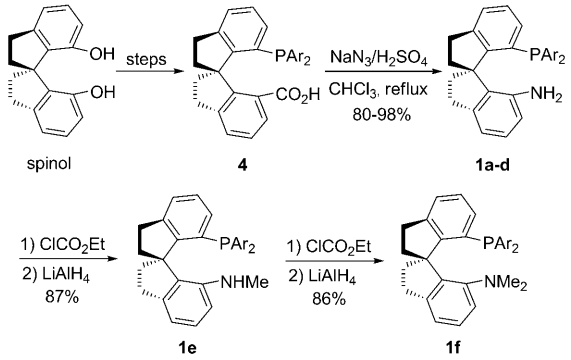
iridium complexes of chiral spiro aminophosphine ligands, especially the ligand with 3,5-di-*tert*-butylphenyl groups on the P atom (**1c**), are effective catalysts for selective hydrogenation of the carbonyl group of α-arylmethylene cycloalkanones, offering the corresponding chiral allylic alcohols with high enantioselectivities (up to 97% *ee*). This result is surprising because the iridium complexes of chiral phosphine-oxazolines (with an sp^2 N atom) were reported to hydrogenate preferentially the carbon–carbon double bond over the coexisting carbonyl group of α,β-unsaturated ketones.[6] The selectivity of the catalysts Ir-**1** on the carbonyl group of conjugate ketones encouraged us to explore the hydrogenation of simple ketones with these chiral spiro iridium catalysts. Herein we describe the asymmetric hydrogenation of ketones catalyzed by iridium complexes of spiro aminophosphine ligands **1**. The reaction produced chiral alcohols with high enantioselectivity (up to 97% *ee*), high turnover number (TON, up to 10000), and high turnover frequency (TOF, up to $3.7\times10^4\ h^{-1}$; Scheme 1). To the best of our knowledge, there are no other reports on the Ir-catalyzed asymmetric hydrogenation of ketones with such high TON and TOF.[7] The structure of the iridium catalyst, as well as a plausible reaction mechanism, are also discussed.

Abstract in Chinese:

*本文研究了手性螺环氨基膦配体铱配合物催化的简单酮化合物的不对称氢化反应, 发现手性螺环胺基膦配体, 特别是磷原子上带有 3,5-二-叔丁基苯基的配体铱配合物是芳基烷基酮不对称氢化反应的高效手性催化剂。在 KOtBu 为碱和温和的反应条件下, 催化剂 Ir-(R)-**1c** 可以高对映选择性地氢化酮, 得到手性醇化合物. 催化剂的对映选择性达到 97% ee, 转化数和转化频率分别达到 10,000 和 $3.7\times10^4\ h^{-1}$. 对催化剂 Ir-(R)-**1c** 的 X-射线结构分析表明配体(R)-**1c** 中的 3,5-二-叔丁基是催化剂获得高反应活性和高对映选择性的关键因素之一. 我们应用 ESI-MS 和 NMR 等谱学方法研究了活性催化剂的结构, 发现反应中较先形成的配合物[IrH_2((R)-**1c**)]是活性催化剂物种. [IrH_2((R)-**1c**)]在反应过程中逐渐转化为无活性的配合物[IrH_2((R)-**1c**)]. 本文还提出了一个可能的反应机理.*



Scheme 2. Synthesis of spiro aminophosphine ligands.

Results and Discussion

Synthesis of Chiral Spiro Aminophosphine Ligands

The chiral spiro aminophosphine ligands SpiroAP (**1**) were easily prepared from optically pure 1,1′-spirobiindane-7,7′-diol (spinol, Scheme 2).[8] The spinol was converted into the key intermediates, bisarylphosphino-7′-carboxy-1,1′-spirobiindanes **4**, in good yield according to the procedure previously described by our group for the synthesis of spiro phosphine-oxazolines.[9] Compounds **4** underwent a Curtius rearrangement to yield spiro aminophosphine ligands **1a–d** in high yields (80–98%).[5] For investigation of the potential effect of aromatic NH_2 group of the spiro aminophosphine ligands **1** on the catalytic reactions, the ligands with one methyl group (**1e**) and two methyl groups (**1f**) on the nitrogen atom were also synthesized. The spiro amino phosphine ligand **1c** reacted firstly with ethyl chloroformate ($ClCO_2Et$) and was reduced with lithium aluminum tetrahydride ($LiAlH_4$) to yield ligand **1e** in 87% yield. By repeating the aforementioned procedure the ligand **1e** was converted into ligand **1f** in 86% yield.

Iridium-Catalyzed Asymmetric Hydrogenation of Simple Ketones

Although significant progress has been achieved in catalytic asymmetric hydrogenation of simple ketones in the past decades,[10] the search for simple and more efficient chiral catalysts is still an important task in this area. As the iridium complexes of chiral spiro aminophosphines **1** can selectively hydrogenate the carbonyl group of α,β-unsaturated ketones,[5] we envisioned that these chiral spiro iridium complexes will be efficient catalysts for the asymmetric hydrogenation of simple ketones. Thus, we chose acetophenone (**2a**) as a model substrate to examine the catalytic capability of Ir-SpiroAP complexes in the hydrogenation of ketones. The hydrogenation was initially performed in *n*PrOH under 6 atm of H_2 at room temperature with KO*t*Bu as base and Ir-(*R*)-**1** complexes, in situ generated from 0.05 mol% [Ir(cod)Cl]$_2$ and 0.12 mol% (*R*)-**1**, as catalysts (S/C = 1000, [substrate] = 1.5 M, [KO*t*Bu] = 0.005 M). The ligand (*R*)-**1c**, which bears bulky 3,5-di-*tert*-butylphenyl groups on the P atom and showed high enantioselectivity in the asymmetric hydrogenation of α-arylmethylene cycloalkanones, has the highest reactivity and enantioselectivity in the hydrogenation of acetophenone. The hydrogenation was completed within 10 min and the product (*S*)-1-phenylethanol (**3a**) was obtained in quantitative yield with 92% *ee* (Table 1, entry 3). This hydrogenation reaction was extremely rapid with a turnover frequency (TOF) of 37200 h^{-1} (S/C = 3000, 3 min, 62% conversion). The ligand (*R*)-**1d**, which bears 4-methoxy-3,5-di-*tert*-butylphenyl groups on the P atom, also gave good reactivity and enantioselectivity in the reaction (Table 1, entry 4). However, the ligands (*R*)-**1a** and (*R*)-**1b**, which have no bulky 3,5-di-*tert*-butyl groups, exhibited low

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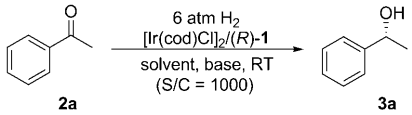
Table 1. Asymmetric hydrogenation of acetophenone (**2a**) catalyzed by Ir-(*R*)-**1**.[a]



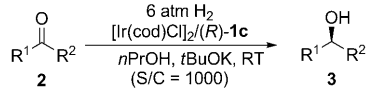
Entry	Ligand	Solvent	Base	*t*	Conv. [%][b]	*ee* [%][c]
1	(*R*)-**1a**	*n*PrOH	KO*t*Bu	4 h	80	33 (*S*)
2	(*R*)-**1b**	*n*PrOH	KO*t*Bu	4 h	23	0
3	(*R*)-**1c**	*n*PrOH	KO*t*Bu	10 min	100	92 (*S*)[d]
4	(*R*)-**1d**	*n*PrOH	KO*t*Bu	4 h	96	86 (*S*)
5	(*R*)-**1e**	*n*PrOH	KO*t*Bu	4 h	37	30 (*R*)
6	(*R*)-**1f**	*n*PrOH	KO*t*Bu	4 h	53	41 (*R*)
7	(*R*)-**1c**	MeOH	KO*t*Bu	4 h	22	36 (*S*)
8	(*R*)-**1c**	EtOH	KO*t*Bu	40 min	100	89 (*S*)
9	(*R*)-**1c**	*n*BuOH	KO*t*Bu	4 h	4	90 (*S*)
10	(*R*)-**1c**	*i*PrOH	KO*t*Bu	15 h	88	76 (*S*)
11	(*R*)-**1c**	THF	KO*t*Bu	15 h	31	46 (*S*)
12	(*R*)-**1c**	*n*PrOH	NaO*t*Bu	20 min	100	91 (*S*)
13	(*R*)-**1c**	*n*PrOH	LiO*t*Bu	20 min	100	90 (*S*)
14	(*R*)-**1c**	*n*PrOH	KOH	20 min	100	91 (*S*)
15[e]	(*R*)-**1c**	*n*PrOH	KO*t*Bu	10 min	100	91 (*S*)
16[f]	(*R*)-**1c**	*n*PrOH	KO*t*Bu	1 h	100	90 (*S*)
17[g]	(*R*)-**1c**	*n*PrOH	KO*t*Bu	10 min	100	92 (*S*)
18[h]	(*R*)-**1c**	*n*PrOH	KO*t*Bu	4 h	100	91 (*S*)

[a] Reaction conditions: 3 mmol scale, [substrate] = 1.5 M, 0.1 mol% catalyst generated in situ by reaction of $[Ir(cod)Cl]_2$ with ligand (L/Ir = 1.2:1) for 1 h, [base] = 0.005 M, 6 atm H_2, at room temperature. [b] Determined by GC. [c] Determined by GC using chiral column Supelco β-dex-225. [d] TOF = 37200 h^{-1} (S/C = 3000, 3 min, 62% conv.). [e] [base] = 0.01 M. [f] [base] = 0.0025 M. [g] L/Ir = 2. [h] S/C = 10000, 30 atm, 35 °C.

reactivities and very low or no enantioselectivities (Table 1, entries 1 and 2). The NH_2 group in chiral spiro aminophosphine ligands **1** was found to be crucial for achieving high reactivity and enantioselectivity. Introduction of one methyl group (**1e**) or two methyl groups (**1f**) onto the nitrogen atom of the ligand dramatically reduced the reactivity and enantioselectivity of the reaction and reversed the configuration of the product (Table 1, entries 5 and 6). The solvent effect was examined and *n*PrOH was found to be the best solvent in terms of reactivity and enantioselectivity (Table 1, entry 3 vs. entries 7–11). EtOH is also a suitable solvent for the hydrogenation, albeit the reactivity and enantioselectivity of reaction are slightly low (Table 1, entry 8). In addition to KO*t*Bu, other bases such as NaO*t*Bu, LiO*t*Bu, as well as KOH also can be used in the hydrogenation of acetophenone (Table 1, entries 12–14). Increasing the concentration of the base from 0.005 M to 0.01 M has little effect on both reactivity and enantioselectivity of the reaction. However, when the concentration of base was decreased to 0.0025 M, the reaction required a longer time and the *ee* value of product became lower (Table 1, entries 15 and 16). Furthermore, changing the ligand/iridium ratio (L/Ir) from 1.2:1 to 2:1 has no influence to the reaction (Table 1, entry 17). This indicated that the active catalyst contains only one aminophosphine ligand. The activity of the catalyst Ir-(*R*)-**1c** is remarkable, the catalyst loading can be lowered to 0.01 mol% (S/C = 10000) without diminishing the enantioselectivity of the reaction (Table 1, entry 18).

A variety of alkyl aryl ketones **2** can be hydrogenated by catalyst Ir-(*R*)-**1c** to produce the corresponding chiral alcohols **3** in excellent yields with high enantioselectivities (91–97% *ee*, Table 2). The ketones with methyl, ethyl, and

Table 2. Asymmetric hydrogenation of ketones by Ir-(*R*)-**1c**.[a]



2 3

Entry	R^1	R^2	**3**	*t*	Yield [%][b]	*ee* [%][c]
1	C_6H_5	Me	**3a**	10 min	>99	92 (*S*)
2	C_6H_5	Et	**3b**	1.5 h	99	93 (*S*)
3	C_6H_5	Bn	**3c**	1.5 h	98	94 (*S*)
4	4-$CH_3C_6H_4$	CH_3	**3d**	40 min	>99	93 (*S*)
5	4-FC_6H_4	CH_3	**3e**	10 min	>99	96 (*S*)
6	4-ClC_6H_4	CH_3	**3f**	10 min	>99	95 (*S*)
7	4-BrC_6H_4	CH_3	**3g**	10 min	>99	94 (*S*)
8	3-$CH_3OC_6H_4$	CH_3	**3h**	2.5 h	>99	94 (*S*)
9	3-ClC_6H_4	CH_3	**3i**	10 min	99	94 (*S*)
10	3-BrC_6H_4	CH_3	**3j**	10 min	>99	94 (*S*)
11	3-$CF_3C_6H_4$	CH_3	**3k**	10 min	>99	93 (*S*)
12[d]	2-$CH_3C_6H_4$	CH_3	**3l**	4 h	99	91 (*S*)
13[d]	2-$CH_3OC_6H_4$	CH_3	**3m**	4 h	99	91 (*S*)
14	2-ClC_6H_4	CH_3	**3n**	10 min	>99	95 (*S*)
15	3,4-$(CH)_4C_6H_3$	CH_3	**3o**	15 min	99	97 (*S*)
16	2-furyl	CH_3	**3p**	3 h	>99	91 (*S*)
17[d]	2-thienyl	CH_3	**3q**	2 h	98	91 (*S*)
18[e,f]	*c*-Hex	CH_3	**3r**	10 h	98	81 (*R*)
19[f]	α-tetralone		**3s**	4 h	95	97 (*S*)

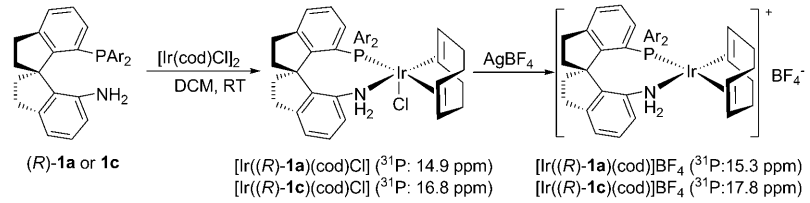
[a] Reaction conditions are the same as those in Table 1, entry 3. [b] Yield of isolated product. [c] Determined by GC or HPLC. [d] S/C = 400. [e] MeOH as solvent and $NaNH_2$ as a base. [f] S/C = 100.

benzyl groups are suitable substrates for the reaction, with acetophenone being the most reactive (Table 2, entries 1–3). However, the ketones with a bulky alkyl group such as *i*Pr and *c*-Hex could not be hydrogenated under the same reaction conditions. Generally, ketones with an electron-withdrawing substituent on the aromatic ring have high reactivity, and the ketones with an electron-donating group, especially at the *ortho* position, on the aromatic ring have lower reactivity. But all aromatic ketones gave high enantioselectivity (Table 2, entries 4–15). Heteroaryl ketones 2-acetylfuran (**2p**) and 2-acetylthiophene (**2q**) and cyclic aromatic ketones (**2s**) also can be hydrogenated by the catalyst Ir-(*R*)-**1c** to the corresponding alcohols with good enantioselectivities (Table 2, entries 16, 17, and 19). However, the Ir-(*R*)-**1c** catalyst was less efficient for the hydrogenation of aliphatic ketones such as *c*-hexylmethylketone (Table 2, entry 18).

Structures of Iridium Complexes of Spiro Aminophosphine Ligands

To understand the structure of the iridium catalysts with ligands SpiroAP, we synthesized the complexes Ir-(*R*)-**1a** and Ir-(*R*)-**1c**. Ligand (*R*)-**1a** or **1c** (2.0 equiv) reacted with $[Ir(cod)Cl]_2$ (1.0 eq) in dichloromethane (DCM) at room temperature for 1 h to form neutral iridium complexes [Ir((*R*)-

1a)(cod)Cl] (^{31}P NMR: $\delta = 14.9$ ppm) and [Ir ((*R*)-**1c**)-(cod)Cl] (^{31}P NMR: $\delta = 16.8$ ppm) as reddish brown solids (Scheme 3). After exchanging the chlorine of complexes with $AgBF_4$, the cationic iridium complexes [Ir((*R*)-**1a**)-(cod)]BF_4 (^{31}P NMR: $\delta = 15.3$ ppm) and [Ir((*R*)-**1c**)-(cod)]BF_4 (^{31}P NMR: $\delta = 17.8$ ppm) were obtained. These cationic iridium complexes were easily crystallized from the mixed solvent of DCM and Et_2O, which were suitable for X-ray fraction analysis. The crystal structures of the cationic iridium complexes [Ir((*R*)-**1a**)(cod)]BF_4 and [Ir((*R*)-**1c**)-(cod)]BF_4[11] were shown in Figure 1.



Scheme 3. Syntheses of iridium complexes of ligands (*R*)-**1a** and **1c**.

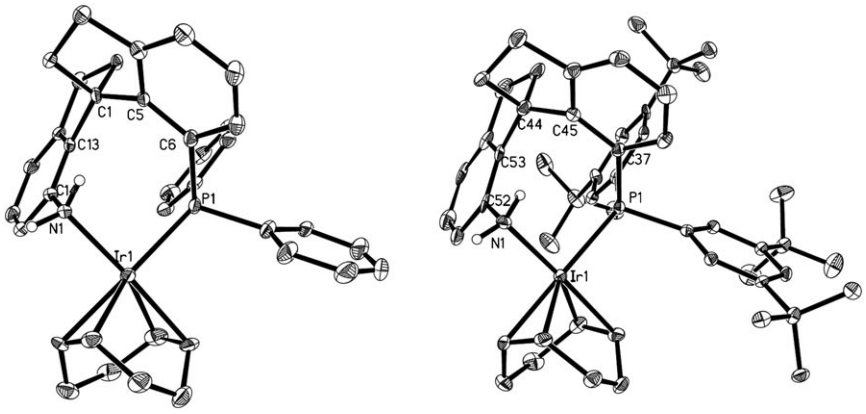


Figure 1. ORTEP diagram of [Ir((*R*)-**1a**) (cod)]BF_4 (left) and [Ir ((*R*)-**1c**) (cod)]BF_4 (right). Thermal ellipsoids shown at the 30% probability level. Selected bond lengths [Å] and angels [°]: for [Ir ((*R*)-**1a**) (cod)]BF_4, Ir1-P1 2.3455 (17), Ir1-N1 2.128(5); P1-Ir1-N1 91.29(15), C6-P1-Ir1 113.7(2), C14-N1-Ir1 102.3(4); for [Ir((*R*)-**1c**) (cod)]BF_4, Ir1-P1 2.3449 (18), Ir1-N1 2.122(5); P1-Ir1-N1 91.70(14), C37-P1-Ir1 114.0(2), C52-N1-Ir1 99.5(3).

As seen from Figure 1, the spiro aminophosphine ligands (*R*)-**1a** and **1c** coordinated to iridium atom with phosphorus and nitrogen atoms via a conformationally restricted eight-membered heterometal ring. The Ir–N bond lengths of the complexes [Ir((*R*)-**1a**)(cod)]BF_4 (2.128 Å) and [Ir((*R*)-**1c**)-(cod)]BF_4 (2.122 Å) are comparable with those in the reported complexes [Ir((1*S*,2*S*)-Ph_2PCH(Ph)CH(Me)NHBn)-(cod)]BF_4 (**I**, 2.140 Å) and [Ir((1*R*,2*S*)-Ph_2PCH(Ph)CH(Me)NHMe)(cod)]BF_4 (**II**, 2.137 Å).[4a] But the Ir–P bond lengths of the complexes [Ir((*R*)-**1a**)-(cod)]BF_4 (2.346 Å) and [Ir((*R*)-**1c**)(cod)]BF_4 (2.345 Å) are apparently longer than those in the complexes **I** and **II** (2.279 Å and 2.298 Å, respectively). Furthermore, the bite angles (P-Ir-N) of both complexes [Ir((*R*)-**1a**)(cod)]BF_4 (91.29°) and [Ir((*R*)-**1c**)(cod)]BF_4 (91.70°) are also obviously larger than those in the complexes **I** and **II** (83.0° and 83.7°, respectively). These characteristics of bonding structure might be attributed to the steric hindrance of ligands and the large chelate rings formed by the spiro aminophosphine ligands.

Compared with the crystal structures of complexes [Ir((*R*)-**1a**)(cod)]BF_4 and [Ir((*R*)-**1c**)-(cod)]BF_4, we found that the major difference between them is that the 3,5-di-*tert*-butyl groups on the *P*-phenyl rings of ligand (*R*)-**1c** constructed a crowded and therefore more effective chiral environment around the metal center. These *tert*-butyl groups, together with the rigid biindane backbone of the ligand, directed the approach of the substrate toward iridium, the active site of the catalyst. This structure character of complex [Ir((*R*)-**1c**)-(cod)]BF_4 interprets its higher enantioselectivity over the complex [Ir((*R*)-**1a**)(cod)]BF_4 in the iridium-catalyzed asymmetric hydrogenation of simple ketones, as well as previously reported cyclic α,β-unsaturated ketones.[5] When the crystals of these two complexes were used to catalyze the hydrogenation of acetophenone under the same reaction conditions, nearly identical results with in situ generated catalysts were obtained ([Ir((*R*)-**1a**)-(cod)]BF_4: 1 h, 100% conv., 31% *ee*; [Ir((*R*)-**1c**)(cod)]BF_4: 10 min, 100% conv., 91% *ee*).

The complex [Ir((*R*)-**1c**)-(cod)]BF_4 is a catalyst precursor instead of active catalyst in the hydrogenation of ketones. To investigate the active catalytic species in the reaction and understand the reaction mechanism, we prepared complex [Ir((*R*)-**1c**)(cod)]Cl in situ from (*R*)-**1c** and $[Ir(cod)Cl]_2$ in *n*PrOH, and treated it with three equivalents KO*t*Bu under ambient H_2 pressure for 12 h to afford a brown solid. The ESI-MS analysis of this brown solid showed that at least two types of iridium hydrides containing ligand (*R*)-**1c** have been formed. One has two ligands and another has one ligand: $[IrH_2((R)\text{-}\mathbf{1c})_2]^+$ ($m/z = 1482$) and $[IrH_2((R)\text{-}\mathbf{1c})]^+$ ($m/z = 838$), respectively.

The oxidative addition of H_2 to complex [Ir((*R*)-**1c**)-(cod)]Cl to form iridium hydride was verified by ^{1}H and ^{31}P NMR spectroscopy. Figure 2 and Figure 3 show ^{1}H and ^{31}P NMR spectra taken at 2 min to 24 h after introducing H_2 to the solution of in situ generated [Ir((*R*)-**1c**)(cod)]Cl complex in *n*PrOH. After treatment with H_2 for 2 min at ambi-

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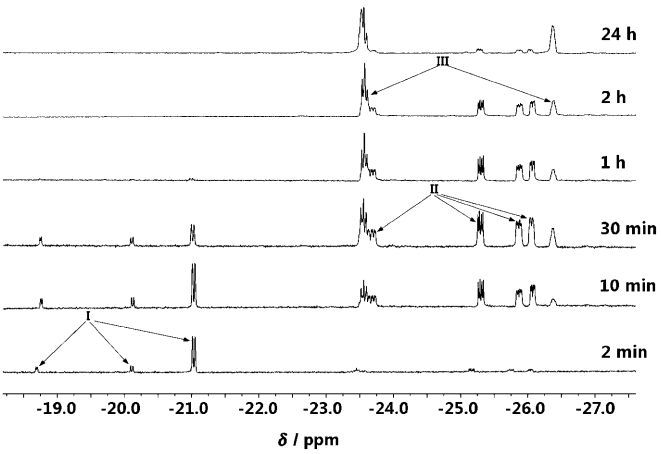


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the hydrogenation of complex [Ir((*R*)-**1c**)(cod)]Cl under ambient H_2 pressure (hydride region) [**I**, **5A** and/or **5B** and their isomers; **II**, **6A** or its isomers; **III**, **7** or its isomers].

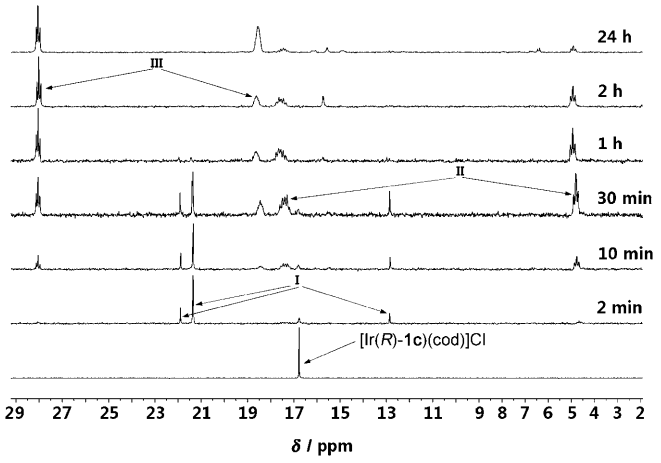
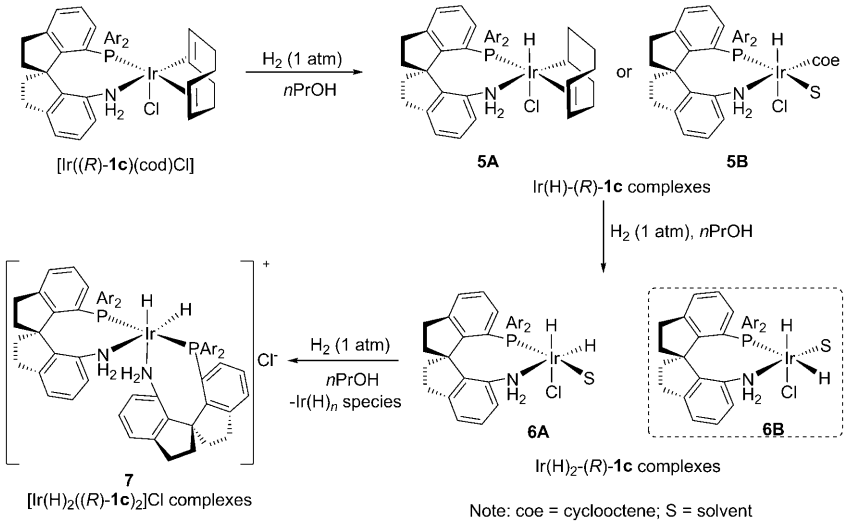


Figure 3. ^{31}P NMR spectra (161 MHz, $CDCl_3$) of the hydrogenation of [Ir((*R*)-**1c**)(cod)]Cl complex under ambient H_2 pressure [**I**, **5A** and/or **5B** and their isomers; **II**, **6A** or its isomers; **III**, **7** or its isomers].

the change of four vinyl-H at 5.65, 5.22, 4.64 and 4.08 ppm for cod to two vinyl-H at 5.00 and 4.61 ppm for coe was observed during the hydrogenation of [Ir((*R*)-**1c**)(cod)]Cl; Scheme 4). In addition to the major signals, several weak signals start to emerge in the range of −26.5 to −23.0 ppm in ^{1}H NMR spectrum, suggesting the formation of other iridium hydride complexes. After a half hour, these weak signals become major double doublet peaks at $\delta = -26.05$ ppm (dd, $^{2}J_{HH} = 6.4$ Hz, $^{2}J_{HP} = 16.4$ Hz), −25.88 ppm (dd, $^{2}J_{HH} = 8.8$ Hz, $^{2}J_{HP} = 19.6$ Hz), −25.30 ppm (dd, $^{2}J_{HH} = 8.8$ Hz, $^{2}J_{HP} = 19.6$ Hz), −23.70 ppm (dd, $^{2}J_{HH} = 6.4$ Hz, $^{2}J_{HP} = 16.4$ Hz), −23.63 ppm (dd, $^{2}J_{HH} = 6.4$ Hz, $^{2}J_{HP} = 16.4$ Hz) in the ^{1}H NMR spectrum, and a triplet at $\delta = 5.01$ ppm (t, $^{2}J_{HP} = 14.5$ Hz) and a multiplet at $\delta = 17.51$ ppm (m) in the ^{31}P NMR spectrum, showing the formation of iridium dihydride complexes. On the contrary, signals for the early formed iridium monohydride complexes became weak in both the ^{1}H NMR spectrum and ^{31}P NMR spectrum. This result clearly indicated that the iridium monohydride complexes **5A** and/or **5B** and their isomers are hydrogenated rapidly to iridium dihydride complexes **6A** and its isomers, which have two hydrides *cis* to the phosphorus atom of the ligand (*R*)-**1c**.[12] Furthermore, the new generated minor triplet and multiplet in both the ^{1}H NMR spectrum and ^{31}P NMR spectrum show the formation of other iridium dihydride complexes. The triplet at $\delta = -23.53$ ppm (t, $^{2}J_{HP} = 16.0$ Hz) in the ^{1}H NMR spectrum and the corresponding triplet at $\delta = 28.15$ ppm (t, $^{2}J_{HP} = 13.5$ Hz) in the ^{31}P NMR spectrum suggested the formation of iridium dihydride complex with two phosphorus donors on the iridium atom. According to the aforementioned ESI-MS analysis result, this new generated iridium dihydride complex is the iridium complex **7** with two (*R*)-**1c** ligands. The multiplet signals at $\delta = -26.37$ ppm (m) in the ^{1}H NMR spectrum and at $\delta = 18.64$ ppm (m) in the ^{31}P NMR spectrum may be attributed to the isomer of iridium dihydride complex **7**.

ent atmosphere, the ^{1}H NMR spectrum exhibits three doublets at $\delta = -23.1$ ppm (d, $^{2}J_{HP} = 15.6$ Hz, major), −21.10 ppm (d, $^{2}J_{HP} = 13.2$ Hz, minor), and −18.70 ppm (d, $^{2}J_{HP} = 8.0$ Hz, minor), and the ^{31}P NMR spectrum exhibits three singlets at $\delta = 21.77$ ppm (s, major), 22.27 ppm (s, minor), and 13.21 ppm (s, minor). These indicated the formation of iridium monohydride complexes **5A** and/or **5B** or their isomers with a cyclooctene (coe) unit coordinating to the iridium atom (π and σ fashion in **5A**, σ fashion in **5B** and the isomers;



Scheme 4. Hydrogenation of [Ir((*R*)-**1c**)(cod)]Cl complex.

After treatment of the solution of complex [Ir((*R*)-**1c**)-(cod)]Cl with H_2 for 1 h, the signals of iridium monohydride complexes **5A** and/or **5B** nearly disappeared and the intensity of the signals of iridium dihydride complexes **7** increased distinctly. Finally, the iridium dihydride complexes **7** became major species and the iridium dihydride complex **6A** and its isomers presented as minor species after reaction with H_2 for 24 h.

Attempts to grow crystals of iridium dihydride complexes with ligand (*R*)-**1c** were unsuccessful. Fortunately, we obtained the crystal of iridium dihydride complex $[Ir(H)_2((R)$-**1a**$)_2]Cl$ with two (*R*)-**1a** ligands by reacting $[Ir(cod)Cl]_2$ with four equivalents (*R*)-**1a** in DCM for 1 h and then with H_2 (1 atm) for 12 h. The NMR measurements of the crystal sample of $[Ir(H)_2((R)$-**1a**$)_2]Cl$ showed the hydride signal as a triplet at $\delta = -23.13$ ppm (t, $^2J_{HP} = 14.8$ Hz) in the ^1H NMR spectrum and the phosphorus signal also as a triplet at $\delta = 31.24$ ppm (t, $^2J_{HP} = 10.9$ Hz) in the ^{31}P NMR spectrum. These NMR spectra are similar to those of the complex in situ generated from the reaction of [Ir((*R*)-**1c**)-(cod)]Cl with H_2 (1 atm) for 2 or 24 h (major signals, ^1H NMR: −23.53 ppm, triplet, $^2J_{HP} = 16.0$ Hz; ^{31}P NMR: 28.15 ppm, triplet, $^2J_{HP} = 13.5$ Hz), and therefore verified the structure of iridium dihydride complex **7** (Scheme 4). The crystal structure of $[Ir(H)_2((R)$-**1a**$)_2]Cl$[13] is shown in Figure 4.

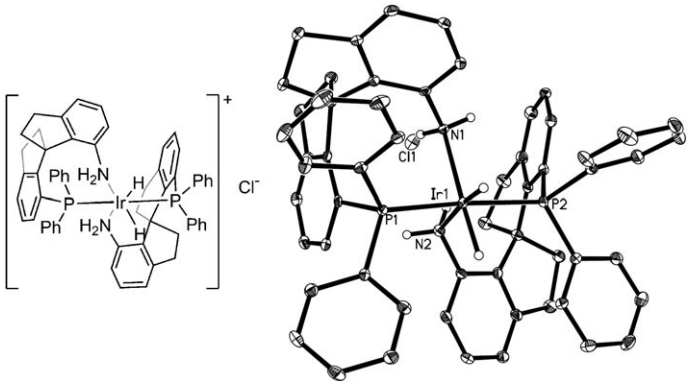


Figure 4. ORTEP diagram of $[Ir(H)_2((R)$-**1a**$)_2]Cl$. Thermal ellipsoids shown at the 30% probability level. Selected bond lengths [Å] and angels [°]: Ir1-N2 2.243(3), Ir1-N1 2.256(3), Ir1-P1 2.3094(11), Ir1-P2 2.3191(11), Ir1-H1 1.54(5), Ir1-H2 1.59(4); N2-Ir1-N1 84.43(12), N2-Ir1-P1 94.62(9), N1-Ir1-P1 91.29(9), N2-Ir1-P2 90.49(9), N1-Ir1-P2 95.20(9), P1-Ir1-P2 172.10(4), N2-Ir1-H1 95.0(17), N1-Ir1-H1 177.2(16), P1-Ir1-H1 91.4(16), P2-Ir1-H1 82.1(16), N2-Ir1-H2 173.4(17), N1-Ir1-H2 102.1(17), P1-Ir1-H2 86.4(16), P2-Ir1-H2 87.8(16), H1-Ir1-H2 78(2).

In the crystal structure of complex $[Ir(H)_2((R)$-**1a**$)_2]Cl$, two spiro aminophosphine ligands (*R*)-**1a** coordinated to the iridium atom in a way such that two phosphorus atoms coordinated in a *trans* fashion and two nitrogen atoms in a *cis* fashion. The space around the iridium atom of the complex is very crowded. The bite angles (P-Ir-N) in $[Ir(H)_2((R)$-**1a**$)_2]Cl$ (N1-Ir1-P1 91.29°, N2-Ir1-P2 90.49°) are nearly the same as that in $[Ir((R)$-**1a**$)(cod)]BF_4$ (91.29°). However, the Ir–N bond lengths of $[Ir(H)_2((R)$-**1a**$)_2]Cl$ (2.256 and 2.243 Å) are obviously longer than that of $[Ir((R)$-**1a**$)-(cod)]BF_4$ (2.128 Å), while the Ir–P bond lengths of $[Ir(H)_2((R)$-**1a**$)_2]Cl$ (2.309 and 2.319 Å) are slightly shorter than that of $[Ir((R)$-**1a**$)(cod)]BF_4$ (2.346 Å). Two N atoms and two hydrides in $[Ir(H)_2((R)$-**1a**$)_2]Cl$ are in a plane and the H1-Ir1-H2 bond angle is 78°, which is far from 90°.

The crystal of the complex $[Ir(H)_2((R)$-**1a**$)_2]Cl$ was tested as catalyst for the hydrogenation of acetophenone under the standard reaction conditions and was found to be ineffective. In the presence of base KO*t*Bu, the hydrogenation provided (*R*)-**3a** in <1% conversion with 7% *ee* after 14 h. Furthermore, the configuration of the product is opposite to that obtained by the catalyst in situ generated from [Ir-(cod)Cl]$_2$ and (*R*)-**1a** (4 h, 80% conv., 33% *ee* (*S*); Table 1, entry 1). This result demonstrated that the iridium dihydride complexes with one spiro aminophosphine ligand, such as **6A** and/or its isomers (Scheme 4), although they have not been isolated, are the active catalytic species for the hydrogenation. The active iridium dihydride complexes with one ligand were slowly transformed into inactive iridium dihydride complexes with two ligands such as complex **7** under hydrogen atmosphere. This fact is consistent with the result of study on the reaction rate of hydrogenation of acetophenone catalyzed by Ir-(*R*)-**1c**.

Possible Mechanism of Iridium-Catalyzed Hydrogenation of Ketones

The reaction rate of the hydrogenation of acetophenone was investigated. Figure 5 shows a typical profile of hydrogenation of **2a** catalyzed by Ir-(*R*)-**1c** in *n*PrOH at S/C = 10000. The reaction performed very fast at the first stage, and the conversion of substrate **2a** was up to 67% in 25 min. The reaction rate was subsequently lowered, and the conversion of substrate increased only 22% in the following 25 min. The reaction became very sluggish after 50 min. The *ee* value of

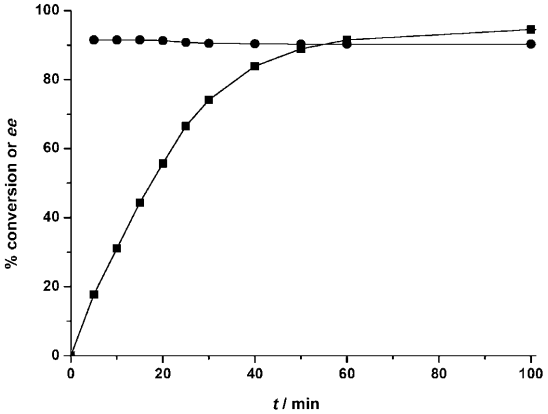


Figure 5. Reaction profile for the asymmetric hydrogenation of acetophenone, catalyzed by Ir-(*R*)-**1c** at S/C = 10000 [Reaction conditions are the same as those in Table 1, entry 18; the line labeled with a square (■) is the conversion–time curve and the line labeled with dot (●) is the *ee* value–time curve].

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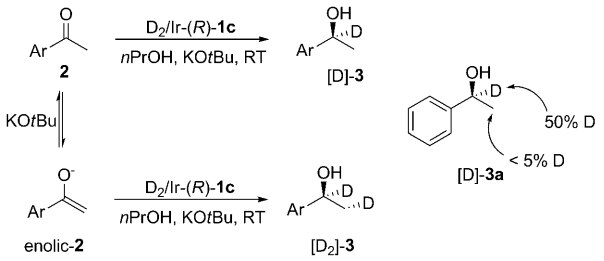
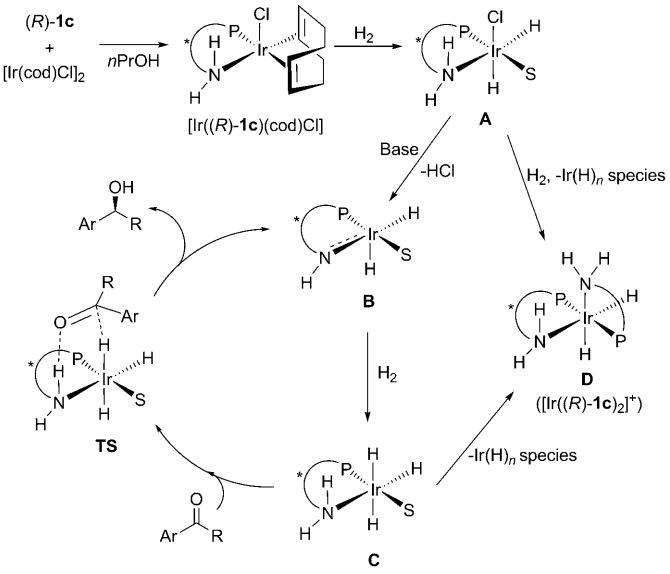
the hydrogenation product **3a** was also slightly decreased as the reaction proceeded. In the beginning of the hydrogenation, the *ee* value of product was 91.5%, which became 90.3% after 100 min. These results obviously indicated that the active catalytic species was slowly transformed into inactive or low-active catalytic species during the reaction.

In the hydrogenation of acetophenone, the base KO*t*Bu is needed to activate the catalyst. Ketones can exist as an enolic tautomers under basic condition (Scheme 5). Thus,



Scheme 5. Hydrogenation of alkyl aryl ketones with D_2.



Scheme 6. Proposed mechanism for the hydrogenation of ketones catalyzed by Ir-(*R*)-**1c** catalyst.

the hydrogen can be added either directly to the carbonyl group of the ketone or to the carbon–carbon double bond of its enolic tautomer to form a chiral alcohol. The best way to discriminate whether the hydrogenation of the ketone proceeds via the ketone form or enolate form is by carrying out the reaction with D_2. The hydrogenation of acetophenone with D_2 under the optimal reaction conditions yielded [D]-**3a** with approximate 50% deuteration at the α-position. The formation of the nondeuterated product is due to the exchange of isotopes between protic solvent and D_2.[14] This result showed that the hydrogen was mainly added to the carbonyl group of the ketone, which was consistent with the observation in the deuteration of (*E*)-2-benzylidenecyclohexanone.[5] It is worthy to mention that no hydrogenation of ketone took place under the basic reaction conditions in the absence of hydrogen; thus, transfer hydrogenation can be ruled out.

To explain the observations in the hydrogenation of ketones catalyzed by Ir-(*R*)-**1c** we propose a mechanism involving a "metal–ligand bifuncational" interaction of catalyst with substrate (Scheme 6).[15] The spiro aminophosphine ligand (*R*)-**1c** reacted firstly with $[Ir(cod)Cl]_2$ to form complex [Ir((*R*)-**1c**)(cod)Cl]. This iridium complex was transformed into iridium dihydride complex **A** under H_2 atmosphere. With the help of a strong base such as KO*t*Bu, the iridium dihydride complex **A** lost one molecule of HCl to generate an Ir-amide complex **B**, the active catalyst involved in the catalytic cycle. This step explains the fact that the NH_2 group of the spiro aminophosphine ligands **1** is crucial for the catalyst to obtain high enantioselectivity and reactivity in the reaction. The Ir-amide complex **B** was further hydrogenated to iridium trihydride complex **C**. This iridium trihydride complex transferred a hydridic Ir–H and a protic N–H unit to the carbonyl group of the ketone via a six-membered cyclic transition state (TS) to produce chiral alcohol, and regenerated the Ir-amide complex **B**. The active iridium catalyst species such as iridium dihydride complex **A** and iridium trihydride complex **C** are not very stable under hydrogen atmosphere, and can form relatively stable cationic iridium complexes **D** with two ligands, which is nearly inactive for the hydrogenation of ketone (Scheme 6). Generally, the use of the spiro aminophosphine ligands with larger substituents on the *P*-phenyl rings is helpful to prevent the formation of such stable and inactive iridium hydride species.

In the aforementioned catalytic cycle, ketone interacts with iridium trihydride complex **C** from the direction perpendicular to the plane defined by nitrogen, phosphorus, and iridium atoms to form a six-membered cyclic transition state. As one of the *tert*-butyl groups of the ligand (*R*)-**1c** in the crystal structure of $[Ir((R)\text{-}\mathbf{1c})(cod)]BF_4$ shields the bottom face of the catalyst, the ketone approaches the active center of catalyst favorably from the top face (Figure 6). To avoid steric hindrances from the *tert*-butyl group and the biindane backbone of the ligand on the top face of the catalyst, the ketone preferably combines with the catalyst at the *Re* face to form a favorable six-membered transition state (TS). The hydridic Ir-H and protic N-H units of the catalyst are then simultaneously transferred to the carbonyl–oxygen double bond of the ketone, leading to the chiral alcohol product with *S* configuration, which is consistent with the experimental results.

Conclusions

In conclusion, the iridium catalysts bearing a chiral spiro aminophosphine ligand, especially the ligand (*R*)-**1c** with 3,5-di-*tert*-butylphenyl groups on the P atom, are highly efficient for the asymmetric hydrogenation of simple ketones,

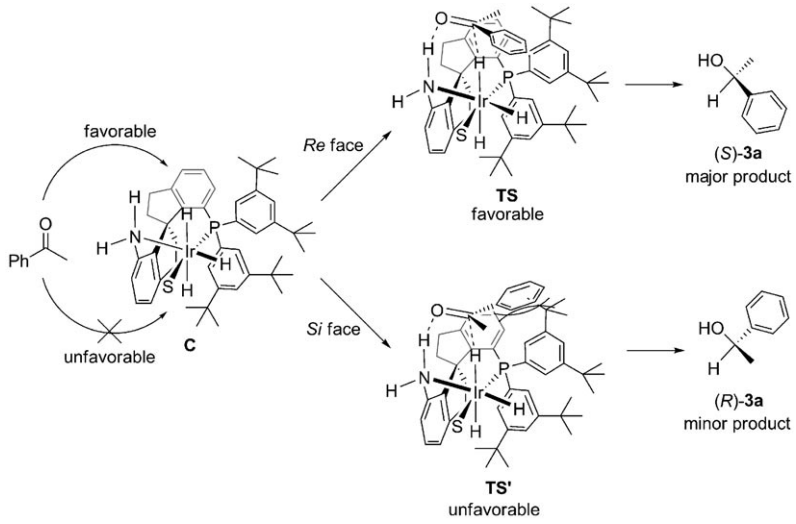


Figure 6. Stereochemistry of the hydrogenation of acetophenone.

offering the chiral secondary alcohols with high enantioselectivities (up to 97% *ee*) and high activities (TON up to 10000, TOF up to 37200 h^{-1}). The active catalyst is iridium dihydride containing one chiral spiro aminophosphine ligand, which was slowly transformed to an inactive iridium dihydride complex with two ligands. The 3,5-di-*tert*-butyl groups on the *P*-phenyl rings of the ligand (*R*)-**1c** play an important role for controlling the enantioselectivity of the catalyst and preventing the formation of inactive iridium complexes. Investigations on the active catalyst species and the reaction rate support the reaction mechanism involving a six-membered cyclic transition state. The iridium complex of chiral spiro aminophosphine ligand (*R*)-**1c** represents a highly efficient iridium catalyst for the asymmetric hydrogenation of simple ketones and α,β-unsaturated ketones, and has a high potential for application in other asymmetric hydrogenation reactions.

Experimental Section

General

All reactions and manipulations which are sensitive to moisture or air were performed in an argon-filled glovebox (VAC DRI-LAB HE 493) or using standard Schlenk techniques. Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin. $Pd(OAc)_2$, $[Ir(cod)Cl]_2$, dppb (1,4-bis(diphenylphosphino)butane), dppp (1,3-bis(diphenylphosphino)propane), and ketones were purchased from Aldrich or Acros. Acyclic unsaturated ketones and some other substrates were synthesized according to literature methods. Anhydrous THF and toluene were distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2, DMSO, *i*PrOH, *n*PrOH, *n*BuOH, iPr_2NEt, and NEt_3 were freshly distilled from calcium hydride. Anhydrous MeOH and EtOH were freshly distilled from magnesium turnings. Melting points were measured on an RY-I apparatus and are uncorrected. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded with a Varian or Bruker spectrometer at 400 MHz (^1H NMR), 100 MHz (^{13}C NMR), and 162 MHz (^{31}P NMR) in $CDCl_3$ or a Bruker spectrometer at 300 MHz (^1H NMR), 75 MHz (^{13}C NMR), and 121 MHz (^{31}P NMR) in $CDCl_3$ or CD_2Cl_2. Chemical shifts were reported in ppm downfield from internal Me_4Si and external 85% H_3PO_4. Optical rotations were determined using a Perkin–Elmer 241 MC polarimeter. HRMS were recorded on APEXII and ZAB-HS spectrometer. GC analyses were performed using a Hewlett Packard Model HP 6890 Series. HPLC analyses were performed using a Hewlett Packard Model HP 1100 instrument. X-ray diffraction analysis was performed on a Bruker Smart-1000 X-ray diffraction meter.

*Synthesis of N-Methylated Spiro Aminophosphoine Ligands (R)-**1e** and **1f***

Synthesis of (*R*)-**1e**: Ethyl chloroformate (60 mg, 0.55 mmol) was added slowly to a dry Schlenk tube containing a solution of (*R*)-**1c** (300 mg, 0.47 mmol) and pyridine (120 μL, 1.49 mmol) in 2 mL dry toluene at 0°C under nitrogen atmosphere. When the addition was complete, the reaction mixture was stirred at room temperature overnight. After dilution with 20 mL ethyl acetate, the mixture was washed sequentially with 5% HCl and brine and dried with anhydrous Na_2SO_4. The organic solution was then concentrated in vacuum to afford a white solid. This white solid was dissolved in 3 mL dry THF and was added to a suspension of $LiAlH_4$ (64 mg, 1.69 mmol) in 1 mL dry THF at 0°C. After the addition was complete, the mixture was stirred under reflux overnight. The mixture was cooled to 0°C and a small amount of water was carefully added to quench the reaction. After dilution with 20 mL ethyl acetate, the reaction mixture was washed sequentially with 20 mL 5% NaOH and brine and dried with anhydrous Na_2SO_4. The solvent was removed in vacuum and the obtained crude product was separated by chromatography on silica gel (petroleum ether/ethyl acetate/triethylamine = 20:1:0.2) to afford (*R*)-**1e** (267 mg, 87%) as an oil (which solidified after standing at room temperature for a long time). $[\alpha]_D^{20} = +142$ ($c = 0.16$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.69$–7.32 (m, 11H, Ar-H), 6.09 (d, $J = 8.0$ Hz, 1H, Ar-H), 2.92–3.10 (m, 4H, CH_2), 2.10–2.39 (m, 5H, CH_2, NH), 2.07 (s, 3H, NCH_3), 1.24 (s, 18H, $C(CH_3)_3$), 1.16 ppm (s, 18H, $C(CH_3)_3$). ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -20.03$ ppm (s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.8$ (d, $J = 25.3$ Hz), 148.9 (d, $J = 7.1$ Hz), 148.7 (d, $J = 6.1$ Hz), 144.3 (d, $J = 2.9$ Hz), 143.0, 142.9, 137.6 (d, $J = 12.1$ Hz), 134.7 (d, $J = 13.0$ Hz), 133.7, 133.5, 133.1 (d, $J = 2.0$ Hz), 133.0, 131.4 (d, $J = 3.0$ Hz), 127.2, 127.0, 126.6, 126.4, 125.9, 124.8, 121.2, 120.1, 112.6, 106.8, 60.5 (d, $J = 3.2$ Hz), 38.0 (d, $J = 3.6$ Hz), 34.3, 33.8, 33.6, 30.4, 30.3, 28.7, 28.3 ppm. HRMS (ESI) calcd for $C_{46}H_{61}NP$ $[M+H]^+$: 658.4536; found: 658.4544.

Synthesis of (*R*)-**1f**: The N-dimethylated spiro aminophosphine ligand (*R*)-**1f** was synthesized from (*R*)-**1e** in 86% yield by using same procedure as that for (*R*)-**1e**. $[\alpha]_D^{20} = +135$ ($c = 0.20$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.68$–7.18 (m, 12H, Ar-H), 2.89–3.10 (m, 4H, CH_2), 2.65–2.73 (m, 1H, CH_2), 2.31–2.38 (m, 1H, CH_2), 2.10–2.18 (m, 2H, CH_2), 2.06 (s, 6H, NCH_3), 1.11 (s, 18H, $C(CH_3)_3$), 1.07 ppm (s, 18H, $C(CH_3)_3$). ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -17.17$ ppm (s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.3$ (d, $J = 26.3$ Hz), 150.5, 148.8 (d, $J = 6.1$ Hz), 148.6 (d, $J = 6.0$ Hz), 145.3 (d, $J = 3.4$ Hz), 144.9 (d, $J = 3.1$ Hz), 142.9 (d, $J = 8.0$ Hz), 137.4 (d, $J = 12.1$ Hz), 136.0 (d, $J = 13.5$ Hz), 132.8, (d, $J = 2.0$ Hz), 132.4 (d, $J = 21.0$ Hz), 127.0, 126.8, 126.0, 125.0, 123.9, 120.6, 120.3, 119.3, 118.7, 118.4, 61.8 (d, $J = 2.9$ Hz), 44.1, 41.5 (d, $J = 5.8$ Hz), 40.5, 33.7 (d, $J = 6.8$ Hz), 30.6, 30.3, 28.7 ppm. HRMS (ESI) calcd for $C_{47}H_{63}NP$ $[M+H]^+$: 672.4693; found: 672.4695.

Asymmetric Hydrogenation of Ketones

General procedure for asymmetric hydrogenation of ketones (S/C = 1000): The catalyst precursor $[Ir(cod)Cl]_2$ (1.0 mg, 1.5 μmol), ligand (*R*)-**1c** (2.3 mg, 3.6 μmol), and *n*PrOH (1.5 mL) were added to a 30 mL hy-

drogenation vessel under nitrogen atmosphere. The mixture was stirred for 1.0 h at room temperature (25~30 °C) to give a clear light-red solution. The vessel was placed in an autoclave and purged with hydrogen by pressurizing to 1 atm and releasing the pressure. This procedure was repeated three times and the solution was stirred under 1 atm H_2 for another 0.5 h. After releasing the pressure, ketone (3 mmol) and a solution of KO*t*Bu in *n*PrOH (0.02 mmol mL^{-1}, 0.5 mL, 10 μmol) were added through the injection port. The autoclave was then pressurized to 6 atm H_2 and the reaction solution was stirred at room temperature (25–30 °C) until no obvious hydrogen pressure drop was observed. The reaction mixture was filtered through a short silica gel column, and the filtrate was analyzed by GC to determine the conversion. The solvent in the filtrate was removed to determine the yield. The enantioselectivity of the product was determined by chiral GC or HPLC.

Acknowledgements

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[1] a) A. Pfaltz, S. Bell in *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 1193; b) G.-Q. Lin, Y.-M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, Wiley, New York, **2001**; c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; d) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.

[2] Selected papers: a) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345; b) B. Alejandro, A. Pfaltz, *Chem. Eur. J.* **2009**, *15*, 2266; c) J. Mazuela, J. J. Verendel, M. Coll, S. Benjamín, A. Börner, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2009**, *131*, 12344; d) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Angew. Chem.* **2008**, *120*, 10287; *Angew. Chem. Int. Ed.* **2008**, *47*, 10133; e) A. Wang, B. Wustenberg, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 2330; *Angew. Chem. Int. Ed.* **2008**, *47*, 2298; f) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 7208; g) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595; h) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402.

[3] For a review, see: a) D. Amoroso, T. W. Graham, R. Guo, C.-W. Tsang, K. Abdur-Rashid, *Aldrichimica Acta* **2008**, *41*, 15; for selected papers, see: b) A. Saitoh, T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1997**, *8*, 3567; c) A. Saitoh, K. Achiwa, K. Tanaka, T. Morimoto, *J. Org. Chem.* **2000**, *65*, 4227; d) R. Guo, A. J. Lough, R. H. Morris, D. Song, *Organometallics* **2004**, *23*, 5524; e) K. Abdur-Rashid, R. Guo, A. J. Lough, R. H. Morris, D. Song, *Adv. Synth. Catal.* **2005**, *347*, 571; f) R. Guo, A. J. Lough, R. H. Morris, D. Song, *J. Am. Chem. Soc.* **2005**, *127*, 516; g) X.-P. Hu, H.-L. Chen, Z. Zheng, *Adv. Synth. Catal.* **2005**, *347*, 541; h) W. Chen, W. Mbafor, S. M. Roberts, J. Whittall, *Tetrahedron: Asymmetry* **2006**, *17*, 1161; i) W. Zeng, G.-Y. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750; j) M. Ito, A. Osaku, C. Kobayashi, A. Shiibashi, T. Ikariya, *J. Am. Chem. Soc.* **2007**, *129*, 290; k) M. Ito, C. Kobayashi, A. Himizu, T. Ikariya, *J. Am. Chem. Soc.* **2010**, *132*, 11414.

[4] a) L. Dahlenburg, R. Götz, *Eur. J. Inorg. Chem.* **2004**, 888; b) L. Dahlenburg, R. Götz, *Inorg. Chem. Commun.* **2003**, *6*, 443; c) L. Dahlenburg, R. Götz, *J. Organomet. Chem.* **2001**, *619*, 88.

[5] J.-B. Xie, J.-H. Xie, X.-Y. Liu, W.-L. Kong, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 4538.

[6] a) S.-M. Lu, C. Bolm, *Angew. Chem.* **2008**, *120*, 9052; *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; b) S.-M. Lu, C. Bolm, *Chem. Eur. J.* **2008**, *14*, 7513; c) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Adv. Synth. Catal.* **2010**, *352*, 103; also see reference [2d].

[7] For other examples of Ir-catalyzed asymmetric hydrogenations of ketones, see: a) H.-Y. Jiang, C.-F. Yang, C. Li, H.-Y. Fu, H. Chen, R.-X. Li, X.-J. Li, *Angew. Chem.* **2008**, *120*, 9380; *Angew. Chem. Int. Ed.* **2008**, *47*, 9240; b) G. Liu, M. Yao, J. Wang, X. Lu, M. Liu, F. Zhang, H. Li, *Adv. Synth. Catal.* **2008**, *350*, 1464; c) E. Le Roux, R. Malacea, E. Manoury, R. Poli, L. Gonsalvi, M. Peruzzini, *Adv. Synth. Catal.* **2007**, *349*, 309; d) Z.-R. Dong, Y.-Y. Li, J.-S. Chen, B.-Z. Li, Y. Xing, J.-X. Gao, *Org. Lett.* **2005**, *7*, 1043; e) X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 3318.

[8] a) V. B. Birman, A. L. Rheingold, K.-C. Lam, *Tetrahedron: Asymmetry* **1999**, *10*, 125; b) J.-H. Zhang, J. Liao, X. Cui, K.-B. Yu, J.-G. Deng, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, L.-W. Chung, T. Ye, *Tetrahedron: Asymmetry* **2002**, *13*, 1363.

[9] S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886.

[10] For reviews, see: a) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40; b) T. Ohkuma, *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 1070. For selected papers, see: c) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703; d) T. Ohkuma, M. Koizumi, H. Doucet, T. Pharm, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529; e) M. J. Burk, W. Hems, D. Herberg, C. Malan, A. Zanotti-Gerosa, *Org. Lett.* **2000**, *2*, 4173; f) J. Wu, H. Chen, W.-H. Kwok; R.-W. Guo, Z.-Y. Zhou, C.-H. Yeung, A. S. C. Chan, *J. Org. Chem.* **2002**, *67*, 7908; R.-W. Guo, Z.-Y. Zhou, C.-H. Yeung, A. S. C. Chan, *J. Org. Chem.* **2002**, *67*, 7908; g) J. Wu, J.-X. Ji, R.-W. Gio, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963; h) J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404; i) A. Hu, H. L. Ngo, W. Lin, *Org. Lett.* **2004**, *6*, 2937; j) D. G. Genov, D. J. Ager, *Angew. Chem.* **2004**, *116*, 2876; *Angew. Chem. Int. Ed.* **2004**, *43*, 2816; k) Y. Xu, N. W. Alcock, G. J. Clarkson, G. Docherty, G. Woodward, M. Wills, *Org. Lett.* **2004**, *6*, 4105; l) Y. Liang, Q. Jing, X. Li, L. Shi, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 7694; m) Q. Jiang, X. Zhang, J. Sun, K. Ding, *Adv. Synth. Catal.* **2005**, *347*, 1193; n) H. Huang, T. Okuno, K. Tsuda, M. Yoshimura, M. Kitamura, *J. Am. Chem. Soc.* **2006**, *128*, 8716; o) W. Li, G. Hou, C. Wang, Y. Jiang, X. Zhang, *Chem. Commun.* **2010**, *46*, 3979; p) W. Li, X. Sun, L. Zhou, G. Hou, S. Yu, X. Zhang, *J. Org. Chem.* **2009**, *74*, 1397.

[11] Crystal data for {[Ir((*R*)-**1a**)(cod)]BF_4}$_2$·Et_2O: $C_{37}H_{38}BF_4IrNP$, M_r = 806.66, orange platelet, 0.26×0.24×0.08 mm^3, monoclinic, *C*2, *a* = 35.564(13), *b* = 13.185(5), *c* = 15.581(6) Å, α = 90, β = 96.064, γ = 90°, *V* = 7265(5) Å^3, ρ_{calcd} = 1.475 g cm^{-3}, μ = 3.765 mm^{-1}, *F*(000) = 3200, *Z* = 8, $Mo_{K\alpha}$ radiation, λ = 0.71070 Å, *T* = 113(2) K, 1.84 < θ < 27.81°. 31673 reflections collected, 16372 unique reflections, R_1 = 0.0439. CCDC 789251. Crystal data for {[Ir((*R*)-**1c**)(cod)]BF_4}$_2$·Et_2O: $C_{110}H_{150}B_2F_8Ir_2N_2OP_2$, M_r = 2136.28, orange block, 0.18×0.16×0.12 mm^3, monoclinic, $P2_1$, *a* = 13.263(3), *b* = 15.339(3), *c* = 25.508(5) Å, α = 90, β = 100.85, γ = 90°, *V* = 5096.7(18) Å^3, ρ_{calcd} = 1.392 g cm^{-3}, μ = 2.703 mm^{-1}, *F*(000) = 2196, *Z* = 2, $Mo_{K\alpha}$ radiation, λ = 0.71073 Å, *T* = 113(2) K, 1.56 < θ < 25.02°. 38394 reflections collected, 17094 unique reflections, R_1 = 0.0506. CCDC 755829 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] If the hydrides are *trans* to the phosphorus atom of the ligand in the iridium complex like in **6B**, larger coupling constants of 150–200 Hz would be expected. For a review, see: a) J. P. Jesson in *Transition Metal Hydrides* (Ed.: E. L. Muetterties), Marcel Decker, New York, **1971**, pp. 75–201; b) R. V. Parish, *NMR; NQR; EPR and Mössbauer Spectroscopy in Inorganic Chemistry*, Ellis Horwood Ltd., New York, **1990**. For selected papers, see: c) C. Mazet, S. P. Smidt, M. Meuwly, A. Pfaltz, *J. Am. Chem. Soc.* **2004**, *126*, 14176; d) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem.* **2009**, *121*, 5245; *Angew. Chem. Int. Ed.* **2009**, *48*, 5143.

[13] Crystal data for [$Ir(H)_2$((*R*)-**1a**)$_2$]Cl(solvent): $C_{65}H_{78.50}ClIrN_2O_{5.50}P_2$, M_r = 1265.39, colorless prism, 0.22×0.12×0.08 mm^3, orthorhombic, $P2_12_12_1$, *a* = 10.3016, *b* = 18.1525(6), *c* = 32.4774(11) Å, α = 90, β = 90,

$\gamma = 90°$, $V = 6073.3(3)$ Å^3, $\rho_{calcd} = 1.348$ g cm^{-3}, $\mu = 2.346$ mm^{-1}, $F(000) = 2602$, $Z = 4$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71070$ Å, $T = 113(2)$ K, $1.7 < \theta < 27.9°$. 42608 reflections collected, 14291 unique reflections, $R_1 = 0.0362$. CCDC 789252 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] For recent reviews on heterolytic H_2 activation, see: a) D. Sellmann, A. Fürsattel, J. Sutter, *Coord. Chem. Rev.* **2000**, *200*, 545; b) G. J. Kubas, *Metal Dihydrogen and σ-Bond Complexes*, Kluver Actdemic/Plenum Publishers, New York, **2001**, chapt. 9 and 10.

[15] For the "metal–ligand bifuncational" mechanism in $RuCl_2$(diphosphine)(diamine)-catalyzed hydrogenation of ketones, see: a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490; b) K. Abdur-Rashid, M. Faatz, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2001**, *123*, 7473; c) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104.

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