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Citation	Advanced synthesis & catalysis <a href="https://doi.org/10.1002/adsc.202000615">https://doi.org/10.1002/adsc.202000615</a>
Issue Date	2020-11-04
Doc URL	<a href="http://hdl.handle.net/2115/83157">http://hdl.handle.net/2115/83157</a>
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# Iridium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones Controlled by Alcohol Hydrogen-Bonding and $sp^3$ -C–H Noncovalent Interactions

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Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

**Abstract.** Iridium-catalyzed enantioselective transfer hydrogenation of ketones with formic acid was developed using a prolinol-phosphine chiral ligand. Cooperative action of the iridium atom and the ligand through alcohol–alkoxide interconversion is crucial to facilitate the transfer hydrogenation. Various ketones including alkyl aryl ketones, ketoesters, and an aryl heteroaryl ketone were competent substrates. An attractive feature of this catalysis is efficient discrimination between the alkyl and aryl substituents of the ketones, promoting hydrogenation with the identical sense of enantioselection regardless of steric demand of the alkyl substituent and thus resulting in a rare case of highly enantioselective transfer hydrogenation of *tert*-alkyl aryl ketones. Quantum chemical calculations revealed that the  $sp^3$ -C–H/ $\pi$  interaction between an  $sp^3$ -C–H bond of the prolinol-phosphine ligand and the aryl substituent of the ketone is crucial for the enantioselection in combination with O–H...O/ $sp^3$ -C–H...O two-point hydrogen-bonding between the chiral ligand and carbonyl group.

**Keywords:** transfer hydrogenation • iridium • chiral catalyst • C–H/ $\pi$  interaction • nonclassical hydrogen bond

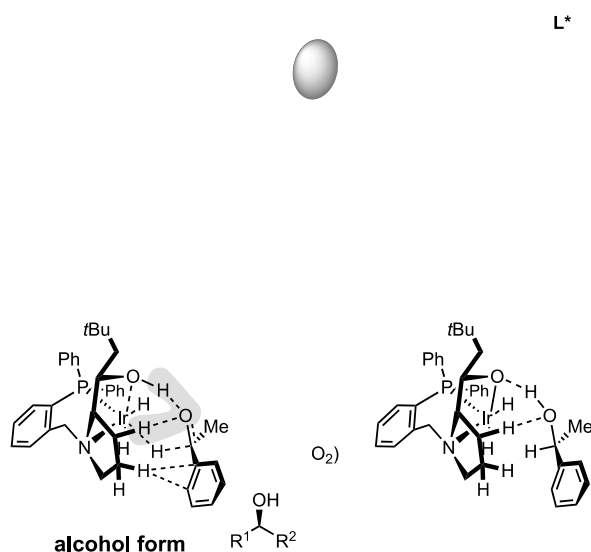
Enantioselective transfer hydrogenation of ketones has been widely studied as a method for the synthesis of chiral secondary alcohols. A common approach toward developing catalysts for the transfer hydrogenation is to employ the cooperative action of metals and ligands for outer-sphere activation of the ketone.<sup>[1]</sup> The Noyori–Ikariya-type chiral ruthenium amide catalyst system is a representative approach.<sup>[2]</sup> The key to its catalysis is the amine–amide interconversion in the ligand that induces both the

abstraction of two H atoms from 2-propanol and the protonative hydride reduction of the carbonyl group resulting in the hydrogenation of simple ketones.<sup>[2d–f]</sup> A few catalytic systems based on interconversion of other functional groups in the ligands have also been proposed, including cyclopentadienol–cyclopentadienone,<sup>[3]</sup> aromatization–dearomatization,<sup>[4]</sup> and carboxylic acid–carboxylate.<sup>[5]</sup> Despite the significant advances in the enantioselective transfer hydrogenation, the reactions are sensitive to steric bulkiness.<sup>[6,7]</sup> More specifically, only a few catalysts induced high enantioselectivity for the transfer hydrogenation of *tert*-alkyl aryl ketones, and those catalysts did not show sufficient enantioselectivity for the reaction of substrates with smaller alkyl groups such as acetophenone.<sup>[6b,c]</sup> Thus, the development of more general transfer hydrogenation catalysts remains a challenge.

Previously, we developed prolinol-phosphine chiral ligands for use in the copper-catalyzed enantioselective alkynylation of aldehydes and  $\alpha$ -ketoesters with terminal alkynes, in which cooperation of the ligand hydroxyl group and the copper center was proven by quantum chemical calculations (Scheme 1).<sup>[8]</sup> The calculations also showed the presence of O–H...O/ $sp^3$ -C–H...O two-point hydrogen-bonding between the chiral ligand and the carbonyl group. Combined with these hydrogen-bonding interactions, dispersive ligand–substrate attractions explained the enantioselectivity of the copper catalysis.<sup>[8,9]</sup> The prolinol-phosphine chiral ligands were also used successfully for the enantioselective Kinugasa reaction,<sup>[10]</sup> the copper-catalyzed coupling between nitrones and terminal alkynes to produce enantioenriched 1,3,4-trisubstituted  $\beta$ -lactams, based

on the assumption that O–H...O/sp<sup>3</sup>–C–H...O two-point hydrogen-bonding between the prolinol-phosphine and the oxyanion of the nitron occurred as a crucial catalyst–substrate interaction. Along this line, we envisioned that the concept of O–H...O/sp<sup>3</sup>–C–H...O two-point hydrogen-bonding may be extended to metal-catalyzed outer-sphere enantioselective hydrogenation of carbonyl compounds, in which hydrogen-bonding between a protic site of a chiral ligand and a carbonyl group is essential.<sup>[11]</sup>

Herein, we report the iridium-catalyzed enantioselective transfer hydrogenation of ketones with formic acid<sup>[12]</sup> enabled by alcohol–alkoxide interconversion<sup>[13]</sup> of a prolinol-phosphine chiral ligand (Scheme 1).<sup>[14,15]</sup> This catalytic system efficiently discriminates between the aryl substituent and the alkyl substituent of the ketone by an attractive noncovalent interaction between a nonpolar sp<sup>3</sup>–C–H bond of the chiral ligand and the  $\pi$  system of the aryl substituent of the ketone (sp<sup>3</sup>–C–H/ $\pi$  interaction), achieving excellent enantioselection of the same sense regardless of steric demand of the alkyl substituent.



**Scheme 1.** Applications of Chiral Prolinol-Phosphine Ligands for the Enantioselective Cu-catalyzed Alkynylation of Carbonyl Compounds (Previous Work) and Ir-catalyzed Transfer Hydrogenation of Ketones (Present Work).

We commenced the investigation with acetophenone (**1a**) as the model substrate (Table 1). Various chiral prolinol-phosphines (**L**) were examined for their ability to induce catalytic activity and enantioselectivity in the reaction of **1a** (0.2 mmol) and formic acid (2.0 eq) in the presence of [IrCl(cod)]<sub>2</sub> (1 mol%), chiral ligand (2.5 mol%), and KO<sup>t</sup>-Bu (5 mol%) in THF (1 mL) at 25 °C over 6 h (entries 1–6). The ligands (**L1** and **L3**) bearing primary or tertiary

alcohol moieties did not promote the reaction at all (entries 1, 3).<sup>[16]</sup> In contrast, **L2** bearing a secondary alcohol moiety gave chiral secondary alcohol **2a** with significant enantioselectivity (85% ee), albeit in low yield (11%) (entry 2). Encouraged by this result, further screening of secondary alcohol ligands was conducted focusing on the influence of  $\alpha$ -substituents of the hydroxy group. Both the product yield and enantioselectivity were slightly improved by employing *tert*-butyl-substituted ligand **L4** (entry 4, 19%, 89% ee). Even better yield and enantioselectivity were obtained with **L5** bearing a neopentyl group (entry 5, 46%, 92% ee). On the other hand, the reaction was completely inhibited by replacing the hydroxy group of **L5** with a methoxy group (**L5-OMe**), indicating the critical role of the alcoholic site (entry 6).

Screening of solvents revealed that the use of ethereal solvents was crucial, as no reaction occurred with other types of solvents such as toluene, dichloromethane, 2-propanol, *N,N*-dimethylformamide, and acetonitrile. The optimal solvent was cyclopentyl methyl ether (CPME), affording the product in 87% yield with 94% ee (entry 7). Effect of the base was also significant. While the reaction did not proceed at all with LiO<sup>t</sup>-Bu or NaO<sup>t</sup>-Bu (entries 8 and 9), K<sub>2</sub>CO<sub>3</sub> improved the enantioselectivity to 96% ee (entry 10, 82% yield).<sup>[17,18]</sup>

**Table 1.** Optimization of Enantioselective Transfer Hydrogenation.<sup>[a]</sup>

entry	ligand	solvent	base	yield (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	<b>L1</b>	THF	KO <sup>t</sup> -Bu	0	–
2	<b>L2</b>	THF	KO <sup>t</sup> -Bu	11	85
3	<b>L3</b>	THF	KO <sup>t</sup> -Bu	0	–
4	<b>L4</b>	THF	KO <sup>t</sup> -Bu	19	89
5	<b>L5</b>	THF	KO <sup>t</sup> -Bu	46	92
6	<b>L5-OMe</b>	THF	KO <sup>t</sup> -Bu	0	–
7	<b>L5</b>	CPME	KO <sup>t</sup> -Bu	87	94
8	<b>L5</b>	CPME	LiO <sup>t</sup> -Bu	0	–
9	<b>L5</b>	CPME	NaO <sup>t</sup> -Bu	0	–
10	<b>L5</b>	CPME	K <sub>2</sub> CO <sub>3</sub>	82	96
11	<b>L5</b>	CPME	–	0	–
12 <sup>[d]</sup>	<b>L5</b>	CPME	–	83	95

**L1**

**L2**

**L3**

**L4**

**L5**

**L5-OMe**

[a] Condition: [IrCl(cod)]<sub>2</sub> (1 mol%), ligand (2.5 mol%), base (5 mol%), **1a** (0.20 mmol), HCO<sub>2</sub>H (0.40 mmol), solvent (1 mL), 25 °C, 6 h. [b] Yield of the isolated product.

[c] The enantiomeric excess was determined by HPLC analysis. [d]  $[\text{Ir}(\text{OMe})(\text{cod})]_2$  was used instead of  $[\text{IrCl}(\text{cod})]_2$ .

The following two experiments are supportive of a mechanism involving an iridium alkoxide species. First, the reaction did not proceed at all in the absence of the external base additive, which was used in a catalytic amount in the parent reaction (Table 1, entry 11). Second, the effect of  $[\text{Ir}(\text{OMe})(\text{cod})]_2$  in the absence of a base additive was comparable to that of the  $[\text{IrCl}(\text{cod})]_2/\text{KO}t\text{-Bu}$  system (entry 12).

Under the optimized conditions, various ketones including alkyl (hetero)aryl ketones, an aryl heteroaryl ketone, and keto esters were hydrogenated to form the corresponding secondary alcohols in a highly enantioselective manner. Thus, the enantioselective transfer hydrogenation of ketones (**1**) with formic acid (2 equiv) was conducted in the presence of  $[\text{IrCl}(\text{cod})]_2$  (1 mol%), **L5** (2.5 mol%), and  $\text{K}_2\text{CO}_3$  (5 mol%) in CPME at 25 °C or 40 °C over 6 h (Table 2). Chiral secondary alcohols were obtained in high enantioselectivities with both electron-donating (**2b**, 81%, 96% ee; **2c**, 93%, 93% ee) and withdrawing (**2d**, 70%, 95% ee; **2e**, 77%, 94% ee) substituents at the *para*-position of the phenyl ring of acetophenone. Ketone **1f** bearing an *ortho*-methyl group on the phenyl ring was also compatible giving **2f** in >99% yield with 97% ee. Sterically more demanding acetophenones were competent (**2g**, 97%, 93% ee; **2h**, 79%, 95% ee). Heteroaryl ketones reacted with good enantioselectivities (**2i**, >99%, 86% ee; **2j**, >99%, 86% ee). A cyclic ketone was also amenable (**2k**: >99%, 87% ee).

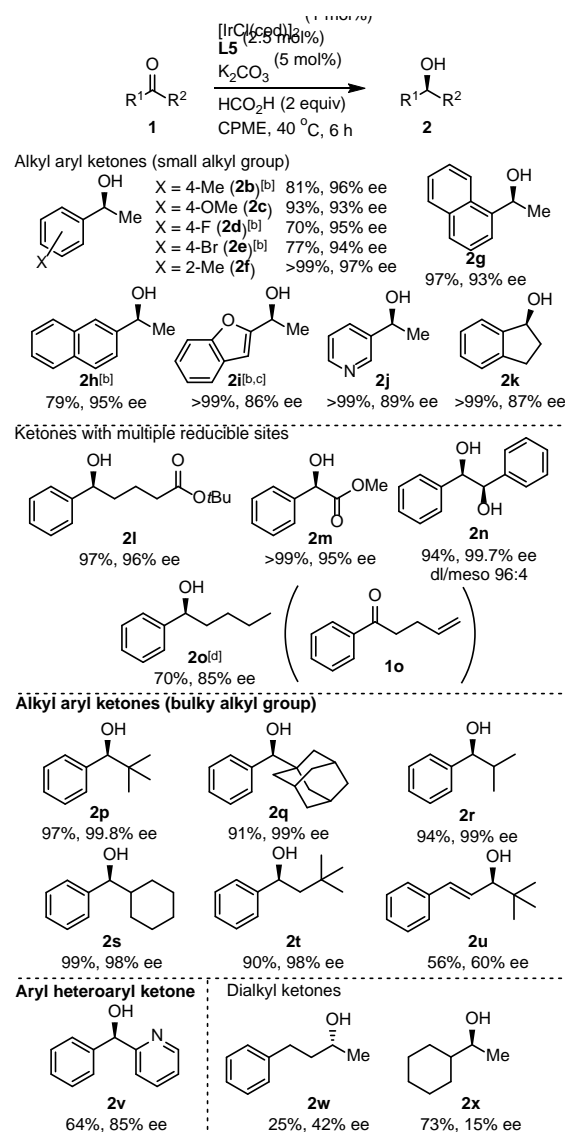
Chemoselectivity was assessed using ketones including other reducible moieties. Reduction of ketonic carbonyl groups proceeded exclusively in the presence of an ester moiety regardless of the relative location of the two functional groups (**2l**: 97%, 96% ee; **2m**: >99%, 95% ee). Benzil **1n** underwent twofold reduction to produce (*R,R*)-1,2-diphenyl-1,2-diol (**2n**) in a 96:4 diastereomeric ratio with 99.7% ee. However, the isolated terminal C–C double bond in **1o** was completely reduced during the enantioselective carbonyl hydrogenation over 24 h to give saturated alcohol **2o** (70%, 85% ee).

Excellent discrimination between the aryl group and the bulky alkyl group with the same catalyst is a significant feature of this reaction. The reaction of *tert*-butyl phenyl ketone (**1p**) proceeded smoothly, giving (*S*)-2,2-dimethyl-1-phenylpropanol (**2p**) in 99.8% ee. Interestingly, hydrogenation of acetophenone and *tert*-butyl phenyl ketone occurred on the same prochiral face, regardless of the reversal of the relative steric demand between the phenyl and the alkyl substituents of the carbonyl group. This result cannot be explained by a steric repulsion model alone, but rather, suggests that the enantioselection is due to attractive forces between the catalyst and the aromatic ring of the substrate.<sup>[2e,19]</sup> Similarly, sterically demanding adamantyl- (**2q**: 91%, 99% ee), isopropyl- (**2r**: 94%,

99% ee), cyclohexyl- (**2s**: 99%, 98% ee), and neopentyl-substituted (**2t**: 90%, 98% ee) alcohols were obtained from the corresponding ketones with the same level of enantioselection. Conjugated enone **1u** with a bulky alkyl group also underwent smooth hydrogenation to afford **2u** (56%), although the enantioselectivity dropped to 60% ee and the competitive 1,4-reduction was significant (17% NMR yield).

This reaction was applicable to 2-benzoylpyridine (**1v**), affording (*R*)-phenyl-(2-pyridyl)methanol (**2v**) in 64% yield with 85% ee.<sup>[20]</sup> Since the steric demand of the phenyl and pyridyl groups is almost the same, the enantioselectivity is likely due to the difference in electron density of the aromatic rings.

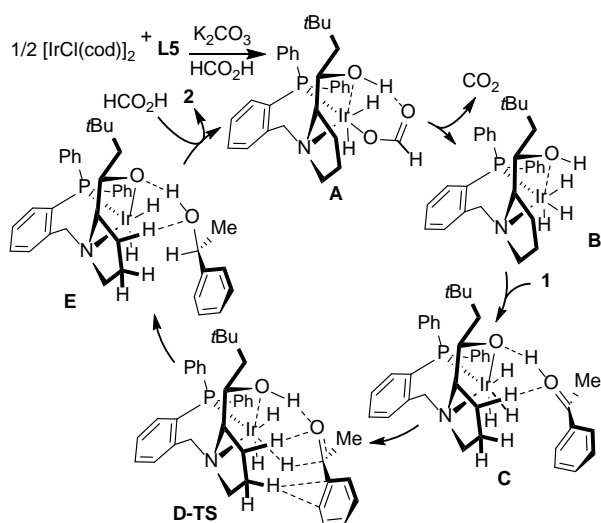
**Table 2.** Scope of Ketones (**1**).<sup>[a]</sup>



[a] Condition:  $[\text{IrCl}(\text{cod})]_2$  (1 mol%), **L5** (2.5 mol%),  $\text{K}_2\text{CO}_3$  (5 mol%), **1** (0.20 mmol),  $\text{HCO}_2\text{H}$  (0.40 mmol), CPME (1 mL), 40 °C, 6 h. Yield of the isolated product. The enantiomeric excess was determined by HPLC analysis. [b] Reaction was conducted at 25 °C. [c] Reaction time was 12 h. [d] Reaction time was 24 h.

Dialkyl ketones such as phenethyl methyl ketone (**1w**) and cyclohexyl methyl ketone (**1x**) showed decreased reactivity and enantioselectivity (**2w**: 25%, 42% ee; **2x**: 73%, 15% ee) compared with the alkyl aryl ketones. These results are in accord with the proposed importance of attractive interactions between the chiral ligand and the aryl group of the ketones.

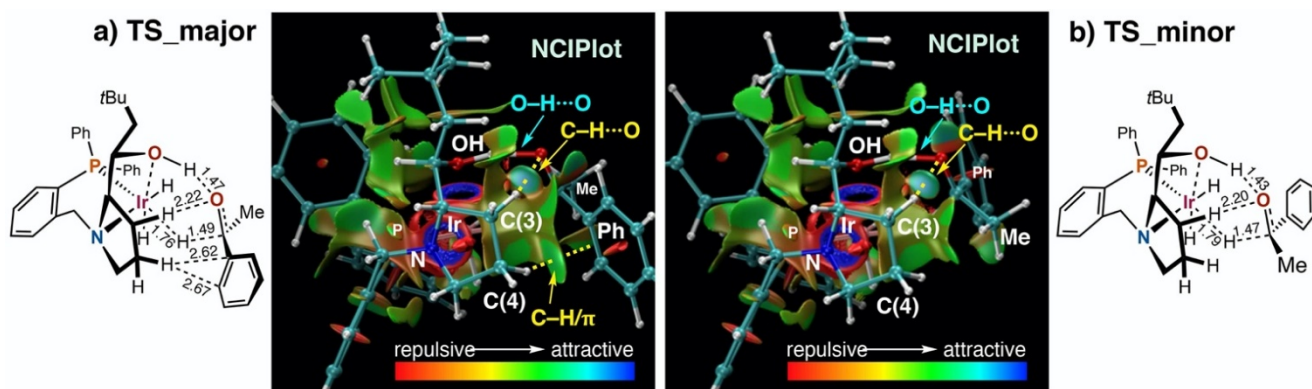
We propose a catalytic cycle involving alcohol-alkoxide interconversion as shown in Scheme 2. An iridium-**L5** complex enters into the catalytic cycle in the form of dihydrido-iridium(III) formate **A** upon reaction with  $K_2CO_3$  and formic acid.<sup>[21]</sup> The formate (**A**) undergoes decarboxylation to form iridium trihydride **B**, in which prolinol-phosphine ligand **L5** presents an alcoholic hydrogen bond donor site. Next, complex **B** captures ketone **1** through  $OH\cdots O/sp^3-C-H\cdots O$  two-point hydrogen-bonding to form **C**. Nucleophilic attack of one of the three hydrides on the iridium center to the carbonyl carbon and cooperative protonation of the developing oxyanion with the ligand O-H group through **D-TS** affords alkoxoiridium(III) complex **E**. Instantaneous protonation of **E** with formic acid releases the secondary alcohol product **2** with regeneration of **A**.



Scheme 2. Proposed Catalytic Cycle.

We performed DFT calculations at the B3LYP+D3(BJ)/def2SVP level of theory<sup>[22]</sup> for the hydride attack of the carbonyl group (**C-D-TS-E** in Scheme 2), which is likely the enantioselectivity-determining step, employing **L5** as the ligand and **1a** as the ketone. For the pyrrolidine ring in **L5**, we examined the three most stable conformers based on our previous DFT studies on the copper-catalyzed enantioselective alkynylation of aldehydes.<sup>[8a]</sup> The most stable transition states (**D-TS**) leading to the major [(*S*)-**2a**] (**TS\_major**) and minor [(*R*)-**2a**] (**TS\_minor**) enantiomeric products are shown in Figures 1a and 1b, respectively, with the plot of weak noncovalent interactions given by the NCIPLOT program<sup>[23]</sup> [see Supporting Information for the bond critical point (BCP) analyses of the quantum theory of atoms in molecule (QTAIM)]. The activation Gibbs free energy leading to the major enantiomer (Scheme 2, **C** to **D-TS**) is 24.1 kJ mol<sup>-1</sup> at 298.15 K. **TS\_major** is 9.8 kJ mol<sup>-1</sup> lower in Gibbs free energy than **TS\_minor**, in accord with the excellent experimental enantioselection (96% ee, Table 1, entry 10) favoring the *S* product.

As expected, one of the nonpolar  $sp^3-C-H$  bonds located  $\beta$  to the N atom (the 3-position of the pyrrolidine ring) of **L5** donates a nonclassical hydrogen bond to the carbonyl oxygen of the ketone in both transition states, resulting in  $O-H\cdots O/sp^3-C-H\cdots O$  two-point hydrogen-bonding, which orients the carbonyl group to accept the nucleophilic attack of the Ir-bound equatorial hydride *cis* to the N atom in a well-defined manner (Figure 1). In addition, Figure 1a shows that a C-H/ $\pi$  interaction occurs between a nonpolar C( $sp^3$ )-H bond at the 4-position of the pyrrolidine ring and the aromatic ring of the ketone in **TS\_major** and that the alkyl (Me) group is positioned outward from the steric environment of the catalyst. On the other hand, the aromatic substituent in **TS\_minor** does not cause attractive interactions, while the alkyl group is located proximal to the pyrrolidine framework of the chiral ligand. These interpretations of the computational results explain the experimental observations that only aryl ketones were efficiently hydrogenated with high enantioselectivity, while the reaction broadly tolerated various aryl ketones regardless of steric demand of the carbonyl alkyl group with the identical sense of enantioselection.



**Figure 1.** Geometrical features and plots of noncovalent interactions (NCIPlot) of the transition states leading to (a) the major enantiomer and (b) the minor enantiomer. Atomic distances are given in Å.

The present work demonstrates that cooperative action of a metal and ligand through alcohol–alkoxide interconversion can facilitate enantioselective transfer hydrogenation of ketones and shows that the O–H...O/sp<sup>3</sup>-C–H...O two-point hydrogen-bonding provided by the metal-bound prolinol-phosphine chiral ligand, which was previously proposed for copper catalysis,<sup>[8,10]</sup> is preserved in the iridium-catalyzed enantioselective transfer hydrogenation of ketones with formic acid. Additionally, in the present Ir catalysis, the pyrrolidine framework of the ligand causes an sp<sup>3</sup>-C–H/ $\pi$  interaction with the carbonyl-substituted aromatic rings, allowing efficient prochiral face selection for the reaction of various alkyl aryl ketones. The tolerance toward various ketones regardless of the steric demand of the alkyl group is a significant feature of this catalysis. Thus, we confirmed that the concept of ligand–substrate noncovalent interactions involving nonpolar sp<sup>3</sup>-C–H bonds serves as a versatile guiding principle for the design of enantioselective catalysis, the significance of which had not been previously demonstrated.

## Experimental Section

**A General Procedure for Iridium(I)-Catalyzed Transfer Hydrogenation of Ketones:** In a glove box, **L5** (2.2 mg, 0.0050 mmol) was placed in a screw vial containing a magnetic stirring bar. CPME (1 mL), [IrCl(cod)]<sub>2</sub> (1.3 mg, 0.0020 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.4 mg, 0.010 mmol) were added to the vial and the mixture was stirred at room temperature for 5 minutes to give a pale yellow solution. Formic acid (18.4 mg, 0.40 mmol) and ketone **1a** (24.0 mg, 0.20 mmol) were added sequentially. The vial was sealed with a screw cap and taken out from the glove box. After stirring for 6 h at 25 °C, the mixture was quenched with saturated K<sub>2</sub>CO<sub>3</sub> aq. and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous MgSO<sub>4</sub>. After filtration, the filtrate was evaporated under reduced pressure to give a crude mixture. Flash chromatography on silica gel (0–10% EtOAc/hexane) gave **2a** (19.7 mg, 0.16 mmol) in 82% yield. The ee value (96% ee) was determined by HPLC analysis on a chiral stationary phase: CHIRALCEL® OD-H column 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 5:95, 1.0 mL/min, 40 °C, 220 nm UV detector, retention time = 7.6 min for (*R*) isomer and 8.4 min for (*S*) isomer.

## Acknowledgements

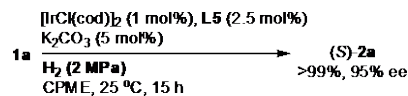
This work was supported by MEXT KAKENHI Grant Number JP15H05801 (to M.S.) and JP18H04233 (to S.M.) in Precisely Designed Catalysts with Customized Scaffolding, by JSPS KAKENHI Grant Number JP18H03906 in Grant-in-Aid for Scientific Research (A) to M.S., and by the Sakura Science Plan through “Collaborative research activity course” from JST (Number: S2018F0228129) to S.M. S.J. thanks the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Ministry of Higher Education, Science, Research and Innovation.

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