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Iridium Catalysts with f-Amphox Ligands: Asymmetric Hydrogenation of Simple Ketones

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Supporting Information

ABSTRACT: A series of modular and rich electronic tridentate ferrocene aminophosphoxazoline ligands (f-amphox) have been successfully developed and used in iridium-catalytic asymmetric hydrogenation of simple ketones to afford corresponding enantiomerically enriched alcohols under mild conditions with superb activities and excellent enantioselectivities (up to 1 000 000 TON, almost all products up to >99% ee, full conversion). The resulting chiral alcohols and their derivatives are important intermediates in pharmaceuticals.

Catalytic asymmetric hydrogenation of prochiral ketones is one of the most powerful and convenient methods to approach chiral alcohols, which are important structural motifs in many pharmaceutical products,[1] such as ezetimine, duloxetine, aprepitant, crizotinib, and montelukast (Figure 1). Owing to this great importance, much effort has been devoted to developing efficient catalytic methodologies to access chiral alcohols in the last decades.

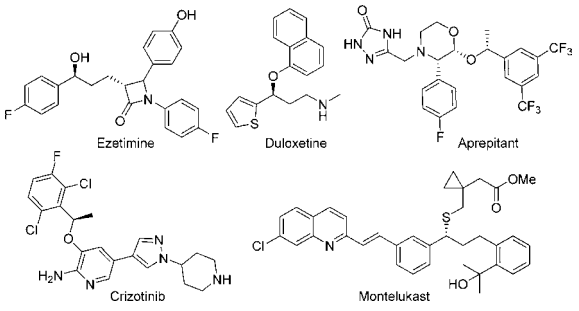

Figure 1. Related chiral pharmaceuticals containing key chiral structural motifs.

The production of enantioenriched chiral compounds was first reported by Knowles et al. in 1968.[2] The milestone research work was reported by Noyori and co-workers in the 1990s, who developed highly effective catalytic system BINAP−ruthenium−diamine complexes for the asymmetric hydrogenation of ketones.[3] The exceptionally high reactivities and enantioselectivities due to the cooperative action of the Ru−H and NH_2 group through metal−ligand bifunctional mechanism involving "NH effect". Promoted by these exciting results, major progress has been made over the past decades. We have proposed an exploration of tridentate ligands for simple ketones. In 1998, our group utilized the strategy of "NH effect" in the first chiral tridentate bis(oxazolinylmethyl)amine (ambox) ligands and applied in Ru-catalyzed transfer hydrogenation of simple ketones.[4] Later our group developed more sterically hindered chiral tridentate NNN Indan-ambox ligand, and the asymmetric hydrogenation of various ketones was achieved up to 97% ee catalyzed by chiral ruthenium−Indan−ambox complex.[5] The N−H moiety of the Indan-ambox ligand of the ruthenium catalyst is crucial for achieving high activity and enantioselectivity. Recently, Zhou and co-workers developed another tridentate spiro pyridine−aminophosphine ligands SpiroPAP.[6] Chiral alcohols were produced with up to 99.9% ee and 4 550 000 TON in the iridium−SpiroPAP catalytic system, although multistep complicated reactions were involved to synthesize these ligands. Despite the great success that has been achieved, it is still necessary to develop effective and readily available ligands especially for asymmetric hydrogenation of various simple ketones. Based on our experience in this area, we made effort to design and synthesize electron-donating and steric hindered ligands for asymmetric hydrogenation of various ketones to achieve excellent enantioselectivities and activities. We introduced a chiral ferrocenylphosphine motif to replace one oxazoline in ambox (aminobisoxazoline) ligands forming air-stable and high active ferrocene aminophosphoxazoline (f-amphox) ligands (Figure 2). Herein we have successfully developed a novel modular electron-donating tridentate ligands f-amphox and applied them in iridium-catalytic asymmetric hydrogenation of various ketones with excellent enantioselectivities and high activities.

The modular chiral f-amphox ligands were easily made via three-step reaction using the commercially available (*S*)-Ugi's

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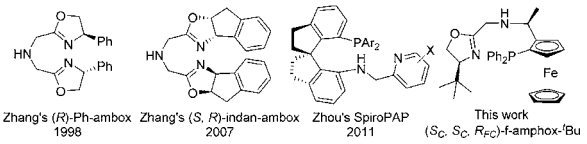
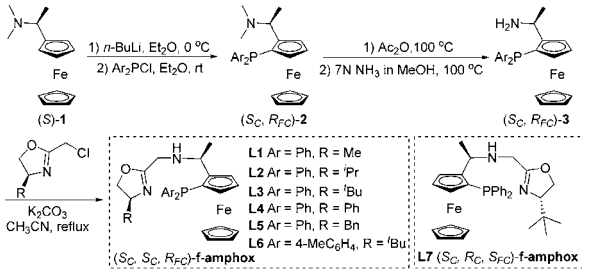


Figure 2. Examples of excellent NH−tridentate ligands in asymmetric hydrogenation of ketones.

amine (Scheme 1). A series of chiral f-amphox ligands **L1**−**L6** were efficiently prepared according to the simple synthetic

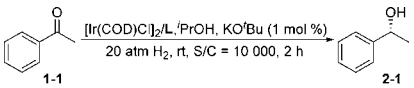
Scheme 1. Synthetic Route of f-Amphox Ligands L1−L7



route.[7−9] (S_C, R_{FC})-**3** was easily obtained[7] and subsequently reacted with various 2-chloromethyloxazoline[8] in the presence of K_2CO_3 as hydrogen chloride scavenger generating the desired f-amphox ligands **L1**−**L6** in good yields.[9] In addition, we synthesized ligand **L7**, which is the diasteroisomer of ligand **L3** to investigate the relationship between enantioselectivity and configuration of ligand.

With the chiral f-amphox ligands **L1**−**L7** in hand, we began our studies by evaluating them for asymmetric hydrogenation of acetophenone **1**−**1** serving as the model substrate with the catalyst generated *in situ* by mixing $[Ir(COD)Cl]_2$ with ligands **L1**−**L7** in ^{i}PrOH. As shown in Table 1, ligands **L1**−**L6** displayed

Table 1. Asymmetric Hydrogenation of Acetophenone 1-1 Catalyzed by Ir/L1−L7 Complexes[a]



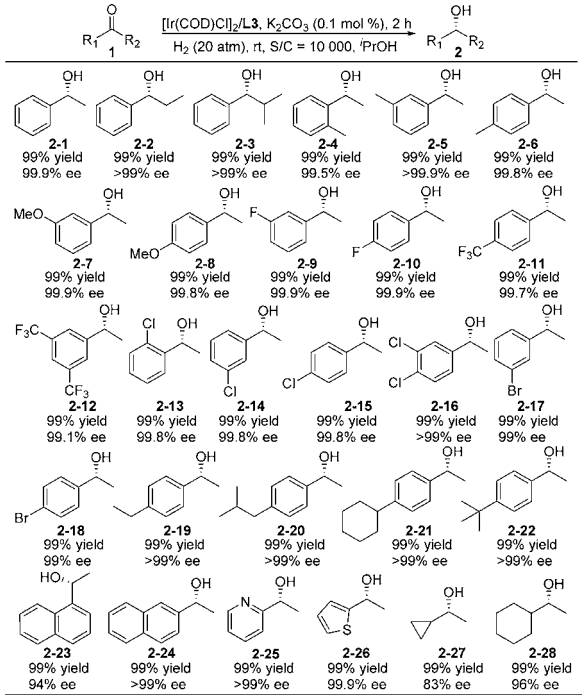
entry	ligand	conversion (%)[b]	ee (%)[c]
1	**L1**	>99	99.1
2	**L2**	>99	99.6
3	**L3**	>99	99.9
4	**L4**	>99	98.9
5	**L5**	>99	95.6
6	**L6**	65	91.8
7	**L7**	45	54.4

[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 M, 0.001 mmol % $[Ir(COD)Cl]_2$, 0.0021 mmol % ligand, [KO^{t}Bu] = 0.002 M, solvent volume = 1.0 mL, room temperature (25−30 °C). [b]Determined by GC. [c]Determined by GC on a Supelco chiral β-dex-120 solid phase.

high reactivities and excellent enantioselectivities (Table 1, entries 1−6). The ligand **L3** afforded the best result with 99.9% ee and >99% conversion (Table 1, entry 3). Ligand screening results demonstrated that the substituents on the oxazoline and P-phenyl ring had a significant effect on the enantioselectivity. Low enantioselectivity and reactivity was obtained when the ligand **L7** was applied into this transformation (Table 1, entry 7). It is shown that the configuration of the ligand is very critical for enantioselectivity and reactivity.

Encouraged by these excellent results, a study of the reaction with $[Ir(COD)Cl]_2$/ligand **L3** was performed in various solvents and bases. The results were summarized in the Supporting Information. With the optimized conditions in hand (S/C = 10 000, Ir-amphox **L3**/20 atm H_2/0.1 mol % K_2CO_3/room temperature), a series of alkyl aryl ketones were hydrogenated smoothly to get various chiral alcohols in quantitative yields with 94−99.9% ee (Scheme 2). The substrates bearing electron-

Scheme 2. Asymmetric Hydrogenation of Various Ketones with Ir-L3[a]



[a]The yield was isolated yield. ee was determined by GC or HPLC on chiral stationary phase (see the Supporting Information).

donating groups (**1**−**4** ≈ **1**−**8**, **1**−**19** ≈ **1**−**22**) and electron-withdrawing groups (**1**−**9** ≈ **1**−**18**) on the phenyl ring performed well with excellent results, and the position of the substituent groups on the phenyl group of the substrates had little influence on the reactions. It is worth noting that the reduction of heterocyclic aromatic ketones (**1**−**25** ≈ **1**−**26**) can also achieve >99% ee. To our delight, more challenging substrates aliphatic ketones, such as cyclopropyl methyl ketone (**1**−**27**) and cyclohexyl methyl ketone (**1**−**28**) were also proceeded efficiently (83%−96% ee).

As we expected, Ir-**L3** complex is very stable and highly active. When the catalyst loading was decreased to 0.0002 mol % (S/C = 500 000), the product (*R*)-**2**−**1** was obtained in >99% ee and >99% conversion within only 36 h at room temperature under an initial hydrogen pressure of 50 atm. When the catalyst loading was further lowered to 0.0001 mol % (S/C = 1 000 000), the reaction still proceeded well under 80 atm H_2 pressure and provided (*R*)-**2**−**1** in >99% ee with >99% conversion within only 48 h (Scheme 3). We found that our catalytic system Ir-amphox **L3** has more advantages than previous reported catalytic system.[10] We used K_2CO_3 as the base, which is weaker than KO^{t}Bu and owned stronger tolerance of base sensitive group. For more challenging

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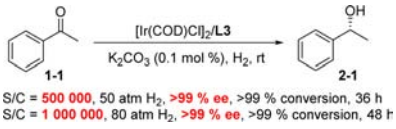
Scheme 3. Asymmetric Hydrogenation of Acetophenone 1−1 with High S/C



substrate 2-pyridyl ketone **1−25**, our catalytic system displayed higher activity and enanoselectivity and did not need to add additive borate to block pyridine. In addition, our chiral f-amphox ligands were synthesized from much more easily available materials, such as chiral amino alcohol, chlorodiphenylphosphine.

Density functional theory calculations as implemented in the Gaussian 09 series of programs[11] have been applied to gain further insights into mechanism and the origins of enantioselectivity for reactant **1−1** with ligand **L3** based on the previous study of mechanism.[12] All stationary points are optimized at B3LYP/6-31G(d)[13] level of theory (LANL08(f) basis set for Ir atom[14]). The harmonic vibrational frequencies were computed at the same level of theory to check whether the optimized structure is at an energy minimum or a transition state and to evaluate the corrections of enthalpy and Gibbs free energy. Solvent effects were computed by PCM salvation model[15] at the M05-2*X*/6-311+G(d,p)[16] level of theory (LANL08(f) basis set for Ir atom) using the gas phase optimized structures. The values given by kcal/mol are the M05-2X calculated relative free energies in DCM solvent.

As shown in Figure 3, there are two possible conformational 7 isomers of the active catalyst hydrideiridium(III) species, which is *endo*-**CP1** and *exo*-**CP4**. The isomerization barrier from **CP1** to **CP4** is only 10.9 kcal/mol via transition state **TS4**. The conformation of iridium-contained six-membered ring for **CP1** and **CP4** is boat type, although the six atoms of that ring are almost on the same plane. In conformational isomer **CP4**, the methyl group on C4 is equatorial, which leads to a strong static repulsion toward neighbored C2 and C6 moieties. Therefore, the relative free energy of **CP4** is 8.4 kcal/mol higher than its conformational isomer **CP1**. The coordination of one molecule hydrogen on complex **CP1** generates an octahedral intermediate **CP2** with 14.0 kcal/mol endothermic. The hydrogenation on the *Re*-face of N5 takes place via a concerted four-membered ring type transition state **TS1**, which is a hydride iridium intermediate **CP3**. The overall activation free energy of this step is 24.1 kcal/mol. In another case, the corresponding hydrogenation on the *Si*-face of N5 could occur from intermediate **CP4** to afford intermediate **CP6** with an activation free energy of 28.4 kcal/mol via transition state **TS6**. The computational results indicate that the formation of intermediate **CP3** is kinetically and thermodynamically favorable. The hydrogenation of acetophenone **1−1** with intermediate **CP3** could take place via transition state **TS2** or **TS3**, which forms the major product b-R or its enantioisomer **2−1′**, respectively. The relative enthalpy of **TS2** is 1.8 kcal/mol lower than that of **TS3**. Therefore, **2−1** is the major product, and the theoretical predicated ee% is 90.1%, which is a little lower than that of experimental observation. Moreover, the calculated free energy difference in gas phase is 3.0 kcal/mol, which indicates 99% ee. Therefore, the computational deviation of enatioselectivity would be attributed to the solvent effect calculation. The geometry information on **TS2** and **TS3** is shown in Figure 3. In transition state **TS2**, the lengths of forming C−H bond and breaking Ir−H bond are 1.65 and 1.79 Å, which are significantly longer and shorter than the corresponding typical single bonds, respectively. However, the lengths of the forming O−H bond and breaking N−H bond are 1.92 and 1.03 Å, respectively, which are closed to a corresponding typical intermediate **CP3** and phenylethanol with dehydrogenated intermediate **CP1**. Therefore, the hydrogenation step could be descripted as a polarized concerted hydride transfer followed by N−H···O hydrogen bond. Moreover, intrinsic reaction coordinate calculations indicate that transition state **TS2** linked the reactant acetophenone with hydrogenated proton transfer. In geometry information on transition state **TS3**, the distance between the phenyl group of reacting acetophenone and the equatorial phenyl of ligand is only

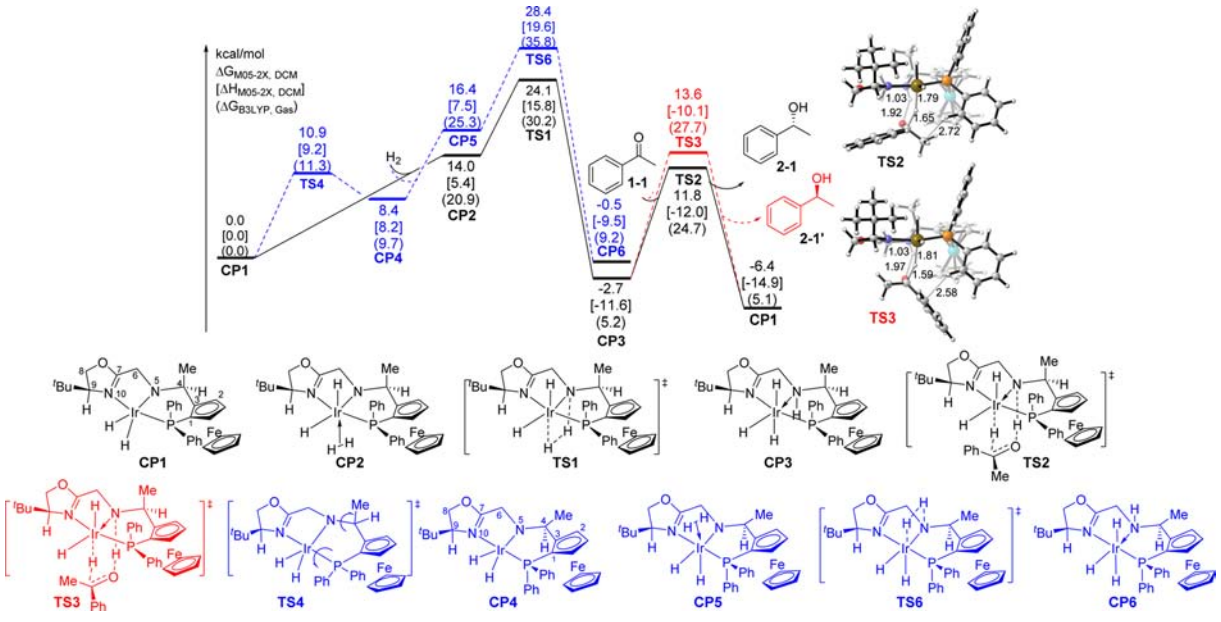


Figure 3. DFT computed energy surfaces of the indium-catalyzed asymmetric hydrogenation of acetophenone. The values given by kcal/mol are the M05-2X calculated relative free energies in DCM solvent. The values in brackets are the M05-2X calculated relative enthalpy in DCM solvent. The values in parentheses are the B3LYP calculated relative free energies in gas phase. Distances in geometry information are valued in Å.

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2.58 Å, which indicates a significant repulsion. Therefore, the relative energy of transition state **TS3** is higher than that of **TS2**.

To better illustrate the steric repulsions at different regions of hydrogenation step, a bottom-view 2D contour map along the *z*-axis of the van der Waals surface of intermediate **CP3** is plotted in Figure 4. In this map, the *z*-axis is defined as the reacting Ir−H

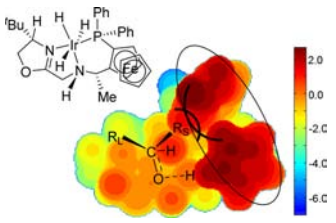

Figure 4. Bottom-view 2D contour maps of the van der Waals surface of intermediate **CP3**. Distances are valued in Å. Negative distance (blue) indicates the atoms on complex is farther away from substrate; positive distance (red) indicates the atoms on complex is closer to substrate.

bond. The 2D contour map clearly indicates that the right part is occupied by the cyclopentadinene moiety and equatorial phenyl group in ligand, which block the right part when the hydrogenation takes place. Therefore, when acetophenone reacts with intermediate **CP3**, the larger group should be arranged at left.

In summary, we have successfully developed a series of modular and electron-donating tridentate ferrocene aminophosphoxazoline ligands (f-amphox) for iridium-catalytic asymmetric hydrogenation of various simple ketones. Excellent enantioselectivities (up to 99.9% ee) and superb activities (up to 1 000 000 TON) has been achieved using Ir-f-amphox catalyst. The great performance of the reaction and the easy preparation of the catalyst make this asymmetric hydrogenation highly practical, and it should have a great impact in the field of asymmetric hydrogenation and organic chemistry. Further investigation for challenging substrates is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01290.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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