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Iridium-Catalyzed Highly Enantioselective Hydrogenation of Exocyclic α,β-Unsaturated Carbonyl Compounds

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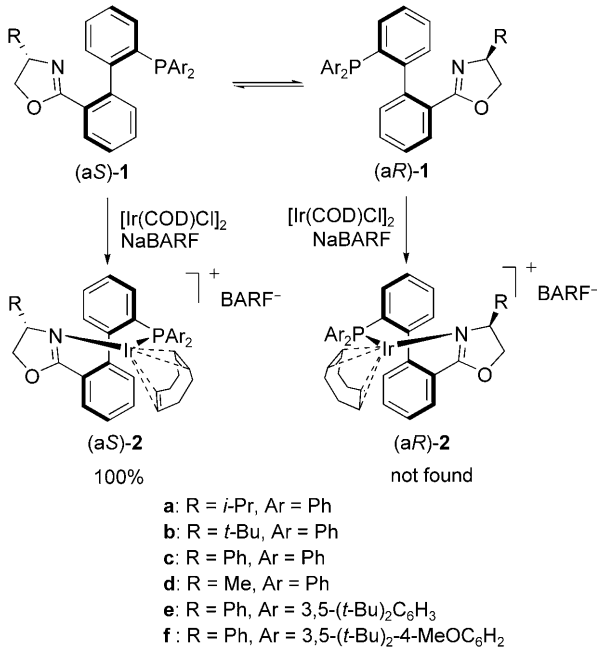
Abstract: By using the iridium complex of a phosphine-oxazoline ligand with an axis-unfixed biphenyl backbone, a highly enantioselective hydrogenation of the C=C bond of exocyclic α,β-unsaturated carbonyl compounds to afford α-chiral cyclic ketones, lactones and lactams was developed.

Keywords: asymmetric synthesis; cyclic carbonyl compounds; hydrogenation; iridium; oxazoline

Cyclic carbonyl compounds with α-chiral carbon centers are an important group of compounds in organic synthesis and medicinal chemistry.[1] For the synthesis of these optically active compounds, enzyme-mediated reactions and chemical syntheses from optically active starting materials have usually been used.[2,3] However, most of the reported methods are limited in substrate scope, and high enantioselectivity has seldom been obtained. The most straightforward and simplest approach to these compounds would be asymmetric hydrogenation of cyclic α,β-unsaturated carbonyl compounds but much less efforts have been focused on this option.[4,5] In most recent years, iridium complexes with chiral phosphine-oxazoline ligands have attracted much attention because of their easy availability and high reactivity and enantioselectivity in the hydrogenation of unfunctionalized olefins[6] or olefin substrates with less strongly coordinating groups[7–10]. In this context, Zhou found that the C=C bond of an α,β-unsaturated carboxylic acid could be hydrogenated with high enantioselectivity by using an iridium spirophosphine-oxazoline (SIPHOX) complex;[8] Bolm and Hou found that the C=C bond of α,β-unsaturated ketones can be hydrogenated with high enantioselectivity by using an iridium phosphine-oxazoline (PHOX) complex;[9] Hou further investigated the enantioselective hydrogenation of α,β-unsaturated amides by using an iridium complex derived from ferrocenylphosphine-oxazoline (Fc-PHOX).[10] However, there are few examples focused on the establishment of α-chiral carbon centers of cyclic carbonyl compounds, especially for lactones and lactams, *via* asymmetric hydrogenation.[4,9] Even in these limited examples, the asymmetric hydrogenation is strongly substrate dependent and there is no general solution for different kinds of cyclic substrates. Herein, we disclose our preliminary results of the highly enantioselective hydrogenation of exocyclic α,β-unsaturated carbonyl compounds by using an iridium complex with axis-unfixed biphenylphosphine-oxazoline ligands **1** (Scheme 1).



Scheme 1. Complexation behavior of ligands **1a–f**.

In the past decade, chiral phosphine-oxazoline ligands with an axis-fixed binaphthyl backbone were developed and showed excellent chirality transfer properties in asymmetric catalysis.[11] However, in most cases, only one of the two diastereomers of the ligands works effectively due to the configurationally matching-mismatching effect. Bearing this in mind, a novel class of phosphine-oxazoline ligands **1** with an axis-unfixed biphenyl backbone was developed by us in recent years, which exist as an equilibrium mixture of diastereomers in solution as a result of rotation around the internal bond of the biphenyl. When these ligands coordinated to Pd(II), interestingly, only one of the two possible diastereomeric complexes was formed and showed excellent enantioselectivities in Pd-catalyzed asymmetric allylic alkylation.[12] This result indicated that all of the ligands could be fully and effectively utilized in the asymmetric catalysis.

Based on the above results, the complexation behavior of our ligands **1** with $[Ir(COD)Cl]_2$ in CH_2Cl_2 at ambient temperature followed by counterion exchange with NaBARF was investigated (Scheme 1). As expected, all of the ligands **1a–f** afforded only one of the two possible diastereomeric complexes **2a–f**, respectively, according to their ^1H NMR and ^{31}P NMR spectra. The formed diastereomer **2a** was easily crystallized from chloroform/hexane and the X-ray diffraction analysis showed that it has an *S* configuration in its axial chirality (Figure 1).[13]

With these complexes in hand, the asymmetric hydrogenation of exocyclic α,β-unsaturated ketone **3a** was initially investigated by using 1 mol% of the Ir complex **2a** in toluene under 20 atm of H_2 pressure at room temperature. To our delight, it provided ketone **4a** in full conversion and 96% *ee* after 24 h (Table 1, entry 1), which indicated that the reaction preferentially reduces the C=C bond under the aforementioned conditions. Screening of the solvents revealed that toluene and dichloromethane were the more suitable solvents than TBME and MeOH in this reaction,

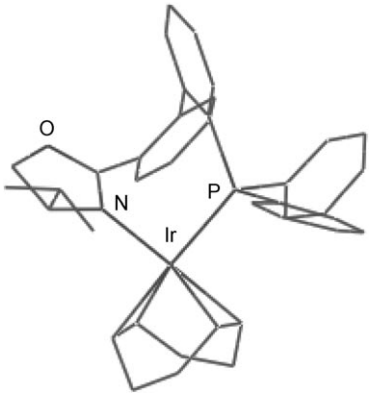
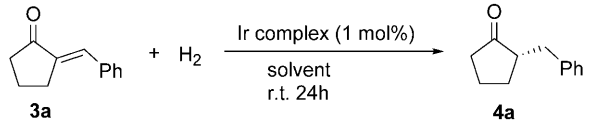


Figure 1. X-ray structure of complex (a*S*)-**2a**. The anion and hydrogen atoms are omitted for clarity.

Table 1. Optimization of the reaction conditions.[a]



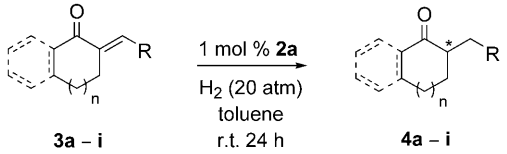
3a 4a

Entry	Complex	Solvent	Pressure [atm]	Conversion [%][b]	*ee* [%][c]
1	**2a**	toluene	20	100	96
2	**2a**	CH_2Cl_2	20	100	94
3	**2a**	TBME[d]	20	100	85
4	**2a**	MeOH	20	100	30
5	**2a**	toluene	10	85	96
6	**2a**	toluene	50	100	96
7[e]	**2a**	toluene	20	100	95
8[f]	**2a**	toluene	20	57	93
9[g]	**2a**	toluene	20	10	95
10[h]	**2a**	toluene	20	9	99
11	**2b**	toluene	20	100	82
12	**2c**	toluene	20	100	86
13	**2d**	toluene	20	100	91
14	**2e**	toluene	20	100	83
15	**2f**	toluene	20	100	78

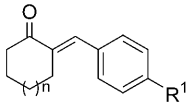
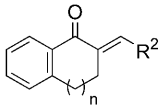
[a] *Reaction conditions:* **3a** (0.25 mmol), catalyst (1 mol%), solvent (2.0 mL). All of the reactions were carried out under hydrogen at room temperature for 24 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC using a chiral Daicel Chiralcel OJ-H column.
[d] TBME: *tert*-butyl methyl ether.
[e] Reaction time was 1 h.
[f] Catalyst loading was 0.2 mol%.
[g] Catalyst counterion was Cl^-.
[h] Catalyst counterion was PF_6^-.

while toluene showed somewhat higher enantioselectivity (Table 1, entries 1–4). The hydrogen pressure has some effect on the reactivity and little effect on the enantioselectivity (Table 1, entries 1, 5, 6). Shortening the reaction time also afforded full conversion and almost the same enantioselectivity (Table 1, entry 7). However, a lower catalyst loading gave a lower conversion and slightly decreased enantioselectivity even after 24 h (Table 1, entry 8). Moreover, a screening of catalyst counterions was carried out. When the counterions of the complex **2a** were changed to Cl^- and PF_6^-, the conversions were decreased to 10% and 9%, although the enantioselectivities went up to 95% *ee* and 99% *ee*, respectively (Table 1, entries 9 and 10). On the basis of these results, the reaction conditions described in entry 1 were chosen for screening of other Ir complexes with different substituents either on the oxazoline ring or on the phosphine phenyl ring. The results indicated that the enantioselectivity in the asymmetric hydrogenation of **3a** was greatly affected by the properties of the substituents on the oxazoline ring and the P-

Table 2. Hydrogenation of exocyclic α,β-unsaturated ketones **3a–i**.[a]



3a – i **4a – i**

Entry	Substrate		Conversion [%][b]	*ee* [%][c]
1		**3a** n = 0, R^1 = H	100	96 (*S*)
2		**3b** n = 1, R^1 = H	100	75 (*S*)
3		**3c** n = 2, R^1 = H	100	70 (*S*)
4		**3d** n = 0, R^1 = F	100	96 (–)
5		**3e** n = 0, R^1 = OMe	100	95 (–)
6		**3f** n = 0, R^2 = Ph	100	95 (–)
7		**3g** n = 1, R^2 = Ph	100	75 (+)
8		**3h** n = 0, R^2 = cyclohexane	100	67 (+)
9		**3i** n = 0, R^2 = *i*-Pr	100	71 (+)

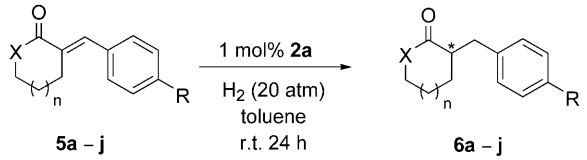
[a] *Reaction conditions:* substrate (0.25 mmol), catalyst (1 mol%), toluene (2.0 mL). All of the reactions were carried out under hydrogen at room temperature for 24 h.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC using Chiral Daicel Chiralcel OJ-H or OD-H column.

phenyl ring and ligand **1a** is the best one for the hydrogenation of **3a** (Table 1, entries 11–15).

Then, several other exocyclic α,β-unsaturated ketones **3b–i** were examined with complex **2a** under the above optimized conditions. All of the substrates afforded the corresponding chiral cyclic ketones with full conversions (Table 2). The reduction of enones **3a–c** with different ring sizes gave the corresponding ketones in 96% *ee*, 75% *ee* and 70% *ee*, respectively (Table 2, entries 1–3), which revealed that ring size has a significant effect on the enantioselectivity. Substrates **3d**, **e** with different substituents on the aryl ring were hydrogenated in 96% *ee* and 95% *ee*, respectively, which showed that the substituent pattern has little effect on the enantioselectivity (Table 2, entries 4 and 5). Substrates **3f** with an indanone skeleton and **3g** with a tetralone skeleton gave 95% *ee* and 75% *ee*, respectively (Table 2, entries 6 and 7). Substrates with aliphatic substituents of the indanone skeleton gave 67% *ee* and 71% *ee*, respectively (Table 2, entries 8 and 9).

Encouraged by the above exciting results for exocyclic α,β-unsaturated ketones, we extended the substrate scope to exocyclic α,β-unsaturated lactones and lactams. Enantiopure lactones and lactams with α-chiral carbon centers play a significant role in organic synthesis and medicinal chemistry, yet their preparation through enantioselective hydrogenation was rarely reported,[4] especially for lactones, for which only one report has appeared but which is limited to two aliphatic substrates.[4a] Hydrogenation of lactones **5a–c** gave **6a–c** in full conversions and excellent enantioselectivities of 95% *ee*, 94% *ee* and 94% *ee*, respectively (Table 3, entries 1–3). When the ring size was changed from 5- to 6-membered, the enantioselectivity decreased to 71% *ee* (Table 3, entry 4). The hydrogenation of lactam substrates was initially tested with **5e** under the above reaction conditions, and to our disappointment, it gave no conversion, probably because of its poor solubility in toluene (Table 3, entry 5). Then, the amide nitrogen atom was protected with an Ac or Bn group to improve its solubility in toluene. The hydrogenation of the resulting substrates **5f** and **5g** proceeded smoothly and excellent enantioselectivities of 97% *ee* and 98% *ee*, respectively, were obtained (Table 3, entries 6 and 7). Similar to the exocyclic α,β-unsaturated ketones and lactones, substrates **5h** and **5i** with different substituent patterns also gave an excellent enantioselectivity of 98% *ee* (Table 3, entries 8 and 9). However, the substrate with

Table 3. Hydrogenation of exocyclic α,β-unsaturated lactones and lactams **5a–j**.[a]



5a – j **6a – j**

Entry	Substrate	Conversion [%][b]	*ee* [%][c]
1	**5a** X = O, n = 0, R = H	100	95 (–)
2	**5b** X = O, n = 0, R = OMe	100	94 (–)
3	**5c** X = O, n = 0, R = F	100	94 (–)
4	**5d** X = O, n = 1, R = H	100	71 (+)
5	**5e** X = NH, n = 0, R = H	–	–
6	**5f** X = NAc, n = 0, R = H	100	97 (–)
7	**5g** X = NBn, n = 0, R = H	100	98 (–)
8	**5h** X = NBn, n = 0, R = OMe	100	98 (–)
9	**5i** X = NBn, n = 0, R = F	100	98 (–)
10	**5j** X = NBn, n = 1, R = H	100	53 (+)

[a] *Reaction conditions:* substrate (0.25 mmol), catalyst (1 mol%), toluene (2.0 mL). All of the reactions were carried out under hydrogen at room temperature for 24 h.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC using a chiral Daicel Chiralcel AD-H column.

a 6-membered ring only gave a moderate enantioselectivity (Table 3, entry 10).

In conclusion, we have developed a highly enantioselective hydrogenation of exocyclic α,β-unsaturated carbonyl compounds by using an iridium complex of phosphine-oxazoline ligands with an axis-unfixed biphenyl backbone. The C=C bond of 5-membered exocyclic α,β-unsaturated carbonyl compounds was hydrogenated with full conversions and excellent enantioselectivities. To the best of our knowledge, this is the first example of the highly enantioselective hydrogenation of exocyclic α,β-unsaturated carbonyl compounds including ketones, lactones and lactams by using the same catalyst.

Experimental Section

General Procedure for the Hydrogenation

Complex **2a** (4.0 mg, 0.0025 mmol) and substrate (0.25 mmol) were placed in a 5-mL tube equipped with a magnetic stirrer bar. This tube was then put into a nitrogen-filled autoclave. Solvent (2.0 mL) was added to the mixture under a nitrogen atmosphere. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed), and finally pressurized to 20 atm. The reaction mixture was stirred for 24 h, and then the hydrogen gas was slowly released. The conversion of the substrate was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, and the product was purified by chromatography using a petroleum/ethyl acetate mixture (10:1) as eluents. The enantiomeric excess was determined by HPLC on a Chiral Daicel Chiralcel column. The HPLC conditions and the spectral data of all compounds are provided in the Supporting Information.

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[13] **Crystallographic data for (a*S*)-2a:** $C_{70}H_{52}BF_{24}IrNOP$, $M_r = 1613.11$, $T = 293(2)$ K, orthorhombic, P2(1)2(1)2(1), $a = 12.7654(7)$ Å, $b = 14.2837(8)$ Å, $c = 37.502(2)$ Å, $\beta = 90.00(2)°$, $V = 6838.0(7)$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.567$ Mg m^{-3}, $\mu = 2.085$ mm^{-1}, 36314 reflections collected, 9927 independent reflections ($R_{int} = 0.0955$), Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0485$, $wR_2 = 0.0937$. CCDC 762042 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

