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COMMUNICATION

Design of Oxa-Spirocyclic PHOX Ligands for the Asymmetric Synthesis of Lorcaserin via Iridium-Catalyzed Asymmetric Hydrogenation

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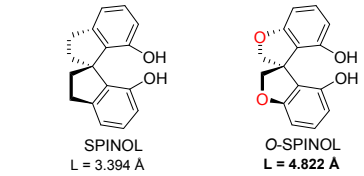
Phosphine-oxazoline (PHOX) ligands are a very important class of privileged ligands in asymmetric catalysis. A series of highly rigid oxa-spiro phosphine-oxazoline ligands (O-SIPHOX) based on O-SPINOL were synthesized efficiently, and their iridium complexes were synthesized by coordination of the ligands O-SIPHOX to $[Ir(cod)Cl]_2$ in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate (NaBArF). The cationic iridium complexes showed high reactivity and excellent enantioselectivity in the asymmetric hydrogenation of 1-methylene-tetrahydro-benzo[d]azepin-2-ones (up to 99% yield, up to 99% ee). The key intermediate of an anti-obesity drug Lorcaserin could be efficiently synthesized with this protocol.

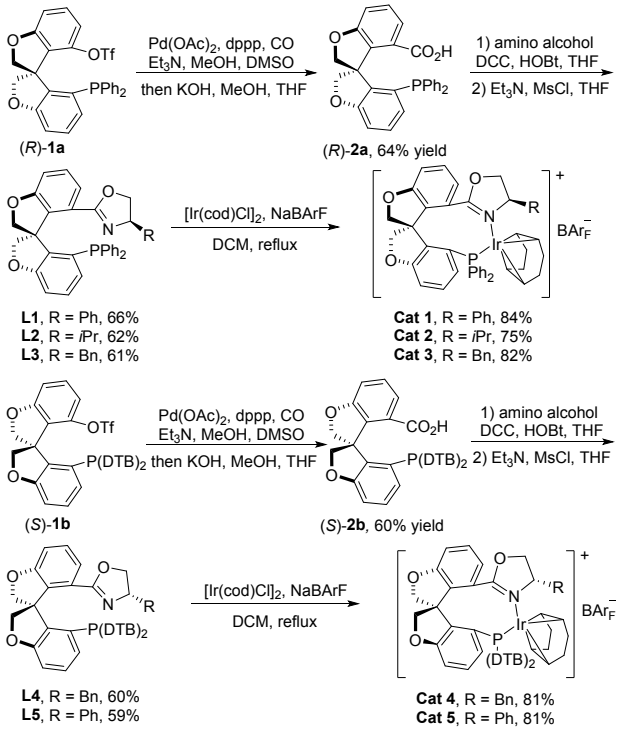
Ever since their first introduction by Helmchen,[1] Pfaltz,[2] and Williams's group[3] in 1993, phosphine-oxazoline ligands (PHOX) have found extensive applications in asymmetric catalysis,[4] and varieties of chiral phosphine-oxazoline ligands such as SimplePHOX,[5] SIPHOX,[6] SpinPHOX,[7] BPPHOX[8] and HMSI-PHOX[9] have been designed and synthesized. As the chiral analogues of the Crabtree's catalyst, one of the most recognized uses of the PHOX ligands is iridium-catalyzed asymmetric hydrogenation of unfunctionalized olefins[10] and imines.[11] In 2006, Zhou and coworkers reported the synthesis of highly rigid spiro phosphine-oxazoline ligands based on spirobiindane skeleton, termed as SIPHOX, and their application in the asymmetric hydrogenation of imines.[6] The SIPHOX ligands showed excellent reactivities and enantioselectivities for a wide range of α,β-unsaturated carboxylic acids[12] and imines.[6, 13]

In 2018, we reported the efficient synthesis of a structurally unique oxa-spirocyclic diphenol, termed as *O*-SPINOL, and the application of the *O*-SpiroPAP ligand in the dynamic kinetic resolution of Bringmann lactones.[14] Subsequently, the diphosphine ligand *O*-SDP [15] based on *O*-SPINOL was also synthesized and applied in ruthenium-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids. The introduction of oxygen atom to the spirobiindane skeleton makes a great difference on the reactivity and enantioselectivity of the resulting ligands. We envisioned that the *O*-SIPHOX ligands based on *O*-SPINOL will show different properties compared with SIPHOX.



L: the distance between the two phenolic oxygen atoms
* The data are collected from the corresponding crystal structures.

Figure 1. Comparison of the structures of SPINOL and *O*-SPINOL.



dppp: 1,3-Bis(diphenylphosphino)propane; DCC: dicyclohexyl carbodiimide; HOBt: 1-Hydroxybenzotriazole.

Scheme 1. Synthesis of the *O*-SIPHOX ligands.

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A series of *O*-SIPHOX ligands were synthesized from known compound (*R*)-**1a**[15] (**L1**-**L3**) and (*S*)-**1b**[14] (**L4** and **L5**) according to previously reported procedures (Scheme 1).[6] After carbonylation, condensation and subsequent cyclization, the *O*-SIPHOX ligands (**L1**-**L5**) were obtained in moderate yields. The iridium catalysts (**Cat 1** to **Cat 5**) were feasibly synthesized by coordination of *O*-SIPHOX to $[Ir(cod)Cl]_2$ in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate (NaBArF) in high yields.

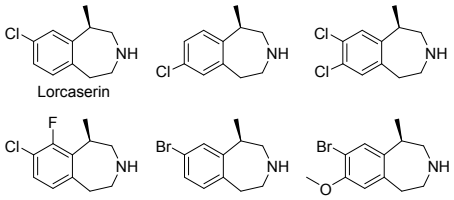
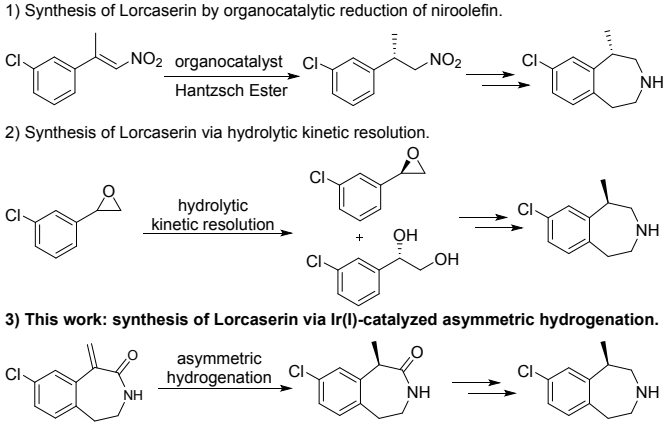


Figure 2. Structures of some 5-HT_{2C} receptor agonists for the treatment of obesity.

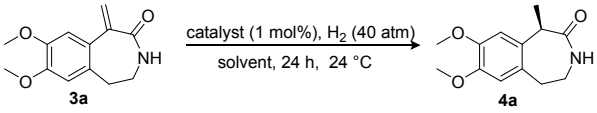
On the other hand, tetrahydrobenzazepines are widely found in many biologically active compounds and drug molecules. Among them, Lorcaserin is an anti-obesity drug developed by Arena pharmaceutical companies. Lorcaserin hydrochloride is a selective 5-HT_{2c} receptor agonist that has been approved by the US Food and Drug Administration (FDA) in 2012 as an anti-obesity drug.[16] Many anti-obesity drugs such as sibutramine, dexfenfluramine etc. were withdrawn from the market because of the risk of the heart;[17] however, Lorcaserin was found to be the best safety of currently available medications with low cardiovascular risk.[18]



Scheme 2. The development in the asymmetric synthesis of Lorcaserin.

Obesity has reached an alarming level in the world, with 13% of adults being obese and 39% being overweight.[19] The development of highly efficient and selective methods for the synthesis of Lorcaserin allows of no delay. During the last decade, many efforts have been devoted to the synthesis of Lorcaserin.[20] Industrially, Lorcaserin was synthesized by the chemical resolution of its racemates. Quantitative amount of resolving reagent was needed to obtain the optically active Lorcaserin, and the highest yield is limited to 50%. To increase the efficiency of the synthesis, some asymmetric synthetic routes were developed recently. In 2016, an asymmetric synthetic route was reported, organocatalytic reduction of nitroolefin with Hantzsch ester was utilized to the synthesis of the key intermediate. Enantiopure Lorcaserin was obtained in 8 steps, which greatly limited its practical application (Scheme 2a).[20e] In 2019, Muthukrishnan and coworkers reported a more practical synthesis of Lorcaserin with hydrolytic kinetic resolution of epoxide as the key step (Scheme 2b).[20a] Despite these advances in the asymmetric synthesis of Lorcaserin, the development of more efficient synthetic route to Lorcaserin and its derivatives is highly desirable. Herein, we report a highly efficient and enantioselective synthesis of Lorcaserin and its derivatives via iridium-catalyzed asymmetric hydrogenation of 1-methylene-tetrahydro-benzo[d]azepin-2-ones (Scheme 2c).

Table 1. Optimization of the reaction conditions.



3a 4a

entry[a]	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**Cat 1**	*i*PrOH	99	-84
2	**Cat 2**	*i*PrOH	46	-88
3	**Cat 3**	*i*PrOH	33	-75
4	**Cat 4**	*i*PrOH	50	92
5	**Cat 5**	*i*PrOH	96	87
6	**Cat 6**	*i*PrOH	26	76
7[d]	Rh(I)/**L8**	*i*PrOH	33	3
8[d]	Rh(I)/**L9**	*i*PrOH	90	71
9[d]	Rh(I)/**L10**	*i*PrOH	99	55
10[d]	Rh(I)/**L11**	*i*PrOH	38	25
11[d]	Rh(I)/**L12**	*i*PrOH	5	5
12[d]	Rh(I)/**L13**	*i*PrOH	48	0
13[d]	Rh(I)/**L14**	*i*PrOH	83	44
14[d]	Rh(I)/**L15**	*i*PrOH	74	40
15	**Cat 5**	MeOH	99	97
16	**Cat 5**	EtOH	84	97
17	**Cat 5**	DCM	74	97
18	**Cat 5**	THF	99	97
19	**Cat 5**	dioxane	99	98
20	***Cat 5***	***toluene***	***99***	***98***
21	**Cat 7**	toluene	99	90

[a] The reactions were conducted on 0.1 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC. [d] $Rh(nbd)_2BF_4$ was used as the Rh(I) precursor. THF = tetrahydrofuran, DCM = dichloromethane.

We synthesized compound **3a** according to reported procedures.[21] The optimization of the reaction conditions was conducted with compound **3a** as a model substrate, and the results were summarized in Table 1. Using *i*PrOH as solvent, we evaluated the efficacy Ir-*O*-SIPHOX catalyst in the presence of 40 atm H_2. 99% yield and 84% ee were achieved with **Cat 1** as catalyst. The yield dropped sharply for **Cat 2** and **Cat 3** (Table 1, entries 1-3). With **Cat 4** as catalyst, compound **4a** was produced in 92% ee, albeit with only 50% yield, the yield was increased to 96% for **Cat 5**, whereas, the ee was dropped to 87% (Table 1, entries 4-5). Only 26% yield and 76% ee were achieved for **Cat**

6 (Table 1, entry 6). The Rh(I)/diphosphine catalytic system was also evaluated, and the yields and enantioselectivities were not satisfactory for a wide range of electron-donating diphosphine ligands such as DuanPhos, BPE, BDPP, WudaPhos and JosiPhos (Table 1, entries 7-11). Axially chiral diphosphine ligands BINAP, SEGPHOS, BIPHEP could not give better results either (Table 1, entries 12-14). Next, we put our attention to the screening of solvents. Various protic and non-protic solvents were screened. 99% yield and 97% ee were achieved with MeOH as solvent and **Cat 5** as catalyst (Table 1, entry 15). The yield was dropped to 84% with retention of the enantioselectivity in the presence of EtOH (Table 1, entry 16). Non-protic solvents such as DCM, THF, dioxane and toluene were also evaluated (Table 1, entries 17-20), and excellent yields and enantioselectivities were achieved (99% yield and 97% ee for THF, 99% yield and 98% ee for dioxane and toluene). Toluene and dioxane were identified as the best solvents. It is noteworthy that **Cat 7**, the analogous catalyst of **Cat 5**, could only produce compound **4a** in 90% ee (Table 1, entry 21).

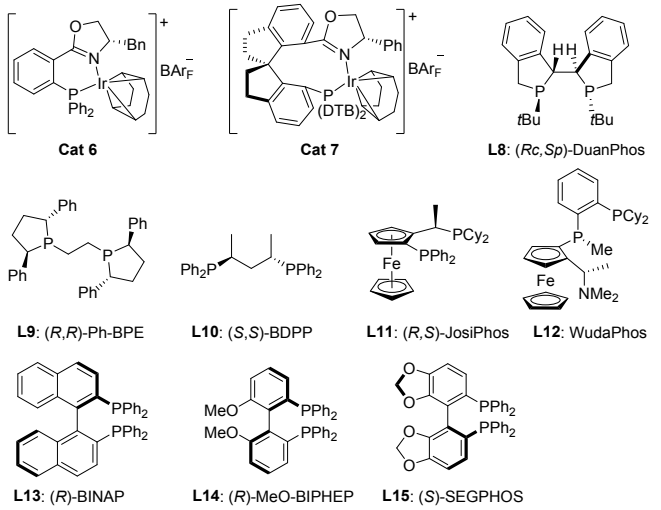
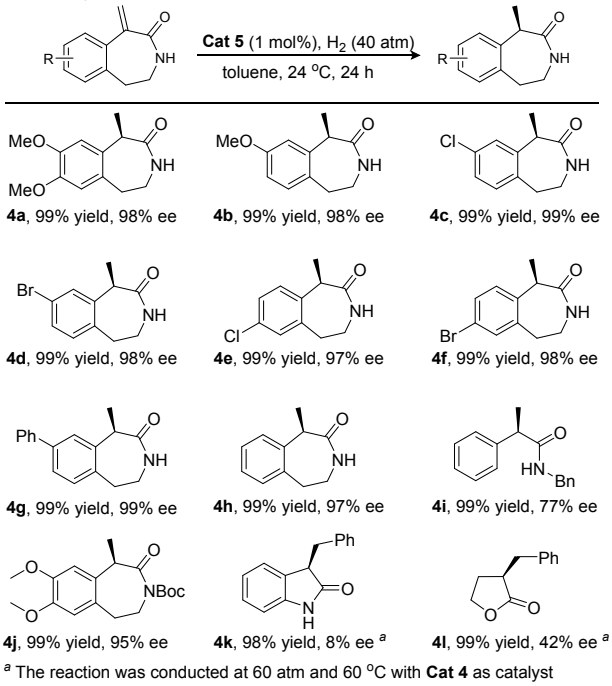


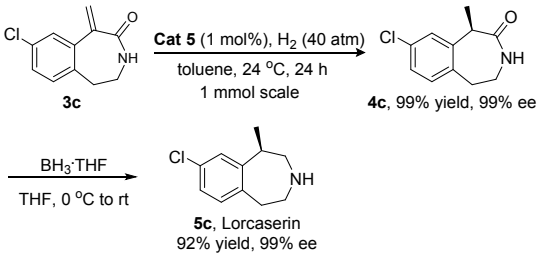
Figure 2. Structures of the catalysts or ligands that were screened.

With the optimal reaction conditions in hand, we next evaluated the substrate scope of the current reaction, and the results were summarized in Scheme 3. For the methoxy or dimethoxy substituted substrate **3a** and **3b**, 99% yield and 98% ee were achieved respectively. Product **4c**, a key intermediate of Lorcaserin, was produced in 99% yield and 99% ee, and 99% yield and 98% ee were observed for the 8-bromo substrate **3d**. The 7-Cl (**3e**, 99% yield, 97% ee) and 7-Br (**3f**, 99% yield, 98% ee) substrates were suitable substrates for the current reaction either. The reaction also worked well for 7-phenyl substrate **3g** (99% yield, 99% ee) and the unsubstituted substrate **3h** (99% yield, 97% ee). Only 77% ee was achieved for the non-cyclic substrate **3i**. The reaction also worked well for the *N*-substituted substrate **3j** (99% yield, 95% ee). Only 8% and 42% ee were achieved for the unsaturated lactam **3k** and lactone **3l** respectively at 60 °C with **Cat 4** as the catalyst, indicating that the lactam **3k** and lactone **3l** [22] were not suitable substrates for the current catalytic system possibly due to the nature of the ligand (rigidity and longer P-N distance). The absolute configuration of the product was unambiguously confirmed by the X-ray structure of compound **4e** (CCDC number 1974701). Compared with the current catalytic system, the Co/BPE system recently developed in our group is very effective for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids,[23a] however, the it has no activity for the α,β-unsaturated ester or amide. The Ni/BPE system recently developed in our group[23b] also works well for the asymmetric hydrogenation of α,β-unsaturated carbonyl compounds.[23c] The use of very electron-rich ligands was necessary to achieve high activity.

The synthetic elaboration of the current reaction was demonstrated by its application in the asymmetric synthesis of anti-obesity drug Lorcaserin. The asymmetric hydrogenation of **3c** could be operated on 1 mmol scale with retention of the yield and enantioselectivity, providing compound **4c** with 99% yield and 99% ee. Lorcaserin could be obtained after a single step reduction of intermediate **4c** according to reported procedure (Scheme 4).[24]



Scheme 3. Substrate scope.



Scheme 4. Synthetic application.

In conclusion, we have designed and synthesized a series of PHOX ligands, termed as *O*-SIPHOX based on *O*-SPINOL skeleton. The *O*-SIPHOX ligands showed excellent reactivity and enantioselectivity in iridium-catalyzed asymmetric hydrogenation of 1-methylene-tetrahydro-benzo[d]azepin-2-one derivatives, the products of which are key intermediates for

a wide range of 5-HT_{2c} receptor agonists. The anti-obesity drug Lorcaserin could be efficiently synthesized by this protocol.

ACKNOWLEDGMENT

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Conflicts of interest

The authors declare no competing financial interests.

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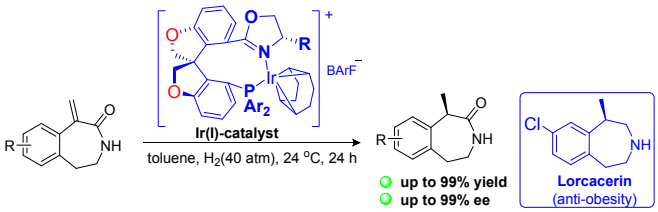

A series of highly rigid oxa-spiro phosphine-oxazoline ligands (O-SIPHOX) based on O-SPINOL were synthesized efficiently, and their iridium complexes were synthesized by coordination of the ligand O-SIPHOX to $[Ir(cod)Cl]_2$ in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate (NaBArF). The cationic iridium complexes showed high reactivity and excellent enantioselectivity in the asymmetric hydrogenation of 1-methylene-tetrahydro-benzo[d]azepin-2-ones (up to 99% yield, up to 99% ee). The key intermediate of an anti-obesity drug Lorcaserin could be efficiently synthesized with this protocol.

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