Asymmetric Synthesis

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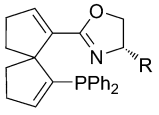
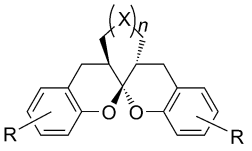
Catalytic Asymmetric Synthesis of Aromatic Spiroketals by SpinPhox/Iridium(I)-Catalyzed Hydrogenation and Spiroketalization of α,α′-Bis(2-hydroxyarylidene) Ketones**

Xiaoming Wang, Zhaobin Han, Zheng Wang, and Kuiling Ding**

Recently, the chemistry of chiral aromatic spiroketals has received much attention because they are key substructures in biologically active natural products,[1] pharmaceuticals,[2] and chiral ligands in transition-metal-catalyzed reactions.[3] Although several methods for the preparation of aromatic spiroketals have been reported,[4–8] the direct catalytic, enantioselective synthesis of aromatic spiroketals has not yet been achieved. On the other hand, transition-metal-catalyzed asymmetric hydrogenations have long held a respected position in modern organic synthesis.[9] In particular, the iridium-catalyzed asymmetric hydrogenation of the C=C bonds of either functionalized or unfunctionalized olefin derivatives has lately been an important topic in asymmetric catalysis.[10] We have recently reported a class of highly efficient iridium(I) catalyst complexes with spiro[4.4]-1,6-nonadiene-based chiral phosphine–oxazoline ligands (SpinPHOX, **1**) for the enantioselective hydrogenation of *N*-aryl or alkyl imines and α-aryl-β-substituted acrylic acids.[11] Herein, we report the first catalytic enantioselective synthesis of aromatic spiroketals **2** through the SpinPHOX/Ir^{I}-promoted asymmetric hydrogenation of α,α′-bis(2-hydroxyarylidene) ketones and spiroketalization of hydrogenation products.



SpinPHOX (**1**)



2: X = CH_2 or O
n = 0, 1, or 2

This research was inspired by the excellent performance of Ir^{I} complexes of phosphine-oxazoline ligands in the asymmetric hydrogenation of the C=C bond of α,β-unsaturated ketones independently reported by the groups of Bolm[12a] and Hou[12b]. We also found that SpinPHOX/Ir^{I} demonstrated excellent enantioselectivity and catalytic activity in the hydrogenation of α,α′-bis(2-methoxybenzylidene)-cyclohexanone (> 99 % *ee*, d.r. = 92:8).[13] This result encouraged us to attempt the catalytic asymmetric synthesis of aromatic spiroketals **2** by sequential hydrogenation of α,α′-bis(2-hydroxyarylidene) ketones followed by spontaneous spiroketalization of the optically active hydrogenation products. After screening a variety of Ir^{I} catalysts to check the viability of this transformation,[14] we decided to employ chiral Ir^{I} complexes of phosphine–oxazoline ligands to catalyze the hydrogenation of prochiral α,β-unsaturated ketone **3a**, which bears two hydroxy groups. In principle, three diastereomeric spiroketals might be formed (*cis*-**2a**, *trans*-**2a,** and *trans*-**2a′**; Table 1). As shown in entry 1, we were pleased to find that the hydrogenation of **3a**, in the presence of 1 mol % of Ir^{I}-(*R*,*S*)-**1a**, proceeded smoothly to give the corresponding, optically active spiroketal *trans*-**2a** in 83 % yield, with a d.r. of 87:13 (*trans*-**2a**/*cis*-**2a**) and 87 % *ee* for the *trans* isomer, thus demonstrating the feasibility of this catalytic, asymmetric hydrogenation strategy for the synthesis of optically active spiroketals. The structures of both *cis*-**2a** and *trans*-**2a** were confirmed by X-ray diffraction analysis (Figure 1).[20] However, *trans*-**2a′** was not observed in the ^{1}H NMR spectrum of the crude product mixture, indicating that the diastereoselectivity of the spiroketalization is completely controlled by the chirality of the *trans*-hydrogenated intermediate.

With these initial results in hand, we turned to optimization of the Ir^{I} catalysts by screening a list of chiral phosphine–oxazoline ligands, including PHOX and SpinPHOX. As summarized in Table 1, the chirality of the spiro backbone of the SpinPHOX ligands plays a dominant role in determining the sense of the asymmetric induction (entries 1–10). Moreover, the substituent on the oxazoline fragment also has a substantial impact on the levels of asymmetric induction and catalytic activity. Ir^{I}/(*S*,*S*)-**1c** turned out to be optimal among the catalysts screened, in terms of the efficiency and selectivity of the reaction, leading to formation of (−)-**2a** in 92 % yield with 98:2 d.r. and greater than 99 % *ee* (entry 6). On the other hand, hydrogenation with catalyst Ir^{I}/(*R*,*S*)-**1e** afforded (+)-**2a** with 96:4 d.r. and greater than 99 % *ee* of the major isomer, albeit with a lower yield (79 %; entry 9). When Pfaltz's Ir^{I}/PHOX catalysts (R = *t*Bu, *i*Pr; entries 11, 12) were applied, Ir^{I}/*i*Pr-PHOX was found to be ineffective under the reaction conditions (entry 12), while Ir^{I}/*t*Bu-PHOX afforded excellent enantioselectivity (> 99 % *ee*), but with only modest activity (entry 11).

[*] X. M. Wang, Dr. Z. B. Han, Dr. Z. Wang, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P. R. China)
E-mail: kding@mail.sioc.ac.cn

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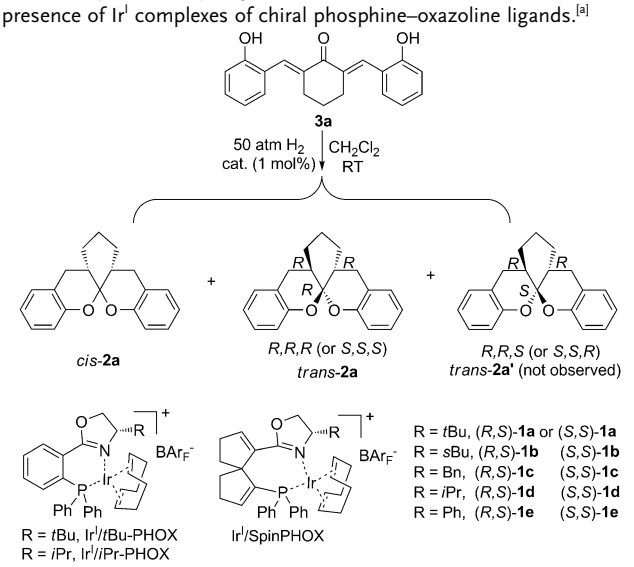
Table 1: Asymmetric hydrogenation and spiroketalization of **3a** in the presence of Ir^{I} complexes of chiral phosphine–oxazoline ligands.[a]



Entry	Catalyst	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ir^{I}/(*R*,*S*)-**1a**	83	87:13	87(+) (15)
2	Ir^{I}/(*S*,*S*)-**1a**	14	54:46	60(−) (1)
3	Ir^{I}/(*R*,*S*)-**1b**	91	95:5	84(+)
4	Ir^{I}/(*S*,*S*)-**1b**	80	83:17	84(−) (4)
5	Ir^{I}/(*R*,*S*)-**1c**	91	91:9	75(+) (12)
6	Ir^{I}/(*S*,*S*)-**1c**	92	98:2	>99(−)
7	Ir^{I}/(*R*,*S*)-**1d**	0	–	–
8	Ir^{I}/(*S*,*S*)-**1d**	73	75:25	81(−) (3)
9	Ir^{I}/(*R*,*S*)-**1e**	79	96:4	>99(+)
10	Ir^{I}/(*S*,*S*)-**1e**	31	75:25	98(−) (5)
11	Ir^{I}/*t*BuPHOX	24	93:7	>99(+)
12	Ir^{I}/*i*PrPHOX	0	–	–

[a] Reaction conditions: **3a** (0.1 mmol), Ir^{I} catalyst (0.001 mmol, 1 mol%), H_2 (50 atm), CH_2Cl_2 (2 mL), room temperature for 24 h. [b] Yield of isolated *trans*-**2a.** [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC for *trans*-**2a**. The *ee* values of the corresponding *cis*-**2a** are given in parentheses.

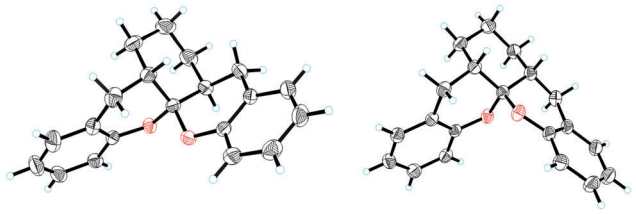
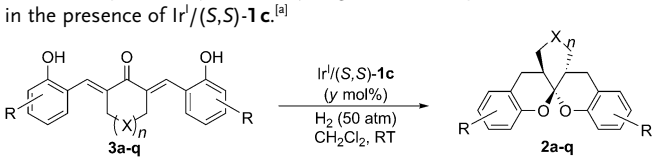


Figure 1. X-ray structures of *trans*-**2a** (left) and *cis*-**2a** (right). C gray, H blue, O red.

Having established complex Ir^{I}/(*S*,*S*)-**1c** as the optimal catalyst, we next examined its adaptability in the asymmetric hydrogenation of various α,α′-bis(2-hydroxyarylidene) ketones. As shown in Table 2, a number of α,α′-bis(2-hydroxyarylidene) cyclohexanones (**3a**–**3o**) can be readily hydrogenated, followed by spiroketalization, to afford the corresponding optically active, aromatic spiroketals in high yields with excellent diastereo- and enantioselectivities. The reaction proceeded well with substrates having *ortho*-, *meta*-,

Table 2: Sequential asymmetric hydrogenation and spiroketalization of **3** in the presence of Ir^{I}/(*S*,*S*)-**1c**.[a]



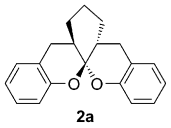
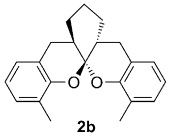
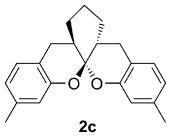
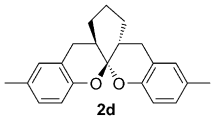
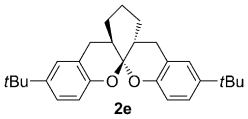
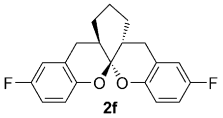
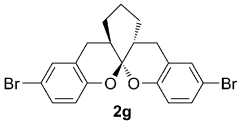
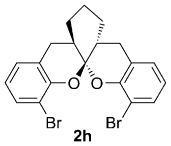
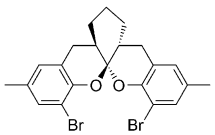
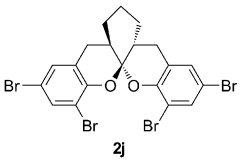
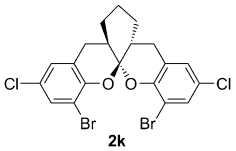
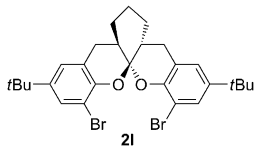
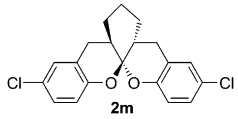
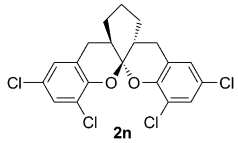
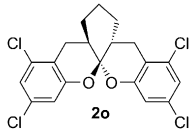
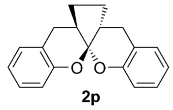
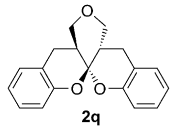
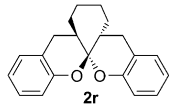
Entry	Product	*y*	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 **2a**	1	92	98:2	>99
2	 **2b**	1	94	95:5	98
3	 **2c**	1	92	93:7	>99
4	 **2d**	2	90	92:8	>99
5	 **2e**	3	81	97:3	98
6	 **2f**	3	90	97:3	95
7	 **2g**	2	88	98:2	>99
8	 **2h**	1	93	94:6	>99
9	 **2i**	1	96	98:2	>99
10	 **2j**	5	92	94:6	>99
11	 **2k**	3	86	98:2	>99

Table 2: (Continued)

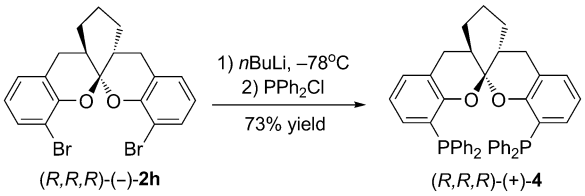
Entry	Product	γ	Yield [%][b]	d.r.[c]	*ee* [%][d]
12	 **2l**	3	85	95:5	>99
13	 **2m**	1	91	95:5	98
14	 **2n**	1	95	98:2	>99
15	 **2o**	3	85	89:11	96
16[e]	 **2p**	3	83[f]	66:34	26
17	 **2q**	3	85[f]	75:25	96
18[e]	 **2r**	3	81[f]	66:34	>99

[a] Reaction conditions, unless otherwise stated: substrate (0.1 mmol), catalyst Ir^{I}/(*S*,*S*)-**1c** (1–5 mol%), CH_2Cl_2 (2 mL), room temperature for 24 h. [b] Yield of isolated *trans* product. [c] d.r. = *trans*/*cis*, determined by ^1H NMR spectroscopy. [d] The *ee* value of the *trans* isomer was determined by chiral HPLC. [e] Catalyst Ir^{I}/(*R*,*S*)-**1a** was used. [f] The total yield of *cis* and *trans* products.

or *para*-methyl groups on the phenyl rings and gave the corresponding products **2b–d** in 90–94% yield with 98–>99% *ee*, indicating the high adaptability of the catalyst to variation in the steric environment of the substrates.

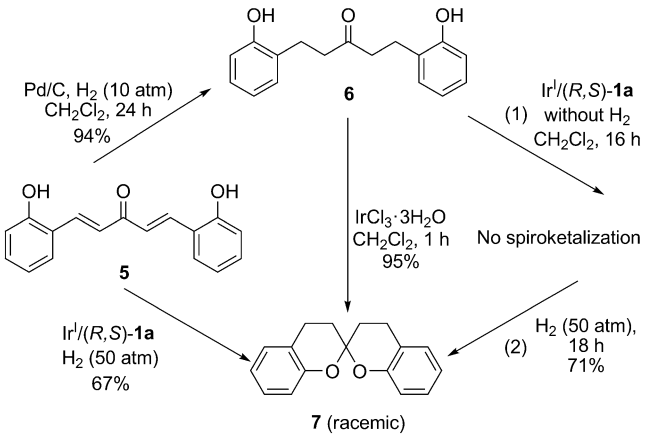
Electron-donating or -withdrawing substituents on the phenyl ring of the substrates have little impact on the yield and enantioselectivity of the reaction. The introduction of halogen substituents, in particular chloro or bromo variants, onto the substrates allows for direct construction of the corresponding halogen-substituted, enantioenriched, aromatic spiroketals **2f–o** (95–>99% *ee*), thus providing an excellent opportunity for further modification of the spiroketal motifs. The absolute configuration of (−)-**2h** was established to be (*R*,*R*,*R*) by X-ray crystal diffraction analysis. The absolute configurations of the analogous products were deduced by comparing their CD spectra with that of (*R*,*R*,*R*)-(−)-**2h**.[13] Finally, the effect of the cycloketone moiety of the substrates on the catalytic reaction was investigated for cyclopentanone, tetrahydropyran-4-one, and cycloheptanone derivatives **3p–r**. As shown in Table 2, catalyst Ir^{I}/(*S*,*S*)-**1c** showed moderate activity in the hydrogenation of **3q** (with a tetrahydropyran-4-one skeleton) to give **2q** in 85% yield. Although the diastereoselectivity was only modest (75:25), the enantiomeric excess of the major diastereomer still remained high (96% *ee*). Similarly, the hydrogenation of **3r** (with a cycloheptanone backbone) gave the corresponding spiroketal (+)-**2r** in 80% yield with a 17:83 d.r. and 98% *ee* of the minor *trans* isomer. Alternatively, the use of catalyst Ir^{I}/(*R*,*S*)-**1a** afforded (−)-**2r** in 81% yield with a 66:34 d.r. and more than 99% *ee* of the major *trans* isomer. Although no reaction occurred in the hydrogenation of cyclopentanone derivative **3p** with catalyst Ir^{I}/(*S*,*S*)-**1c** (3 mol%), catalyst Ir^{I}/(*R*,*S*)-**1a** was effective, affording the corresponding spiroketal (+)-**2p** in 83% yield, albeit with poor diastereo- and enantioselectivity.

To demonstrate the potential of this highly efficient catalytic asymmetric reaction, product **2h** was employed for the preparation of a new type of spiroketal-based diphosphine ligand **4**. As showed in Scheme 1, enantiopure (*R*,*R*,*R*)-(+)-**4** could be readily obtained in 73% yield by a one-step transformation from (*R*,*R*,*R*)-(−)-**2h**, providing a facile and practical approach to the access of chiral diphosphine ligands, which might be useful for asymmetric catalysis.[15]



Scheme 1. Preparation of the chiral diphosphine ligand **4.**

To gain more information on the catalytic process, bis-(phenol) product **6**, obtained by hydrogenation of **5** using Pd/C as catalyst, was further treated with 1 mol% of catalyst Ir^{I}/(*R*,*S*)-**1a** in CH_2Cl_2 at room temperature for 16 h in the absence of H_2 (Scheme 2).[16] No spiroketalization was observed under these conditions. However, 18 h after introduction of H_2 (50 atm) to the reaction system, spiroketaliza-



Scheme 2. Experimental studies on plausible reaction pathways in the catalytic synthesis of aromatic spiroketals.

tion product **7** was isolated in 71% yield, which is close to the results obtained from direct hydrogenation of **5** using Ir^I/(*R*,*S*)-**1a** as catalyst. On the other hand, the direct use of $IrCl_3 \cdot 3H_2O$ (10 mol%) as a catalyst for the spiroketalization of **6**, in the absence of hydrogen, afforded **7** in 95% yield (Scheme 2). These results imply that the spiroketalization was probably promoted by an Ir^{III} species resulting from a reaction between H_2 and the Ir^I precatalyst. It is well known that chiral dihydroxy ketones can be readily cyclized in the presence of Lewis or Brønsted acids to form spiroketals.[17] However, the chiral α carbon atoms of the ketone will easily undergo racemization under acidic conditions. In fact, this racemization did occur when the cyclization of the hydrogenation product (with >99% *ee*) of α,α′-bis(2-methoxybenzylidene)cyclohexanone was carried out by demethylation with BBr_3, which was followed by spontaneous spiroketalization. The major spiroketalization product isolated was racemic *cis*-**2a** (71%), while the expected, optically active *trans*-**2a**, with an enantiomeric excess of 15%, constitutes only 10% of the product mixture.[13] Although we cannot rule out the possibility of Brønsted acid promotion of the diastereoselective spiroketalization of diphenolic ketones, some kind of high-valent iridium species seems more likely to be involved; both the use of various Ir^I or Ir^{III} species as Lewis acids for electrophilic activation[18] and the acidity of Ir–H intermediates in hydrogantion systems[19] are well known. Finally, as shown in entry 1 of Table 1, *cis*-**2a**, resulting from the *cis* hydrogenation intermediate (*meso* isomer) in the hydrogenation of **3a**, has an *ee* value of 15%. This result is evidence for the involvement of a chiral iridium species in the spiroketalization reaction.

In conclusion, we have developed the first catalytic, enantioselective synthesis of aromatic spiroketals **2** through the asymmetric hydrogenation of α,α′-bis(2-hydroxyarylidene) ketones and subsequent spiroketalization of the resulting hydrogenated, bisphenolic ketones using Ir^I/SpinPHOX as catalyst. The iridium complexes were found to play a dual catalytic role in the reaction, acting as catalysts for both the hydrogenation of C=C bonds and the spiroketalization of the hydrogenated ketone-bearing bis(phenol) moieties without racemization of the chiral α-carbon centers. The present methodology provides an efficient synthesis of optically active aromatic spiroketals and will stimulate future work on the synthesis and application of aromatic spiroketal-based chiral functional molecules.

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Keywords: asymmetric catalysis · hydrogenation · iridium · P,N ligands · spiroketals

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