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Practical Asymmetric Catalytic Synthesis of Spiroketals and Chiral Diphosphine Ligands

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This article is dedicated to Professor Irina Petrovna Beletskaya for her contribution to metal-catalyzed reactions.

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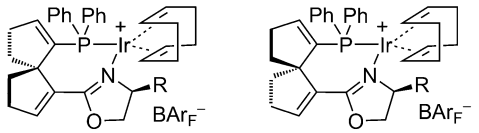
Abstract: A practical procedure has been developed for efficient synthesis of chiral aromatic spiroketals and the relevant diphosphine ligands. The procedure includes first asymmetric hydrogenation of readily available α,α′-bis(2-benzyloxyarylidene) ketones catalyzed by the Ir(I)/SpinPHOX (*S*,*S*)-**1a** (0.5–1 mol%) and subsequent hydrogenative deprotection of the resultant benzyl ethers catalyzed by palladium on carbon (Pd/C), as well as simultaneous spiroketalization of the corresponding diphenolic ketones by (*S*,*S*)-**1a** in one pot. The corresponding chiral aromatic spiroketals (*R*,*R*,*R*)-**4a–j** have been obtained in high yields (77–94%) with good diastereoselectivities (*trans*/*cis* = 81/19 to 96/4), and excellent enantioselectivities for the *trans* products (97–>99% *ee*). In addition, the reaction of aromatic spiroketal difluoride (*R*,*R*,*R*)-**4b** with potassiodiarylphosphide ($KPAr_2$) in refluxing tertahydrofuran (THF) has also provided an alternative and practical synthesis of chiral spiroketal-based diphosphine (SKP) ligands in 78–95% yields on multigram scale.

Keywords: asymmetric catalysis; diphosphine ligands; hydrogenation; iridium; spiroketals

Introduction

The aromatic spiroketals have attracted considerable attention because of their unique structural motifs occurring in many bioactive natural products,[1] pharmaceuticals,[2] and ligands in transition metal-catalyzed reactions.[3] Despite the fact that numerous approaches have been developed for the synthesis of various spiroketals,[4–8] the direct catalytic enantioselective synthesis of chiral spiroketals is only a recent event and documented examples are still rather limited so far.[9–13] We have recently developed the first catalytic enantioselective synthesis of aromatic spiroketals by a tandem hydrogenation and spiroketalization of α,α′-bis(2-hydroxyarylidene) ketones using Ir(I)/SpinPHOX **1**[14] (Figure 1) as the catalyst.[10] This methodology led to the development of a type of spiroketal-based diphosphine ligand (SKPs),[15] which demonstrated excellent performance in Pd-catalyzed asymmetric allylic amination of a variety of racemic Morita–Baylis–Hillman adducts[3f] and Au(I)-catalyzed stereoselective cyclopropanation of olefins with diazooxindoles.[3j] List and co-worker independently reported an elegant example of spiroacetal synthesis *via* a catalytic asymmetric spiroketalization of various hydroxyl enol ethers using structurally confined chiral imidodiphosphoric acids as the catalysts.[11] A similar procedure using BINOL-derived chiral phosphoric acids as the catalysts for the stereoselective acetalization various achiral and chiral cyclic enol ethers have also been reported by Nagorny and co-workers.[12] Very recently, Gong et al. developed a gold(I)/chiral phosphoric acid relay catalysis for highly efficient



R = Bn, (*S*,*S*)-**1a**
R = Ph, (*S*,*S*)-**1b**
R = *s*-Bu, (*S*,*S*)-**1c**
R = *i*-Pr, (*S*,*S*)-**1d**

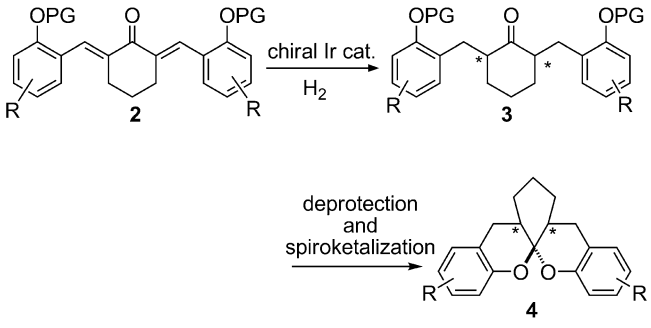
R = Bn, (*R*,*S*)-**1a**
R = Ph, (*R*,*S*)-**1b**
R = *s*-Bu, (*R*,*S*)-**1c**
R = *i*-Pr, (*R*,*S*)-**1d**

Figure 1. Ir(I)/SpinPHOX catalysts (*S*,*S*)- and (*R*,*S*)-**1a–d**.

access to aromatic spiroacetals from a three-component reaction of salicylaldehydes, anilines, and alkynols.[13]

Although our previously reported catalytic system has provided an efficient synthesis of a variety of optically active aromatic spiroketals,[10] the methodology still suffers from some limitations. Specifically, the α,α′-bis(2-hydroxyarylidene) substrates bearing strongly electron-donating substituents on the phenyl rings were found to be difficult to prepare *via* the direct aldol condensation of the corresponding salicylaldehydes and cyclohexanone, thus limiting the bis(2-hydroxyarylidene) substrate scope in the reaction. Moreover, the catalyst loadings employed in the hydrogenation–spiroketalization were usually high (1–5 mol%) for certain substrates. Herein, we wish to report an improved method for the catalytic enantioselective synthesis of aromatic spiroketals with special attention on the efficient access to the aromatic spiroketals with electron-donating substituents. Meanwhile, an alternative and practical approach for the synthesis of chiral spiroketal-based diphosphine ligands (SKPs) on the multigram scale has also been developed.

With regards to the limitations in our previous protocol, we speculated that both the free phenolic OH groups and the electron-donating groups in the salicylaldehydes might negatively influence their aldol reactivity towards the ketone substrates. Furthermore, the purification of resultant α,α′-bis(2-hydroxyarylidene) substrates seems also a challenging issue because of their strong polarities and poor crystalline properties. In this context, we envisioned that modification of the OH sites with suitable protecting groups[16] might circumvent the problems. Such a protecting group (PG) should allow for their ready synthesis and separation, high diastereo- and enantioselective hydrogenation (from **2** to **3**), as well as facile deprotection and subsequent spiroketalization to the corresponding enantioenriched aromatic spiroketals **4** (Scheme 1).



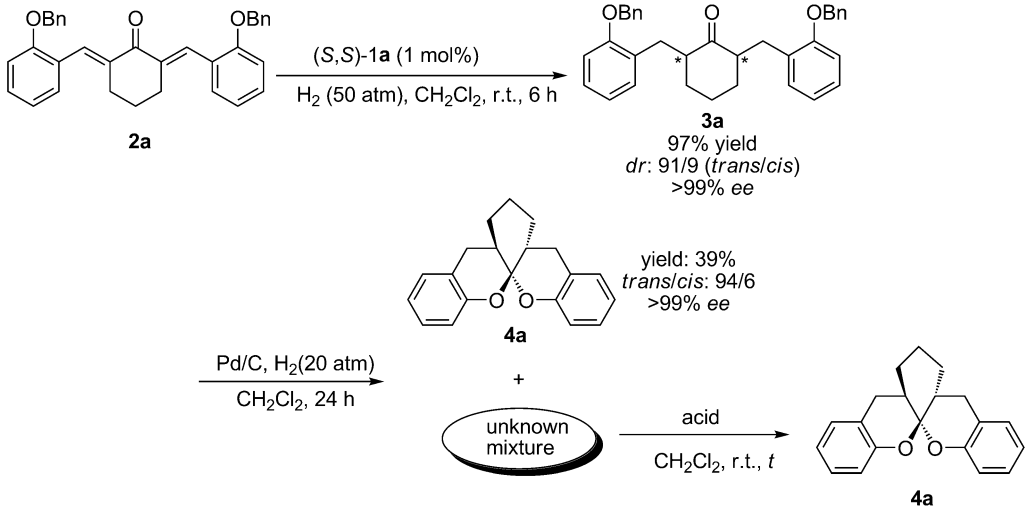
Scheme 1. Proposed synthesis of spiroketals (**4**) *via* asymmetric hydrogenation of protected bis(2-hydroxyarylidenes (**2**) followed by deprotection–spiroketalization of **3**. PG = protecting group.

Results and Discussion

We have previously examined the reaction of α,α′-bis(2-methoxyarylidene) ketone, a substrate protected by the methyl group, using the afore-mentioned strategy.[10] Although the hydrogenation catalyzed by (*S*,*S*)-**1a** proceeded smoothly to give the corresponding product in 90% yield with a diastereomeric ratio (*dr* = *trans*/*cis*) of 92:8 and 99% *ee* for the *trans* isomer, the subsequent demethylation–spiroketalization using BBr_3 proved to be not successful, resulting in only a modest yield (10%) of *trans* spiroketal product with a low *ee* value (15%).[10] Accordingly, we moved to test the viability of using TBS-protected substrate **S2** in the synthesis (for details, see the Supporting Information). In this case, the hydrogenation of **S2** proceeded smoothly as well, to afford the corresponding hydrogenation product **S3** in high yield (94%) with excellent diastereoselectivity (*trans*/*cis* = 18/1) and nearly perfect chiral induction (>99% *ee*). Unfortunately, subsequent attempts to desilylate **S3** with HF·pyridine, $Et_3N{\cdot}3HF$, $BF_3{\cdot}OEt_2$, or TBAF led to an intractable mixture in each case, from which neither the desilylated product nor the targeted acetal **4a** could be isolated (see the Supporting Information).

Gratifyingly, the results obtained with benzyl-protected bis(2-hydroxyarylidene) **2a** proved to be promising as shown by the results summarized in Table 1. As expected, the hydrogenation of **2a** in the presence of (*S*,*S*)-**1a** afforded **3a** in excellent yield (97%) with high diastereoselectivity (*trans*/*cis* = 91/9) and excellent *ee* (>99%). Subsequent Pd/C-catalyzed hydrogenative deprotection of isolated **3a** resulted in only the partial formation of the spiroketal product (*R*,*R*,*R*)-**4a** in 39% yield and nearly enantiopure *trans*-isomer, together with an unidentifiable mixture that may be composed of the bisphenolic product, hemiketals, and some tautomers formed thereof. Obviously, the presence of Pd/C catalyst alone was not effective enough for the clean transformation of the debenzylation product to **4a**. It is well-known that Lewis or Brønsted acids can significantly promote the cyclization of chiral dihydroxy ketones and analogues to spiroketals.[4] Accordingly, several acids including Brønsted acid $TsOH{\cdot}H_2O$ or Lewis acidic $IrCl_3{\cdot}3H_2O$ or $BF_3{\cdot}OEt_2$ were tested by addition into the unknown mixture mentioned above. Indeed, the use of the acids resulted in a complete transformation of the mixture to the target spiroketal (*R*,*R*,*R*)-**4a**, although HOAc was found to be less effective for the reaction even after a prolonged reaction time (24 h, entry 4). While both $TsOH{\cdot}H_2O$ and $IrCl_3{\cdot}3H_2O$ led to (*R*,*R*,*R*)-**4a** with a high *dr* ratio (93/7 and 95/5, respectively) and >99% *ee* for the *trans*-isomer (entries 1 and 2), the *dr* value using $BF_3{\cdot}OEt_2$ declined dramatically to 44:56 (entry 3), presumably caused by B(III)-

Table 1. Asymmetric hydrogenation of **2a** and hydrogenative debenzylation and spiroketalization of **3a**.



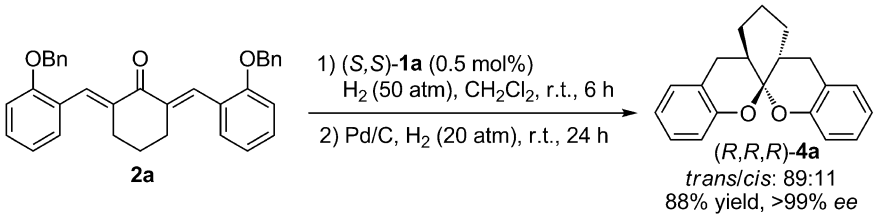
Entry	Acid	Time *t* [h]	Conversion[a] [%]	*dr*[b]	*ee*[c] [%]
1	$TsOH{\cdot}H_2O$	1	> 99	93:7	> 99
2	$IrCl_3{\cdot}3H_2O$	10	> 99	95:5	> 99
3	$BF_3{\cdot}OEt_2$	1	> 99	44:56	97
4	HOAc	24	0	–	–

[a] Determined by ^1H NMR.
[b] *dr* = *trans*/*cis*, determined by ^1H NMR.
[c] Determined by chiral HPLC for *trans*-**4a**.

induced enolization–isomerization of the ketonic substrates during the cyclization. $TsOH{\cdot}H_2O$ turned out to be optimal for this transformation, leading to the clean transformation to spiroketal (*R*,*R*,*R*)-**4a** with excellent *dr* and > 99 % *ee* in 1 h.

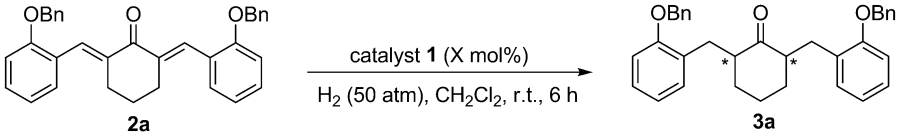
In our previous work on the catalytic enantioselective synthesis of aromatic spiroketals,[10] the Ir complexes were found to play a dual role in the reaction, i.e., to catalyze the asymmetric hydrogenation of α,α′-bis(2-hydroxyarylidene)s and to promote the spiroketalization of the resulting hydrogenated bisphenolic ketones as well. The spiroketalization was proposed to be induced either by the high-valent Lewis acidic Ir species[17] or by the acidic Ir–H intermediates[18] generated in the reaction systems. For the reaction of benzyl-protected bis(2-hydroxyarylidene) **2a**, we further explored the possibility to effect the second use of the Ir complex (*S*,*S*)-**1a** for the acceleration of spiroketalization of the dihydroxy ketone generated from the subsequent Pd/C-catalyzed hydrogenative debenzylation step. Thus, the reaction mixture from the (*S*,*S*)-**1a**-catalyzed hydrogenation of **2a**, without isolation of the intermediate product **3a** and removal of catalyst (*S*,*S*)-**1a**, was directly submitted to the Pd/C-catalyzed hydrogenative debenzylation and spiroketalization. In this case, the corresponding spiroketal was obtained in 88% isolated yield with 89:11 *dr* and > 99 % *ee*, indicating that such a one-pot procedure can provide an efficient access to enantioenriched spiroketals (Scheme 2).

Encouraged by these preliminary results, we switched to screen the chiral Ir(I)/SpinPHOX catalysts (*S*,*S*)- and (*R*,*S*)-**1a–d** (Figure 1) for the asymmetric hydrogenation of **2a**. The reactions were conducted in dichloromethane for 6 h under a hydrogen pressure of 50 atm, and the results are shown in



Scheme 2. One-pot procedure for the synthesis of (*R*,*R*,*R*)-**4a**.

Table 2. Catalyst screening for the asymmetric hydrogenation of α,α′-bis(2-benzyloxyarylidene) ketone **2a**.[a]



2a **3a**

Entry	Catalyst (X mol%)	Conversion[b] [%]	*dr*[c]	Yield[d] [%]	*ee*[e] [%]
1	(*S,S*)-**1a** (1)	>99	91:9	87	>99 (−)
2	(*R,S*)-**1a** (1)	69	83:17	51	>99 (+)
3	(*S,S*)-**1b** (1)	>99	56:44	44	>99 (−)
4	(*R,S*)-**1b** (1)	77	84:16	62	>99 (+)
5	(*S,S*)-**1c** (1)	>99	82:18	81	>99 (−)
6	(*R,S*)-**1c** (1)	>99	90:10	80	>99 (+)
7	(*S,S*)-**1d** (1)	>99	68:31	67	98 (−)
8	(*R,S*)-**1d** (1)	16	ND	15	ND
9	(*S,S*)-**1a** (0.5)	>99	91:9	87	>99 (−)
10	(*S,S*)-**1a** (0.2)	>99	90:10	84	>99 (−)
11	(*S,S*)-**1a** (0.1)	20	ND	18	ND

[a] *Reaction conditions:* $P(H_2)=50$ atm, **2a** (0.1 mmol), Ir(I) catalyst (0.1–1 mol%), CH_2Cl_2 (2 mL), room temperature, 6 h.
[b] Determined by ^{1}H NMR.
[c] dr = *trans*/*cis*, determined by ^{1}H NMR.
[d] Yield of isolated *trans*-**3a**.
[e] The *ee* value of the *trans*-**3a** was determined by chiral HPLC.

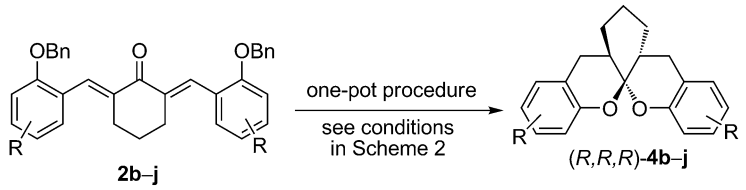
Table 2. Excellent *ee* values (98–>99%) were obtained for the *trans*-**3a** in most cases, with the sense of the asymmetric induction being dictated by the chirality of the spiro backbone of the SpinPHOX ligands (entries 1–8). On the other hand, the catalytic activity and the diastereoselectivity (*dr*) varied dramatically with the change of the substituents at the oxazoline fragments of the ligands. In terms of both the catalytic efficiency and the diastereoselectivity, (*S,S*)-**1a** proved to be the optimal catalyst, affording (−)-*trans*-**3a** in 87% yield with a *dr* of 91:9 and >99% *ee* (entry 1). By contrast, (*R,S*)-**1c** was found to be optimal for the production of (+)-*trans*-**3a**, a yield of 81% with 90:10 *dr* and >99% *ee* being obtained in this case (entry 6). Under the otherwise identical conditions, the catalyst loading of (*S,S*)-**1a** can be decreased from 1.0 to 0.5 or 0.2 mol%, respectively, without significant deterioration in substrate conversions or product *dr* and *ee* values (entries 9 and 10 *vs.* 1). Further lowering the catalyst loading to 0.1 mol%, however, led to a dramatic decline of the conversion to 20% (entry 11).

With the optimized catalysts in hands, we proceeded to extend the one-pot procedure (Scheme 2) to the synthesis of other aromatic spiroketals. The benzyl-protected bis(2-hydroxyarylidenes) **2b–j** were readily obtained in good yields from the aldol condensation of the corresponding benzylated salicylaldehydes with cyclohexanone, and were easily purified by simple recrystallization. Substrates **2b–j** proved to be well amenable to the one-pot procedure for the synthesis of spiroketals. As shown in Table 3, α,α′-bis(2-benzyloxyarylidene) ketones **2b–j** were first submitted to asymmetric hydrogenation catalyzed by (*S,S*)-**1a**, subsequently to hydrogenative debenzylation of the resultant benzyl ethers catalyzed by Pd/C, and simultaneously to spiroketalization of the diphenolic ketones by (*S,S*)-**1a** again in the presence of H_2, leading to the formation of the corresponding chiral aromatic spiroketals (*R,R,R*)-**4b–j** in high overall yields (77–94%) with good diastereoselectivities (*trans*/*cis* = 81/19 to 96/4), and excellent enantioselectivities for the *trans* products (97–>99% *ee*). It is noteworthy that aromatic spiroketals with strongly electron-donating groups (OH, OMe, or OEt) on the phenyl rings are readily accessible using this protocol (entries 3–6), while the aromatic spiroketals (*R,R,R*)-**4e** with free phenolic hydroxy functionality may find utility as chiral ligand or organocatalyst for asymmetric synthesis.[19] Meanwhile, as shown in entry 9, the transformation of the substrate with different substituents on each phenyl ring also proceeds smoothly to the corresponding product (*R,R,R*)-**4j** with good yield, high *dr* and excellent *ee*.

Encouraged by the results obtained above, we further extended the methodology to a large-scale synthesis of the spiroketal-based diphosphine ligands (SKPs),[3f] to demonstrate the practical synthetic utility of the one-pot catalytic approach. As shown in Scheme 3, the key synthetic intermediate (*R,R,R*)-**4b** was prepared by following the protocol with a slight modification. Benzylation of 3-fluoro-2-hydroxybenzaldehyde (**5**, 100 g) followed by aldol condensation with cyclohexanone in one pot, afforded 151 g of (2*E*,6*E*)-2,6-bis(2-(benzyloxy)-3-fluorobenzylidene)cy-

clohexanone (**2b**) in total 81% yield. Compound **2b** was readily purified by recrystallization from 90% aqueous ethanol, thus obviating the need for cumbersome column chromatography. For the transformation of large quantities of **2b** to (*R*,*R*,*R*)-**4b**, a catalytic amount of TsOH was used along with Pd/C to facilitate the spiroketalization of the debenzylated product. By using this procedure, 50 g of **2b** was smoothly transformed to 24.8 g of (*R*,*R*,*R*)-**4b** (79% overall yield) with excellent enantiopurity (>99% *ee*). The aromatic spiroketal difluoride (*R*,*R*,*R*)-**4b** was easily converted into the spiroketal-based diphosphine ligands (*R*,*R*,*R*)-**6a–c** in good yields (78–95%) in up to tens of grams scales, by reaction with either $KPPh_2$ or KH and $HPAr_2$ in refluxing THF (Scheme 3).[20] In comparison with the previous approach for the synthesis of SKP ligands, this method is obviously more convenient with higher total yields, and is particularly amenable to the practical synthesis of these compounds in large scales.

Table 3. Synthesis of various chiral aromatic spiroketals *via* a one-pot procedure.[a]



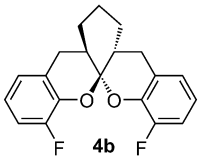
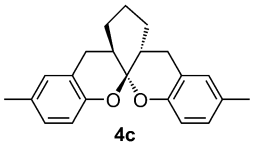
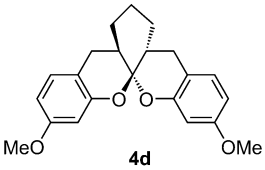
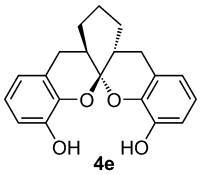
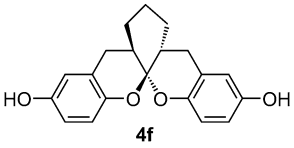
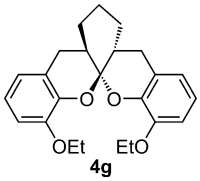
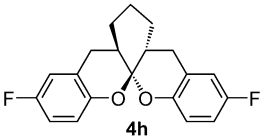
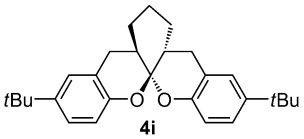
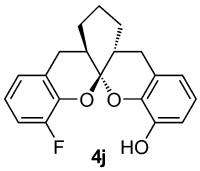
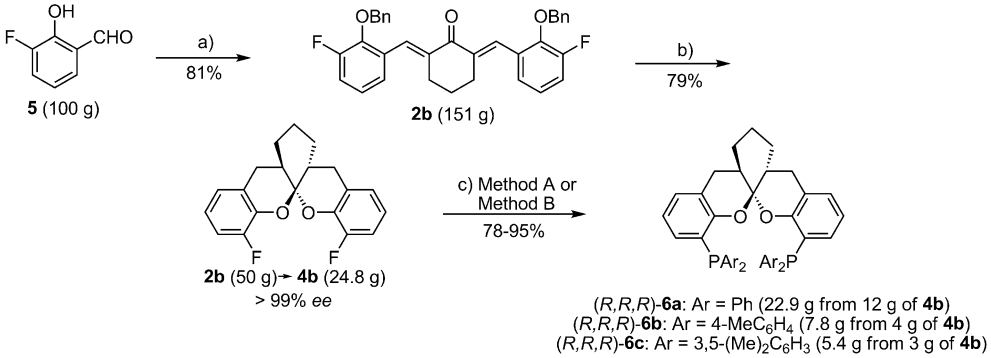
Entry	Product	*dr*[b]	Yield [%][c]	*ee* [%][d]
1	 **4b**	96:4	93	>99
2	 **4c**	88:12	77	>99
3	 **4d**	81:19	80	>99
4[e]	 **4e**	92:8	80	>99
5	 **4f**	81:19	78	>99
6	 **4g**	92:8	90	>99
7	 **4h**	96:4	94	>99

Table 3. (Continued)

Entry	Product	*dr*[b]	Yield [%][c]	*ee* [%][d]
8	 **4i**	88:12	85	97
9	 **4j**	89:11	86	98

[a] *Reaction conditions:* substrate **2a–j** (0.3 mmol), $P(H_2)=50$ atm, (*S,S*)-**1a** (0.5–1.0 mol%), CH_2Cl_2 (5 mL), room temperature, 6 h. The resulting mixture, after release of H_2, was submitted to debenzylation and spiroketalization by charging with 5% Pd (10–30% wt/wt), $P(H_2)=20$ atm, room temperature, 24 h.
[b] *dr* = *trans*/*cis*, determined by ^{1}H NMR.
[c] Yield of isolated *trans* product.
[d] The *ee* value of the *trans* isomer was determined by chiral HPLC.
[e] 1 mol% of (*S,S*)-**1a** was used.



Scheme 3. Practical asymmetric synthesis of the spiroketal compound (*R,R,R*)-**4b** and chiral SKP ligands (*R,R,R*)-**6a–c**: a) BnBr, K_2CO_3, DMF; then cyclohexanone, aqueous NaOH; b) (*S,S*)-**1a** (0.2 mol%), H_2 (65 atm), CH_2Cl_2, room temperature, 20 h; then Pd/C, H_2 (20 atm), room temperature, 24 h; then $TsOH{\cdot}H_2O$ (0.1 equiv,), room temperature, 1 h. c) Method A for (*R,R,R*)-**6a** synthesis: $KPPh_2$ in refluxing THF, 6 h. Method B for **6b–c** synthesis: $HPAr_2$, KH, in refluxing THF, 6 h.

Conclusions

In summary, an improved procedure has been developed for the efficient synthesis of chiral aromatic spiroketals and the relevant diphosphine ligands. The procedure includes first asymmetric hydrogenation of readily available α,α′-bis(2-benzyloxyarylidene) ketones catalyzed by (*S,S*)-**1a** (0.5–1 mol%) and subsequent hydrogenative deprotection of the resultant benzyl ethers catalyzed by Pd/C, as well as simultaneous spiroketalization of the corresponding diphenolic ketones by (*S,S*)-**1a** in one pot. The corresponding chiral aromatic spiroketals (*R,R,R*)-**4a–j** has been obtained in high yields (77–94%) with good diastereoselectivities (*trans*/*cis* = 81/19 to 96/4), and excellent enantioselectivities for the *trans* products (97–>99% *ee*). The ease of preparation of the substrates combined with the lower catalytic loading has provided a straightforward and convenient route to the preparation of the chiral spiroketals. Remarkably, the reaction of aromatic spiroketal difluoride (*R,R,R*)-**4b** with $KPAr_2$ in refluxing THF has also provided an alternative and facile synthesis of chiral SKP ligands in 78–95% yields in up to tens of grams scales. This synthetic advance will definitely stimulate future researches on the applications of this type of molecular platform from both academic and industrial communities.

Experimental Section

One-Pot Procedure for the Synthesis of Chiral Aromatic Spiroketals (*R,R,R*)-4a–j, General Procedure

To a glass tube containing the substrate **2** (0.3 mmol), Ir(I)-(*S,S*)-**1a** catalyst (0.5–1 mol%) and a magnetic stirring bar

was added anhydrous CH_2Cl_2 (5 mL) under an argon atmosphere. The tube was transferred into a Parr autoclave in a glovebox, the autoclave was then purged three times with hydrogen and finally pressurized to 50 atm. The reaction mixture was stirred at room temperature for 6 h. After carefully releasing H_2 into a hood, an amount of 5% Pd/C (10–30% wt/wt relative to **2**) was added slowly into the reaction mixture, and the autoclave was again purged three times with H_2 and finally pressurized to 20 atm. The reaction mixture was stirred at room temperature for 24 h, and then the hydrogen gas was released in a hood. The conversion of substrates and *dr* values of the products were determined by ^{1}H NMR analysis of an aliquot of the crude mixture. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate as the eluent to afford the spiroketal products (*R*,*R*,*R*)-**4a–i**. The *ee* values of the spiroketals were determined by chiral HPLC.

Procedure for Catalytic Asymmetric Synthesis of (*R*,*R*,*R*)-4b on a Large Scale

Benzyl bromide (102.4 mL, 0.85 mol) was added dropwise to a solution of 3-fluoro-2-hydroxybenzaldehyde (**5**) (100 g, 0.71 mol) and anhydrous K_2CO_3 (197 g, 1.4274 mol) in DMF (200 mL) at room temperature. After the reaction mixture had been stirred for 2 h, TLC detection indicated the completion of the reaction. To the stirred reaction mixture was added aqueous NaOH (20 wt%, 228 mL, 1.42 mol), followed by the dropwise addition of cyclohexanone (35.5 mL, 0.34 mol). The resulting mixture was stirred at room temperature for 19 h, followed by addition of H_2O (300 mL) to afford a yellow precipitate which was filtered off, washed with distilled H_2O, and dried under vacuum. The crude product was purified by recrystallization from the 90% aqueous ethanol to afford **2b** as yellow crystalline solid; yield: 151 g (81%).

Under an argon atmosphere, CH_2Cl_2 (130 mL) was added into a 250-mL vial containing **2b** (50 g, 0.095 mol), Ir(I)-(*S*,*S*)-**1a** catalyst (315 mg, 0.2 mol%) and the magnetic stirring bar. The vial was then transferred into a Parr autoclave in a glovebox, which was purged three times with hydrogen and finally pressurized to 65 atm. The resulting mixture was stirred at room temperature for 20 h. The residual H_2 was carefully released into a hood, and 5% Pd/C (3.0 g, 6% wt/wt based on substrate **6**) and $TsOH{\cdot}H_2O$ (1.82 g, 0.0095 mol) were added slowly into the reaction mixture. The autoclave was again purged 3 times with H_2 and finally pressured to 2 atm, and allowed to react further for 24 h. The hydrogen gas was released into a hood, and the mixture was filtered through a short pad of celite. The solvent of the filtrate was removed under vacuum, and the residue was purified by recrystallization from the ethyl acetate/petroleum ether mixed solvent to afford (*R*,*R*,*R*)-**4b** as a white crystalline solid; yield: 24.8 g (>99% *ee*).

Procedure for Large-Scale Preparation of the SKP Ligand (*R*,*R*,*R*)-6a (Method A)

To a 500-mL three-neck flask equipped with magnetic stirring bar were added (*R*,*R*,*R*)-**4b** (12 g, 0.036 mol) and $KPPh_2$ (168 mL, 0.084 mol, 0.5 M in THF) under a stream of argon. The mixture was heated at reflux for 6 h and then cooled down to room temperature, followed by addition of water (200 mL). The resulting mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were dried over sodium sulfate. After removal of sodium sulfate solids by filtration, the filtrate was concentrated under vacuum. Purification of the residue by flash chromatography [SiO_2: ethyl acetate/petroleum ether (1:50, v/v)] afforded the diphosphine product (*R*,*R*,*R*)-**6a** as a white solid; yield: 22.9 g (95%); >99% *ee* by chiral HPLC).

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References

[1] For recent reviews, see: a) M. Brasholz, S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2007**, 3801; b) J. Sperry, Z. E. Wilson, D. C. K. Rathwell, M. A. Brimble, *Nat. Prod. Rep.* **2010**, *27*, 1117. For selected examples, see: c) Y.-C. Hu, X.-F. Wu, S. Gao, S.-S. Yu, Y. Liu, J. Qu, J. Liu, Y.-B. Liu, *Org. Lett.* **2006**, *8*, 2269; d) P.-L. Huang, S.-J. Won, S.-H. Day, C.-N. Lin, *Helv. Chim. Acta* **1999**, *82*, 1716; e) X. Zhang, L. Shan, H. Huang, X. Yang, X. Liang, A. Xing, H. Huang, X. Liu, J. Su, W. Zhang, *J. Pharm. Biomed. Anal.* **2009**, *49*, 715; f) A. Trani, C. Dallanoce, G. Panzone, F. Ripamonti, B. P. Goldstein, R. Ciabatti, *J. Med. Chem.* **1997**, *40*, 967; g) C. Puder, S. Loya, A. Hizi, A. Zeeck, *Eur. J. Org. Chem.* **2000**, 729; h) T. Ueno, H. Takahashi, M. Oda, M. Mizunuma, A. Yokoyama, Y. Goto, Y. Mizushina, K. Sakaguchi, H. Hayashi, *Biochemistry* **2000**, *39*, 5995.

[2] M. D. Weingarten, J. A. Sikorski, N. Raymond, L. Ni, Z. Ye, C. Q. Meng, *Patent* WO 2008/140781 A1, November 20, **2008**.

[3] a) Z. Freixa, M. S. Beentjes, G. D. Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz, P. W. N. M. van Leeuwen, *Angew. Chem.* **2003**, *115*, 1322; *Angew. Chem. Int. Ed.* **2003**, *42*, 1284; b) Z. Freixa, P. C. J. Kamer, M. Lutz, A. L. Spek, P. W. N. M. van Leeuwen, *Angew. Chem.* **2005**, *117*, 4459; *Angew. Chem. Int. Ed.* **2005**, *44*, 4385; c) C. Jiménez-Rodríguez, F. X. Roca, C. Bo, J. Benet-Buchholz, E. C. Escudero-Adán, Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2006**, 268; d) X. Sala, E. J. G. Suárez, Z. Freixa, J. Benet-Buchholz, P. W. N. M. van Leeuwen, *Eur. J. Org. Chem.* **2008**, 6197; e) J. Li, G. Chen, Z. Wang, R. Zhang, X. Zhang, K. Ding, *Chem. Sci.* **2011**, *2*, 1141; f) X. Wang, F. Meng, Z. Han, Y. Chen, L. Liu, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 9410; *Angew. Chem. Int. Ed.* **2012**, *51*, 9276; g) X. Jia, Z. Wang, C. Xia, K. Ding, *Chem. Eur. J.* **2012**, *18*, 15288; h) X. Jia, Z. Wang, C.

Xia, K. Ding, *Catal. Sci. Technol.* **2013**, *3*, 1901; i) O. Jacquet, N. D. Clement, C. Blanco, M. M. Belmonte, J. Benet-Buchholz, P. W. N. M. Van Leeuwen, *Eur. J. Org. Chem.* **2012**, 4844; j) Z. Cao, X. Wang, T. Chen, X. Zhao, J. Zhou, K. Ding, *J. Am. Chem. Soc.* **2013**, *135*, 8197.

[4] For reviews, see: a) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617; b) K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227; c) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406.

[5] For examples of aromatic spiroketal synthesis *via* Brønsted or Lewis acid catalyzed cyclization of a bisphenolic dihydroxyketone intermediate, see: a) T. Tanaka, M. Miyayguchi, R. K. Mochisuki, S. Tanaka, M. Okanoto, Y. Kitajima, T. Miyazaki, *Heterocycles* **1987**, *25*, 463; b) T. Capecchi, C. B. D. Koning, J. P. Michael, *Tetrahedron Lett.* **1998**, *39*, 5429; c) T. Capecchi, C. B. D. Koning, J. P. Michael, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2681; d) K. Y. Tsang, M. A. Brimble, J. B. Bremner, *Org. Lett.* **2003**, *5*, 4425; e) K. Y. Tsang, M. A. Brimble, *Tetrahedron* **2007**, *63*, 6015; f) S. P. Waters, M. W. Fennie, M. C. Kozlowski, *Tetrahedron Lett.* **2006**, *47*, 5409; g) S. Sörgel, C. Azap, H.-U. Reissig, *Org. Lett.* **2006**, *8*, 4875; h) M. A. Brimble, C. L. Flowers, M. Trzoss, K. Y. Tsang, *Tetrahedron* **2006**, *62*, 5883; i) Y. Xin, H. Jiang, J. Zhao, S. Zhu, *Tetrahedron* **2008**, *64*, 9315; j) C. Venkatesh, H.-U. Reissig, *Synthesis* **2008**, 3605; k) D. C. K. Rathwell, S.-H. Yang, K. Y. Tsang, M. A. Brimble, *Angew. Chem.* **2009**, *121*, 8140; *Angew. Chem. Int. Ed.* **2009**, *48*, 7996; l) F. Wang, M. Qu, X. Lu, F, Chen, F. Chen, M. Shi, *Chem. Commun.* **2012**, *48*, 6259.

[6] For selected examples of aromatic spiroketal synthesis *via* ring closure of the hydroxyl enol ethers, see: a) D. H. Qin, R. X. Ren, T. Siu, C. S. Zheng, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4845; *Angew. Chem. Int. Ed.* **2001**, *40*, 4709; b) W. Wei, L. Li, X. Lin, H. Li, J. Xue, Y. Li, *Org. Biomol. Chem.* **2012**, *10*, 3494.

[7] For examples of aromatic spiroketal synthesis *via* hetero-Diels–Alder reactions, see: a) G. Zhou, D. Zheng, S. Da, Z. Xie, Y. Li, *Tetrahedron Lett.* **2006**, *47*, 3349; b) X. Li, J. J. Xue, C. S. Huang, Y. Li, *Chem. Asian J.* **2012**, *7*, 903. For a review, see: c) M. A. Rizzacasa, A. Pollex, *Org. Biomol. Chem.* **2009**, *7*, 1053.

[8] For examples of other miscellaneous routes to aromatic spiroketals, see: a) S. Akai, K. Kakiguchi, Y. Nakamura, I. Kuriwaki, T. Dohi, S. Harada, O. Kubo, N. Morita, Y. Kita, *Angew. Chem.* **2007**, *119*, 7602; *Angew. Chem. Int. Ed.* **2007**, *46*, 7458; b) K.-L. Wu, E. V. Mercado, T. R. R. Pettus, *J. Am. Chem. Soc.* **2011**, *133*, 6114; c) C. C. Lindsey, K. L. Wu, T. R. R. Pettus, *Org. Lett.* **2006**, *8*, 2365; d) Y. Zhang, J. Xue, Z. Xin, Z. Xie, Y. Li, *Synlett* **2008**, 940; e) P. J. Choi, D. C. K. Rathwell, M. A. Brimble, *Tetrahedron Lett.* **2009**, *50*, 3245.

[9] A. K. Franz, N. V. Hanhan, N. R. Ball-Jones, *ACS Catal.* **2013**, *3*, 540.

[10] X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 960; *Angew. Chem. Int. Ed.* **2012**, *51*, 936.

[11] a) I. Čorić, B. List, *Nature* **2012**, *483*, 315. For a highlight of the works reported in refs.[10,11a], see: b) M. Wilsdorf, H. U. Reissig, *Angew. Chem.* **2012**, *124*, 9624; *Angew. Chem. Int. Ed.* **2012**, *51*, 9486.

[12] Z. Sun, G. A. Winschel, A. Borovika, P. Nagomy, *J. Am. Chem. Soc.* **2012**, *134*, 8074.

[13] H. Wu, Y.-P. He, L.-Z. Gong, *Org. Lett.* **2013**, *15*, 460.

[14] a) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345; b) Y. Zhang, Z. Han, F. Li, K. Ding, A. Zhang, *Chem. Commun.* **2010**, *46*, 156; c) Z. Han, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2011**, *353*, 1584; d) J. Shang, Z. Han, Y. Li, Z. Wang, K. Ding, *Chem. Commun.* **2012**, *48*, 5172; e) J.-H. Xie, Q.-L. Zhou, *Acta Chim. Sinica* **2012**, *70*, 1427.

[15] The spiro backbone has been recognized as a privileged structure for the construction of chiral ligands; see: a) *Privileged Chiral Ligands and Catalysts*, (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**; b) A. S. C. Chan, W. Hu, C.-C. Pai, C.-P. Lau, Y. Jiang, A. Mi, M. Yan, J. Sun, R. Lou, J. Deng, *J. Am. Chem. Soc.* **1997**, *119*, 9570; c) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581; d) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32; e) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, H. Sasai, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285.

[16] M. Schelhaas, H. Waldmann, *Angew. Chem.* **1996**, *108*, 2192; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2056.

[17] a) S. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225; b) X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree, *Org. Lett.* **2005**, *7*, 5437; c) G. Onodera, T. Toeda, N. Toda, D. Shibagishi, R. Takeuchi, *Tetrahedron* **2010**, *66*, 9021; d) L. D. Field, B. A. Messerle, S. L. Wren, *Organometallics* **2003**, *22*, 4393; e) J. H. H. Ho, R. Hodgson, J. Wagler, B. A. Messerle, *Dalton Trans.* **2010**, *39*, 4062. For examples of transition metal complex-catalyzed acetalizations, see: f) F. Gorla, L. M. Venanzi, *Helv. Chim. Acta* **1990**, *73*, 690; g) M. Cataldo, E. Nieddu, R. Gavagnin, F. Pinna, G. Strukul, *J. Mol. Catal. A* **1999**, *142*, 305; h) Q. Jiang, H. Rüegger, L. M. Venanzi, *Inorg. Chim. Acta* **1999**, *290*, 64; i) M. Sülü, L. M. Venanzi, *Helv. Chim. Acta* **2001**, *84*, 898; j) C. Crotti, E. Farnetti, N. Guidolin, *Green Chem.* **2010**, *12*, 2225.

[18] a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249; b) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595; c) P. Cheruku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659; d) Y. Zhu, K. Burgess, *Adv. Synth. Catal.* **2008**, *350*, 979; e) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113; f) G. S. McGrady, G. Guilera, *Chem. Soc. Rev.* **2003**, *32*, 383; g) X. Qi, L. Liu, Y. Fu, Q. Guo, *Organometallics* **2006**, *25*, 5879.

[19] a) J. M. Brunel, *Chem. Rev.* **2007**, *107*, PR1; b) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; c) J. Inanaga, H. Furuno, T. Hayano, *Chem. Rev.* **2002**, *102*, 2211; d) Y. Chen, S. Yekta, A. Yudin, *Chem. Rev.* **2003**, *103*, 3155.

[20] O. Herd, A. Hessler, K. P. Langhans, O. Stelzer, W. S. Sheldrick, N. Weferling, *J. Organomet. Chem.* **1994**, *475*, 99.

