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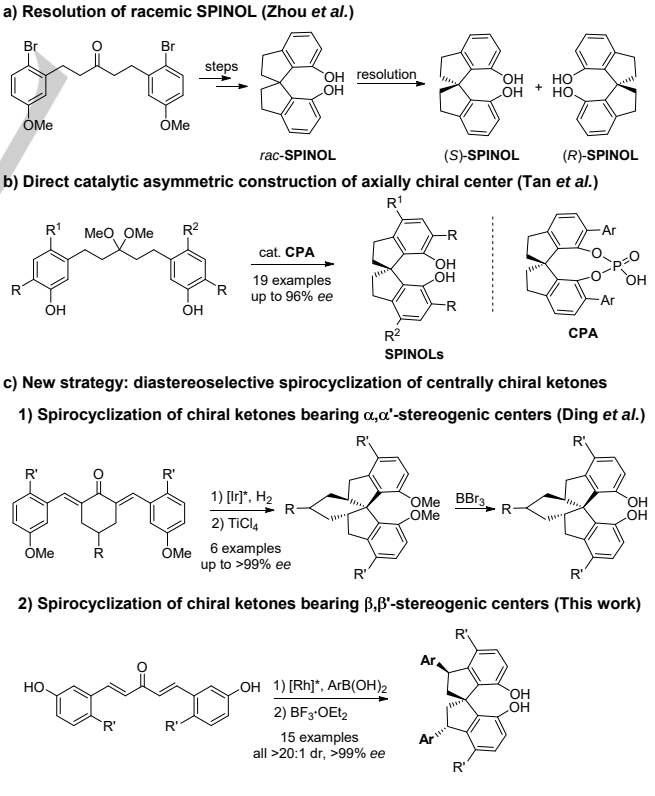
Enantioselective Synthesis of 3,3'-Diaryl-SPINOLS by Rh-Catalyzed Asymmetric Arylation–BF_3-Promoted Spirocyclization Reactions

Long Yin,[#] Junhao Xing,[#] Yuhan Wang, Yue Shen, Tao Lu,* Tamio Hayashi,* and Xiaowei Dou*

Abstract: *Enantioselective synthesis of a series of C_2-symmetric 3,3'-diarylated 1,1'-spirobiindane-7,7'-diols (3,3'-Diaryl-SPINOLS) was developed via a sequential Rh-catalyzed two-fold asymmetric conjugate arylation–BF_3-promoted diastereoselective spirocyclization process (>20:1 dr and >99% ee for all the examples). Some phosphoramidite ligands were prepared from the 3,3'-Ph-SPINOL and applied to several catalytic asymmetric reactions, where the 3,3'-diarylated ligands showed higher enantioselectivities than the privileged non-substituted ones.*

The privileged chiral structures are highly important in asymmetric catalysis, as they constitute the backbone of a large amount of useful chiral catalysts and ligands.[1] As an example, 1,1′-spirobiindane-7,7′-diol (SPINOL)[2] represents one of the privileged axially chiral structures: since the venerable pioneering work of Zhou and coworkers,[3] a variety of new ligands, catalysts, and chiral reagents based on the SPINOL structure have been developed,[4,5] and they proved to be highly useful in broad types of asymmetric transformations.[6] Despite the significance of SPINOLs, available methods to access enantioenriched SPINOLs are rather limited. The classical approach to enantioenriched SPINOLs relies on optical resolution of racemic SPINOLs using resolving agents (Scheme 1a).[7,8] Asymmetric construction of the axially chiral SPINOLs remained a formidable task for a long time, until recently, the first catalytic asymmetric synthesis of SPINOL derivatives was achieved by Tan and coworkers.[9] In Tan's work, direct asymmetric construction of the axially chiral center was realized by chiral phosphoric acid-catalyzed intramolecular spirocyclization of 1,5-diphenolic-3-ketal substrates (Scheme 1b). We envisioned that a new strategy, i.e., construction of the axially chiral center by diastereoselective spirocyclization of centrally chiral reagents, may be developed as an alternative approach to SPINOL derivatives. During the course of our study, the Ding group reported a related strategy to prepare chiral SPINOL derivatives.[10] Chiral cyclic ketones bearing α,α′-stereogenic centers were produced by iridium-catalyzed asymmetric hydrogenation, and those chiral ketones then underwent $TiCl_4$-promoted spirocyclization to give the spirobiindanes, which upon treatment with BBr_3 gave 2,2′-cyclohexyl-fused SPINOL derivatives (Scheme 1c-1). It was also demonstrated that the 2,2′-cyclohexyl-fused SPINOL-derived ligands showed similar enantioselectivities as the privileged non-substituted ones. Herein, we report a highly diastereo- and enantioselective synthesis of 3,3′-diarylated SPINOL derivatives (3,3′-Diaryl-SPINOLS), which was achieved via a sequential Rh-catalyzed two-fold asymmetric conjugate arylation–BF_3-promoted diastereoselective spirocyclization process (Scheme 1c-2). The new method reported here tolerates phenolic substrates to gives SPINOL derivatives directly. More importantly, the 3,3′-diaryl substitutions were found to be beneficial for development of new SPINOL-based phosphoramidite ligands, which showed higher enantioselectivities than the non-substituted ones in several different types of reactions.



Scheme 1. Approaches to enantioenriched SPINOL derivatives.

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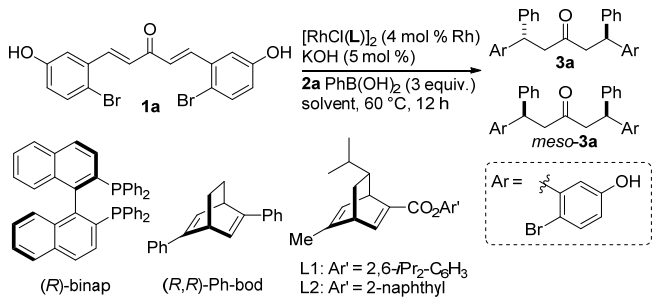
To realize the direct asymmetric synthesis of SPINOLs by diastereoselective spirocyclization, a highly diastereo- and enantioselective synthesis of centrally chiral phenolic ketones is a necessary prerequisite. The rhodium-catalyzed asymmetric conjugate arylation of α,β-unsaturated ketones with arylboronic acids has proved to be one of the most reliable methods to generate ketones bearing β-benzylic chiral centers.[11] We then speculated that the target chiral ketones might be generated by rhodium-catalyzed two-fold asymmetric conjugate arylation of easily prepared α,α′-bis(arylidene)ketones. We commenced our investigation with the rhodium-catalyzed asymmetric conjugate phenylation of (1*E*,4*E*)-1,5-bis(2-bromo-5-hydroxyphenyl)penta-1,4-dien-3-one (**1a**), and the results are summarized in Table 1.

Table 1. Rhodium-catalyzed asymmetric addition of $PhB(OH)_2$ (**2a**) to (1*E*,4*E*)-1,5-bis(2-bromo-5-hydroxyphenyl)penta-1,4-dien-3-one (**1a**).[a]

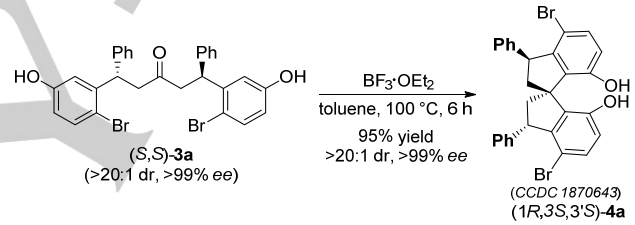


Entry	L	Solvent	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	(*R*)-binap	toluene/H_2O (10:1)	<5	--	--
2	(*R*,*R*)-Ph-bod	toluene/H_2O (10:1)	92	2.5:1	87
3	L1	toluene/H_2O (10:1)	90	>20:1	>99
4	L2	toluene/H_2O (10:1)	95	>20:1	>99
5	L2	dioxane/H_2O (10:1)	94	>20:1	99
6	L2	THF/H_2O (10:1)	94	16:1	99
7	L2	DCE/H_2O (10:1)	95	19:1	>99
8[e]	L2	toluene/H_2O (2:1)[f]	99	>20:1	>99
9[e,g]	**L2**	**toluene/H_2O (2:1)[f]**	**99**	**>20:1**	**>99**
10[e,h]	L2	toluene/H_2O (2:1)[f]	78	>20:1	>99
11[h]	L2	toluene/H_2O (2:1)[f]	95	>20:1	>99

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), and Rh catalyst (4 mol % Rh), KOH (20 mol %) in solvent (1.1 mL) at 60 °C for 12 h. [b] Isolated yield of **3a** and *meso*-**3a**. [c] The ratio of **3a**:*meso*-**3a**, determined by HPLC and ^{1}H NMR analysis. [d] The *ee* value of **3a**, determined by HPLC analysis on a chiral stationary phase column. [e] no KOH. [f] toluene/H_2O (1.0 mL/0.5 mL) was used as the solvent. [g] 2 mol % Rh was used. [h] 1 mol % Rh was used.

At first, (*R*)-binap ligated rhodium catalyst was tested, however, only negligible amount of the desired two-fold conjugate phenylation product **3a** was detected (Table 1, entry 1). In contrast to the ineffective chiral bisphosphine ligand, chiral diene ligands were found to be superior. (*R,R*)-Ph-bod[12] ligated rhodium catalyst gave a promising result: the desired β,β′-phenolic ketone **3a** was obtained in a high yield with a good enantioselectivity, albeit with a poor diastereoselectivity (entry 2). Other chiral diene ligated catalysts were then investigated, and to our delight, chiral dienes L1 and L2 (both are derived from (*R*)-α-phellandrene)[13] ligated catalysts gave excellent dr and *ee* values (entries 3 and 4, >20:1 dr, >99% *ee*), and the less bulky one showed higher catalytic reactivity (entry 4, 95% yield). A screening of different solvents proved toluene to be the best (entries 4 to 7). It was found that the non-basic reaction conditions[14] worked well for the current reaction, and the yield of **3a** was improved to 99% (entry 8). The catalyst loading can be reduced to 2 mol % Rh under non-basic conditions without affecting the results (entry 9). The yield decreased when the catalyst loading was further reduced to 1 mol % Rh, and additional KOH was found to be beneficial for a higher yield (entries 10 and 11). It is noteworthy that entry 10 gave **3a** in 78% yield with unreacted **1a**, and no mono phenylation product was observed, indicating a higher reactivity of the mono phenylation intermediate than **1a** in the current reaction system.

With enantioenriched **3a** (>20:1 dr, >99% *ee*) in hand, we set out to explore the spirocyclization of **3a**. After extensive studies of the reaction conditions, boron trifluoride diethyl etherate was found to promote the spirocyclization efficiently, and SPINOL derivative **4a** was generated in a high yield with excellent diastereocontrol (Scheme 2, 95% yield, >20:1 dr, >99% *ee*). The structure of **4a** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[15]



Scheme 2. Spirocyclization of **3a** to 3,3′-Ph-SPINOL derivative **4a**.

Next, with the non-basic conditions for asymmetric conjugate arylation, and with boron trifluoride diethyl etherate for spirocyclization, the scope of the 3,3′-Diaryl-SPINOLS synthesis was investigated (Scheme 3).[16] Arylboronic acids bearing variable substitutions at different positions were found to be suitable in the current method, and >20:1 dr and >99% *ee* were observed in all the investigated cases. For instance, in addition to the simple phenylboronic acid (**4a**), arylboronic acids bearing electron-donating groups at the *meta*- or *para*-positions worked well (**4b** – **4d**). The structure of the products was further confirmed by single-crystal X-ray diffraction analysis of **4c**.[15] Electron-withdrawing group substituted arylboronic acid was also tolerated, albeit the yield was lower (**4e**, 67% yield). Halogen-substituted arylboronic acids worked equally well (**4f** – **4i**). 3,5-Disubstituted arylboronic acid and 2-naphthylboronic acid were verified, and the corresponding SPINOL derivatives were obtained in moderate yields (**4j** and **4k**). It should be pointed out that the relatively lower yields of **4e**, **4i**, **4j** and **4k** were mainly due to the low conversion at the spirocyclization step. At last, α,α′-bis(arylidene)ketones bearing different substitutions were tested, and those substrates bearing -OMe, -Cl, and -F substitutions were well-tolerated (**4l** – **4o**). Iodide substitution can be easily installed to the *ortho*-position of the

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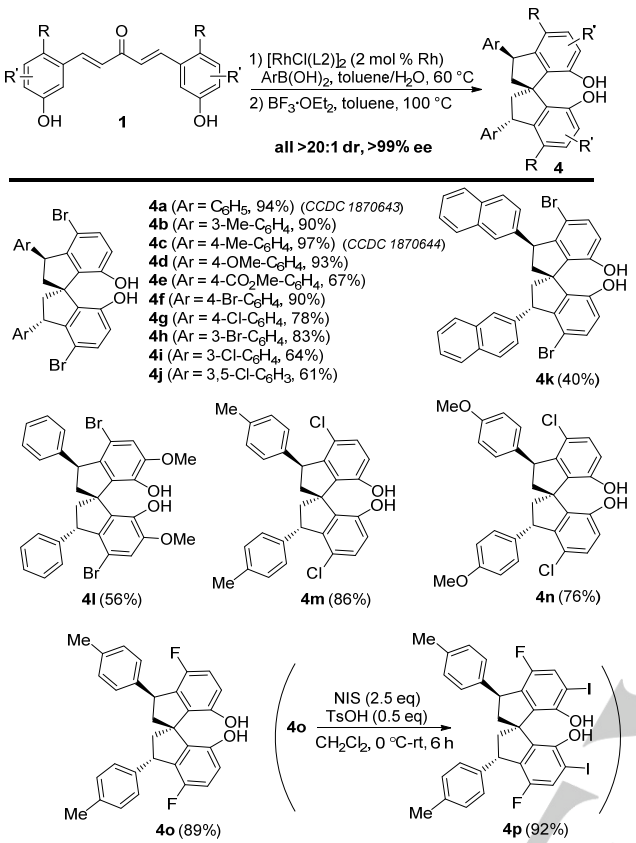
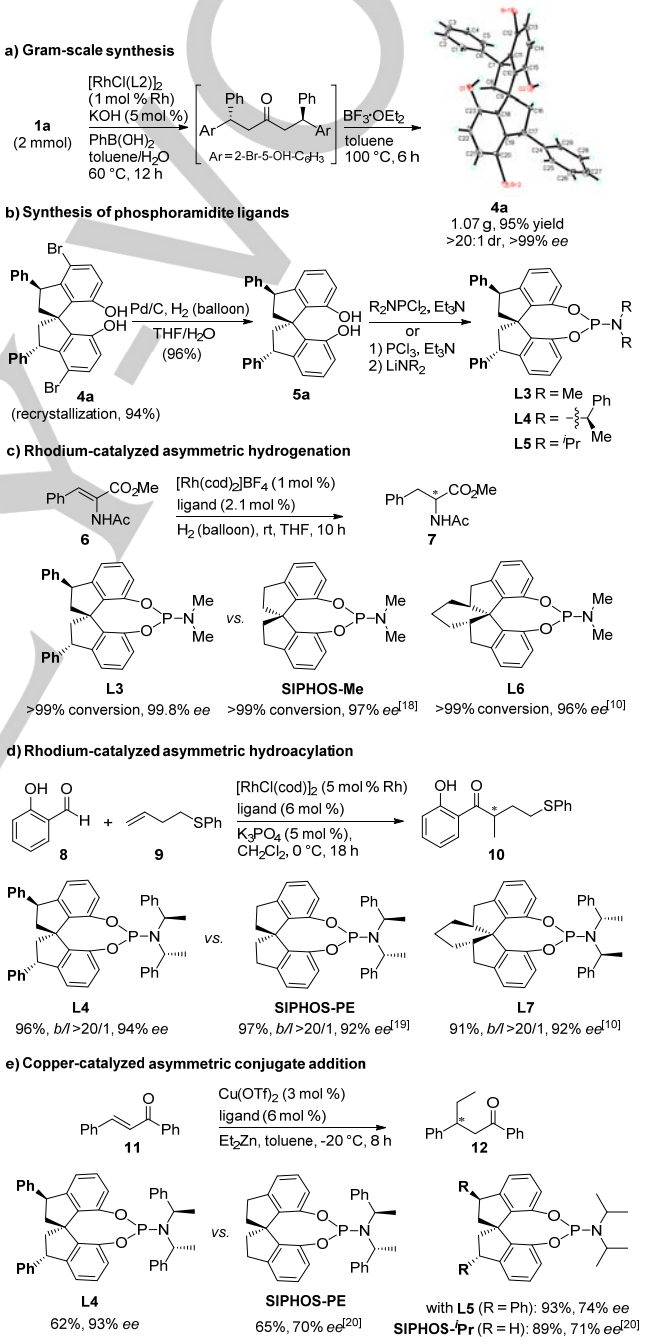
phenolic OH group, producing a useful intermediate for further cross-couplings (**4p**).



Scheme 3. Scope of the 3,3′-Diaryl-SPINOLS synthesis.

Underscoring the utility of our protocol, a gram-scale synthesis of **4a** was conducted. As shown in Scheme 4a, with 1 mol % Rh catalyst loading, **4a** was produced in a high yield with excellent diastereo- and enantiocontrol (1.07 g, 95% yield, >20:1 dr, >99% *ee*). From the X-ray structure of **4a**, it can be clearly seen that the phenyl substitutions are located on the same side as the OH groups. We envisioned this special spatial arrangement should have great influence on the selectivities of the SPINOL-based ligands/catalysts. At this stage, we prepared several 3,3′-Ph-SPINOL-based phosphoramidite ligands[17] (Scheme 4b) and examined their performance in metal-catalyzed asymmetric transformations. As shown in Scheme 4, phosphoramidite ligands **L3**, **L4**, and **L5** were used for direct comparison with their non-substituted congeners, and they were found to give higher enantioselectivities in several different types of reactions. At first, the cationic rhodium-catalyzed asymmetric hydrogenation of aminocinnamic acid derivative **6** was tested, and gratifyingly, using **L3** as the chiral ligand, a higher enantioselectivity was achieved than the privileged **SIPHOS-Me**[18] and Ding's 2,2′-cyclohexyl-fused **L6**[10] (Scheme 4c, 99.8% *ee* vs. 97% *ee* and 96% *ee*). When **L4** was applied to the rhodium-catalyzed asymmetric acylation reaction between salicylaldehyde **8** and homoallylic sulfide **9**,[19] the chiral ketone **10** was generated in a higher *ee* value, without affecting the high yield and excellent branched/linear selectivity (Scheme 4d). **SIPHOS-^{i}Pr** was identified as the best SIPHOS-type ligand in the copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcone **11**,[20] and its 3,3′-diphenylated congener **L5** showed a higher enantioselectivity (74% *ee* vs. 71% *ee*). Moreover, **L4** further improved the enantioselectivity to 93% *ee*, which is much higher than the *ee* value obtained (70% *ee*) with the corresponding **SIPHOS-PE** (Scheme 4e).



Scheme 4. Gram-scale synthesis, phosphoramidite ligand preparation and applications.

In summary, we have developed the enantioselective synthesis of a series of 3,3′-Diaryl-SPINOLS, and the present method features readily available reagents, easy operation, and excellent diastereo- and enantiocontrol. More importantly, the 3,3′-Diaryl-SPINOLS-based phosphoramidite ligands showed higher enantioselectivities than the privileged SPINOL-based ones in several different types of reactions, indicating great potentials of the newly developed 3,3′-Diaryl-SPINOLS in ligand/catalyst development. Further studies on understanding the origin of higher enantioselectivities of 3,3′-Diaryl-SPINOLS-based phosphoramidite ligands, as well as development of other 3,3′-Diaryl-SPINOLS-based ligands/catalysts are currently ongoing in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis • rhodium • conjugate addition • spirocyclization • SPINOL

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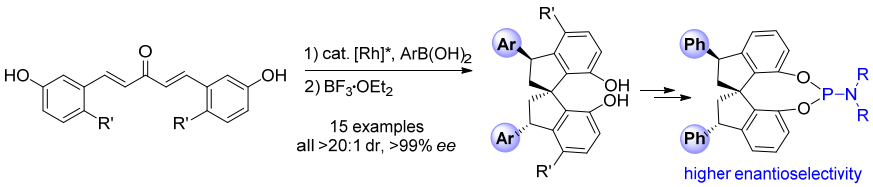

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Enantioselective Synthesis of 3,3'-Diaryl-SPINOLS by Rh-Catalyzed Asymmetric Arylation–BF_3-Promoted Spirocyclization Reactions

Enantioselective synthesis of a series of 3,3'-diarylated 1,1'-spirobiindane-7,7'-diols (3,3'-Diaryl-SPINOLS) was developed via a sequential Rh-catalyzed two-fold asymmetric conjugate arylation–BF_3-promoted diastereoselective spirocyclization process. Some phosphoramidite ligands were prepared from the 3,3'-Ph-SPINOL and applied to several catalytic asymmetric reactions, where the 3,3'-diarylated ligands showed higher enantioselectivities than the privileged non-substituted ones.