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Communication

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Design and synthesis of chiral *oxa*-spirocyclic ligands for Ir-catalyzed direct asymmetric reduction of Bringmann's lactones with molecular H_2

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Supporting Information Placeholder

ABSTRACT: *We herein present a facile and column-free synthetic route towards a structurally unique oxa-spirocyclic diphenol, termed as O-SPINOL. Features of the synthesis include the construction of the all-carbon quaternary center at an early stage, a key double intramolecular S_NAr step to introduce the spirocycles and the feasibility of operating on >100 g scale. Both enantiomers of O-SPINOL can be easily accessed through optical resolution with L-proline by control of the solvent. The chiral tridentate ligand O-SpiroPAP derived from O-SPINOL has been successfully synthesized and applied in the iridium-catalyzed asymmetric hydrogenation of bridged biaryl lactones under mild reaction conditions, providing valuable and enantioenriched axially chiral molecules in excellent yields and enantioselectivities (up to 99% yield and >99% ee). This method represents a rare example of constructing axially chiral molecules by direct reduction of esters with H_2.*

The development of efficient chiral ligands for transition-metal (TM) catalyzed asymmetric synthesis continues to stimulate intense research effort.[1] Due to their configurational rigidity and stability, chiral spiro ligands, complementary to axially chiral biaryl ligands, have exhibited tremendous potential and efficacy in asymmetric transformations.[2] Since the pioneering work reported by Chan, Jiang and Sasai et al,[3] chiral spiro ligands have become an appealing and powerful tool in TM catalysis. Notably, great advances in this field have been witnessed since Zhou and co-workers' seminal contribution[2a-2c] on chiral spiro ligands based on 1,1'-spirobiindane-7,7'-diol (SPINOL) (**I**, Figure 1) which was first reported by Birman and coworkers.[4] A large number of ligands such as SDP,[5a-5b] SIDIM,[5c] SpiroAP,[5d] SpiroPAP,[5e] SpiroBox[5f] and SIPhox[5g] derived from SPINOL have been synthesized and applied, rendering SPINOL as a privileged ligand scaffold in asymmetric TM catalysis.[6]

The modulation of the SPINOL skeleton is extremely challenging due to the lack of efficient synthetic route towards the spirocyclic scaffold. We expected that the replacement of one carbon atom with a more electronegative oxygen atom would lead to interesting and unique properties because of the shorter nature of C-O bond, especially the C(sp^2)-O bond (Eq A, Figure 1). In addition to the effort devoted to SpinPHOX with Ding and coworkers,[7] we also developed a six-membered *O*-containing spirocyclic diphenol and spiro phosphoramidite ligands.[8] *Herein, we disclose our preliminary results on the design and concise synthesis of structually unique oxa-spirocyclic ligand O-SPINOL*[9] *and the development of chiral O-SpiroPAP ligand for direct asymmetric reduction of Bringmann's lactones with molecular H_2.*

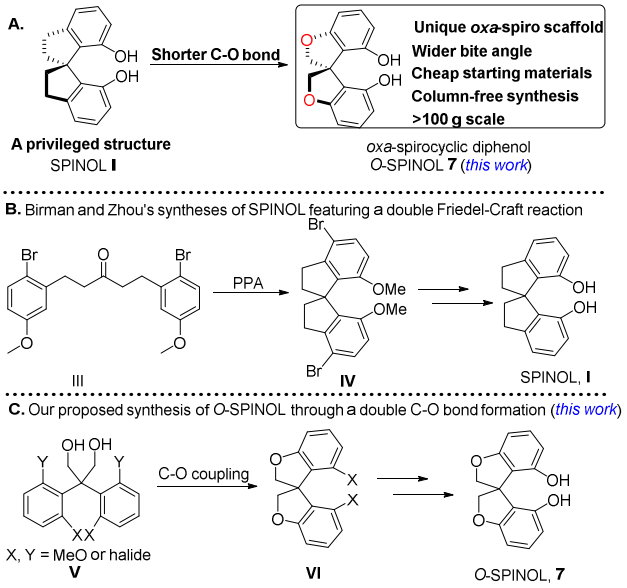


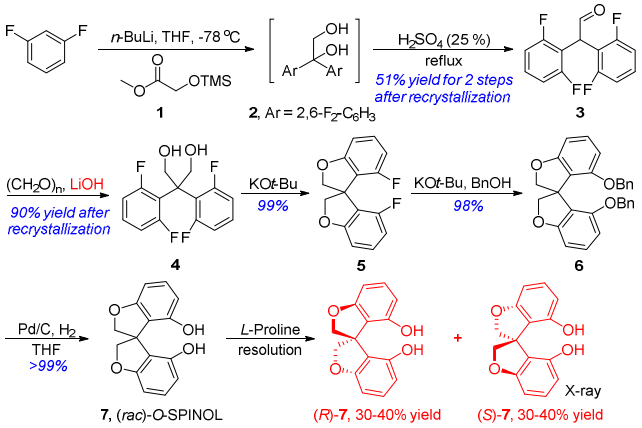
Figure 1. A. Our rational design of *oxa*-spirocyclic diphenol *O*-SPINOL. **B**. Birman and Zhou's synthetic route to SPINOL. **C**. Our proposed synthetic route to *O*-SPINOL.

The key step for the synthesis of SPINOL relies on the acid promoted double intramolecular Friedel-Crafts reaction (Eq B, Figure 1).[4] This method has also been applied in the synthesis of other types of spiro diphenols,[8,10] including an elegant catalytic asymmetric synthesis developed by Tan and coworkers.[11] However, this method failed to assemble the pivotal spirocyclic skeleton of *O*-SPINOL, and resulted in a complex mixture. Since the formation of spirocyclic quaternary carbon center is the key step, we proposed that the quaternary carbon center could alternatively be introduced at an early stage and a subsequent double C-O couling step would produce the spirocycle (Eq C, Figure 1).

Starting from commercially available 1,3-diflurobenzene,[12] diaryl-substituted acetaldehyde **3** could be accessed through a two-step sequence in decent yield after recrystallization, without the isolation of intermediate **2**. Key compound diol **4** was obtained in

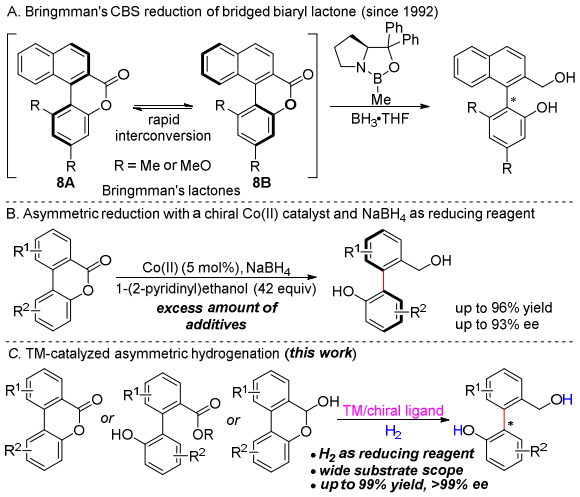
high yield via a modified aldol/Cannizzaro cascade reaction between **3** and paraformaldehyde.[13] To our delight, the subsequent intra- and intermolecular double S_NAr reactions worked well and quantitatively furnished spiro compound **6**, which was hydrogenated under Pd/C to give racemic diphenol **7**. Unfortunately, the resolving reagent *N*-benzylcinchonidinium chloride which is very effective for the resolution of SPINOL did not work for *O*-SPINOL. Instead, Both enantiomers of *O*-SPINOL was efficiently resolved with *L*-Proline. A crystal structure of (*S*)-SPINOL[14] was obtained to further confirm its structure and absolute configuration (for details see the Supporting Information).

Scheme 1. Column-free synthesis and optical resolution of racemic *O*-SPINOL.



On the other hand, because of their ubiquitous existence in naturally occurring compounds and extensive utilities as key elements in catalyst designs, atropisomeric biaryls have attracted increasing attention.[15] Among the synthetic methods toward them, dynamic kinetic resolution (DKR)[16] of configurationally unstable "bridged biaryl lactone", originally developed by Bringmann,[17] represents a unique and efficient strategy. Due to a rapid equilibrium between two atropoisomers (**8A** and **8B**, Eq A, Scheme 2), Bringmann's lactones could be stereoselectively reduced in the presence of a chiral catalyst, affording chiral biaryl diols with good conversion and high enantioselectivity. However, stoichiometric amount of CBS reagent is generally required to accomplish full conversion[17e] and only one catalytic example has been reported.[17a] A catalytic asymmetric reduction was later realized with $NaBH_4$ as reducing reagent by Yamada *et al*, wherein a chiral cobalt catalyst was introduced yet requiring large excess amount of additives (Eq B, scheme 2).[18] Very recent contributions from Akiyama[19] and Wang[20] et al disclosed the feasibility of applying organocatalysis in the DKR of Bringmann's lactones. Despite these advances, a direct and efficient TM-catalyzed asymmetric reduction of Bringmann's lactones with more atom-economic H_2 remains unknown. A formidable challenge is, however, anticipated since the reduction of esters with a chiral metal catalyst is rarely studied.[21]

Scheme 2. DKR of Bringmann's lactones via asymmetric reduction.

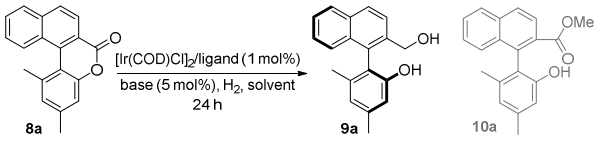


To test our idea, chiral tridentate ligands, such as f-amphox (**L1**),[22c] f-amphol (**L2**)[22b] and f-ampha (**L3**)[22a] which are highly efficient for Ir-catalyzed asymmetric hydrogenation of ketones,[22] were first investigated in Ir-catalyzed asymmetric hydrogenation of model substrate **8a** under 80 atm of H_2. Disappointedly, alcoholysis product **10a** was quantitatively formed when using **L1** as ligand, K_2CO_3 as base and MeOH as solvent, without detection of the desired product **9a** (entry 1, Table 1), indicating that alcohol solvent was not suitable for the current transformation. Iridium complexes of **L1**, **L2** and **L3** could not catalyze the current reaction in THF either (Table 1, entries 2-4). In addition, the Noyori catalyst **L6** was also evaluated,[22d] but the desired product was still not detected (entry 5, Table 1). We then turn our attention to seeking more reactive catalysts. Inspired by Zhou and Xie's work,[5e] we synthesized an *O*-SPINOL based tridentate PNN ligand **L4** according to a modified procedure (for details see the Supporting Information) and tested its catalytic activity towards hydrogenation of **8a**. To our great delight, product **9a** was obtained in 50% yield and 98% ee under the conditions of **L4** as ligand and *t*BuOK as base, combined with alcoholysis products. Encouraged by this result, weak base such as K_2CO_3 and Cs_2CO_3 were then screened (entries 7-8, Table 1). Gratifyingly, in both cases, product **9a** was obtained quantitatively with excellent enantioselectivity at 45 °C. The influence of temperature was also evaluated, and the reactivity and enantiocontrol remained excellent at 60 °C (96% ee of **9a**, entry 11, Table 1) while decreased yield was observed at 10 °C (entry 10, Table 1). The pressure of hydrogen was subsequently examined at rt, revealing that pressure is essential to the reactivity as no reaction happened under 20 atm pressure (entry 12 *vs* entry 13, Table 1). SpiroPAP **L5** developed by Zhou was also tested under the optimal conditions, giving comparable results (entry 14, Table 1). Besides, the reaction worked well at lower catalyst loading albeit requiring more time for full conversion (entry 15, Table 1). Given both the yield and enantioselectivity of **9a**, the combination of $[Ir(COD)Cl]_2$/**L4** (1 mol%) as catalyst, K_2CO_3 (5 mol%) as base, THF as solvent, 50 atm of H_2 at rt is the optimal condition.

With the optimal conditions in hand, we next examined the substrate generality, and the results were summarized in Scheme 3. Substrates with various substituents (Me, Cl as in **8b**-**8e**) on the phenolic part did not show much difference, affording desired products **9b**-**9e** in excellent yields and ee (95-98% yields, 97->99% ee). Nonetheless, removal of the substituent on the C3 position of the phenolic benzene ring, as exemplified in the cases of **8f** and **8g**, resulted in obvious decrease in the enantiocontrol (79% ee for **9f** and 85% ee for **9g**). Notably, binaphthyl substrates **8h** and **8i** are also well tolerated, affording **9h** with 96% ee and **9i** with >99% ee. Evaluation of the substituent effect on the carbonyl-containing

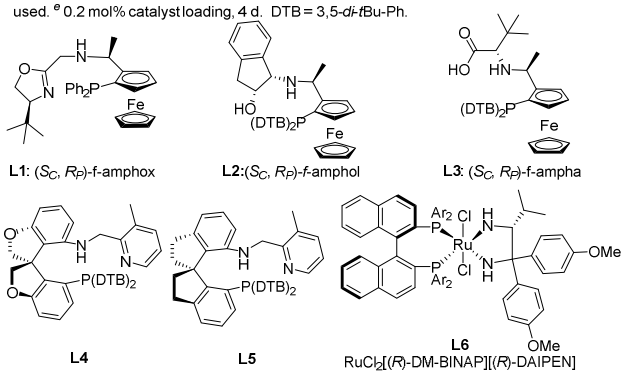
phenyl ring was also conducted (**9j-9l**, 90-96% yields, 91-98% ee). Besides, all reactions worked well for biphenyl substrates **8m-8q** in terms of enantiocontrol, but prolonged reaction time was required for substrates **8o** and **8p** to fulfill good conversions.

Table 1. Optimization of the reaction conditions.



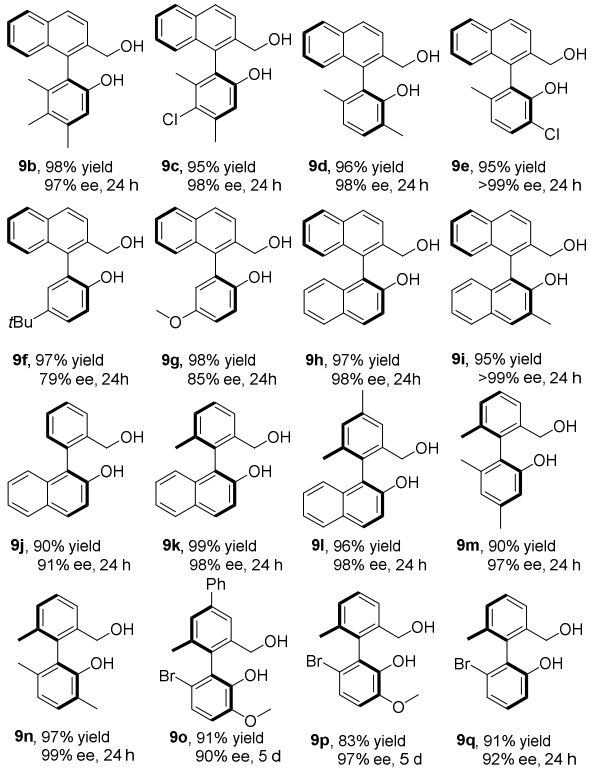
entry[a]	P (atm)	T (°C)	ligand	solvent	base	ee (%)[b]	yield (%)[c]
1	80	rt	**L1**	MeOH	K_2CO_3	--	**10a**, 99%
2	80	rt	**L1**	THF	K_2CO_3	--	--
3	80	rt	**L2**	THF	K_2CO_3	--	--
4	80	rt	**L3**	THF	K_2CO_3	--	--
5[d]	80	rt	--	THF	K_2CO_3	--	--
6	80	rt	**L4**	THF	*t*BuOK	98	**9a**, 50%
7	80	45	**L4**	THF	K_2CO_3	98	**9a**, 98%
8	80	45	**L4**	THF	Cs_2CO_3	97	**9a**, 98%
9	80	rt	**L4**	THF	K_2CO_3	98	**9a**, 98%
10	50	10	**L4**	THF	K_2CO_3	98	**9a**, 84%
11	50	60	**L4**	THF	K_2CO_3	96	**9a**, 98%
12	50	rt	**L4**	THF	K_2CO_3	98	**9a**, 98%
13	20	rt	**L4**	THF	K_2CO_3	--	--
14	50	rt	**L5**	THF	K_2CO_3	97	**9a**, 98%
15[e]	50	rt	**L4**	THF	K_2CO_3	98	**9a**, 98%

[a]The reactions were conducted on 0.05 mmol scale. [b]The ee values were determined by HPLC analysis. [c]Isolated yield. [d]Noyori catalyst $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] was used. [e] 0.2 mol% catalyst loading, 4 d. DTB = 3,5-*di*-*t*Bu-Ph.

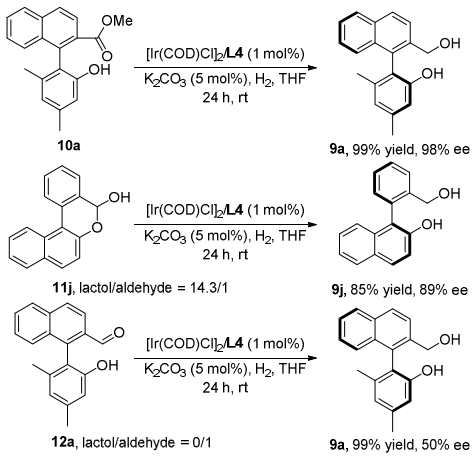


To gain further insight into the asymmetric induction process, compounds **10a**, **11j** and **12a** were prepared and subjected to the standard reaction conditions (Scheme 4). Interestingly, **10a** was quantitatively transformed to **9a** in the same enantioselective manner compared to that from **8a**, suggesting in situ generation of compound **8a** from **9a** under basic conditions. Similar stereo output was obtained for substrates **11j** and **8j**, indicating that the reaction of **8j** probably goes through a lactol intermediate. Importantly, for the hydroxyl aldehyde **12a**, product **9a** was obtained with dramatically decreased ee compared to that from **8a**.

Scheme 3. Substrate scope.



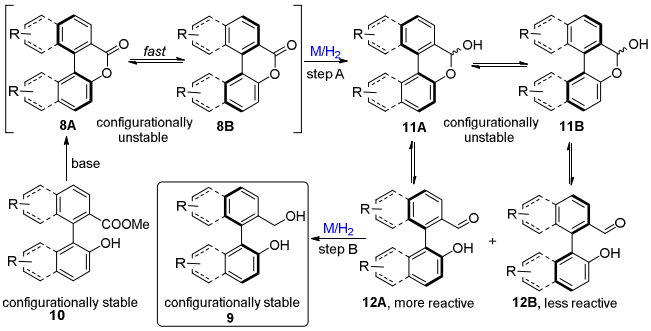
Scheme 4. DKR of hydroxyl ester **10a**, lactol **11j** and hydroxyl aldehyde **12a**.



Based on the literature precedents[17b,18,19,23] and our experimental observations (for more experiments see the Supporting Information), a rationalization of the asymmetric induction was illustrated (Scheme 5). **8A** and **8B** are in a rapid equilibrium with each other, and **8** can also be produced from **10** in the presence of a base. Overall, the asymmetric induction process is highly dependent on the structure of the substrates.[23] The first DKR process (step A) can preferentially produce enantioenriched lactol **11A**, which quickly isomerize to chiral intermediate **12A** for 2,6,2',6'-*tetra*-substituted substrates. Further reduction of enantioenriched **12A** (step B) produced the final product **9** in high enantioselectivity. Whereas, racemization would occur for 2,6,2'-*tri*-substituted lactols due to unstable configuration. Both DKR processes possibly contribute to the enantiocontrol in the reduction of compound **8j**, which is supported by the fact that racemic **11j** was transformed to **9j** with 89% ee. The dramatically decreased enantiocontrol of **12a** versus **8a** implies that the DKR of **12a** is not very effective due to low interconversion rate between the two

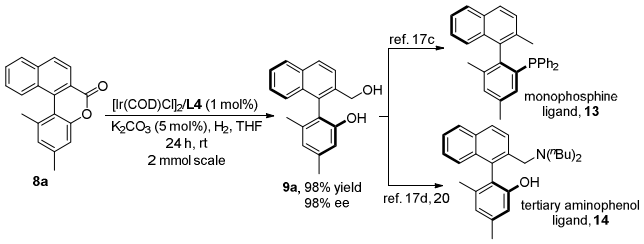
enantiomers of **12a** (For the details see the Supporting Information).[19,24]

Scheme 5. Proposed asymmetric induction mechanism.



The protocol can be easily scaled up to 2 mmol scale at a higher concentration (0.5 M), affording **9a** in quantitative yield and 98% ee (Scheme 6). It is noteworthy that **9a** can be easily elaborated to synthetically useful chiral monophosphine ligand **13**[17c] and chiral aminophenol ligand **14**.[17d,20]

Scheme 6. Scalable synthesis of product **9a** and its synthetic elaborations.



In conclusion, a new *oxa*-spirocyclic scaffold has been designed and synthesized featuring a novel double intramolecular S_NAr reaction from cheap and commercially available starting materials. Both enantiomers of *O*-SPINOL can be divergently resolved on large scale upon the choice of solvents with *L*-Proline. Impressively, the synthesis towards enantiopure *O*-SPINOL relies only on recrystallization and does not need any column chromatography operation. The ligand *O*-SpiroPAP derived from *O*-SPINOL has been successfully synthesized and applied in iridium-catalyzed DKR of Bringmann's lactones via asymmetric hydrogenation, providing an atom-economic and facile method to valuable chiral biaryl molecules. Additionally, some control experiments were also performed to gain insight into the asymmetric induction mechanism.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, spectral data, and analytical data (PDF)

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Notes

The authors declare no competing financial interests.

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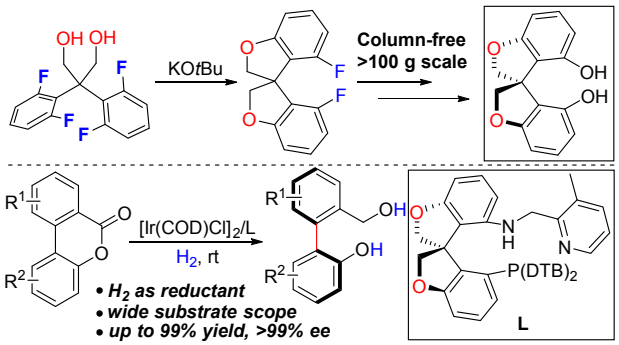
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• H2 as reductant
• wide substrate scope
• up to 99% yield, >99% ee
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