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Development of a C_2-Symmetric Chiral *aza* Spirocyclic Diol

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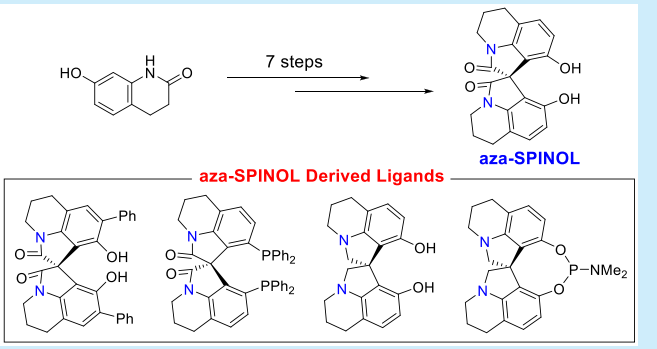
ABSTRACT: A C_2-symmetric chiral spirocyclic diol *aza*-SPINOL containing a spirooxindole scaffold has been designed, synthesized, and optically resolved. The product could be synthesized on gram scale in an overall yield of 22%. Moreover, elaborations of *aza*-SPINOL to other chiral ligands as well as the preliminary investigation of the related bisphosphine ligand in the desymmetrization of bisallylic amide were reported.



Axially chiral 1,1′-spirobiindane-7,7′-diol (SPINOL) was first synthesized and optically resolved by Birman in 1999.[1] Thanks to Zhou's pioneering[2] and subsequent extensive[3] contributions to the development and application of SPINOL-derived ligands and catalysts, chiral 1,1′-spirobiindane has now become one of the most privileged chiral scaffolds in asymmetric catalysis. In order to tune steric and electronic effects of ligands or catalysts, some SPINOL analogues or derivatives have been designed and synthesized, including CHEXDBSPINOL by Venugopal,[4] SBIFOL by Zhou,[5] SBITOL by Zhou,[6] and HMSIOL by Lin.[7] While optically pure SPINOL and its analogues were conventionally obtained by optical resolution, remarkably, their asymmetric syntheses have been recently realized by Ding,[8] Tan,[9] and Dou.[10] Moreover, besides an all-carbon spiro framework, chiral *oxa*-SPINOLs have also been developed, including SBIXOL[11] and *O*-SPINOL[12] by Zhang, and SPIROL by Nagorny.[13] However, *aza*-SPINOLs are still unknown. Herein, we report the first example of *aza*-SPINOL, providing a new chiral skeleton for the development of chiral spirocyclic ligands and catalysts (Figure 1).

It is well-known that the ketone **I** is the key intermediate for the synthesis of SPINOL, which can undergo a twofold Friedel−Crafts reaction to give the chiral spirocyclic intermediate **II** under acidic conditions (Scheme 1a).[1] We proposed that the spirocyclic compound **IV** might be successfully constructed if the 2-oxomalonamide **III** could also undergo the acid-promoted spirocyclization. Further elaborations of **IV** would provide a class of potentially useful C_2-symmetric chiral *aza*-SPINOLs (Scheme 1b). With this proposal in mind, we launched this research and finally succeeded in preparing *aza*-SPINOL **8**. It should be noted that literature surveys indicated while *aza*-SPINOL is still unknown, the spirooxindole skeleton is known. In 2012, Du,

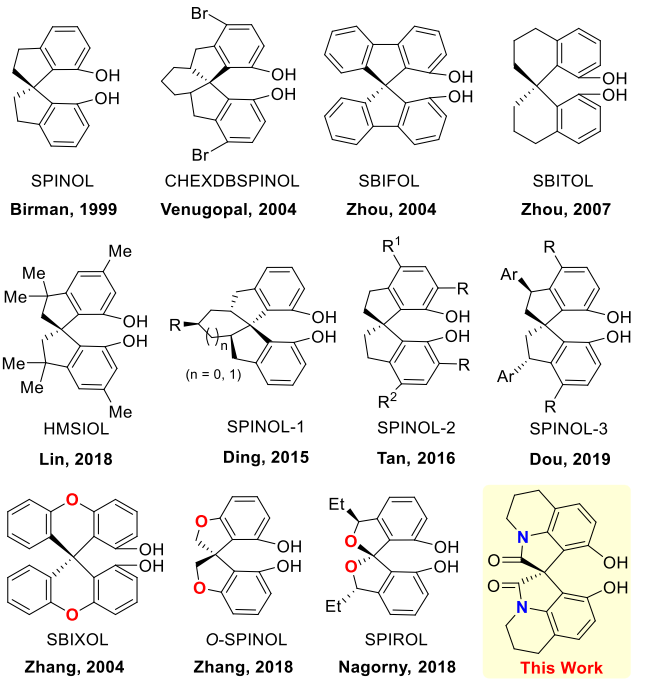


Figure 1. Chiral spirocyclic diols.

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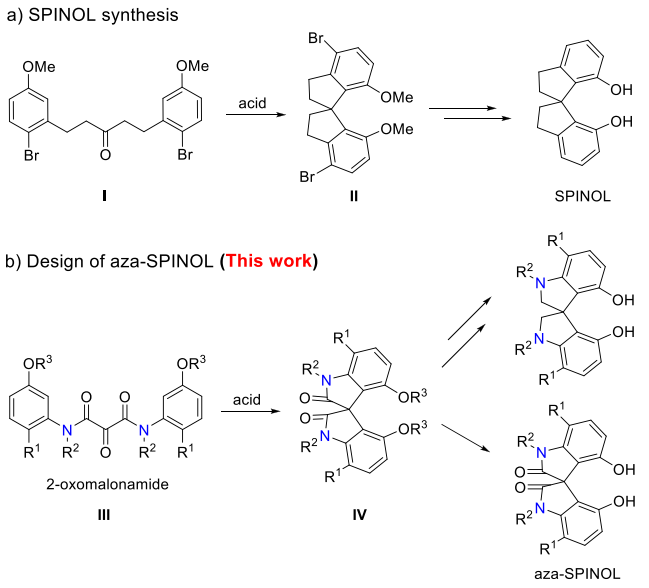
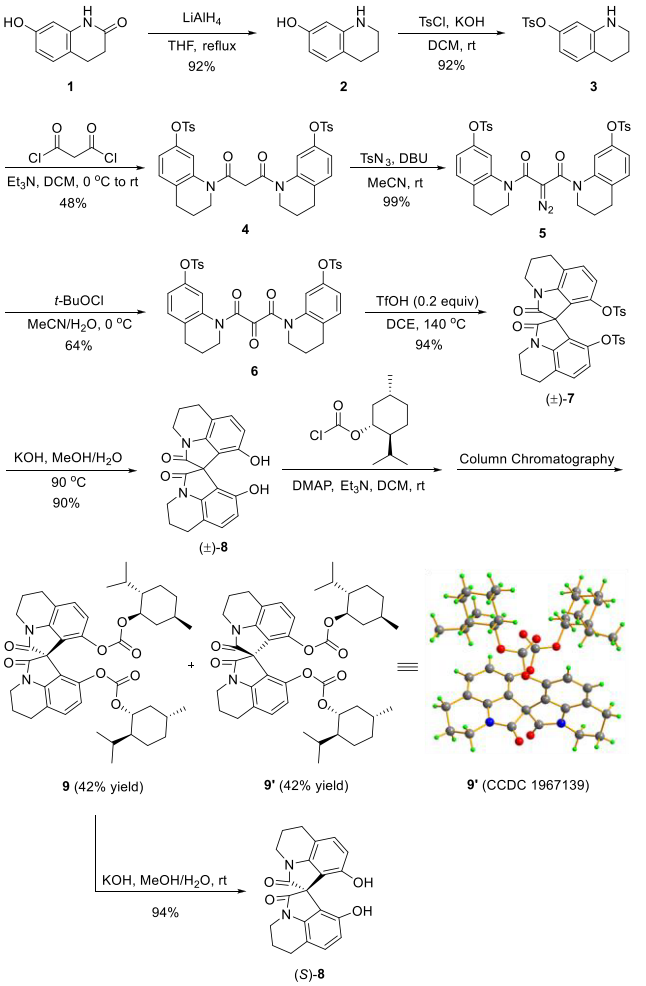
Scheme 1. Design the Synthesis of *aza*-SPINOL



Scheme 2. Synthetic Route for *aza*-SPINOL



Zhao and co-workers synthesized several C_2-symmetric or unsymmetric spirooxindoles via a phenyliodine bis-(trifluoroacetate) (PIFA)-mediated cascade oxidation of N^1,N^3-diphenylmalonamides.[14] Later, this reaction was achieved highly enantioselectively with a chiral organoiodine catalyst by Gong and co-workers.[15] In addition, recently Cai and co-workers developed a copper(I)-catalyzed intramolecular asymmetric double C-arylation for the synthesis of diverse enantioenriched spirooxindoles.[16]

As outlined in Scheme 2, our synthesis starts from commercially available 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one **1**. The secondary amine **2** was prepared by reduction of **1** with $LiAlH_4$. After tosylation, the tosylate **3** was obtained in 92% yield, which was further treated with malonyl chloride in the presence of triethylamine to afford the malonamide **4** in 48% yield. To oxidize the malonamide **4** to the key 2-oxomalonamide intermediate **6**, a two-step procedure was applied. Specifically, the malonamide **4** was first treated with *p*-tosyl azide (TsN_3) to produce the diazo compound **5** quantitatively, which was then oxidized with *t*-BuOCl to give the 2-oxomalonamide **6** in 64% yield.[17] To our delight, promoted by a catalytic amount of trifluoromethanesulfonic acid (TfOH), the successive dual Friedel−Crafts reactions proceeded well to deliver the desired spirocyclic compound **7** in 94% yield. Notably, this reaction could be performed on gram scale without any difficulties. Attempting to directly convert the malonamide **4** into the spirocyclic product **7** by PIFA-mediated tandem oxidation[14] proved unsuccessful. Finally, removal of the tosyl group with KOH afforded the targeted racemic 9,9′-dihydroxy-1,1′-spirooxindole **8** in 90% yield. Furthermore, optical resolution of racemate **8** was efficiently achieved via its bis-L-menthoxycarboxylate as the two diastereomers could be separated by silica gel chromatography. The structure and the absolute configuration of the diastereomer **9′** with the lower R_f value were identified by single-crystal X-ray diffraction. Upon saponification, both of the optically pure enantiomers of *aza*-SPINOL **8** were obtained facilely.

In order to investigate the potential use of this newly developed *aza*-SPINOL in the synthesis of chiral ligands, the counterparts of some classic chiral ligands were selectively prepared (Scheme 3). First, synthesis of 8,8′-disubstituted spirooxindoles was explored. Gladly, 8,8′-diiodination of *aza*-SPINOL (*S*)-**8** proved successful with NIS and TsOH, providing the product (*S*)-**10** in 85% yield. After the Pd/C catalyzed Suzuki coupling[9] with phenylboronic acid, the 8,8′-diphenyl spirooxindole (*S*)-**11** was obtained in 34% yield (Scheme 3a). Second, synthesis of bisphosphine ligand was studied. Treatment of *aza*-SPINOL (*R*)-**8** with trifluoromethanesulfonic anhydride produced the triflate (*R*)-**12** in 92% yield. Then, coupling (*R*)-**12** with diphenylphosphine in the presence of $Pd(OAc)_2$/dppb gave the corresponding bisphosphine (*R*)-**13** in 44% yield (Scheme 3b).[18] Third, the *aza*-SPINOL (*S*)-**14** bearing a spiroindoline scaffold was successfully prepared by reduction of (*S*)-**8** with borane. Moreover, it could be further converted to the corresponding phosphoramidite (*S*)-**15** in 85% yield by refluxing with hexamethylphosphorous triamide in toluene (Scheme 3c).[19]

To show potential application of spirooxindole catalyst in the asymmetric catalysis, the asymmetric catalytic desymmetrization of bisallylic amide **16** with NBS was studied, which was previously reported by Hamashima et al.[20] It was found that, in the presence of 10 mol % of (*R*)-**13**, the oxazoline product **17** was obtained in 55% yield with 72% ee (Scheme 4).

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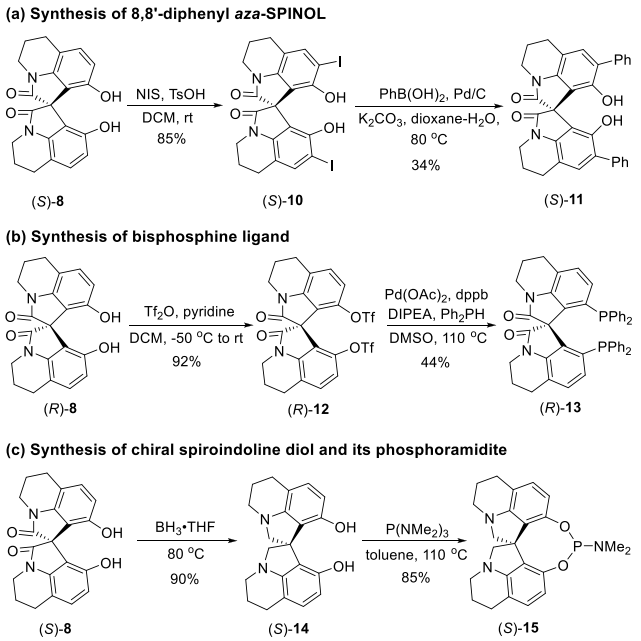
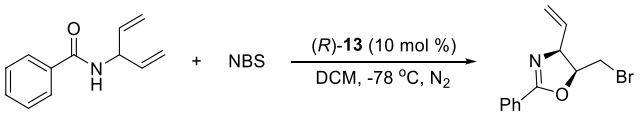
Scheme 3. Elaborations of *aza*-SPINOL 8 to Chiral Ligands



Scheme 4. Application of Chiral Phosphine Ligand in the Desymmetrization of Bisallylic Amide[a]



[a]Under a nitrogen atmosphere, **16** (0.1 mmol), NBS (0.25 mmol), and catalyst (*R*)-**13** (10 mol %) in DCM (1 mL) at −78 °C for 24 h.

In conclusion, we describe the design, synthesis, and optical resolution of a new class of C_2-symmetric chiral spirocyclic diol, namely, *aza*-SPINOL. It could be prepared on gram scale in an overall yield of 22%. In addition, its elaborations to some representative chiral ligands and preliminary application in asymmetric catalysis were explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00858.

Experimental details, characterization data, ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1967139 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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