

Synthesis of New Monodentate Spiro Phosphoramidite Ligand and Its Application in Rh-Catalyzed Asymmetric Hydrogenation Reactions

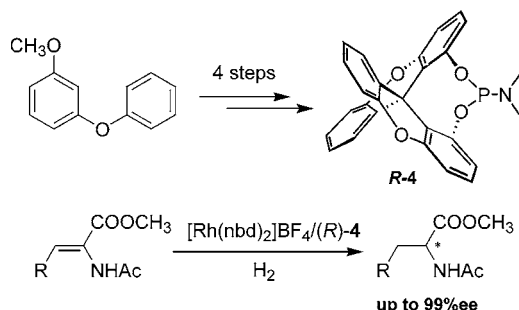
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ABSTRACT



A new spirocyclic diol, 9,9'-spirobixanthene-1,1'-diol, was synthesized in two steps from readily available starting material *m*-phenoxyanisole. Resolution of the racemic diol was achieved by cocrystallization with *N*-benzylcinchonidinium chloride and *N*-benzylquininium chloride in acetonitrile. The corresponding spiro monodentate phosphoramidite ligand has been prepared for Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives and itaconic acid with excellent enantioselectivities (up to >99% ee).

Transition-metal-catalyzed enantioselective hydrogenation is a powerful strategy to synthesize chiral substances from unsaturated starting materials.¹ Since DIOP ligand was discovered by Kagan in 1971,² a large number of bidentate ligands, especially those diphosphine ligands with C₂ symmetry, have been developed for highly efficient asymmetric hydrogenation of various olefins, ketones, and imines.³ In comparison, monodentate ligands had been much less successful due to the conformational flexibility of their metal/ligand complexes. However, recent advances^{4–6} indicated that

monodentate ligands can be effective for asymmetric hydrogenation. For example, MonoPhos has been prepared from BINOL^{5a} and led to excellent enantioselectivities in Rh-catalyzed asymmetric hydrogenation of α - and β -dehy-

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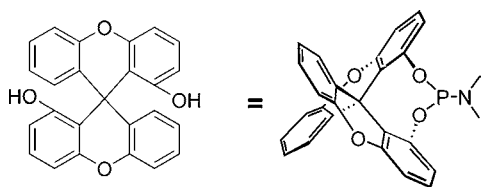
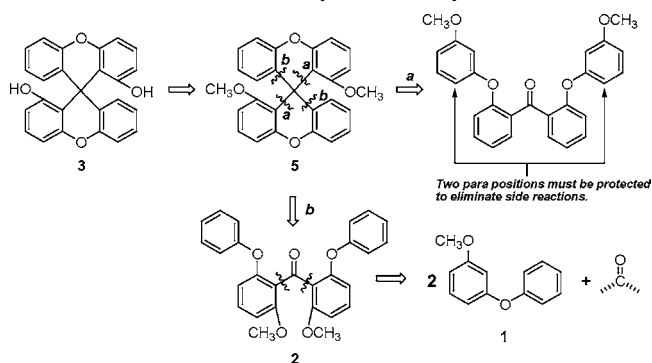


Figure 1. 9,9'-Spirobixanthene-1,1'-diol (**3**).

droamino acid derivatives,^{5b,c} itaconic acid derivatives,^{5b} and enamides.^{5d} Using 1,1-spiroindane-7,7-diol,^{6a} Zhou et al. have prepared a series of spiro monodentate phosphoramidite ligands (SIPHOS), and good to excellent results^{6b-e} have been achieved in asymmetric hydrogenation reactions. During the past few years, our group has examined a variety of readily available ligands with conformational rigidity.⁷ In searching for new structural motifs, we found that 9,9'-spirobixanthene was first synthesized in the 1930s,^{8a} and no further attempts had been made to assemble functional groups onto its aromatic rings.^{8b,c} We therefore modified this spirocyclic framework into a new C_2 -symmetric 9,9'-spirobixanthene-1,1'-diol (**3**, Figure 1), which possesses a larger biting angle and more rigid coordinating structure than BINOL.⁹ This new spirocyclic diol **3** is among the most accessible (two-step synthesis) diols reported to date and can be practical for many applications. Herein we report the facile synthesis and resolution of **3**. To demonstrate its potential role in asymmetric catalysis, spiro monodentate phosphoramidite ligand **4** was prepared, which exhibited excellent enantioselectivity (up to 99% ee) in Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives and itaconic acid.

The original synthesis of 9,9'-spirobixanthene^{8a} involved the reaction of a Grignard reagent with xanthenone to form a tertiary alcohol. Subsequent cyclization in the presence of acetic acid produced the spiran molecule. Considering the C_2 -symmetric structure of **3**, we envisioned double cyclization of ketone¹⁰ would be a more efficient approach. Among the two possible ways (Scheme 1) to disconnect the spirocyclic backbone into its ketone precursor, method a requires

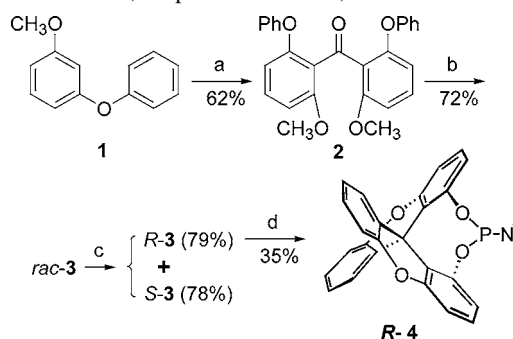
Scheme 1. Retrosynthetic Analysis of **3**



protection with removable substituents on the positions *para* to the methoxy groups in the aromatic ring before cyclization occurs.^{6a} On the other hand, there is no competing cyclization in method b. Therefore, it is a preferred strategy to construct the designed spirocyclic molecule.

Starting from 3-phenoxyanisole (**1**),¹¹ the symmetric ketone **2** was prepared in a moderate yield by linking 2 equiv of lithiated **1** with methyl chloroformate (Scheme 2). Further

Scheme 2. Synthesis of Chiral Monodentate Spiro Ligand via 9,9'-Spirobixanthene-1,1'-diol^a



^a Reagents and conditions: (a) (i) *n*-BuLi, THF, -78°C , (ii) ClCO_2CH_3 , THF, -78°C ; (b) (i) AlCl_3 , toluene, reflux, (ii) concd HCl, reflux; (c) (i) *N*-benzylcinchonidinium chloride, acetonitrile, (ii) *N*-benzylquininium chloride, acetonitrile; (d) hexamethylphosphorus triamide, toluene, reflux.

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treatment of **2** with an acid was expected to produce the spiran precursor **5**. However, several acidic reagents (H_2SO_4 , HCl, polyphosphoric acid, acetic acid, and trifluoroacetic acid) have been tested, and none of them can lead to the desired product. Interestingly, when we tried AlCl_3 , target molecule **3** was formed directly.¹² As a Lewis acid, AlCl_3 can promote not only Friedel–Crafts alkylation but also deprotection of methyl ether. That accounts for the direct formation of **3** from **2** in one pot.

To obtain enantiomerically pure **3**, cocrystallization¹³ of racemic **3** with chiral resolving reagents has been extensively

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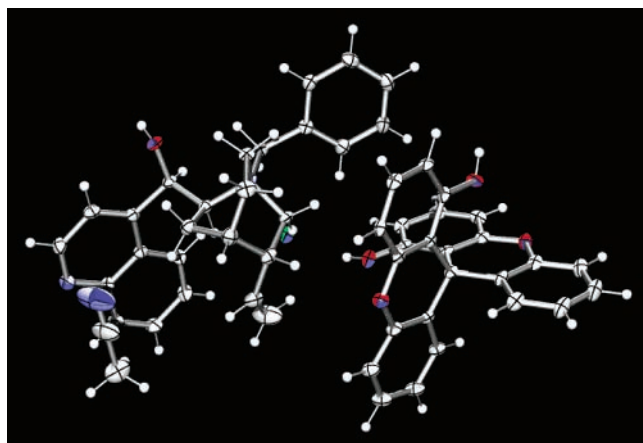


Figure 2. ORTEP representation of molecular complex crystal of (*R*)-**3** and **6**.

studied. The most efficient reagent was found to be *N*-benzylcinchonidinium chloride (**6**), which can precipitate as cocrystals with one enantiomer of **3** in acetonitrile. X-ray diffraction of a single crystal grown from the precipitate revealed a regularly packed molecular complex of **3** and **6** in 1:1 molar ratio (Figure 2). Based on the crystal structure of **6**, the absolute configuration of **3** is assigned as (*R*). The other (*S*) enantiomer of **3** can be obtained from the mother solution by cocrystallization with *N*-benzylquininium chloride.

To demonstrate the utilities of the spirocyclic diol, we have prepared monodentate phosphoramidite derivative **4** for asymmetric hydrogenation reactions. Following the procedure of Monophos synthesis,^{5a} (*R*)-**4** was prepared by reacting (*R*)-**3** with hexamethylphosphorus triamide (HMPT) in refluxing toluene. Then a series of α -dehydroamino acid derivatives **7** were explored as substrates in hydrogenation reactions. The results (Table 1, entries 1–7) confirm excellent enantioselectivities of **4** as a monodentate phosphoramidite ligand in Rh-catalyzed asymmetric hydrogenation reactions of dehydroamino acid derivatives (up to >99% ee). Itaconic acid **9** was also used for hydrogenation, and 97.9% ee was achieved (Table 1, entry 8). This result compares

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Table 1. Rh(I)/(*R*)-4-Catalyzed Asymmetric Hydrogenation of α -Dehydroamino Acid Derivatives and Itaconic Acid^a

| $ \begin{array}{ccc} \begin{array}{c} \text{COOCH}_3 \\ \\ \text{R}-\text{C}=\text{C} \\ \\ \text{NHAc} \end{array} & \xrightarrow[\text{H}_2 \text{ (25 psi)}]{[\text{Rh}(\text{nbd})_2]\text{BF}_4/(\text{R})\text{-4}} & \begin{array}{c} \text{COOCH}_3 \\ \\ \text{R}-\text{C}-\text{C}^* \\ \\ \text{NHAc} \end{array} \\ \mathbf{7} & & \mathbf{8} \end{array} $ | | | |
|--|---|---------------------|----------------------------|
| entry | substrate | ee (%) ^b | configuration ^c |
| 1 ^d | R = H | 98.2 | S |
| 2 | R = Ph | 98.4 | S |
| 3 | R = <i>p</i> -F-Ph | 99.9 | S |
| 4 | R = <i>p</i> -Cl-Ph | 99.1 | S |
| 5 | R = <i>o</i> -Cl-Ph | 99.3 | S |
| 6 | R = <i>m</i> -Br-Ph | 99.8 | S |
| 7 | R = 2-naphthyl | 99.8 | S |
| 8 | $ \begin{array}{c} \text{HOOC} \quad \text{COOH} \\ \diagup \quad \diagdown \\ \text{C}=\text{C} \end{array} $ 9 | 97.9 ^e | S |

^a Refer to the Experimental Section for details. All hydrogenation reactions were performed with 0.1 mmol substrate and 0.001 mmol in situ prepared $[\text{Rh}(\text{nbd})_2]\text{BF}_4/(\text{R})\text{-4}$ in CH_2Cl_2 at room temperature, P_{H_2} = 25 psi. 100% conversion was observed within 12 h. ^b Determined by chiral GC (Chirasil-VAL III FSOT). ^c The *S* absolute configuration was assigned by comparison of optical rotation with reported data. ^d THF/ CH_2Cl_2 (5:1) was used as solvent. ^e The ee was measured through its corresponding methyl ester (chiral GC, Gamma Dex-225).

favorably to those obtained with other monodentate phosphorus ligands (e.g., Monophos, 97% ee;^{5c} SIPHOS, 94.7% ee^{5b}).

In conclusion, we have developed a new C_2 -symmetric spirocyclic diol as a rigid motif for asymmetric catalysis. Initial studies on its corresponding monodentate phosphoramidite ligand showed excellent enantioselectivities in Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives and itaconic acid. With this distinct and readily accessible structural motif, various transition-metal-catalyzed asymmetric reactions can be realized.

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Supporting Information Available: Experimental details and spectroscopic data for all the new compounds and a general hydrogenation procedure. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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