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

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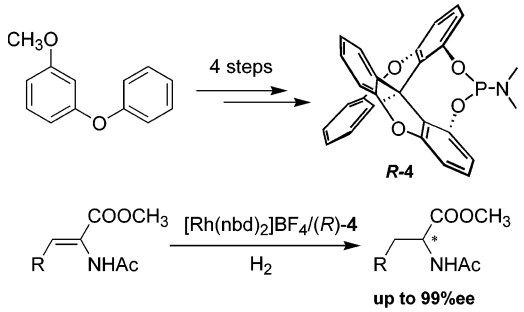
ABSTRACT



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 C_2 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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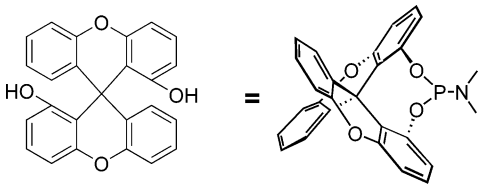
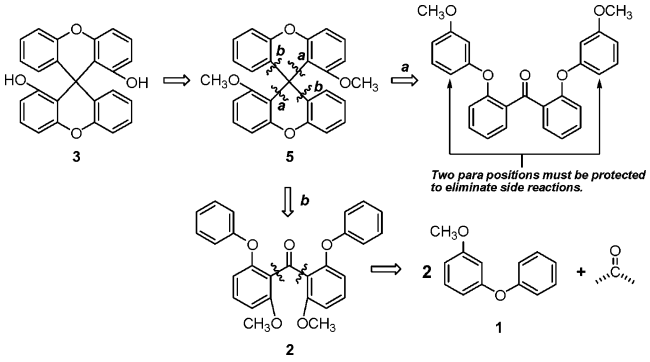


Figure 1. 9,9′-Spirobixanthene-1,1′-diol (**3**).

droamino acid derivatives,[5b,c] itaconic acid derivatives,[5b] and enamides.[5d] Using 1,1-spirobiindane-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 ketone[10] 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

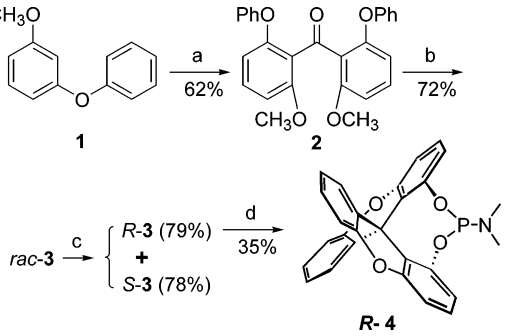
Scheme 1. Retrosynthetic Analysis of **3**



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.

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 Frediel−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**, cocrystallization[13] of racemic **3** with chiral resolving reagents has been extensively

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(9) During the course of our work, synthesis and resolution of 9,9′-spirobifluorene-1,1′-diol was reported by Zhou et al. in a six-step synthesis: Cheng, X.; Hou, G.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2004**, *6*, 2381.

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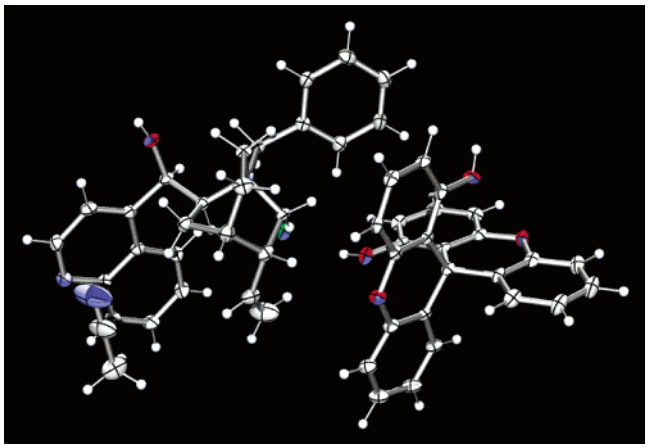
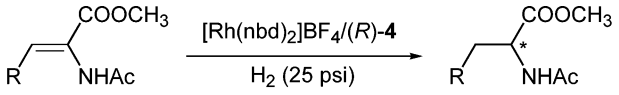


Figure 2. ORTEP representation of molecular complex crystal of (*R*)-**3** and **6**.

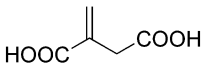
studied. The most efficient reagent was found to be *N*-benzylcinchonidinium chloride (**6**), which can precipitate as cocrystals with one enantiomer of **3** in acetonitrile. X-ray diffraction of a single crystal grown from the precipitate revealed a regularly packed molecular complex of **3** and **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 favorably to those obtained with other monodentate phosphorus ligands (e.g., Monophos, 97% ee;[5e] SIPHOS, 94.7% ee[5b]).

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



7 **8**

entry	substrate	ee (%)[b]	configuration[c]
1[d]	R = H	98.2	*S*
2	R = Ph	98.4	*S*
3	R = *p*-F-Ph	99.9	*S*
4	R = *p*-Cl-Ph	99.1	*S*
5	R = *o*-Cl-Ph	99.3	*S*
6	R = *m*-Br-Ph	99.8	*S*
7	R = 2-naphthyl	99.8	*S*
8		97.9[e]	*S*

9

[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 $[Rh(nbd)_2]BF_4$/(*R*)-**4** in CH_2Cl_2 at room temperature, P_{H2} = 25psi. 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).

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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(12) Other Lewis acids such as BBr_3 and $ZnCl_2$ are unsuccessful for the desired transformation.

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