

## Resolution of Spiro[4.4]nonane-1,6-dione by Chiral Inclusion Complexation

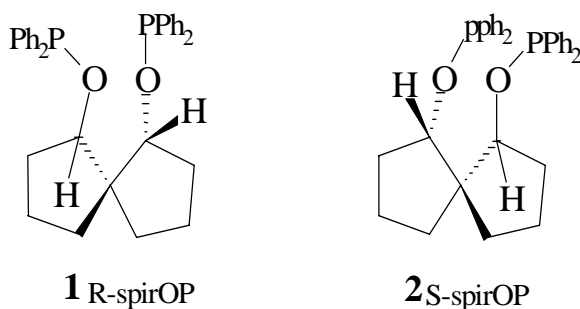
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**Abstract:** The racemic spiro[4.4]nonane-1,6-dione was efficiently resolved through an enantioselective inclusion complexation using chiral host BINOL by simple recrystallization with 31.9~38.4% yield and 100%ee.

**Keywords:** Resolution, chiral inclusion complexation, enantioselectivity.

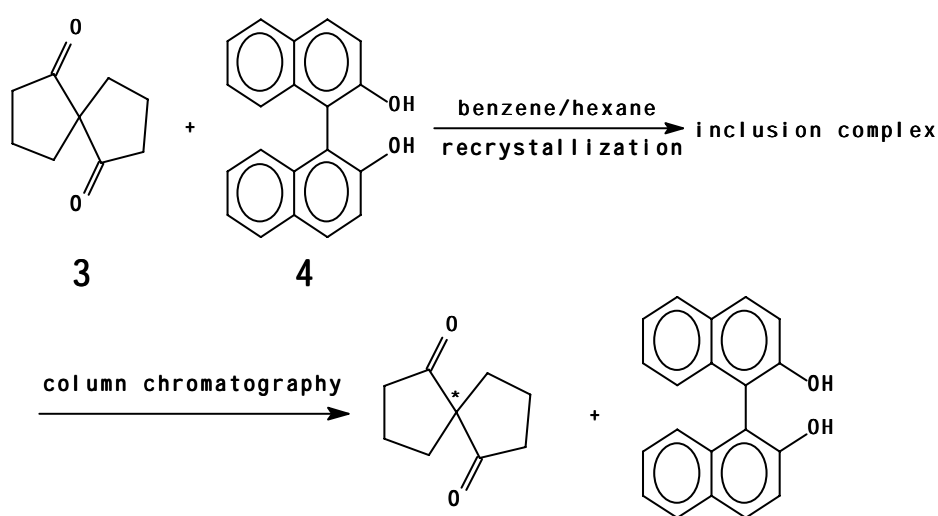
Because of the intrinsically skew orientation of the bicyclic rings in the spirocyclic diones, the chiral spiro[4.4]nonane-1,6-dione may be excellent precursors for useful ligands which can be used in metal-mediated asymmetric synthesis (including asymmetric catalysis). Recently, we reported asymmetric hydrogenation of 2-acetamidoacylic acid using spiro[4.4]nonane-1,6-dione derivatives **1** (or **2**) as chiral ligand gave >99.9% conversion and >99.9% enantiomeric excess<sup>1</sup>.



Because of the potential of the use of optically pure spiro[4.4]nonane-1,6-dione as precursors for useful chiral ligands, there is a great incentive to the preparation of

optically pure spiro[4.4]nonane-1,6-dione. However, reports about the preparation of optically pure spiro[4.4]nonane-1,6-dione are few and the Harada's procedure<sup>2</sup> is better than others for its good repeatability. Our laboratory also make some modifications on the basis of the Harada's procedure, but even in this improved procedure the overall yield of the resolution of racemic spiro[4.4]nonane-1,6-dione is only 23% and the procedure is too tedious for industrialization<sup>3</sup>. Moreover, we found that in the large scale (10 times) of this improved procedure the overall yield is as low as 15% and the enantiomeric excess is only 92.6% (need recrystallization)<sup>4</sup>.

Inclusion crystallization has been used since the early 1980s, to selectively and reversibly include chiral guest molecules in host lattices of chiral molecules<sup>5-6</sup>. Recently, we found this methods is effective for the resolution of racemic spiro[4.4]nonane-1,6-dione, which form inclusion complexes with chiral host compounds (BINOL), and the optically pure spiro[4.4]nonane-1,6-dione are obtained with 31.9~38.4% yield. A solution of **4** and rac-**3** in solvent was kept at appropriate temperature for 72 h, and an inclusion complex was obtained. The crude inclusion complex of **4** and **3** was recrystallized from the same solvent and subsequently separated by column chromatography on silica gel to give optically pure spiro[4.4]nonane-1,6-dione. The compound **4** could be recycled. The e.e. of spiro[4.4]nonane-1,6-dione was determined by GC using CP-chirasil-DEX(25m × 0.25mm, Chrompack company) and ethyl acetate as eluent (**Scheme 1**).

**Scheme 1**

The typical experimental results are summarized in **Table 1**.

**Table 1** resolution of spiro[4.4]nonane-1,6-dione **3** through inclusion complexation with BINOL **4**

entry	4(mmol)	3 (mmol)	benzene:hexane	solvent volumn(ml)	T°	yield(%)	e.e.(%)
1	R-(+),1	2	1:0	1.2	25	0.0	0.0
2	R-(+),1	2	1:1	2.0	25	0.0	0.0
3	R-(+),1	2	1:1	3.0	-25	34.2	100.0 <sup>a</sup>
4	R-(+),5	13.2	1:1	20.0	-25	36.8	100.0 <sup>a</sup>
5	R-(+),15	40.0	1.2:1	12.0	-25	38.4	100.0 <sup>a</sup>
6	S(-),0.6	1.2	1:1	2.0	-25	42.1	100.0 <sup>b</sup>

\*In entry 6, guest **3** is separated from mother liquid which through an enantioselective inclusion complexation by chiral host R-(+)-BINOL.

a. R-(+)- spiro[4.4]nonane-1,6-dione      b. S(-)- spiro[4.4]nonane-1,6-dione

The resolution of racemic spiro[4.4]nonane-1,6-dione was efficiently achieved through chiral inclusion complexation with chiral host BINOL by simple recrystallization with 31.9~38.4% yield and 100%e.e. The factors including temperature, solvent and amounts of chiral host BINOL which can influence the resolution of racemic spiro[4.4]nonane-1,6-dione were studied, the better conditions were showed in **Table 1**.

The IR and <sup>1</sup>H-NMR spectra of the inclusion complex showed that there is hydrogen bond between the OH of chiral host BINOL and the carbonyl of guest spiro[4.4]nonane-1,6-dione in a crystalline state. The study of x-ray structure and the chiral recognition principles in the inclusion complex are in progress.

### Acknowledgments

We thank the National Natural Science Foundation of China (No. 29832020) and the Union Laboratory of Asymmetric Synthesis in Chengdu for financial support of this study.

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7. IR spectrum (differences). Racemic spiro[4.4]nonane-1,6-dione: 1725, 1745cm<sup>-1</sup> (overlap).

R-(+)-BINOL: 3420 (sharp), 3500 (sharp)  $\text{cm}^{-1}$ . Complex: 3420 (broad), 3500 (broad), 1720, 1750  $\text{cm}^{-1}$ .

8.  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ). Racemic spiro[4.4]nonane-1,6-dione:  $\delta$  (ppm) 1.2~2.4 (12H,m).

R-(+)-BINOL:  $\delta$  (ppm) 5.07 (-OH,broad). Complex: 5.20 (-OH,sharp),

Received 7 December 1998