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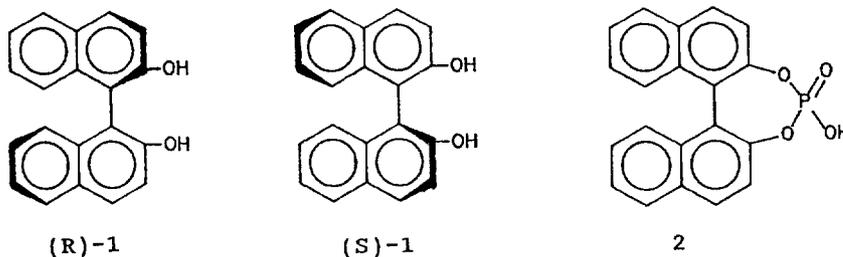
A Simple Convenient Method for the Resolution of Racemic 2,2'-Dihydroxy-1,1'-Binaphthyl Using (S)-Proline

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Abstract: The racemic mixture of 2,2'-dihydroxy-1,1'-binaphthyl has been resolved to obtain the R(+) and S(-) enantiomers in essentially pure forms by refluxing with (S)-proline (1eq.) in benzene in three successive operations.

The enantiomers of 2,2'-dihydroxy-1,1'-binaphthyl, (RS-1), have been useful in several stoichiometric and catalytic enantioselective transformations.¹ Obviously, there have been sustained efforts to develop methods for the synthesis of these important enantiomers in enantiomerically pure forms. Although several methods have been reported for the synthesis of these enantiomers (eg. enantioselective synthesis,²⁻⁴ resolution through crystallization of complexes obtained using chiral trans-1,2-diaminocyclohexane⁵ or certain N-alkylcinchonidium halides,⁶ deracemization-crystallization procedure⁷ and enzymatic resolution^{8,9}), resolution methods based on phosphoric acid 2 and its derivatives have been widely utilized.¹⁰⁻¹³



In addition to requiring several steps for the synthesis and resolution, the cyclic phosphoric acid 2 has to be finally cleaved using LiAlH_4 to obtain 1. We wish to report here a very simple, convenient and novel method of resolution of (RS)-1 utilizing (S)-proline.

Table 1. Separation of Enantiomers of 1 using (S)-Proline.

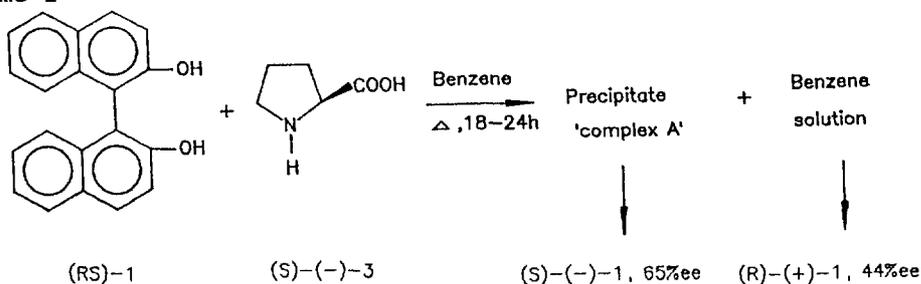
S.No.	Substrate 1 ^a Config., % ee	Product 1 obtained from					
		Precipitate (complex A)			Solution		
		Config.	% ee	yield	Config.	% ee	% yield
1	(RS)-(±), 0 ^b	S	65	43	R	44	51
2	(S)-(-), 10 ^c	S	64	65	R	70	25
3	(S)-(-), 65 ^d	S	87	66	S	06	22
4	(R)-(+), 44 ^e	R	90	45	R	06	41
5	(S)-(-), 87 ^f	S	100 ^h	77	S	35	11
6	(R)-(+), 90 ^g	R	98 ⁱ	70	R	28	18

a) Experiments were carried out using 1:1 mixtures of 1 and (S)-proline in dry benzene and refluxed for 24h. b) (RS)-(±)-1 (5.72g, 20mM), (S)-3 (2.3g, 20mM) and 240 ml of benzene were used. (RS)-(±)-1 was prepared following a reported procedure (ref.16). It was purified by recrystallization from benzene. c) (S)-(-)-1 (1.00g), (S)-(-)-3 (0.40g) and 50 ml of benzene were utilized. d) (S)-(-)-1 (2.50g), (S)-(-)-3 (1.00g) and 105 ml of benzene were used. e) (R)-(+)-1 (2.90g), (S)-(-)-3 (1.20g) and 120 ml of benzene were utilized. f) (S)-(-)-1 (0.90g), (S)-(-)-3 (0.37g) and 50 ml of benzene were used. g) (R)-(+)-1 (0.96g), (S)-(-)-3 (0.39g) and 45 ml of benzene were utilized. h) Enantiomeric excess was determined by HPLC analysis on chiralcel OP column using methanol as solvent. All other % ee values reported here are based on $[\alpha]_D^{25}$ values; maximum $[\alpha]_D^{25} = 34$ (Cl, THF) (ref.13). i) 100% ee based on $[\alpha]_D^{25}$ value. However, presence of 1-2% of the (S)-(-) enantiomer was detected in the HPLC analysis.

In the course of an investigation on the synthesis and utilization of chiral auxiliaries derived from (S)-proline,^{14,15} We have observed that refluxing of a 1:1 mixture of racemic 2,2'-dihydroxy-1,1'-binaphthyl and (S)-proline 3 in benzene leads to a precipitate and a benzene solution (Scheme 1). Upon separation and evaporation of the

benzene solution, a residue containing **1** enriched in (R)-isomer (44% ee) was obtained. The precipitate (complex A) on treatment with ether digests compound **1** leaving behind insoluble (S)-proline. The compound **1** obtained in this way was found to be enriched in (S)-isomer (65% ee).

Scheme 1



Similar experiments with mixtures of (R)-**1** and (S)-**1** enriched in one of the isomers lead to separation of the enantiomers as outlined in Table 1. The racemic **1** can be converted into essentially pure enantiomers in three successive repetitions of the procedure using (S)-proline (entries 1 → 3, 4 → 5, 6). Also, it is of interest to note that both the enantiomers of **1** are obtained in essentially pure forms using the readily accessible natural (S)-proline.

The following is a representative procedure: In a 500 ml RB flask fitted with a reflux condenser, (S)-proline (2.3g, 20mM) and (±)-**1** (5.72g, 20mM) were suspended in dry benzene (240 ml) and refluxed. The slurry becomes homogeneous in 1h and precipitation starts in 3h. After 24h, the reaction flask was brought to room temperature and the precipitate was filtered. It was washed with dry benzene (20 ml). The combined benzene solution was concentrated to obtain a solid. This was extracted into ether by stirring the suspension in anhydrous ether (2x40 ml) leaving behind the insoluble (S)-proline (0.20g). The combined ether extract was concentrated and the residue was purified by column chromatography (hexane:ethyl acetate/80:20) to obtain (R)-(+)-**1**, yield 2.9g (44% ee), $[\alpha]_D^{25} = +15$ (C1, THF). The precipitate (complex A) was then extracted into ether (4x50 ml). The insoluble (S)-proline (1.70g) was separated. The combined ether extract was concentrated and the residue was purified by column chromatography to obtain (S)-(-)-**1**, yield 2.5g, (65% ee) $[\alpha]_D^{25} = -22$ (C1, THF). The recovered (S)-proline fractions were combined and crystallized from ethanol (1.68g, 73%).

We have carried out several experiments in order to examine the nature of the precipitate (complex A, Scheme 1) obtained in the reaction of **1** and (S)-proline. Unfortunately, this material is insoluble in non polar solvents such as benzene, CHCl_3 and CH_2Cl_2 but decomposes in

solvents such as ether, THF and CH₃OH. Although we do not have results at hand to speculate the nature of this precipitate, the method of resolution/enrichment of the enantiomers of this important chiral auxiliary should be synthetically useful. This method should be also economical since most of the (S)-proline (>70%) and the solvents utilized can be recovered and recycled.¹⁷ We are actively pursuing research in delineating the nature of the complexes involved and also in the further development of resolution methods utilizing the readily accessible chiral amino acids and their derivatives.

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17. A referee pointed out that the use of benzene as solvent will limit the utility of this method. We have carried out an experiment with (RS)-1 (5mM) and (S)-proline (5mM) utilizing toluene (60 ml) in place of benzene 80-90°C for 24h following the procedure described in the text and obtained (S)-1 (18% yield, 38%ee) and (R)-1 (66% yield, 12%ee).