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A Novel, Simple Method for Enrichment of Enantiomeric Excess of Scalemic 1,1'-Bi-2-naphthol

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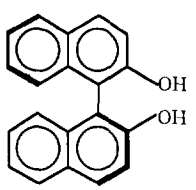
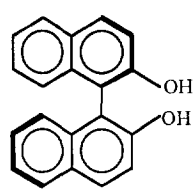
Abstract: Enantiomeric excess of scalemic (i.e nonracemic, 17-86 % ee) 1,1'-bi-2-naphthol are readily enhanced to 90-96 % ee by refluxing with $B(OH)_3$ and TMEDA in acetonitrile, followed by acid hydrolysis of the precipitate.

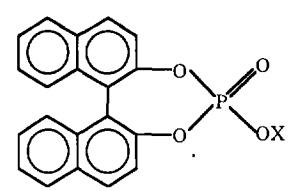
Homochiral 1,1'-bi-2-naphthol **1** has become one of the most important organic compounds. Several useful chiral acid and base catalysts have been prepared from this reagent.[1] Obviously, several methods are available for the synthesis of this compound in enantiomerically pure forms. Generally, resolution of racemic **1** is carried out via the synthesis of diastereomeric phosphate esters **2** which are finally cleaved using $LiAlH_4$ to obtain **1**.[2]



(S) - **1**



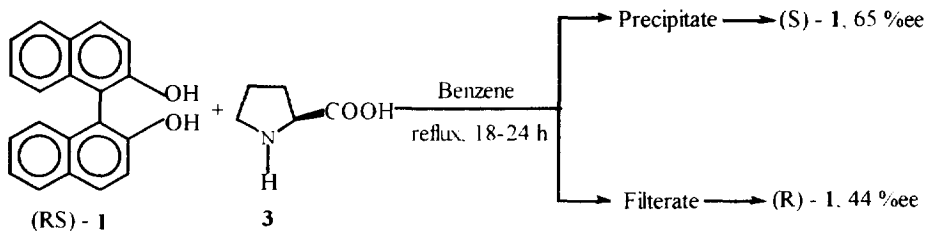
(R) - **1**



2

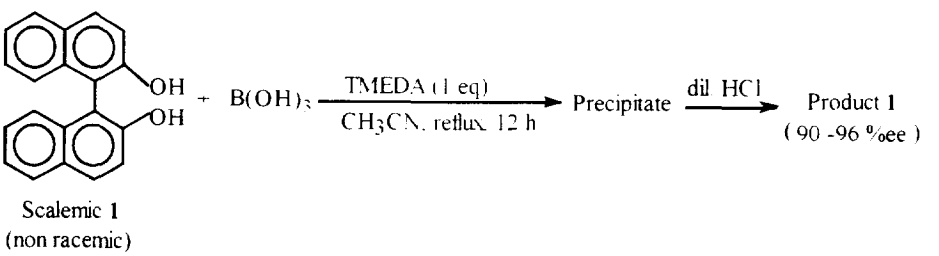
In recent years, Toda etal, Kawashima and Hirata and we have developed direct resolution methods using N-benzylcinchonidium halides,[3] certain chiral diamines[4] and (S)-proline **3**,[5] respectively. The latter method using the readily accessible (S)-proline (Scheme 1) should be attractive for synthetic applications. Unfortunately, this method requires three successive operations, each requiring equimolar amounts of (S)-proline to obtain **1** in enantiomerically pure form.[5] Although the (S)-proline can be readily recovered and recycled, we were looking for a method of upgradation of the enantiomeric excess of scalemic **1** without reusing (S)-proline. We wish to report that this objective is readily achieved by refluxing the scalemic mixtures of **1** with boric acid and TMEDA (N,N,N',N'-tetramethylethylenediamine) in acetonitrile.

Scheme 1:



It has long been recognised that the separation of enantiomers from a scalemic mixture through the synthesis of complexes of the type ML_2 followed by separation and decomposition of the complex should give the L with enhanced enantiomeric excess even if there is no stereoselection in the formation of the ML_2 complexes [6] It was thought that this would be readily realised in the reaction of $B(OH)_3$ with the scalemic diol **1** which is expected to give a complex of the type B_2L_3 (L=1,1'-bi-2-naphthyloxy)[1c] (Scheme 2).

Scheme 2:



Initial experiments using $B(OH)_3$ (2 eq), **1** (3 eq) and TMEDA (1 eq) in benzene or acetonitrile did not give fruitful results (Table 1, entries 1,2). However, when the $B(OH)_3$ was used less than that required for the formation of B_2L_3 type complexes better results were observed (entries 3-6) Finally, very good results were obtained when the experiments were carried out using $B(OH)_3$ equivalent to the excess of the enantiomer present (entries 7-16). The samples of **1** with 94 - 96 % ee can be readily purified to get sample with 100% ee by crystallization from methanol.[3]

The following is the representative procedure A 50 ml RB flask was charged with **1** (5 mmol), $B(OH)_3$ and TMEDA (1 mmol) and acetonitrile (20 ml) was added. The resulting suspension was refluxed for 12 h. Then the reaction mixture was cooled to 25 ^{o}C and filtered. The filterate was concentrated. The precipitate and the residue obtained from the filterate were treated with ether (100 ml) / dil.HCl (20 ml) mixture for 10 min, washed with water (2x10 ml) and brine (10 ml) successively. The aqueous layer was separated and the ether layer was dried over $MgSO_4$, filtered and the solvent was removed to obtain **1.**

Table 1: Upgrading of Enantiomeric Excess of 1,1'-bi-2-naphthol Using $B(OH)_3$ and TMEDA[a]

Entry No.	Substrate 1 Config., % ee		Boric acid mmol	Product 1 obtained from Precipitate Config., % ee		Precipitate Yield (%)[d]	Filterate Config., % ee		Filterate Yield (%)
1.	R	63	2.0[b]	R	74	78	R	40	06
2.	R	34	2.0	R	52	47	S	03	33
3.	R	16	2.0[b]	R	41	28	R	01	56
4.	S	28	2.0[b]	S	59	38	R	03	52
5.	S	18	2.0	S	31	57	S	05	30
6.	R	34	2.0	R	89	38	R	12	48
7.	R	17	0.57	R	89	11	R	03	76
8.	R	34	1.14	R	93	31	S	05	55
9.	R	53	1.80	R	96[c]	30	R	20	53
10.	R	69	2.30	R	95	41	R	52	45
11.	R	76	2.50	R	94	48	R	64	39
12.	S	18	0.60	S	90	13	S	05	75
13.	S	34	1.10	S	96	28	S	01	54
14.	S	53	1.80	S	96	38	S	16	47
15.	S	70	2.30	S	94	52	S	34	36
16.	S	86	2.90	S	94[c]	53	S	74	33

a) All experiments were carried out using 5 mmol of **1** (in entries 1&2 only 3 mmol of **1** was used) in acetonitrile (20 ml) and the contents were refluxed for 12 h. The ee values are based on $[\alpha]_D^{25}$ = 34 (C1, THF) for compound with 100 % ee (ref. 2d. However, Toda et. al. (ref. 3) reported a value of $[\alpha]_D^{25}$ = 33.2 for a sample which was found to be 100 % ee by HPLC analysis).

b) In these experiments benzene (40 ml) was used as solvent and the contents were refluxed for 12h.

c) HPLC analysis on chiralpak OP using methanol as eluent did not detect the presence of 2-3 % of the other enantiomer. However, the enantiomeric purities of 94-96 % ee given in this Table should be at least 96-98 % ee if these results are compared with that reported by Toda et. al. (ref. 3)

d) Yields based on amount of scalemic **1** used. In runs 7 - 16, the yields are expected to be equal to or less than the percentage ee of the starting scalemic mixture since the amounts of boric acid utilized were equivalent to the enantiomer present in excess over the racemic mixture to form the B_2L_3-amine complex.

We have also observed that the experiments utilizing $(C_2H_5)_3N$ in place of TMEDA gave poor results Although attempts made to analyse the nature of the complex formed in the reaction of **1** with $B(OH)_3$ and TMEDA did not give fruitful results,[7] this new method of enrichment of enantiomeric excesses of scalemic **1** should be useful for synthetic applications. In addition, formation of the complex derived from the major enantiomer implies interesting further applications in asymmetric catalysis.[8]

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