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Simple and Efficient Resolution of 1,1'-Bi-2-naphthol

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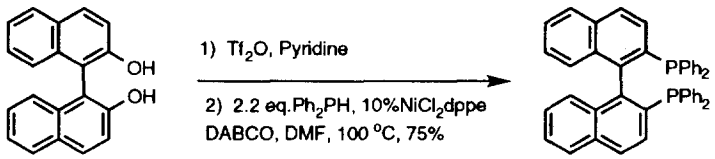
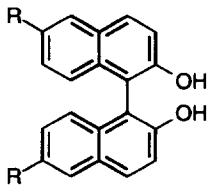
Abstract: Acetonitrile is a crucial solvent for a simple and efficient resolution of 1,1'-bi-2-naphthol using *N*-benzylcinchonidium chloride. Both enantiomers can be easily obtained with ≥95% yield and ≥99% ee.

Both enantiomers of 1,1'-bi-2-naphthol are very useful compounds for various applications : 1) chiral inducing agents for catalytic asymmetric reactions such as Diels-Alder reaction,[1] ene reaction,[2] and Lewis acid-catalyzed reactions;[3] 2) enantioselective reduction of ketones;[4] 3) synthesis of chiral macrocycles[5] and other interesting compounds.[6] Recently, we discovered a new reaction which enabled us to convert directly the chiral ditriflate of 1,1'-bi-2-naphthol to chiral 2,2'-bis(diphenylphosphino)-1,1-binaphthyl (BINAP).[7] In order to

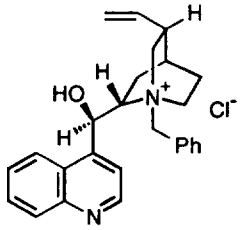


make this reaction even more attractive, we sought an inexpensive, readily available source of both enantiomers of 1,1'-bi-2-naphthol. Although there are numerous reported practical resolutions of 1,1'-bi-2-naphthol, including enzymatic hydrolysis of the diester of 1,1'-bi-2-naphthol,[8] resolution of the cyclic phosphate of 1,1'-bi-2-naphthol, and inclusion complexes with suitable compounds,[9~11] none of these resolutions satisfied our requirements for simplicity (prefer no chemical steps) and low cost. Thus far, the most attractive method for resolution of both enantiomers of 1,1'-bi-2-naphthol appears to be formation of an inclusion complex with (*R,R*)-1,2-cyclohexanediamine,[10] but the commercially available (*R,R*)-1,2-cyclohexanediamine is expensive. Other resolving agents such as (*R,R*) or (*S,S*)-(+)-2,3-dimethoxy-*N,N,N',N'*-tetramethylsuccinamide, and (*R,R*) or (*S,S*)-(+)-*N,N,N',N'*-tetramethyl-2,2'-dimethyl-1,3-dioxolane-trans-dicarboxamide were also reported to form inclusion complexes with 1,1'-bi-2-naphthol, but they must be synthesized from tartaric acid and they are difficult to remove.[11] Recently, Toda *et al.* reported that *N*-benzylcinchonidium chloride readily forms an inclusion complex with one enantiomer of 1,1'-bi-2-naphthol.[12] In this procedure, one enantiomer (*R*) of 1,1'-bi-2-naphthol is crystallized as an inclusion complex with high ee, while the other enantiomer (*S*) remains in the mother liquor with only 42% ee. Since there is no opposite enantiomer of *N*-benzylcinchonidinium chloride

available, the pure (*S*)-enantiomer of 1,1'-bi-2-naphthol appears difficult to obtain using Toda's procedure. However, if the crystallization of the *N*-benzylcinchonidinium complex can be improved to near 100% yield, then the resulting mother liquor should provide near 100% ee of the other enantiomer. This would offer a simple, cheap and efficient resolution of 1,1'-bi-2-naphthol. Here, we report our approach for resolutions of both enantiomers of 1,1'-bi-2-naphthol using *N*-benzylcinchonidinium chloride.

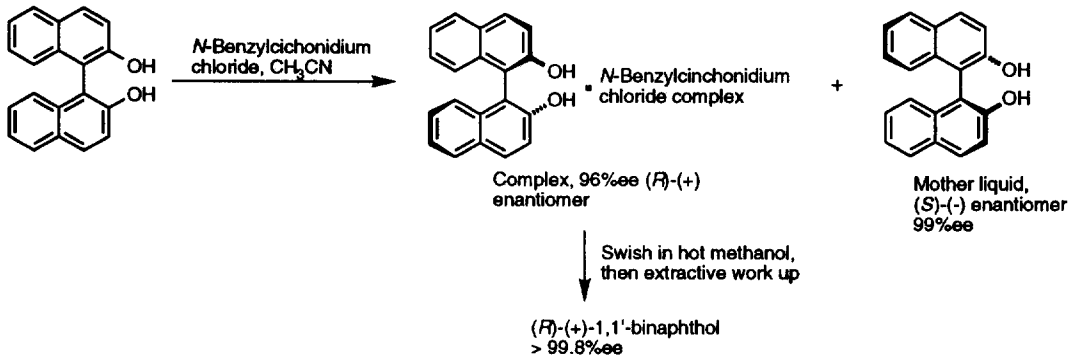


R = H, Br, Me



N-Benzylcinchonidinium Chloride

We believed that the low enantiomeric excess (42% ee) of 1,1'-bi-2-naphthol in the mother liquor using Toda's procedure was due to the nature and volume of solvent. The complex is too soluble in the solvent (MeOH) used by Toda. So, the key to success in this approach is selection of a suitable solvent in which one enantiomer completely forms an inclusion complex with *N*-benzylcinchonidinium chloride and the resulting inclusion complex has very low solubility (< 1%); therefore, one could obtain a high optical purity of the other enantiomer in the mother liquor (>98% ee). There are two other limitations for selecting a suitable solvent: 1) at least one enantiomer of 1,1'-bi-2-naphthol must be completely soluble in that solvent, and 2) it is necessary to have a reasonable solubility of *N*-benzylcinchonidinium chloride in that solvent, so the inclusion complex will be formed favorably. We tried several solvents and found that acetonitrile is an excellent solvent for this resolution. 1,1'-Bi-2-naphthol was successfully resolved with 0.55-0.6 eq. of *N*-benzylcinchonidinium chloride. When carried out at 0°, the mother liquors contained one enantiomer of 99.0% ee (98.6% ee if carried out at room temperature) while the resulting crystalline inclusion complexes were 96% ee of the opposite enantiomer. It is extremely important to get a high ee% for the isomers in the mother liquor, because they are much harder to upgrade by recrystallization. The inclusion complex, on the other hand, is very easy to upgrade to near 100% ee by swishing in hot acetonitrile or alcohol solvents such as methanol or ethanol.



Our procedure can also apply to binaphthol analogs such as 6,6'-dibromo-1,1'-bi-2-naphthol or 6,6'-dimethyl-1,1'-bi-2-naphthol with essentially the same results.[13,14]

In summary, we have developed a simple and efficient resolution for both enantiomers of 1,1'-bi-2-naphthol using *N*-benzylcinchonidinium chloride in acetonitrile. Both enantiomers of 1,1'-bi-2-naphthol can be easily obtained in $\geq$ 95% yield and $\geq$ 99% ee. This procedure represents a much better resolution for 1,1'-bi-2-naphthol than those previously reported.

Experimental

A 500 mL flask, equipped with a magnetic stirring bar and a reflux condenser, is charged with 1,1'-bi-2-naphthol (23.0 g, 80 mmol) and *N*-benzylcinchonidinium chloride (18.6 g, 44 mmol). Acetonitrile (300 mL) is added and the resulting suspension is refluxed for 4 hrs, cooled and stirred at room temperature overnight, then cooled to 0-5 °C and kept at that temperature for 2 hrs, then filtered. The filtrate is concentrated to dryness, then redissolved in ethyl acetate (300 mL), and washed with 1N HCl (2 x 100 mL) and brine (100 mL), respectively. The organic layer is dried over Na_2SO_4, filtered, and concentrated to a light brown solid [10.87 g, 99 wt%, mp 207-210 °C, 95% recovery, 99.0% ee (*S*)-enantiomer $[\alpha]_D^{21}$ = 34.0 (THF, *c* 1)].[15]

The solid is washed with acetonitrile (50 mL). This acetonitrile solution is discarded due to the low ee, ~80% ee, of the (*S*)-enantiomer contained. The resulting solid complex (96% ee, *R* enantiomer) is transferred into a 250 mL flask. Methanol (100 mL) is added and the resulting suspension is refluxed for 24 hrs to upgrade the enantiomeric excess to >99.8% ee.[16] After cooling to room temperature the mixture is filtered and the solid is washed with methanol (20 mL). The solid complex is suspended in a mixture of ethyl acetate (300 mL) and 1N HCl (150 mL) and stirred until complete dissolution occurs (0.5 hr). The solution is transferred into a separatory funnel and the organic layer separated, then washed with 1N HCl (150 mL) and brine (150 mL), respectively. The organic layer is dried over Na_2SO_4, filtered, and concentrated to an off-white crystalline solid [10.97 g, 99 wt%, mp 208-210 °C, 95% recovery, >99.8% ee of (*R*)-enantiomer $[\alpha]_D^{21}$=34.3 (THF, *c* 1)].

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14. Both mother liquors of bromo and methyl analogs had 98~99% ee, and the complexes had 96% ee of the other enantiomers. The complexes can be upgraded to >99.8% ee (our detection limit) by slurrying in refluxing ethanol or methanol. Chiral assay were performed on a Diacel Chiralpak AD column (4.6 x 250 nm) with 15 % EtOH/hexane at a flow rate of 1.0 mL/min. Typical retention times for two enantiomers of 6,6'-dibromo-1,1'-bi-2-naphthol were 11.0 and 16.4 min. respectively, and typical retention times for two enantiomers of 6,6'-dimethyl-1,1'-bi-2-naphthol were 12.0 and 16.4 min. respectively.
15. Enrichment to >99.8% ee is possible by recrystallization from a MTBE/hexane mixture: 1.0 g of (*S*)-1,1'-bi-2-naphthol is dissolved in MTBE (10 mL) then hexane is added (20 mL). The resulting solid is stirred at room temperature for 2 hr, then filtered to provide a white crystalline solid (0.65 g, >99.8% ee, >99 wt% purity).
16. Numerous chiral HPLC columns have been used for determination of chiral purity of 1,1'-bi-2-naphthol.[8,10] We used Diacel Chiralpak OP(+) column (4.6 mm x 250 mm) at room temperature for our chiral assay. Typical retention times of 1,1'-bi-2-naphthol are 14 min (*R* enantiomer) and 20 min (*S* enantiomer) using methanol as an eluting solvent at 0.5 mL/min. Our detection limit of minor enantiomers is around 0.1%.

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