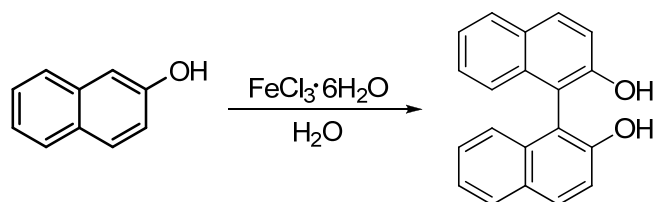


1,1'-二联-2-萘酚的合成与拆分

1,1'-二联-2-萘酚的两种对映体已得到广泛应用：1) 不对称催化反应（例如 Diels-Alder 反应，³ ene 反应，^{4,5}）中的手性诱导试剂或 Lewis 酸；^{6,7} 2) 酮的对映选择性还原；^{8,9} 3) 手性大环^{10,11} 和其它有趣的化合物¹² 的合成。原来报道的拆分方法包括：1) 制成一种联萘酚的环状磷酸酯，拆分并接着进行还原，释放出手性纯联萘酚；¹³⁻¹⁷ 2) 联萘酚二酯的酶水解；¹⁸ 和 3) 与适当的化合物形成包合物。¹⁹⁻²¹ 用氯化 *N*-苄基辛可宁季铵盐制备包合物以得到联萘酚的一种对映体是 Ding 组报道的。² 用乙腈作溶剂包合物溶解度很小，两种异构体都可以以高对映纯度分离得到。

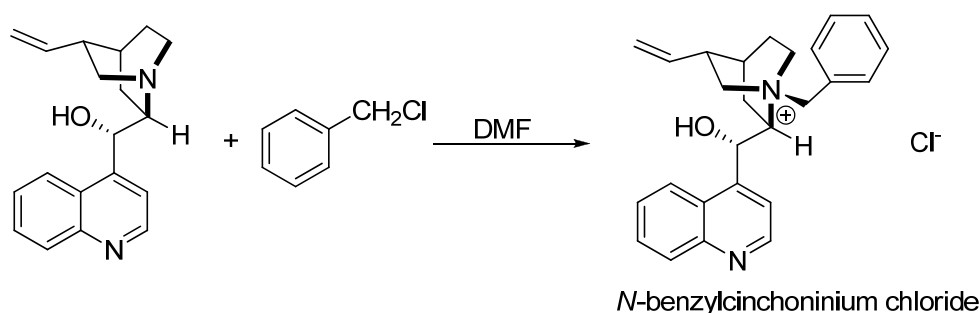
一、操作流程

1、消旋 1,1'-二联-2-萘酚的制备¹



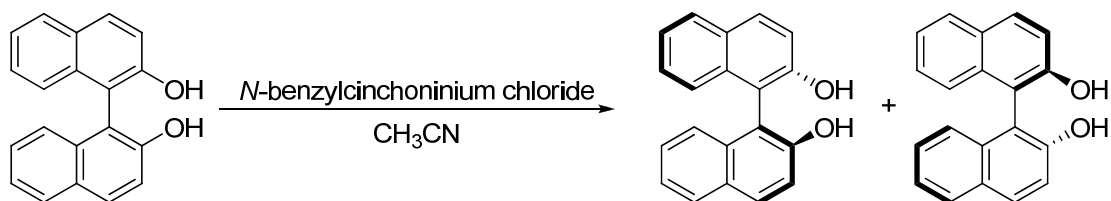
事先粉碎好的 2-萘酚 (Note 1) (1.0 g, 7 mmol) 加入 20 ml 溶解有 3.8 g (14 mmol) FeCl₃ · 6H₂O 的水溶液，在空气氛围中，50℃ 下搅拌 1 小时。粗产物过滤分离，然后用蒸馏水洗涂除去 Fe³⁺ 和 Fe²⁺。产物用甲苯重结晶可得到白色针状的纯产物，产率 95%。

2、氯化 *N*-苄基辛可宁季铵盐的制备²



辛可宁 (11.76 g, 40 mmol) 中加入溶有苄基氯 (Note 2) (7.62 g, 60 mmol) 的 DMF 溶液 80 ml。混合物在 80℃ 下加热搅拌 3 小时。冷却后抽滤收集白色针状晶体，用丙酮洗涤 (2 × 10 mL)，得到产率为 85% 的 *N*-苄基辛可宁季铵盐。Mp 256℃ (dec.) (lit. Mp 248℃). $[\alpha]_{27}^{D} = +165.9$ (c=0.50, H₂O) (lit. $[\alpha]_{27}^{D} = +164.8$ (c=0.716, H₂O)).

3、用氯化 *N*-苄基辛可宁季铵盐拆分消旋的 1,1'-二联-2-萘酚



氯化 *N*-苄基辛可宁季铵盐(20.21 g, 48 mmol)加入消旋 1,1'-二联-2-萘酚(22.88 g, 80 mmol)的乙腈溶液 300ml。混合物回流 4 小时, 然后冷却至室温。所得白色固体抽滤收集, 用乙腈洗涤 (3×20 mL)。这些固体是(R)- (+)-1,1'-二联-2-萘酚与氯化 *N*-苄基辛可宁季铵盐形成的摩尔比率为 1:1 的双组分子晶体。Mp 248°C(dec.)。留在母液中的是富集的(S)- (-)-1,1'-二联-2-萘酚。

将分子晶体分散在稀盐酸 (200 mL of 1 N HCl 和 800 mL of H₂O) 与 300 mL 乙酸乙酯中搅拌 30 分钟, 直到白色固体消失。分出有机层, 用盐水洗涤, 无水 MgSO₄ 干燥。蒸除溶剂后, 残留物用苯重结晶给出产率 80% 的白色棱状(R)- (+)-1,1'-二联-2-萘酚, 99% ee (Chiralcel AS, 0.8 mL min⁻¹, S: 12.43 min; R: 16.06 min.) Mp 208-210°C (lit. 208-210°C)。

$[\alpha]_D^{27} = +32.1$ (c=1.0, THF) (lit. $[\alpha]_D^{21} = +34.3$ (c=1.0, THF)); ¹H NMR (300 MHz, CDCl₃): d

5.05 (s, 2H), 7.15 (d, J=8.11 Hz, 2H), 7.29-7.41 (m, 6H), 7.88 (d, J=8.40 Hz, 2H), 7.96 (d, J=8.92 Hz, 2H). ¹³C NMR (100.61 MHz, CDCl₃): d 110.9, 117.8, 124.1, 124.3, 128.5, 129.5, 131.5, 133.5, 152.8.

母液浓缩至干, 然后重新溶解于 300 mL 乙酸乙酯, 并用 HCl (100 mL, 1 N) 和 50 mL 盐水洗涤。有机层用无水 MgSO₄ 干燥。采用与(R)- (+)-1,1'-二联-2-萘酚相同的重结晶操作流程, 得到产率 78% 的(S)- (-)-1,1'-二联-2-萘酚, 99% ee (Chiralcel AS, 0.8 mL min⁻¹, S: 12.43 min; R:

16.06 min). Mp 208-210°C (lit. 207-210°C), $[\alpha]_D^{27} = -33.5$ (c=1.0, THF) (lit. $[\alpha]_D^{21} = -34$ (c=1.0,

THF))。

合并盐酸提取物, 用 NaHCO₃ 中和得到白色沉淀, 抽滤收集。用甲醇与水混合溶剂重结晶给出 *N*-苄基辛可宁季铵盐晶体, 回收率 > 90%, 可以再用来拆分, 其效率毫无降低。

二、注意事项

1、2-萘酚吸入或食入是有害的。对眼睛, 皮肤和呼吸系统有强烈刺激作用;

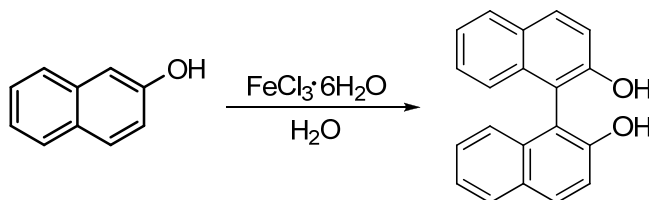
2、苄基氯是催泪剂, 并被用作化学武器。对皮肤有强烈刺激作用。 $d_4^{25} = 1.100$

The synthesis and resolution of 1,1'-bi-2-naphthol

Both enantiomers of 1,1'-bi-2-naphthol are widely used for various applications: 1) chiral inducing agents for catalytic, asymmetric reactions such as the Diels-Alder reaction,³ ene reaction,^{4,5} or as Lewis acids;^{6,7} 2) enantioselective reduction of ketones;^{8,9} 3) synthesis of chiral macrocycles^{10,11} and other interesting compounds.¹² Previously reported resolutions include: 1) making a cyclic phosphate of binaphthol, then resolution and subsequent reduction to release the pure binaphthol;¹³⁻¹⁷ 2) using enzymatic hydrolysis of the diester of binaphthol;¹⁸ and 3) forming inclusion complexes with suitable compounds.¹⁹⁻²¹ The use of *N*-benzylcinchoninium chloride to make inclusion complexes was reported by Ding and co-workers for obtaining one enantiomer of binaphthol.² Using acetonitrile as solvent, in which the inclusion complex has very low solubility, allows for the isolation of both enantiomers with high enantiomeric excess.

1. Procedure

A. The preparation of racemic 1,1'-bi-2-naphthol¹

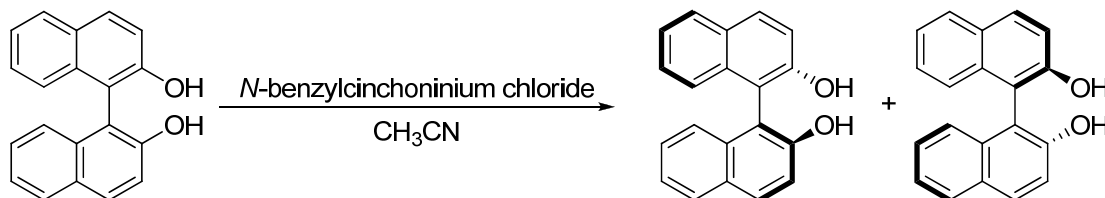


A suspension of powdered 2-naphthol (Note 1) (1.0 g, 7 mmol) in water (20 mL) containing $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (3.8 g, 14 mmol) was stirred at 50°C for 1 h under air atmosphere. The crude product was separated quantitatively by filtration and washed with distilled water to remove Fe^{3+} and Fe^{2+} . Recrystallization of the product from toluene gave pure product as white needles in 95% yield.

B. The preparation of *N*-benzylcinchoninium chloride²

Cinchonine (11.76 g, 40 mmol) was added to the solution of benzyl chloride (Note 2) (7.62 g, 60 mmol) in dimethylformamide (DMF) (80 mL). The mixture was heated at 80°C and stirred for 3 h. The white needle crystals were collected by filtration after cooling, and washed with acetone (2×10 mL) to give *N*-benzylcinchoninium chloride (14.24 g) in 85% yield. Mp 256°C (dec.) (lit. Mp 248°C). $[\alpha]_D^{27} = +165.9$ (c=0.50, H_2O) (lit. $[\alpha]_D^{22} = +164.8$ (c=0.716, H_2O)).

C. Resolution of racemic 1,1'-bi-2-naphthol using *N*-benzylcinchoninium chloride



N-benzylcinchoninium chloride (20.21 g, 48 mmol) was added to the solution of racemic 1,1'-bi-2-naphthol (22.88 g, 80 mmol) in acetonitrile (300 mL). The mixture was heated to reflux for 4 h and then allowed to cool to room temperature. The resulting white solids were collected by filtration and washed with acetonitrile (3×20 mL). The solids were characterized to be two-component molecular crystals of (R)- (+)-1,1'-bi-2-naphthol and *N*-benzylcinchoninium chloride in a 1:1 molar

ratio. Mp 248°C(dec.). The enriched (S)-(-)-1,1'-bi-2-naphthol was left in the mother liquor. A suspension of molecular crystals in acidic water (200 mL of 1 N HCl and 800 mL of H₂O) and ethyl acetate (300 mL) was stirred for 30 min until the white solids disappear. The organic layer was separated, washed with brine, and then dried over MgSO₄. After removal of the solvent, the residue obtained from organic phase was recrystallized from benzene to afford (R)-(+)-1,1'-bi-2-naphthol (9.15 g) in 80% yield based on one enantiomer with 99% ee (Chiralcel AS, 0.8 mL min⁻¹, S: 12.43 min; R: 16.06 min.) as colorless prisms. Mp 208-210°C (lit. 208-210

°C). $[\alpha]_D^{27} = +32.1$ (c=1.0, THF) (lit. $[\alpha]_D^{21} = +34.3$ (c=1.0, THF)); ¹H NMR (300 MHz, CDCl₃):

d 5.05 (s, 2H), 7.15 (d, J=8.11 Hz, 2H), 7.29-7.41 (m, 6H), 7.88 (d, J=8.40 Hz, 2H), 7.96 (d, J=8.92 Hz, 2H). ¹³C NMR (100.61 MHz, CDCl₃): d 110.9, 117.8, 124.1, 124.3, 128.5, 129.5, 131.5, 133.5, 152.8.

The mother liquor was concentrated to dryness, then redissolved in ethyl acetate (300 mL), and washed with HCl (100 mL, 1 N) and brine (50 mL). The organic layer was dried over MgSO₄. Following the same procedure for the recrystallization of (R)-(+)-1,1'-bi-2-naphthol, (S)-(-)-1,1'-bi-2-naphthol (8.92 g) was obtained in 78% yield based on the other enantiomer with 99% ee (Chiralcel AS, 0.8 mL min⁻¹, S: 12.43 min; R: 16.06 min). Mp 208-210°C (lit. 207-210°C),

$[\alpha]_D^{27} = -33.5$ (c=1.0, THF) (lit. $[\alpha]_D^{21} = -34$ (c=1.0, THF)).

Neutralization of the combined HCl extracts with sodium bicarbonate led to white precipitates which are collected by filtration. Recrystallization from methanol-water mixed solvent gave the crystals of *N*-benzylcinchoninium chloride in > 90% recovery (18.5 g), which could be further used for resolution without any decrease in efficiency.

2. Notes

1. 2-naphthol is harmful if swallowed or inhaled, it is eye, skin and respiratory irritant.
2. Benzyl chloride is a lachrymator and has been used as a war gas. It is also very irritating to the

skin. $d_4^{25} = 1.100$

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