A New Method for the Synthesis of Enantiomerically Pure Betti Base

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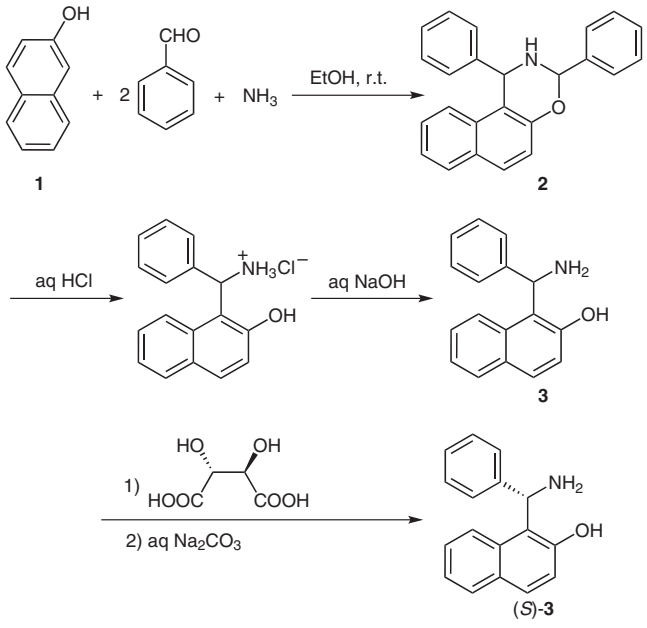
Abstract: We have developed a new method for the synthesis of enantiomerically pure Betti base. By using trifluoroacetic acid to replace the more traditionally used hydrochloride acid, the hydrolysis procedure used in the classical synthesis of racemic Betti base was carried out under milder conditions with an improved yield (up to 96%), which was followed by a new and efficient resolution with using recyclable (*R*)-1,1′-binaphthalene-2,2′-diyl sodium phosphate to provide enantiomerically pure (*S*)-Betti base in 95% yield with up to 99% ee and (*R*)-Betti base in 93% yield with 90% ee in one resolution step.

Key words: Betti base, 1,1′-binaphthalene-2,2′-diyl sodium phosphate, chiral resolution, recycle, asymmetric synthesis

Chiral 1-(α-aminobenzyl)-2-naphthol, known as Betti base, is an excellent aminohydroxy ligand and auxiliary in asymmetric synthesis.[1] Despite the fact that it was firstly reported 100 years ago, this compound remained little exploited for many years. In the last few decades, interest in Betti base has undergone a resurgence because of its unique rigid structure and diversity.[2]



Scheme 1 Classical synthetic route of enantiomerically pure Betti base

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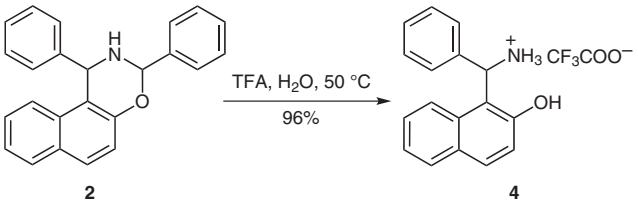
The classical and practical synthesis of enantiomerically pure Betti base is performed as shown in Scheme 1. Firstly, three-component condensation of 2-naphthol (**1**), benzaldehyde, and ammonia (in a ratio of 1:2:1) gives 1,3-diphenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (**2**); acidic hydrolysis of **2** gives Betti base as its hydrochloride. Subsequent neutralization of the hydrochloride with an aqueous solution of sodium hydroxide provides racemic 1-(α-aminobenzyl)-2-naphthol (**3**),[3] which is further resolved with chiral tartaric acid to provide enantiomerically pure Betti base.[4]

Traditionally, the hydrolysis of oxazine **2** consists of steam distillation in hydrochloric acid to remove benzaldehyde.[3,5] However, this hydrolysis procedure is difficult to take to completion even with prolonged reaction times and increased hydrochloric acid concentrations due to the insolubility of oxazine **2** and Betti base hydrochloride. Here, we introduce an improved hydrolysis method with the use of trifluoroacetic acid. The trifluoroacetic acid catalyzes the hydrolysis of **2** and proceeds smoothly to form salt **4** with the hydrolysate under milder conditions in up to 96% yield (Equation 1). The Betti base trifluoroacetate **4** is not only easy to separate by simple filtration because it is almost insoluble in cold dichloromethane, but also is stable and can be stored for extended periods after vacuum drying.



Equation 1 Trifluoroacetic acid catalyzed hydrolysis of **2**

Until now, the reported syntheses of enantiomerically pure Betti base have been mainly based on the resolution of racemic Betti base **3** with chiral tartaric acid. Cardellicchio and co-workers firstly reported resolution via the formation of diastereomeric tartrates in a mixture of ethanol and methanol, which gave the major diastereomeric salt in 90% yield with >98% ee and the other diastereomeric salt in 50% yield with >98% ee.[4] However, this method often gives unsatisfactory chemical yields and enantiomeric excesses in practice. In 2005, Hu and co-workers reported

another resolution of racemic Betti base using L-(+)-tartaric acid in acetone to give (*S*)-Betti base tartrate in 96% yield with >99% ee and (*R*)-*N*,*O*-ketal of Betti base in 94% yield with >99% ee.[6] Alfonsov and co-workers reported a new resolution of Betti base starting from the stable oxazine **2**.[7] In this procedure, one equivalent of **2** was treated with one equivalent of L-(+)-tartaric acid in dichloromethane–methanol to give (*S*)-Betti base tartrate in 85% yield and (*R*)-oxazine **2** in 61% yield without reported enantiomeric excess values.

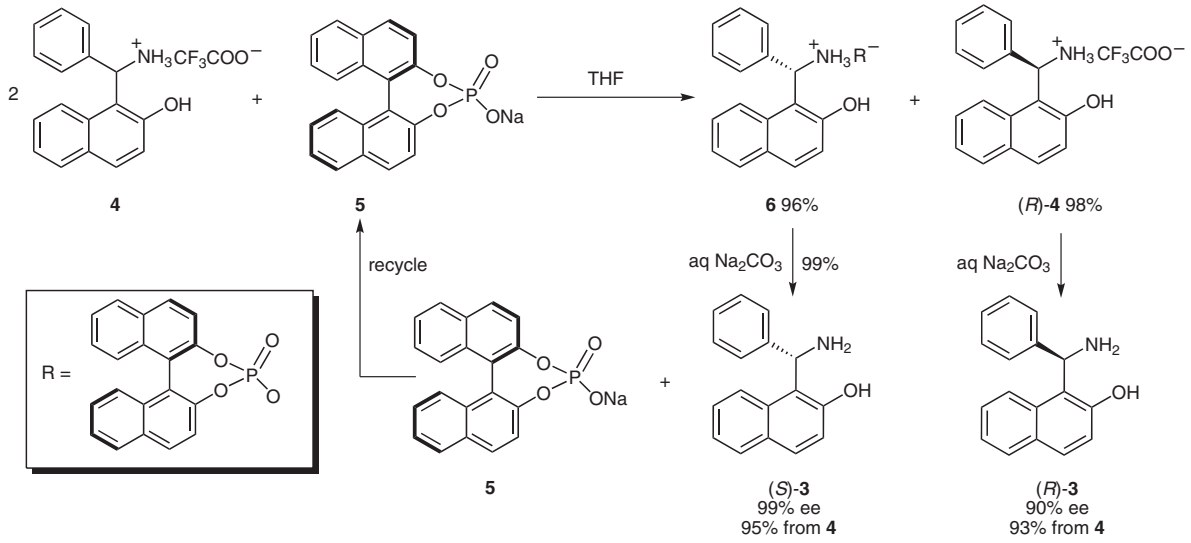
In the above reported resolution procedures, the method of Hu can also give (*R*)-Betti base with good chemical yield and enantiomeric excess, but another resolution process is necessary. In contrast, the resolution method of Cardellicchio can simultaneously provide the two desired enantiomerically pure Betti bases by one-step resolution, but the yield and reproducibility are not satisfactory. In this paper, a one-step resolution method for racemic Betti base with good reproducibility and high chemical yields and enantiomeric excesses of the two enantiomers is reported. A recyclable resolving agent, (*R*)-1,1′-binaphthalene-2,2′-diyl sodium phosphate (**5**) is used to directly separate racemic Betti base trifluoroacetate **4** (Scheme 2). The reaction of two equivalents of **4** with one equivalent of **5** in tetrahydrofuran gives a mixture of (*S*)-Betti base diastereomeric salt **6**, (*R*)-Betti base trifluoroacetate (*R*)-**4**, and sodium trifluoroacetate. The salt **6** is insoluble in tetrahydrofuran and can be easily separated by filtration. Dilution of the mother liquor with water results in the precipitation of salt (*R*)-**4**, which can be obtained by filtration. Neutralization of salt **6** gives the free Betti base (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**3**] and releases the chiral salt **5**. The chiral salt **5** can be recycled from the water phase by simple filtration. The data in Table 1 show that recycled **5** can be efficiently reused without significantly decreasing the yields and enantiomeric excess of (*S*)-Betti base. Following the same procedure for obtaining (*S*)-**3** from salt **6** gives (*R*)-**3** from salt (*R*)-**4**.

In summary, a simple, easily scalable and highly efficient synthetic method of enantiomerically pure Betti base has been developed. One-step resolution of racemic Betti base trifluoroacetate by recyclable (*R*)-1,1′-binaphthalene-2,2′-diyl sodium phosphate provides (*S*)-Betti base in 95% yield with 99% ee and (*R*)-Betti base in 93% yield with 90% ee.

Table 1 Resolution of Betti Base by Recycled (*R*)-1,1′-Binaphthalene-2,2′-diyl Sodium Phosphate (**5**)

Sodium phosphate **5**	Yield (%) of **6**	Yield (%) of (*S*)-**3**	ee (%) of (*S*)-**3**	Recovery (%) of **5**
1st use	96	95	99	–
recycle 1	94	93	99	90
recycle 2	90	89	98	89

(*R*)-1,1′-Bi-2-naphthol, 2-naphthol, and benzaldehyde were purchased from Acros. TFA, $POCl_3$, and other common reagents were purchased from Sinopharm Group Chemical Reagent Co., Ltd. All reagents were used directly without further purification. 1,3-Diphenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (**2**) was prepared according to literature procedures.[3] All solvents used were dried and purified using standard, published methods. Melting points were obtained on a SGW-4 micro melting point apparatus (Precision Scientific Instrument Co., Ltd., Shanghai, China). Optical rotations were measured on SGW-1 automatic polarimeter (Precision Scientific Instrument Co., Ltd., Shanghai, China). ^{1}H, ^{13}C. and ^{31}P NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (Switzerland), using TMS (δ_H or δ_C = 0) as internal standards and 85% H_3PO_4 (δ_P = 0) as external standard. Elemental analyses were performed on Vario MICRO CHON analyzer (Germany ELEMENTAR). ESI-MS spectra were obtained at 70 eV on a Thermo Finnigan DECAX-30000 LCQ Deca XP spectrometer (Switzerland). HPLC analyses were performed on an LC20A chromatograph (Shimadzu, Japan) by using a Chiralcel OD-H column (25 mm × 0.46 mm, 5 μm) (Japan).



Scheme 2 Resolution of Betti base by (*R*)-1,1′-binaphthalene-2,2′-diyl sodium phosphate (**5**)

1-(α-Aminobenzyl)-2-naphthol Trifluoroacetate (4)
To a soln of oxazine **2** (20 g, 59.3 mmol) in CH_2Cl_2 (200 mL) and H_2O (2.1 mL) was added TFA (8.8 mL, 118.6 mmol) dropwise at r.t. The mixture was stirred at 50 °C for 5 h and then cooled to 10 °C and filtered to obtain a solid that was washed with cold CH_2Cl_2 and dried in vacuo to give racemic **4**; yield: 20.7 g (57.0 mmol, 96%); mp 160–162 °C.

IR (KBr): 3290, 3070, 2920, 1675, 1210, 1130 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.02 (br s, 1 H), 8.83 (br s, 3 H), 8.07 (d, *J* = 8.6 Hz, 1 H), 7.90–7.87 (m, 2 H), 7.53–7.49 (m, 3 H), 7.40–7.30 (m, 5 H), 6.32 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7 (q, *J* = 31.2 Hz), 154.1, 138.0, 132.3, 131.2, 129.3, 129.0, 128.6, 128.5, 127.8, 127.6, 123.5, 122.2, 119.1, 117.7 (q, *J* = 299.8 Hz), 114.4, 51.6.

MS (ESI): *m*/*z* (%) = 250 (52) $[M - CF_3COO]^+$, 233 (100).

Anal. Calcd for $C_{19}H_{16}F_3NO_3$: C, 62.81; H, 4.44; N, 3.86. Found: C, 62.71; H, 4.45; N, 3.85.

(*R*)-1,1′-Binaphthalene-2,2′-diyl Sodium Phosphate (5)
A 250-mL Schlenk flask was evacuated, refilled with argon, and charged with a soln of (*R*)-1,1′-bi-2-naphthol (10 g, 34.9 mmol) in pyridine (50 mL). The soln was cooled to 0 °C in an ice bath and $POCl_3$ (6.4 mL, 70 mmol) was added dropwise. When the addition was complete, the mixture was warmed to 60 °C and stirred for 5 h, and then the solvent was completely removed in vacuo. The residue was dissolved in sat. Na_2CO_3 soln (100 mL) and then refluxed for 2 h. After cooling the reaction to r.t., the mixture was filtered. The residue was washed with H_2O and dried in vacuo to give **5** as a powdered colorless solid; yield: 11.2 g (85%); mp >320 °C; $[\alpha]_D^{25}$ –254.3 (*c* 0.82, THF).

IR (KBr): 3630, 3360, 3055, 1250, 1100, 970, 860, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.03 (t, *J* = 8.8 Hz, 4 H), 7.45–7.41 (m, 4 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.7, 150.6, 132.5, 130.8, 130.1, 128.8, 126.5, 124.8, 123.1, 122.2.

^{31}P NMR (162 MHz, DMSO-d_6): δ = 5.3.

MS (ESI): *m*/*z* (%) = 347 (100) $[M - Na]^-$.

Anal. Calcd for $C_{20}H_{12}NaO_4P \cdot 0.5\ H_2O$: C, 63.33; H, 3.45. Found: C, 63.22; H, 3.46.

(*S*)-1-(α-Aminobenzyl)-2-naphthol Diastereomeric Salt 6
To a soln of **4** (2.0 g, 5.5 mmol) in anhyd THF (5 mL) at 50 °C was added a soln of **5** (1.0 g, 2.8 mmol) in anhyd THF (7 mL). The mixture was stirred at 50 °C for 2 h and then stirred at r.t. for 3 h. The sediments were separated by filtration [the mother liquor was retained and used to obtain (*R*)-**4**] and washed with MeOH–Et_2O (1:5, 10 mL), and dried in vacuo to give **6** as a colorless solid; yield 1.58 g (96%); mp 199–201 °C; $[\alpha]_D^{20}$ –286.8 (*c* 1.0, MeOH).

IR (KBr): 3055, 2920, 1500, 1220, 1080, 960 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.22 (br s, 1 H), 8.80 (br s, 3 H), 8.06–7.98 (m, 5 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.71 (d, *J* = 8.9 Hz, 1 H), 7.49–7.26 (m, 16 H), 6.25 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.3, 150.5, 138.0, 132.5, 132.3, 131.0, 130.8, 130.2, 129.2, 128.9, 128.5, 127.6, 126.5, 124.9, 123.4, 123.1, 122.2, 119.1, 114.2, 51.6.

^{31}P NMR (162 MHz, DMSO-d_6): δ = 4.6.

MS (ESI): *m*/*z* (%) = 598 (100) $[M + H]^+$, 250 (52), 233 (60).

Anal. Calcd for $C_{37}H_{28}NO_5P$: C, 74.36; H, 4.72; N, 2.34. Found: C, 74.16; H, 4.73; N, 2.33.

(*S*)-1-(α-Aminobenzyl)-2-naphthol [(*S*)-3]
The salt **6** was suspended in H_2O, followed by the addition of 2 M Na_2CO_3 soln (30mL). Then the mixture was stirred for 30 min and extracted with Et_2O (3 × 20 mL). The Et_2O phase was washed with sat. aq NaCl, dried (Na_2SO_4), and concentrated in vacuo to give (*S*)-**3** as a white solid; yield: 0.65 g (2.6 mmol, 99%); 99% ee [*S*, major];[8] mp 132–133 °C (Lit.[6] 133–134 °C); $[\alpha]_D^{25}$ +55.8 (*c* 4.0, benzene) [Lit.[6] $[\alpha]_D^{25}$ +56.6 (*c* 4.0, benzene)]; R_f = 0.3 (hexanes–EtOAc, 2:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 7.87 (d, *J* = 8.6 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 2 H), 7.37–7.19 (m, 7 H), 7.04 (d, *J* = 8.8 Hz, 1 H), 6.08 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.8, 144.1, 132.3, 129.3, 128.9, 128.2, 127.8, 127.7, 126.7, 122.4, 122.0, 120.8, 117.4, 55.0.

(*R*)-1-(α-Aminobenzyl)-2-naphthol [(*R*)-3]
To the mother liquor from the resolution of racemic **4** was added H_2O (100 mL) dropwise and the mixture was stirred for 2 h. The insoluble substance was separated by filtration, washed with CH_2Cl_2 and dried in vacuo to give crude (*R*)-**4** (0.98 g, 98%). Without purification, the crude (*R*)-**4** was added to 2 M Na_2CO_3 soln (10 mL). Then the mixture was stirred for 30 min and extracted with Et_2O (3 × 10 mL). The Et_2O phase was washed with sat. aq NaCl, dried (Na_2SO_4), and concentrated in vacuo to give (*R*)-**3** as a white solid; yield: 0.64 g (2.5 mmol, 93% yield from **4**); 90% ee [*R*, major].[8]

Recycled (*R*)-1,1′-Binaphthalene-2,2′-diyl Sodium Phosphate (5)
The remaining aqueous phase after extracting (*S*)-**3** was filtered. The residue was washed with H_2O and Et_2O and then dried in vacuo to give **5** (0.9 g, 90%) as a colorless solid. The recycled (*R*)-1,1′-binaphthalene-2,2′-diyl sodium phosphate (**5**) was reused for resolution of racemic 1-(α-aminobenzyl)-2-naphthol trifluoroacetate (**4**).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(8) Measured by chiral HPLC analysis: 20% *i*-PrOH–80% hexane, 1.0 mL/min, t_R = 8.5 min (*S*), 21 min (*R*).

