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*Short Note*

# 1-[(1*S*)-(4-Fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-trifluoromethanesulfonate

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**Abstract:** The complex structure of aminobenzylnaphthols can be easily obtained with the useful Betti reaction. These valuable compounds can give rise to chiral intermediates, that found wide application in asymmetric synthesis. 1-[(1*S*)-(4-Fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-ol **1** was treated with triflic anhydride to yield the corresponding (*S*,*S*)-triflate **2**, which is a valuable intermediate in the future synthesis of aminophosphine, to be used in asymmetric catalysis. Preliminarily structural considerations based upon H(1)-NMR spectroscopy are also reported.

**Keywords:** Betti reaction; aminobenzylnaphthols; chirality; NMR analysis



**Citation:** Cardellicchio, C.; Capozzi, M.A.M. 1-[(1*S*)-(4-Fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-trifluoromethanesulfonate. *Molbank* **2023**, *2023*, M1695. https://doi.org/10.3390/M1695

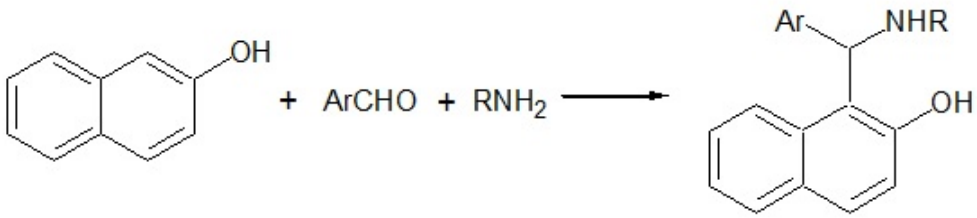
Academic Editor: Nicola Della Ca

Received: 30 May 2023
Revised: 3 July 2023
Accepted: 11 July 2023
Published: 14 July 2023



## 1. Introduction

The Betti reaction [1] is the condensation between 2-naphthol, aryl aldehydes and ammonia, or amines, that join to yield aminobenzylnaphthols (Scheme 1).




**Scheme 1.** Betti reaction between 2-naphthol, aryl aldehydes and amines.

This reaction, discovered by the Italian chemist Mario Betti [2] more than 120 years ago, was seldom applied during the 20th century. However, about 25 years ago, our work [1] initiated a new interest towards this useful process and towards the intermediates that can be obtained therefrom, as witnessed by the many applications that have been published by many research groups all over the world [1,3,4].

Several reasons have contributed to this success. First of all, different aryl groups are present in these aminobenzylnaphthols, together with the amino- and the 2-hydroxynaphthyl-moieties; later, these compounds can easily yield enantiopure materials [1].

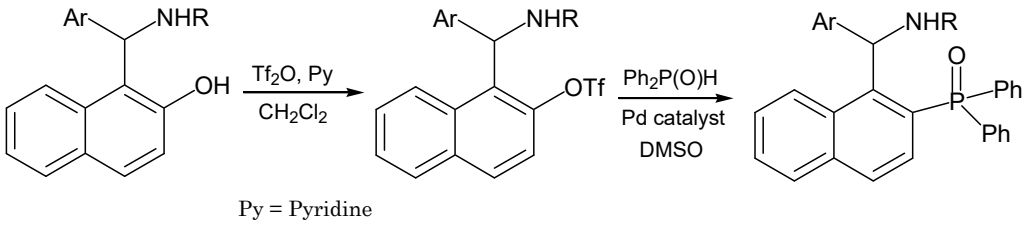
These enantiopure intermediates were applied in asymmetric synthesis both as chiral starting materials and as chiral ligands, due to the simultaneous presence of nitrogen and oxygen, acting as potential metal-coordinating atoms [1]. For example, the enantioselective addition reaction of diethylzinc to aryl aldehydes in the presence of Betti aminobenzyl-naphthols as chiral coordinating ligands [1] was the first reported recent application of these intermediates in asymmetric synthesis.

## 2. Results

New processes in asymmetric synthesis can be applied if the Betti aminobenzyl-naphthols are transformed into a chiral aminophosphine, bearing N and P coordinating

atoms [5–7]. These ligands could coordinate many more transition metals than a simple aminobenzylnaphthol, thus yielding valuable and useful chiral catalysts for very large numbers of asymmetric processes [5–7].

The strategy to this end was to transform the hydroxyl naphthol moiety into a triflate; this species was subjected to a metal catalysed coupling with diphenylphosphine oxide (Scheme 2) [5].



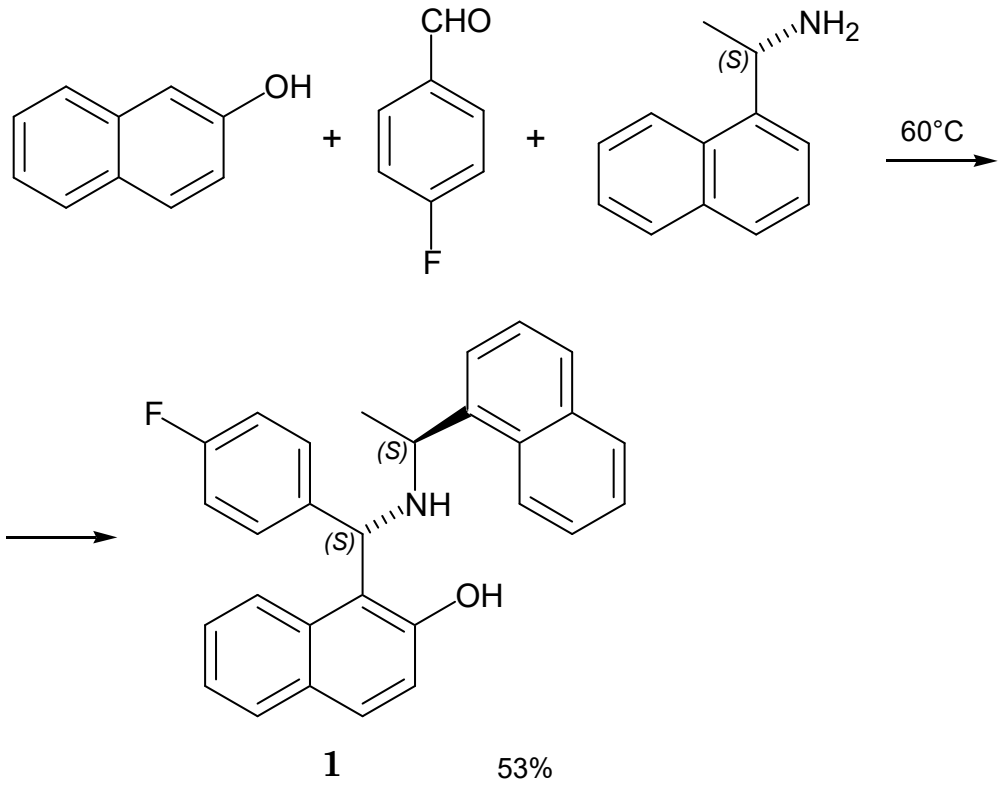

**Scheme 2.** Transformation of a Betti aminobenzylnaphthol into a *N*, *P*-ligand.

The resulting aminophosphine oxide can be reduced by standard methods to the corresponding aminophosphine [5].

In this strategy, the triflation reaction is a crucial step, since it modifies the nucleophilic 2-naphthol hydroxyl group into a potential leaving group for the palladium catalysed cross-coupling reaction.

In this paper, we report on the triflation reaction of the 1-[(1*S*)-(4-fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-ol **1** [8] to yield the corresponding triflate **2**, bearing two stereogenic centres.

The aminobenzylnaphthol 1 was already synthesised by us [8] with the aid of a Betti reaction between 2-naphthol, 4-fluorobenzaldehyde and (*S*)-1-naphthyl-1-ethylamine with a 53% yield (Scheme 3).

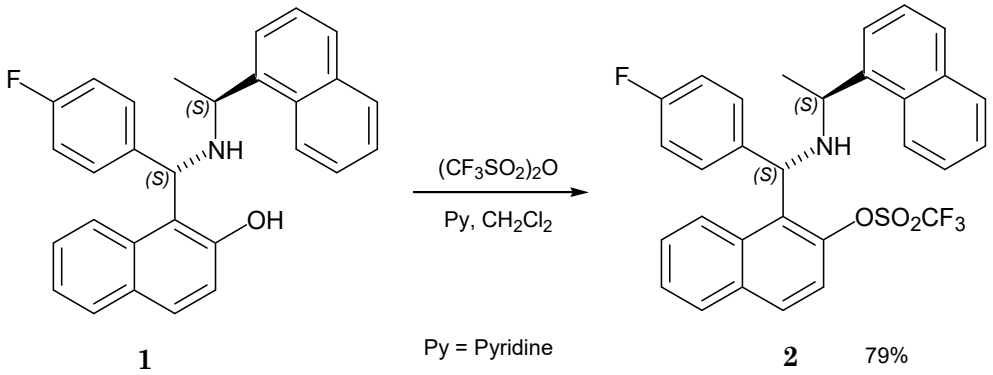



**Scheme 3.** Betti reaction of 2-naphthol, 4-fluorobenzaldehyde and (*S*)-1-naphthyl-1-ethylamine.

This reaction is performed by mixing the reagents for 2 days at 60 °C without any solvent. In principle, a mixture of (*S*,*S*)- and (*S*,*R*)-aminobenzylnaphthols should be obtained. However, upon cooling the reaction mixture, the addition of small amounts of ethanol causes the separation of the (*S*,*S*)-stereoisomer, which was fully characterised [8]. The absolute configuration of the stereogenic centres was attributed with an X-ray diffraction experiment [8]. Moreover, the H(1)-NMR pattern of the (*S*,*S*)- and (*S*,*R*)-aminobenzylnaphthols is peculiar [9], and can be used to discriminate among the stereoisomers.

Investigating the crystal structures [8,10] of these aminobenzylnaphthols revealed the presence first of an intramolecular OH···N hydrogen bond, and later of short and cooperating CH···π interactions [11]. The construction of the crystal structure is based upon all of these interactions.

The triflation reaction that involves the (*S*,*S*)-aminobenzylnaphthol **1** that was depicted in Scheme 3 was performed by us. We added trifluoromethanesulfonic anhydride with pyridine, using dichloromethane as a reaction solvent at room temperature (Scheme 4).




**Scheme 4.** Triflation of the Betti aminobenzylnaphthol **1**.

Since the reaction does not involve the stereogenic centres, and the conditions that caused their scrambling in similar compounds are absent [12,13], it is reasonable to believe that the obtained triflate species **2** maintained the same (*S*,*S*)-configuration. As a further point of interest, as previously reported [14,15], the functionalisation of the naphthol hydroxyl moiety always has relevant consequences on the crystal structures, because it inhibits the formation of the intramolecular OH···N hydrogen bond and causes a new rearrangement of the aryl group in the molecule [14,15].

The H(1)-NMR spectrum of the triflate **2** (Supplementary Materials) describes structural variations that occur by blocking the naphthol hydroxyl moiety. We observed that the hydrogen atom close to the two aryl groups moves lowfield (5.65 ppm for the triflate), in comparison with 5.49 ppm of the starting aminobenzylnaphthol [9]. On the other hand, the signal related to the naphthylethylamine moiety moves upfield (4.39–4.34 multiplet and 1.38 ppm for the triflate), in comparison with the signals of the starting material (5.01–4.77 multiplet and 1.66 ppm) [9]. Waiting for the completion of an X-ray diffraction investigation, these NMR data seem to suggest a different arrangement of the aryl groups of the triflate, as a direct consequence of the triflation reaction.

## 3. Materials and Methods

Chemicals were used as received. NMR spectra were recorded on a Bruker AM500 spectrometer. MS Spectra were performed with an Agilent HPLC QTOF spectrometer via direct infusion of the samples.

Pyridine (40 µL, 0.5 mmol) and 1-[(1*S*)-(4-Fluorophenyl)-((1′*S*)-1′-naphthalen-1-yl-ethylamino)-methyl]-naphthalen-2-ol **1** [8] (0.21 g, 0.5 mmol) were dissolved in 8 mL of dichloromethane. Trifluoromethanesulfonic anhydride (84 µL, 0.5 mmol) was added to this solution. The mixture was reacted for 16 h at room temperature. The reaction was quenched with a solution of hydrochloric acid 1 N and then it was extracted three times with

dichloromethane. The organic extracts were washed with a solution of sodium carbonate 1 M and then evaporated under vacuo. The residual was crystallised from methanol/ethyl acetate 7:3 yielding 0.22 g (0.385 mmol, 79% isolated yield) of **2**.

mp = 151–152 °C.

$[\alpha]_D$ = + 46.3 (c = 0.8, $CHCl_3$).

$^1$H-NMR ($CDCl_3$, 500 MHz) δ 7.93–7.74 (m, 7 H, $H_{Ar}$), 7.50–7.29 (m, 8 H, $H_{Ar}$), 6.99–6.93 (m, 2 H, $H_{Ar}$), 5.65 (s, 1 H, $CHAr_2$), 4.39–4.34 (m, 1 H, CHMe), 2.50–2.40 (m, 1 H, NH), 1.38 (d, $^3J$ = 6.2 Hz, 3 H, $CH_3$).

$^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 161.7 (d, $^1J$= 246 Hz, $C_{Ar}F$), 145.9 ($C_{Ar}$), 140.1 ($C_{Ar}$), 138.3 ($C_{Ar}$), 134.1 ($C_{Ar}$), 133.3 ($C_{Ar}$), 131.4 ($C_{Ar}$), 131.1 ($C_{Ar}$), 130.6 ($C_{Ar}$), 129.2 ($C_{Ar}$), 128.8 ($C_{Ar}$), 128.3 (d, $^3J$ = 8.2 Hz, $C_{Ar}$), 127.5 ($C_{Ar}$), 127.3 ($C_{Ar}$), 126.7 ($C_{Ar}$), 125.7 ($C_{Ar}$), 125.4 ($C_{Ar}$), 125.2 ($C_{Ar}$), 125.1 ($C_{Ar}$), 123.2 ($C_{Ar}$), 122.6 ($C_{Ar}$), 119.3 ($C_{Ar}$), 118.0 (q, $^1J$ = 320 Hz, $CF_3$), 115.1 (d, $^2J$ = 20.6 Hz, $C_{Ar}$), 55.0 ($CHAr_2$), 51.6–51.4 (broad, CHMe), 24.7 ($CH_3$).

HRMS (ESI-TOF), *m*/*z*: calcd for $C_{30}H_{23}F_4NO_3SNa$ [M + Na], 576.1232, found 576.1240.

**Supplementary Materials:** The following supporting information can be downloaded online. Spectral properties of the title compound.

**Author Contributions:** C.C. and M.A.M.C. contributed in the same way to all the steps of the work. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** The project Fibre e tessuti intelligenti ed ECOsostenibili per l'abbigliamento TECnico e l'alta moda (ECOTEC) is gratefully acknowledged for technical support.

**Conflicts of Interest:** The authors declare no conflict of interest.

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