SYNTHESIS AND RESOLUTION OF RACEMIC 2-AMINO-2′-HYDROXY-1,1′-BINAPHTHYL

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Dedicated to the memory of Dr Zdenek Arnold.

The title compound **3** has been prepared via a highly selective, Cu(II)-mediated cross-coupling of 2-aminonaphthalene **1** and 2-naphthol **2** and resolved into enantiomers via crystallization of diastereoisomeric salts with (1*S*)-(+)-10-camphorsulfonic acid. The method has been optimized and the use of chromatography eliminated.
Key words: Binaphthyls; Oxidative coupling; Resolution.

C_2-Symmetrical, 2,2′-disubstituted 1,1′-binaphthyls, such as BINOL **5**, BINAP, etc., which all have identical groups in positions 2 and 2′, are established ligands for use in asymmetric catalysis[1]. On the other hand, their congeners with non-identical substituents in these positions (which are no longer C_2-symmetrical) have only recently emerged. Among them, Hayashi's MOP (with OMe and PPh_2 groups)[2] and our amino alcohol **3** (NOBIN) (refs[3–5]), have risen to prominence[2,6]. Whereas C_2-symmetrical 1,1′-binaphthyls, such as BINOL **5**, are readily synthesized via an efficient oxidative coupling of the appropriate naphthol (e.g. **2**) (refs[1,7]), non-symmetrical derivatives are generally more difficult to obtain since their preparation requires a selective transformation of one of two identical functional groups[2,8].

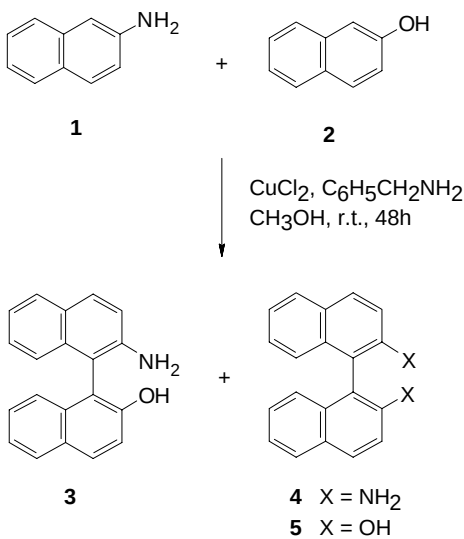
Recently, we have described a highly chemoselective oxidative cross-coupling between two different naphthyl derivatives[3–5,9] and rationalized the observed selectivity in terms of frontier orbital theory[5]. In short, the most selective cross-coupling can be expected for those pairs of reactants where one component is electron-rich (and, therefore, easily oxidized), whereas the other partner is relatively electron-poor (e.g., due to an electron-withdrawing group)[5]. Thus, for instance, typical pairs for successful cross-coupling are 2-aminonaphthalene and 3-methoxycarbonyl-2-naphthol (71%) (ref.[5]), 2-naphthol and 3-methoxycarbonyl-2-naphthol (81%) (refs[5,9]), or 2-aminonaphthalene and 2-naphthol (85%) (refs[3,5]). For further examples of selective cross-coupling see ref.[9]. The latter

coupling (**1** + **2** → **3**; Scheme 1) can be modified to produce the amino alcohol **3** in an enantiomerically enriched form (46% ee), by carrying out the oxidative coupling with a complex of $CuCl_2$ and a chiral amine, such as α-methylbenzylamine[4]. Enantiomerically pure **3** is then obtained by recrystallization[4].

The amino alcohol **3** proved to be an excellent scaffold for building chiral titanium(IV) complexes that have been shown to be superior to other catalysts in aldol-type condensations, such as the Mukaiyama reaction[6]. However, a drawback, which attenuates the wider use of **3**, is the practicality of its preparation. Clearly, the asymmetric coupling process (**1** + **2**) (ref.[4]), although excellent on a small scale, may appear less suitable for larger-scale operations. Therefore we explored an alternative route, namely the resolution of the racemic **3** into enantiomers. Herein, we describe an optimized procedure for obtaining larger quantities of (*R*)-(+)-**3** and (*S*)-(–)-**3** via the latter approach.

RESULTS AND DISCUSSION

The oxidative cross-coupling of 2-aminonaphthalene **1** and 2-naphthol **2** was carried out at room temperature for 48 h in the presence of a stoichiometric amount of an *in situ* generated complex of copper(II) chloride and benzylamine in methanol. The amino alcohol **3** (NOBIN) thus obtained was contaminated by small quantities of the products arising from self-coupling of each of the starting materials, i.e., the diamine **4** and diol **5**,



SCHEME 1

and by other impurities (mainly of inorganic nature). Although these byproducts can be easily separated by flash chromatography[3], for the large-scale synthesis of **3** an alternative method was required. We reasoned that the individual components may be separated owing to their different acid-basic properties.

As expected, the diamine **4** was separated as an insoluble solid by digesting the crude coupling product with concentrated methanolic KOH, which converted **3** and **5** into the soluble naphtholates. The pH of the solution was then adjusted to ≈8 in order to precipitate a mixture of **3** and **5**. The latter precipitate was treated with concentrated HCl in ethanol and the resulting hydrochloride of **3** and the neutral **5** were partitioned between water and toluene. The amino alcohol **3** was then released from its water-soluble hydrochloride by treatment with aqueous ammonia and crystallized from toluene to give the product of sufficient purity for further resolution into enantiomers.

Originally, good resolution of (±)-**3** was attained by fractional crystallization of the diastereoisomeric salts with (1*S*)-(+)-10-camphorsulfonic acid (CSA). However, on a larger scale, the latter procedure proved capricious. After numerous experiments, it turned out that the efficiency of the resolution was crucially dependent on the source and quality of the CSA used, the best specimen originating from Fluka which, apparently, contains least water. The success of the resolution has been found to be dependent on the batch of camphorsulfonic acid used. Furthermore, the chemical purity of (±)-**3** proved to be no less important. Thus, in particular, **4** has to be completely removed prior to the resolution, since this byproduct, even if present in quantities as low as 1%, not only co-crystallizes with the desired salt, but also nucleates the crystallization of its diastereoisomer(!), which substantially lowers the diasteroisomeric purity of the final crop.

The amount of the solvent (chlorobenzene and ethanol in a 10 : 1 ratio) required has to be tested first on a small scale before scaling up. We have noticed that if the resolution gave more than ca 60% of the salt precipitate, related w/w to the starting (±)-**3**, the resulting enantiomeric purity of NOBIN was lower.

In an optimized procedure, solid (+)-CSA (Fluka) was added to a suspension of (±)-**3** of >99% purity in a chlorobenzene–ethanol mixture (10 : 1), preheated to 110 °C. The suspension had quickly dissolved and within 10–15 min at 110 °C the salt begun to precipitate. The heating was then discontinued and the stirred mixture was allowed to cool to room temperature. The desired optically active base was liberated from the precipitated salt on treatment with pyridine; single recrystallization of the crude base from benzene produced the enantiomerically pure (*S*)-(–)-**3** in 30% overall yield. Decomposition of the diastereoisomeric salt that remained in the solution afforded (*R*)-(+)-**3** of 75% enantiomeric purity in 66% yield[12].

In conclusion, we have developed an optimized procedure for an alternative preparation of both enantiomers of the amino alcohol **3** via the cross-coupling of **1** and **2** followed by purification of the crude, racemic product and its resolution into enantiomers

by means of camphorsulfonic acid. The importance of the quality of the resolving agent and of the chemical purity of (±)-**3** to be resolved has been demonstrated. Since chromatographic purification has been avoided, this protocol is suitable for a large-scale preparation of NOBIN **3**.

EXPERIMENTAL

Optical rotations were measured with an error of <±0.5°. All solvents used for the reactions or for crystallization experiments were degassed by purging with argon (20 min; 60 ml/min). (1*S*)-(+)-10-Camphorsulfonic acid was purchased from Fluka.

2-Amino-2′-hydroxy-1,1′-binaphthyl (±)-**3**

Preparation of the crude 2-amino-2′-hydroxy-1,1′-binaphthyl (±)-**3**. To a stirred solution of copper(II) chloride dihydrate (50 g, 0.3 mol) in degassed methanol (250 ml) was added a solution of benzylamine (128.6 g, 1.2 mol) in degassed methanol (250 ml). The resulting solution was purged with argon for 5 min and a mixture of 2-aminonaphthalene (14.3 g, 0.1 mol) and 2-naphthol (14.4 g, 0.1 mol) in degassed methanol (1 l) was then added. After stirring at room temperature for 48 h under argon, the mixture was first acidified with concentrated HCl (150 ml), stirred for 10 min, then treated with concentrated aqueous ammonia (200 ml), and finally poured into water (4.5 l). The resulting precipitate was isolated by suction and washed with methanol (100 ml). After air-drying, ca 28 g of the crude product was obtained. This procedure was repeated for 8 times to give 224 g of the crude product in total.

Removing 2,2′-diamino-1,1′-binaphthyl **4** *from the crude NOBIN* **3**.To a suspension of crude NOBIN (224 g) in methanol (500 ml) was added a 20% solution of KOH in methanol (1 700 ml). The mixture was stirred at room temperature for 5 h and then filtered through celite. The solid material was washed with methanol (100 ml) and the filtrate was poured into a vigorously stirred 15% aqueous HCl (1.5 l). The resulting suspension was neutralized by adding concd aqueous ammonia (100 ml) to reach pH ≈8 and the precipitate was isolated by suction and washed with methanol (100 ml). Air-drying of the latter material yielded 125 g of crude NOBIN **3**.

Removing BINOL **5** *from NOBIN* **3**. Water (950 ml) was added to a solution of NOBIN (125 g), free of the diamine **4**, in a mixture of ethanol (2.5 l) and concentrated HCl (300 ml), and the solution was extracted with toluene (3 × 1 l). The aqueous phase was then poured into a mixture of water (4 l) and concentrated aqueous ammonia (500 ml), and the resulting precipitate was isolated by suction. Air-drying of the latter material afforded 103 g of purified NOBIN **3** contaminated by 2,2′-diamino-1,1′-binaphthyl **4** (3%) and BINOL **5** (≤1%), as revealed by GCMS.

Crystallization of NOBIN **3** *from toluene*. The purified NOBIN (103 g) was refluxed in toluene (5 l) for 30 min and the hot solution was filtered. On cooling to room temperature, the filtrate furnished pure, crystalline NOBIN (85 g). Concentration of the mother liquors yielded a second crop of crystalline NOBIN (13 g). In total, this whole procedure afforded 98 g (43%) of pure (>99%), racemic NOBIN **3**.

Resolution of Racemic NOBIN **3**

To a stirred suspension of (±)-NOBIN **3** (5.70 g) in a mixture of chlorobenzene (160 ml) and ethanol (16 ml), preheated to 110 °C, was added solid (1*S*)-(+)-10-camphorsulfonic acid (5.00 g). The resulting clear solution was further stirred at 110 °C until a precipitate begun to form (10–15 min); heating was then discontinued and the mixture was stirred overnight. The precipitate was isolated by suction

and washed with dichloromethane (20 ml) and dried to afford the corresponding salt (3.53 g). The latter salt was dissolved in pyridine (5 ml) and the solution was poured into hot water (300 ml, 70 °C). Hot water is essential for obtaining a solid product. If cold water is used, a less easy-to-handle paste is formed. The product was isolated by suction, washed with water (50 ml), and air-dried to yield (*S*)-(–)-NOBIN (1.88 g; 33%): $[\alpha]_D$ –116° (*c* 1.5; THF). Crystallization from benzene (40 ml) afforded the enantiomerically pure (*S*)-(–)-**3** (1.71 g; 30 %): $[\alpha]_D$ –120° (*c* 1.5; THF, ≈100% ee).

The diastereoisomeric salt obtained from the solution (7.06 g) was worked up in the same manner to yield (*R*)-(+)-**3** (3.76 g; 66%): $[\alpha]_D$ +87 (*c* 1.5; THF; 75% ee). Enantiomerically pure (*R*)-(+)-NOBIN can be obtained from this material via fractional crystallization of this product from benzene[4].

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