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Enantioselective synthesis of (*R*) and (*S*)-[9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol: a furo-fused BINOL derivative

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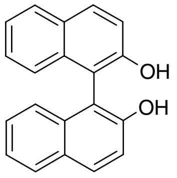
Abstract—The enantioselective synthesis of [9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol, a modified BINOL, was achieved using an inexpensive route. Both enantiomers of [9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol were obtained with satisfactory stereoselectivities by employing two optical antipodes of phenylethylamine as chiral influence in a Cu(II)Cl_2 catalyzed oxidative coupling step.

Though numerous chiral compounds have been developed over the past four decades as chiral auxiliaries, BINOL (**1**) remains one of the best known chiral auxiliaries[1] in asymmetric transformations. The extraordinary success of this molecule in a wide range of asymmetric transformations and chiral recognition has led to the development of modified BINOLs.[2] Several derivatives[3–6] of BINOL (**1**) have been developed in order to modify the steric factors and electronic factors and for provision of additional binding sites (Fig. 1).

Recently we reported[7] the synthesis of a racemic modified BINOL, namely, [9,9′]bi[naphtho(2,1-*b*)furanyl]-8,8′-diol (**3**). The molecule was resolved and the absolute configurations of its enantiomers were determined. The placement of a heteroaryl ring at the sterically hindered, 7,8- and 7′,8′-positions of BINOL (**1**) has given the first example of BINOL derivatives of this type. The stereodiscriminating properties of BINOL derivatives are mostly dependent on the dihedral angle. BINOL **3** exhibited modified steric properties, for example, the dihedral angle was found to be 97° for its diester derivative based on X-ray diffraction studies. In comparison to **1**, BINOL **3** exhibited enhanced fluorescence properties, clearly indicating a modified electronic system. Based on these observations, a number of potential applications in asymmetric transformations and molecular recognition are expected.



1

Figure 1.

Resolution of racemates and asymmetric synthesis are two major routes for obtaining nonracemic compounds. The former entails additional steps hence, asymmetric synthesis, although challenging, is beneficial for practical purposes. Asymmetric syntheses of BINOL and its derivatives have been described by several workers.[1] Oxidative coupling of 2-naphthol derivatives with chiral catalysts has been found to be a convenient route for the nonracemic production of BINOL derivatives. The enantioselective oxidative dimerization of 2-naphthol has been studied with several copper(II) amine complexes as oxidants.[8,9] Although some of the methods described by previous workers give excellent enantioselectivities, most suffer from the use of expensive chiral amines and, in general, chemical yields have been low to moderate. We decided to make use of both enantiomers

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Keywords: Modified BINOL; Chiral HPLC; Oxidative coupling; Phenylethylamine.

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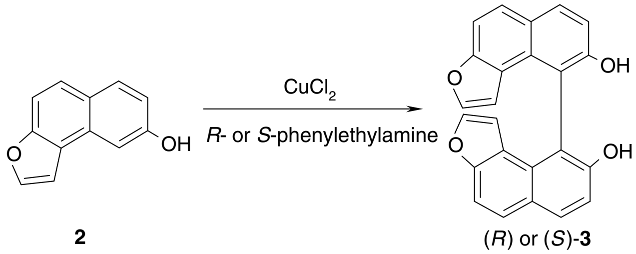

Scheme 1.

of phenylethylamine in a chiral amine–Cu(II)Cl$_2$ oxidative coupling methodology to obtain nonracemic **3**. The selection of phenylethylamine was due to its easy accessibility and low cost compared to other expensive alkaloid derivatives such as sparteine[10,11] used earlier for similar purposes.

The enantioselective synthesis of [9,9′]bi[naphtho(2,1-*b*)-furanyl]-8,8′-diol (**3**) was achieved[12] by coupling naphtho[2,1-*b*]furan-8-ol (**2**) with copper(II) chloride and *R*-(+)- or *S*-(−)-phenylethylamine. Copper(II) chloride and (*R*) or (*S*)-phenylethylamine were used in a 1:4 ratio. The reaction was carried out at 10–20 °C for 24 h under a nitrogen atmosphere. The product was obtained in a 50% yield but with satisfactory enantioselectivity.[12] Notably the extent of enantioselectivities observed was exactly the same when either enantiomer of phenylethylamine was employed as indicated by chiral HPLC. The use of *R*-(+)-phenylethylamine yielded (*R*)-(−)-[9,9′]bi[naphtho[2,1-*b*]furanyl]-8,8′-diol (**3**) in 75% ee, $[\alpha]_{589}^{25}$ +77 (THF, *c* 1) and (*S*)-(−)-phenylethylamine gave (*S*)-(+)-[9,9′]bi[naphtho[2,1-*b*]furanyl]-8,8′-diol (**3**) in 75% ee $[\alpha]_{589}^{25}$ −78 (THF, *c* 1) (Scheme 1).

The new furo-fused BINOL derivative **3** has promising properties such as an enhanced dihedral angle and modified electronic properties. The usefulness of the methodology was established by employing both enantiomers of phenylethylamine to prepare both enantiomers of [9,9′]bi[naphtho[2,1-*b*]furanyl]-8,8′-diol (**3**) via an efficient and practical route.

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12. Copper(II) chloride tetrahydrate (1.60 g; 8.0 mmol) and *S*-(−)-phenylethylamine (3.87 g; 32.0 mmol) were taken in methanol (5 ml) under a nitrogen atmosphere. The solution was allowed to stand for 30 min at 10–20 °C. After the solution had been purged with nitrogen for 5 min, a solution of naphtho[2,1-*b*]furan-8-ol (**2**) (736 mg; 4.0 mmol) in degassed methanol (20 ml) was added, and the mixture was stirred at 10–20 °C for 24 h under nitrogen. The resulting brown precipitate (a modified binaphthol–copper(II)–amine complex) was filtered, dried and transferred to a magnetically stirred mixture of 0.5 N HCl (100 ml) and chloroform (50 ml). After 10 min the brown complex dissolved and the layers became almost colourless. The mixture was transferred to a separating funnel and the chloroform layer was separated and washed with brine (50 ml), dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness to yield a solid. Chiral HPLC using a Chiralcel OD-H column and *iso*-propyl alcohol and hexane as eluents afforded the two enantiomers with retention times of 22.7 and 40 min, respectively, at 276 nm. Evaporation of the solvent gave a solid which on crystallization afforded a pale brown solid (1.92 g), mp 199–200 °C, 50% recovery. The product, (*S*)-(+)-[9,9′]bi[naphtho[2,1-*b*]furanyl]-8,8′-diol (**3**), was obtained in 75% ee $[\alpha]_{589}^{25}$ +77 (THF, *c* 1). When *R*-(+)-phenylethylamine was used for the reaction we obtained levorotatory *R*-[9,9′]bi[naphtho[2,1-*b*]furanyl]-8,8′-diol (**3**) in 75% ee $[\alpha]_{589}^{25}$ −78 (THF, *c* 1).