Synthesis of a Tridentate Ligand for Use in Ti^{IV}-Catalyzed Acetate Aldol Addition Reactions

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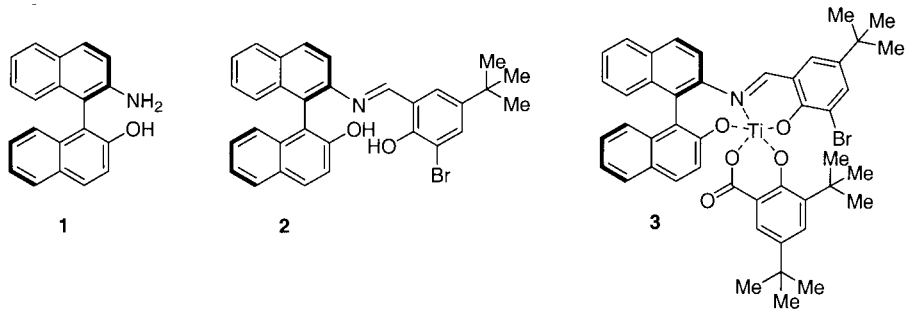
Dedicated to Professor *Jack D. Dunitz* on the occasion of his 80th birthday

A facile, practical synthesis and resolution of (±)-2′-amino-[1,1′-binaphthalen]-2-ol (**1**) is described, as well as the preparation of the tridentate *Schiff* base ligand **2** derived from condensation of **1** with 3-bromo-5-(*tert*-butyl)salicylaldehyde, which has been used in catalytic enantioselective acetate aldol addition reactions.

Introduction. – The identification and development of novel ligands and ligand scaffolds have, in part, fueled advances in catalytic asymmetric synthesis. Indeed, an important outcome of the vast number of studies in this field has been the realization that the reactivity of transition-metal complexes can be substantially and dramatically altered on the basis of the associated ligands [1]. These effects are most notably manifested in the kinetic profile of a reaction, including reaction rate, catalyst loading, and turnover frequency, as well as in various aspects of selectivity (enantio-, diastereo-, and chemoselectivity). Advances in the design and synthesis of chiral catalysts for enantioselective-reaction methodology are dependent on the availability of inexpensive, optically active starting materials. Many of these are prepared from naturally occurring diols, amino acids, amino alcohols, and carbohydrates [2].

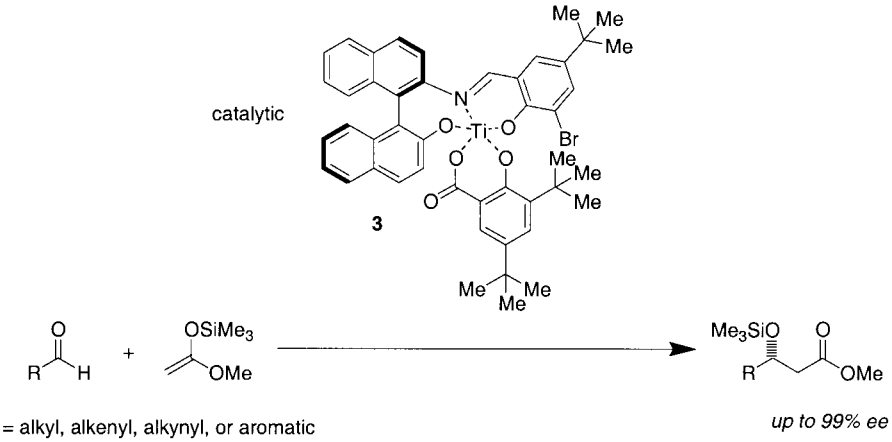
Chiral metal complexes derived from C_2-symmetric substituted 1,1′-binaphthalenes have proven to be remarkably effective as catalysts for asymmetric synthesis. The most widely used substituted binaphthalenes include [1,1′-binaphthalene]-2,2′-diol (BINOL), 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthalene (BINAP), and [1,1′-binaphthalene]-2,2′-diamine [3]. For each of these, both enantiomers are readily available or readily prepared. However, derivatives of unsymmetrical, substituted 1,1′-binaphthalenes such as (+)-(*R*)-2′-amino-[1,1′-binaphthalene]-2-ol (**1**) have only recently been examined for the preparation of chiral metal complexes [4–7]. We have documented the use of (+)-(*R*)-**1** in the preparation of a tridentate ligand **2**, whose derived titanium complex **3** is effective in catalytic enantioselective aldol addition reactions [5]. The unsymmetrical 1,1′-binaphthalene possesses several salient features as a precursor to chiral ligands: *1*) availability of both enantiomers; *2*) ease of derivatization; *3*) amenability to incremental variations in the overall electronics and sterics of the metal-ligand complex.

We have described a tridentate *Schiff*-base ligand prepared from (+)-(*R*)-2′-amino-[1,1′-binaphthalen]-2-ol ((+)-(*R*)-**1**) and 3-bromo-5-(*tert*-butyl)salicylaldehyde (= 3-bromo-5-(*tert*-butyl)-2-hydroxybenzenecarbaldehyde). The orange Ti^{IV} complex **3** derived from **2**, $(i\text{-PrO})_4Ti$, and 3,5-di-(*tert*-butyl)salicylic acid catalyzes (2 mol-%) the



acetate aldol addition of *O*-trimethylsilyl *O*-methyl ketene acetal and aldehydes in good yields and high levels of asymmetric induction (*Scheme*). The Ti^{IV} complex in this catalytic process displays some unique features relative to other Ti^{IV} complexes that have been reported to date pertaining to its wide substrate scope [8]. Indeed, the catalytic process has found numerous applications, including our own synthesis of macrolactin A [9]. Synthesis of the active complex required a practical preparation of optically active, pure 2′-amino-[1,1′-binaphthalen]-2-ol (**1**); however, unlike BINOL and [1,1′-binaphthalene]-2,2′-diamine, the resolution of (±)-2′-amino-[1,1′-binaphthalene]-2-ol has received less attention [6][7]. The utility of this ligand in aldol-addition reactions along with potential other applications that may be identified in the future compel us to document herein the preparation of the tridentate ligand **2** [10].

Scheme 1



Results and Discussion. – The coupling of naphthalen-2-amine and naphthalen-2-ol can be carried out on a large scale to give racemic 2′-amino-[1,1′-binaphthalen]-2-ol. We have found that slight modifications of the procedure reported by *Kočovský* and co-workers reproducibly afford **1** [6]. Thus, stirring a solution of naphthalen-2-amine, naphthalen-2-ol, $PhCH_2NH_2$, and $CuCl_2 \cdot 2\ H_2O$ in deoxygenated MeOH over 48 h

afforded 2′-amino-[1,1′-binaphthalen]-2-ol in 65% yield. In the subsequent experiments involving the resolution of 2′-amino-[1,1′-binaphthalen]-2-ol with camphorsulfonic acid, we observed batch-dependent results. We speculated that this was a function of trace amounts of residual Cu salts, as judged by slight coloration of the product. This problem was addressed by noting that a second washing of the isolated product with acid (HCl) and base (NH_4OH) assures removal of Cu salts from the product, as judged by coloration of the aqueous layers, and, thus, facilitates the subsequent enantiomeric resolution. The resolution is carried out by treating a rapidly stirred solution of (±)-2′-amino-[1,1′-binaphthalen]-2-ol in PhCl/abs. EtOH 5:1 at 65° with (*R*)-camphor-10-sulfonic acid[1]). After initial formation of a precipitate, the well-stirred solution was allowed to slowly cool to room temperature over 1 h and allowed to stand for an additional hour. The isolated filtrate was washed three times with PhCl to afford the camphorsulfonate salt. After the filter cake was suspended in a mixture of CH_2Cl_2 and 5% aqueous $NaHCO_3$ solution, the mixture was stirred rapidly for 10 min, over which time the organic phase became homogeneous. From the organic phase was isolated (+)-(*R*)-2′-amino-[1,1′-binaphthalen]-2-ol in 97% ee. This was conveniently assayed by conversion to the corresponding *Mosher* derivative and analysis of the ^{1}H-NMR spectrum ($CDCl_3$) and integration of MeO peaks (major δ 2.95, minor 2.81 ppm). A subsequent recrystallization of the product (97% ee) from benzene afforded (+)-(*R*)-**1** (73%) with an optical purity of 99% ee as a crystalline solid. Since both (−)-(*R*)- and (+)-(*S*)-camphorsulfonic acids are inexpensive and readily available, either (+)-(*R*)- or (−)-(*S*)-2′-amino-[1,1′-binaphthalene]-2-ol (**1**) can be accessed by the resolution described.

The synthesis of the *Schiff*-base ligand **2** illustrates the ease with which **1** can be derivatized. The conversion of optically pure **1** to the tridentate ligand was readily effected upon condensing with the substituted salicylaldehyde. Thus, treatment of **1** with 3-bromo-5-(*tert*-butyl)salicylaldehyde in absolute EtOH at reflux for 24 h afforded a bright orange crystalline solid, **2**, in 83% yield. This material, in combination with di-(*tert*-butyl)salicylic acid, is suitable for use as a ligand with Ti^{IV} to furnish a complex that may be used as a catalyst for enantioselective addition reactions of aldehydes and silyl ketene acetals.

We have described a facile preparation of the tridentate ligand **2** for use in enantioselective acetate aldol addition reactions. Given the ease with which we have demonstrated access to multi-gram quantities of **2** by the procedure we have described, this should facilitate its use not only as reported but also possibly in further applications.

Experimental Part

(±)-2-Amino-1,1′-binaphthalen]-2-ol ((±)-**1**). MeOH (1.4 l) is deoxygenated in a 2-l flask by bubbling N_2 through for 1 h. In a separate 1-l flask are placed naphthalen-2-ol (5.00 g, 34.7 mmol) and naphthalen-2-amine (*Caution*, handle with care; 5.00 g, 34.7 mmol) in 400 ml of the deoxygenated MeOH. $PhCH_2NH_2$ (37.2 g, 347 mmol) is placed in a 500-ml flask and dissolved in 200 ml of deoxygenated MeOH. To the remaining deoxygenated methanol is added $CuCl_2 \cdot 2H_2O$ (14.8 g, 86.7 mmol). Once all the $CuCl_2$ is dissolved by stirring, the soln. of $PhCH_2NH_2$ is added *via* cannula. After stirring the Cu and $PhCH_2NH_2$ soln. for 10 min at r.t., the

[1]) We have observed that a 3:1 toluene/i-PrOH mixture may be used as an alternative to PhCl/EtOH.

soln. of naphthalen-2-ol and naphthalen-2-amine is added *via* cannula. The soln. is stirred at 23° for 48 h. The precipitate formed is collected with a fritted funnel and washed twice with 50 ml of MeOH. The filter cake is stirred with 100 ml of 37% aq. HCl and 100 ml of H_2O for 30 min. Then 150 ml of a 30% aq. NH_4OH soln. is added slowly followed by 500 ml of H_2O. The precipitate is isolated by filtration and washed twice with 50 ml of H_2O. The solid is stirred again with 50 ml of 37% aq. HCl and 100 ml of H_2O for 10 min. A 30% aq. soln. of NH_4OH (70 ml) is slowly added to the soln. and is then diluted with 300 ml of H_2O. The precipitate is collected by filtration and washed twice with 50 ml of water. The powder obtained is dried *in vacuo* to give 6.44 g (65%) of (±)-**1**.

*(+)-(*R*)-2-Amino-[1,1′-binaphthalen]-2-ol* ((+)-**1**). In an 100-ml flask is placed (±)-**1** (5.00 g, 17.5 mmol) in 55.5 ml of PhCl and 11.1 ml of abs. EtOH. The soln. is heated to 65° with rapid stirring and (*R*)-camphor-10-sulfonic acid (4.24 g, 18.3 mmol, recrystallized from AcOEt prior to use) is added. The dark-colored mixture became homogeneous immediately after addition of the (*R*)-camphor-10-sulfonic acid. Stirring is continued, and heating is maintained at 65° for 30 min, during which time a precipitate began to form. The well-stirred soln. is then allowed to gradually cool to r.t. over 1 h and allowed to stand for an additional hour. The precipitate formed is isolated by filtration and washed three times with 4 ml of PhCl. The filter cake is suspended in a mixture of 50 ml of CH_2Cl_2 and 25 ml of a 5% aq. $NaHCO_3$ soln. The mixture is stirred rapidly for 10 min, over which time the org. phase became homogeneous. The mixture is transferred to a separatory funnel, and the org. layer is separated. The aq. layer is extracted with another 15 ml of CH_2Cl_2. The combined org. layers are dried (Na_2SO_4) and concentrated *in vacuo* to give 2.20 g (88%) of (+)-**1** in 97% ee. A small sample of the unpurified solid was converted to the corresponding (*S*)-MTPA ester (4-(dimethylamino)pyridine, (*R*)-MTPACl, CH_2Cl_2). Analysis by ^{1}H-NMR spectroscopy revealed that it had been formed in 97% ee (ratio of diastereoisomers determined from integration of MeO peaks in ^{1}H-NMR (300 MHz, $CDCl_3$): major δ 2.95, minor 2.81 ppm).

Recrystallization of the product (97% ee) from 20 ml of benzene affords 1.83 g (73%) of (+)-**1** with an optical purity of 99% ee. M.p. 169°. $[\alpha]_D^{19} = +122$ ($c = 1.04$, THF) ([5]: m.p. 171-3°; $[\alpha]_D^{19} = +116$, for 97% ee).

*3-Bromo-5-(*tert*-butyl)salicylaldehyde* (= *3-Bromo-5-(*tert*-butyl)-2-hydroxybenzenecarbaldehyde* Mg (3.60 g, 150 mmol) and $Mg(OMe)_2$ methoxide (682 mg, 0.750 mmol) are placed in a 500-ml flask in 71 ml of anh. MeO and 30 ml of toluene to be heated to reflux for 1.5 h. To the white, cloudy soln. is added 4-(*tert*-butyl)phenol (37.0 g, 250 mmol), and heating is continued for another h. An additional 100 ml of toluene is added, and the MeOH/toluene azeotrope is then removed by distillation (b.p. 63°) from the clear, yellow soln. Once the distillation temp. rises above 100°, heating is temporarily stopped for addition of another 50 ml of toluene to the white suspension. Paraformaldehyde (23.0 g, 750 mmol) is then added in 3–5 g batches over 1 h with resumed heating. The thick, yellow soln. is stirred at 110°, and the low-boiling materials are removed by distillation throughout the addition of the paraformaldehyde. After all the paraformaldehyde is added, heating is continued for another 2 h. The soln. is then cooled to r.t., and diluted with 50 ml of toluene and 250 ml of a 10% aq. H_2SO_4 soln. The mixture is stirred for 1.5 h at 60°. The org. layer is separated, and the aq. layer is extracted with another 50 ml of toluene. The combined org. layers are washed with 150 ml of a 10% aq. soln. of H_2SO_4 and 100 ml of a sat. aq. NaCl soln. After drying (Na_2SO_4), the org. extracts are concentrated. The residue is a yellow oil (31.4 g), which consists of 80% 5-(*tert*-butyl)salicylaldehyde and 20% 4-(*tert*-butyl)phenol. To a 250-ml flask containing a soln. of the crude 5-(*tert*-butyl)salicylaldehyde (31.4 g, 176 mmol) in 90 ml of glacial AcOH is added Br_2 (11.4 ml, 220 mmol) dropwise. The orange soln. is allowed to stir for 24 h at 23°. The soln. is then diluted with 100 ml of H_2O to precipitate the product. The crystals are collected by suction filtration and washed with H_2O (3×50 ml). The yellow solid is recrystallized from hexane/AcOEt 10:1 to give 27.1 g (42% overall) of yellow crystals. M.p. 81°.

Schiff *Base (+)-***2**. In a 25-ml flask, a soln. of (+)-**1** (1.00 g, 3.50 mmol) and 3-bromo-5-(*tert*-butyl)salicylaldehyde (1.08 g, 4.21 mmol) in 10 ml of abs. EtOH is heated at reflux for 24 h. After removal of the volatiles *in vacuo*, the product is isolated by flash chromatography on 100 ml of silica gel (4-cm diameter column) with hexane/AcOEt 4:1. The resulting orange powder is dried under vacuum (1 mm Hg) for 12 h to give 1.53 g (83%) of (+)-**2**. M.p. 164°. $[\alpha]_D^{19} = +22.8$ ($c = 1.00$, $CHCl_3$).

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