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Asymmetric Synthesis of Conformationally Constrained *cis*-1-Amino-1-phenylcyclohexan-2-ol

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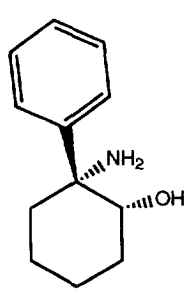
Abstract: A regio- and stereo-controlled synthesis of chiral *cis*-1-amino-1-phenylcyclohexan-2-ol is described. The optically pure diol **4** was converted to the ligand **8** in 80% yield. Copyright © 1996 Elsevier Science Ltd

New chiral *cis*-1,2-aminoalcohols and their applications to asymmetric synthesis continue to be found. For example, we recently reported the syntheses of chiral *cis*-1-amino-2-alcohols **2a-c** (n = 0-2) from either the corresponding chiral epoxides or diols using a *Ritter*-type reaction.[1] The exploration of **2a**, in particular, as chiral auxiliaries and ligands is of great current interest.[2] By increasing the conformational rigidity of the phenylglycinol system selectivities have been shown to increase.[2a] Another means to enhance selectivity would be to increase the steric bulk at the amine, as in **1**. Unfortunately, the preparation of such an amine attached to a chiral tertiary carbon atom with a cis-1,2-relationship to an alcohol is a difficult synthetic task. We reasoned that the Ritter technology could solve this problem. Herein we disclose the first asymmetric synthesis of chiral *cis*-1-amino-1-phenylcyclohexan-2-ol (**1**) from either the chiral epoxide or diol of 1-phenylcyclohexene (**3**).



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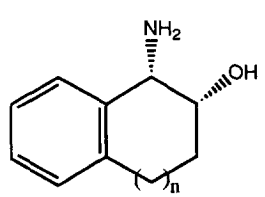
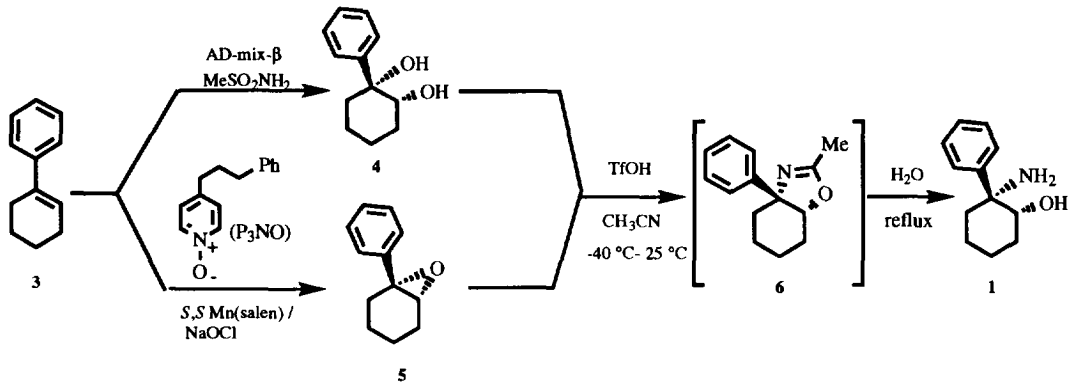


2 n = 0-2

As with our report on the conversion of *cis*-1,2-tetralindiol[1b] to *cis*-1-amino-2-tetralol we envisaged that *cis*-1-amino-1-phenylcyclohexan-2-ol (**1**) could be prepared from diol **4** via the oxazoline intermediate **6**. The racemic diol **4** was prepared according to the literature procedure in >95% yield.[3] NMR studies indicated that 2.0 equivalents of TfOH in acetonitrile at -40 °C followed by warming to room temperature converted diol **4** to a 95:5 mixture of *cis*/*trans* oxazolines **6**. Typically, 5% of 2-phenylcyclohexanone was formed in the reaction. Surprisingly, no other by-products were observed in this reaction. Hydrolysis of the oxazolines yielded *cis* and *trans*-1-amino-1-phenylcyclohexan-2-ol[4] with no epimerization of the aminoalcohol (Scheme 1).

Scheme 1



The salient feature in the asymmetric synthesis of **2a-c** was the stereochemical integrity of the carbon-oxygen bond at C-2. Moreover, from this center, chirality was transferred to the amine-bearing carbon. Analogously, the C-2 carbon of **4** or **5** should make the asymmetric synthesis of **1** feasible. Recently, Sharpless disclosed the synthesis of either antipode of optically pure 1-phenyl-1,2-cyclohexanediol (**4**).[5] The (1*R*, 2*R*)-enantiomer of **4** was subjected to the amination procedure to provide the *cis*-methyloxazoline intermediate **6** with >95% selectivity. The oxazoline was hydrolyzed by addition of water, removal of the acetonitrile by distillation, and heating the mixture at 100 °C for 4 h to give an 80% assay yield of *cis*-1-amino-1-phenylcyclohexan-2-ol. Neutralization with 50% NaOH provided a 70% yield of pure crystalline *cis*-amino alcohol **1** [m.p. 128 °C, $[\alpha]^{25}_D = -30.8°$ (c 1, $CHCl_3$)]. The optical purity of the *cis*-amino alcohol **1** was determined to be >99% by derivatization as the *tert*-butyl carbamate and HPLC analysis using chiral pack-AD column (92:8 hexane/ethanol). In addition, the single-crystal X-ray structure determination of *cis*-amino alcohol **1** confirmed the stereochemistry (Figure 1)[6] as (1*R*, 2*R*)-1-amino-1-phenylcyclohexan-2-ol. As with the benzocycloalkanes[1b], the C-2 hydroxyl group directed the stereochemistry to the C-1 position.

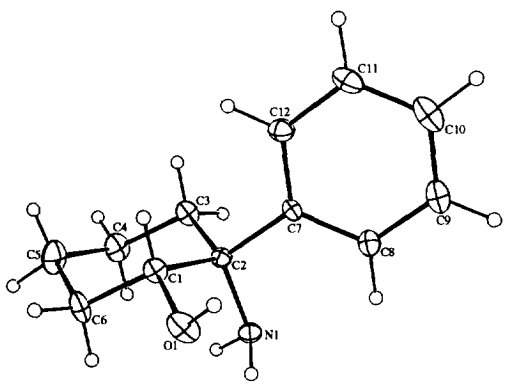
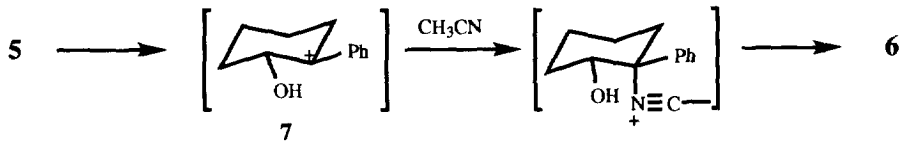


Figure 1. Perspective view (ORTEP) showing the crystallographic labels for compound **1**.

Chiral epoxides can also undergo a Ritter-type reaction to produce oxazolines.[1] However, the 6-membered-ring analogue 1,2-tetralin oxide only gave an ~1:1 mixture of *cis*/*trans*-oxazolines of compound **2b**.[1b] Therefore, we were not hopeful in obtaining for a selective-amination process with chiral 1-phenylcyclohexene oxide. Notwithstanding, the (1*R*, 2*R*)-1-phenylcyclohexene oxide was prepared in 92% e.e. and 60% yield using Jacobsen's procedure with (*S*,*S*)-Mn(salen)/NaOCl.[7] Gratifyingly, the corresponding *cis*-methyloxazoline **6** was obtained with >95% *cis*-selectivity when the (1*R*, 2*R*)-1-phenyl-1,2-epoxide was exposed to the triflic acid reaction. Hydrolysis gave (1*R*, 2*R*)-1-phenyl-1-aminocyclohexan-2-ol with >95% *cis*-selectivity and 92% e.e.[8] The high *cis*-selectivity for this conversion is due to the locked conformation of the incipient carbenium ion **7** and the directing effect of the hydroxyl group. Axial attack of the nitrile affords the preferred stereochemistry with the phenyl ring and C-2 oxygen in the equatorial positions.



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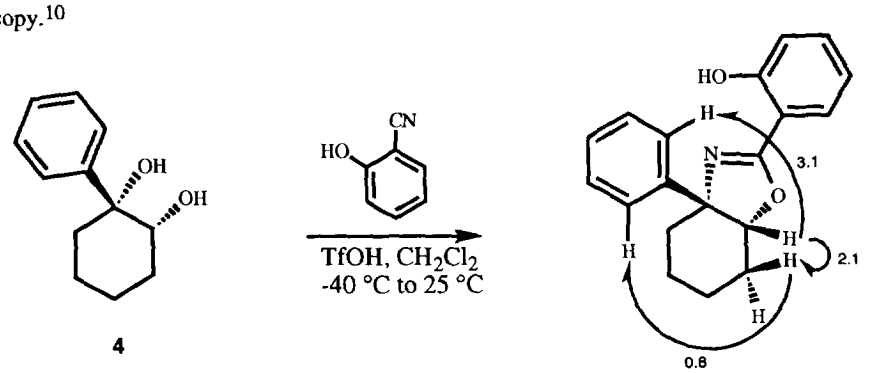
The successful formation of the *cis*-methyloxazoline **6** led us to investigate the synthesis of the more constrained potential bi-dentate ligand **8**.[9] When the diol **4** was exposed to five equivalents of 2-cyanophenol in the presence of two equivalents of triflic acid at -40 °C, followed by warming to room temperature, an 80% yield of **8** was realized. The *cis*-stereochemistry of the oxazoline **8** was determined by using NOE difference spectroscopy.[10]



4 8

In summary, we have developed a practical synthesis of chiral *cis*-1-amino-1-phenylcyclohexan-2-ol and a related bi-dentate ligand in a single step from the epoxide or diol of 1-phenylcyclohexene. This technology is applicable to the synthesis of other conformationally constrained amino alcohols and their derivatives possessing different steric and electronic properties.[11]

Experimental

Proton and carbon-13 spectra was recorded in CD_3CN and $CDCl_3$ on a Bruker AM-400 spectrometer at a frequency of 400.13 and 100.61 MHz respectively. The chemical shifts for **1** are reported in ppm relative to residual CD_2HCN for proton (d= 1.93 ppm) and CD_3CN for carbon (d=1.3 ppm). The 1-phenylcyclohexene epoxide and diol Ritter reactions were monitored by Spectra Physics HPLC with a reverse phase HPLC assays on a Zorbax® RX-C8 column, 4.6 mm x 25 cm, at 220 nm, mobil phase A: aqueous / acetonitrile = 65 /35 (aqueous = 0.01 M potassium dihydrogenphosphate, 0.002 M sodium hexanesulfonate), or B: aqueous / acetonitrile = 40 / 60 (aqueous = 0.01 M phosphate at pH = 5.0), 1.0 mL/min. A chiral assay was performed on Spectra Physics HPLC with a Chiral Pac-AD , 4.6 mm x 25 cm, at 254 nm, mobil phase = hexane /ethanol = 98/2, 1 mL/min(Retation time of racemic *tert*-butyl carbamate of **1**: 8.3 min; 9.0 min; Retation time of (1*R*,2*R*)-*tert*-butyl carbamate of **1**: 8.3 min). All the solvents were purchased from Fisher Scientific Co.,

Preparation of (*1R, 2R*)-1-amino-1-phenylcyclohexane-2-ol from diol 4:

Diol **4**[5] (>99.5 e.e, 10 mmol) and acetonitrile (16.5 mL) is charged using a three-necked flask under nitrogen atmosphere and cooled to -40 °C. To this slurry triflic acid (20 mmol) is added while maintaining the internal temperature at <-30 °C. The reaction mixture is warmed to 22 °C and aged for 1.0 h. Water (16.5 mL) is added to the reaction mixture and aged for 10 minutes. The reaction mixture is concentrated until the internal temperature reaches 100 °C by atmospheric distillation and the aqueous reaction mixture is then refluxed at 100 °C for 5.0 h. After cooling to 22 °C, CH_2Cl_2 (10.0 mL) is added and stirred for 10 minutes. The two phases were separated. The aqueous layer was adjusted to pH 13 by controlled addition of 50% NaOH at 0 °C. The slurry was filtered and the product was washed with cold water(2x5mL). Amino alcohol **1** was dried at 40 °C in a vacuum oven for 24h to produce a 70% yield. The optical purity of amino alcohol **1** is >99.5 % e.e. mp 128 °C; $[\alpha]^{25}_D$ = -30.8 (c 1, $CHCl_3$); ^1H NMR (400.12MHz, CD_3CN) δ 7.53 (m, 2H), 7.47 (m, 2H), 7.42 (m, 1H), 4.37 (dd, J=7.2,4.2, 1H), 3.86 (br s, 1H), 2.24 (m, 1H), 2.09 (m, 1H), 1.79-1.55 (om, 4H), 1.54-1.38 (om, 2H); ^{13}C NMR (100.16MHz, CD_3CN) δ 138.1, 130.0, 129.9, 127.3, 70.1, 64.2, 32.3, 29.9, 21.7, 21.3. Anal. Calcd for $C_{12}H_{17}ON$: C, 75.36; H, 8.96; N, 7.32 Found: C, 75.50; H, 8.91; N, 7.23.

Preparation of (*1R, 2R*)-1-amino-1-phenylcyclohexane-2-ol from epoxide 5:

Epoxide **5**[7,8b] (10 mmol, 93% e.e.) and acetonitrile (16.5 mL) is charged using a three-necked flask under nitrogen atmosphere and cooled to -40 °C. To this solution triflic acid (20 mmol) is added while maintaining the internal temperature at <-30 °C. The reaction mixture is warmed to 22 °C and aged for 1.0 h. Water (16.5 mL) is added to the reaction mixture and aged for 10 minutes. The reaction mixture is concentrated until the internal temperature reaches 100 °C by atmospheric distillation and the aqueous reaction mixture is then refluxed at 100 °C for 5.0 h. After cooling to 22 °C, CH_2Cl_2 (10.0 mL) is added and stirred for 10 minutes. The two phases were separated. The aqueous layer was adjusted to pH 13.0 by controlled addition of 50% NaOH at 0 °C. The slurry was filtered and the product was washed with cold water(2x5mL). Amino alcohol **1** was dried at 40 °C in a vacuum oven for 24h to produce a 65% yield. The optical purity of amino alcohol **1** is 93% e.e. $[\alpha]^{25}_D$ = -27.5 (c 1, $CHCl_3$). The amino alcohol **1** was crystallized from H_2O/EtOH(1:1) to provided >99% e.e.

Preparation of ligand 8:

To a suspension of diol **4** (1 mmol) and 2-hydroxy benzonitrile (5 mmol) in dichloromethane (4 mL) at -40 °C, trifluoromethanesulfonic acid (2 mmol) was added dropwise to give a homogeneous solution. The reaction was allowed to reached room temperature and then stirred for 2h. The pale-yellow solution was cooled to 5 °C and poured into ice-cold saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$, then water. The organic phase was dried (Na_2SO_4) and evaporated. Column chromatography on silica gel (ethyl acetate/ hexane 1:6) gave the desired ligand **8** in 80% yield. $[\alpha]^{25}_D$ = -103.0 (c 1, $CHCl_3$). ^1H NMR (400.12MHz, $CHCl_3$) δ 12.48 (br s, 1H), 7.72 (dd, J=7.9, 1.6, 1H), 7.48 (m, 2H), 7.44-7.35 (om, 3H), 7.29 (m, 1H), 4.83 (t, J=3.6, 1H), 2.23 (m, 1H), 2.11 (m, 1H), 2.01(m, 1H), 1.92 (m, 1H), 1.70-1.56 (om, 4H); ^{13}C NMR (100.16MHz, $CHCl_3$) δ 164.6, 160.2, 146.5, 133.4, 128.6, 128.2, 127.1, 125.3, 118.6, 116.8, 110.9, 84.0, 73.0, 35.0, 25.3, 18.0, 16.3. Anal. Calcd for $C_{19}H_{19}O_2N$: C, 77.79; H, 6.52; N, 4.77. Found: C, 77.81; H, 6.51; N, 4.80.

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†† Author to whom correspondence regarding X-ray structure determinations should be addressed.

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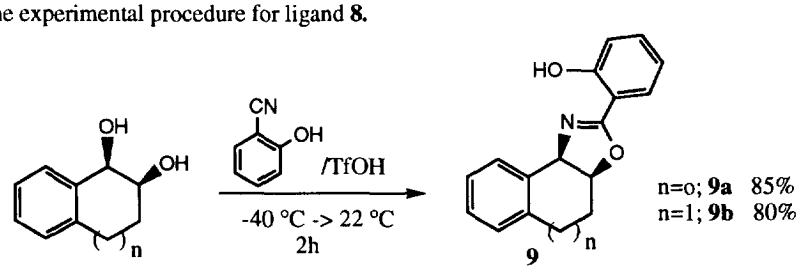
(8) (a) Jacobsens's AE with *S,S* manganese salen catalyst provides the same sense of induction for compound **1** as Sharpless' AD-mix-β catalyst. (b) For practical reasons, P_3NO (4-(3-phenylpropyl)pyridine N-oxide) can be substituted for expensive 4-PPNO in Jacobsen's procedure.[1b] The benefit of P_3NO in manganese salen's see: "The Role of 4-(3-Phenylpropyl)pyridine N-Oxide (P_3NO) in the Manganese-Salen-Catalyzed Asymmetric Epoxidation of Indene" Senanayake, C. H.; Smith, G.B; Fredenburgh, L. E.; Ryan, K. M.; Liu, J.; Roberts, F. E.; Hughes, D.L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. submitted to *Tetrahedron Lett.*

The Preparation of P_3NO as follows: A 500-mL, three-necked flask equipped with an overhead paddle stirrer, thermocouple, condenser, nitrogen atmosphere and cooled by means of a water bath, was charged with water (63.5 mL), methanol (125 mL), and oxone (37.5 g). The pH of the slurry was 1.4 due to the bisulfate salts in oxone. To this slurry 4-(3-phenylpropyl)-pyridine (12.5 g) was added over 5 min. The mixture was then maintained at pH = 5.5 by the addition of 5 N sodium hydroxide solution while controlling the temperature at ≤ 35 °C. The temperature was controlled by water cooling and by the rate of addition of the sodium hydroxide: The progress of the reaction was monitored by HPLC assay. Upon completion of the reaction (< 1 area % by HPLC), the salts were removed by filtration and the cake was washed with 50 mL of methanol. The combined filtrate and washes were treated with 1 M sodium metabisulfite solution (12 mL) and stirred for 0.5 h. The quenched solution was then adjusted to pH = 10.0 with 5 N sodium hydroxide solution and further aged for 1 h. The solution was concentrated *in vacuo* (26 in Hg, 50 °C) to a final volume of 75 mL. The resulting slurry was cooled to 20 °C, the product was filtered, washed with 50 mL of water, and dried under nitrogen. The yield of 4-(3-phenylpropyl)pyridine *N*-oxide was 93%: m.p.60 °C; ^1H NMR (300MHz, $CDCl_3$) δ 1.81.98(2H, m), 2.3-2.6(4H, m), 7.05(2H, m), 7.12-7.30(5H, m), 8.11(2H, m); ^{13}C NMR (300MHz, $CDCl_3$) δ 31.6, 33.7, 35.0, 126.0, 126.1, 128.4, 128.5, 138.8, 141.1, 142.0. Anal. Calcd for $C_{14}H_{15}ON$: C, 78.84; H, 7.08; N, 6.56. Found: C, 78.80; H, 7.01; N, 6.25.

(9) These types of ligands are becoming extremely valuable in metal-catalyzed asymmetric reactions. For pioneering work in this area, see: (a) Blom, C.; Weickhardt, K. *Helv. Chim. Acta* **1991**, *74*, 717. (b) Blom, C.; Weickhardt, K.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173. (c) Blom, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848. (d) Serrano, J. L.; Sierra, T.; Gonzalez, Y.; Bolm, C.; Weickhardt, K.; Magnus, A.; Moll, G. *J. Am. Chem. Soc.* **1995**, *117*, 8312, and references cited therein.

(10) The curved arrows represent observed NOEs, and the values have been corrected for residual magnetization. The relative stereochemistry of compound **8** was unambiguously established as *cis* by acid hydrolysis to the known amino alcohol **1**.

(11) The viability of this new hydroxy-oxazoline formation process was extended to other optically pure diols, such as, indane and tetralindiol[1b] to provide ligand **9a** and **9b** respectively, by using the identical procedure as described in the experimental procedure for ligand **8.**



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