

Synthesis and Chiroptical Properties of a Novel C_2 -Symmetric Binaphthyl Phosphortriamide ("Chiral HMPA")

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ABSTRACT By use of an asymmetric Ullmann coupling involving chiral naphthalene oxazolines **1**, the title compounds were prepared in good yields and with high diastereoselectivity. Hydrolysis of the binaphthyl oxazolines **2** led to the di-aldehydes **5**, which were transformed into the azepine derivative, **6**. The latter was treated with the appropriate phosphoryl halide to access the chiral HMPA systems **7** and **9**. The CD spectra of the chiral azepine **6** and the chiral phosphoramides **7** and **9** were measured and showed a strong positive CD couplet near 225 nm, consistent with the P axial chirality (S configuration). Semi-empirical CNDO/S molecular orbital calculations of the CD spectrum of **6** satisfactorily reproduced the major features of the observed spectrum. *Chirality* 9:431-434, 1997. © 1997 Wiley-Liss, Inc.

Chiral binaphthyls containing a C_2 -symmetry axis display a wide variety of useful chemical properties such as ligands for transition-metal catalyzed processes, catalytic and stoichiometric asymmetric reactions.¹⁻³ Furthermore, we have previously shown that chiral oxazolines, attached to the binaphthyl nucleus, are readily accessible via Ullmann coupling⁴ and these products can be useful to reach other chiral biaryl systems.

It soon became obvious that these chiral C_2 -symmetric binaphthyls may be useful in the construction of certain chiral phosphoramides: a class of compounds (**7**, **9**) that has both the unique properties of chirality and strong metal ion binding. Chiral phosphoramides have been utilized as mediators in the reduction of ketones⁵ but to date the results have not been outstanding. Recently, Kubota and Koga have shown that chiral binaphthyl amines related to **7** effectively catalyzed allylic transpositions.⁶

Chiral binaphthyls are well-known examples of exciton chirality.^{7a} If the dihedral angle between the naphthyl rings has an absolute value less than 90° , the absolute configuration can be assigned unambiguously from the sign of the exciton couplet in the CD spectrum near 225 nm.⁸ A positive couplet indicates P axial chirality, and a negative couplet indicates M axial chirality. (The sign of a CD couplet is that of the long-wavelength component.) We investigated the CD spectra of **6**, **7**, and **9** experimentally and used the CNDO/S⁹ method to calculate the CD spectrum of **6**.

Our approach to the "chiral HMPA" derivatives **7** and **9** began with our own Ullmann coupling⁴ to give **2** as a 94:6 ratio of diastereomers (Scheme 1). Mild hydrolysis then produced the di-ester **3**, which was reduced to the diol, **4**. Oxidation of the latter using pyridinium dichromate gave

the aldehyde **5** in good yield. Transformation to the chiral azepine **6** took place readily using $\text{NH}_4\text{OAc-NaCNBH}_3$ in methanol at 0°C and was identical to the product obtained previously.¹⁰

Transformation to the chiral phosphoramide **7** was accomplished using bis (dimethylamino) chlorophosphine oxide to give **7** in 90% yield. In a similar fashion, the bis-binaphthyl phosphoramide **9** was obtained by treating **6** with phosphorous oxychloride affording the mono-biaryl dichlorophosphine oxide, **10**. This was followed by addition of another portion of the binaphthyl azepine **6** to furnish **8** in 91% yield. Finally, the last chlorine was replaced by piperidine affording the phosphortriamide **9** after heating at reflux in xylene. The product **9** was obtained in 90% yield as a colorless solid. Purification of both chiral phosphortriamides **7** and **9** was readily accomplished by chromatography (see Materials and Methods) and these then became the subject for experimental and theoretical chiroptical studies.

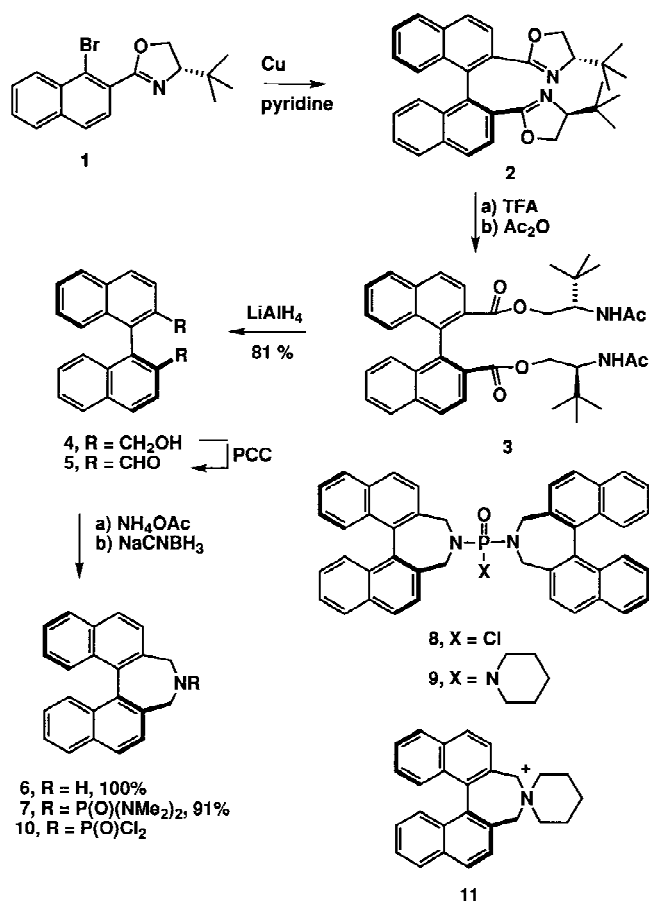
The CD spectra of **6**, **7**, and **9** are presented in Figure 1. Each spectrum is dominated by a strong positive couplet centered at 222 nm, with amplitude A ($\Delta\epsilon_1 - \Delta\epsilon_2$, where $\Delta\epsilon_1$ is the CD at the long-wavelength maximum of the couplet, and $\Delta\epsilon_2$ is the CD at the short-wavelength maximum)^{7b} of +800 for **6**, +870 for **7**, and +1,760 for **9**. The positive sign

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Scheme 1. Synthetic route to titled compound.

of the couplet indicates P axial chirality⁸ and an S absolute configuration. The amplitude for the dimeric binaphthyl **9** is approximately twice that for the two monomeric binaphthyls, as would be expected if the interaction between the

binaphthyl chromophores is weak. In addition to the intense positive couplet associated with the naphthalene B_b¹¹ band near 220 nm, weaker bands at longer wavelengths are observed. These are a negative band near 300 nm, assigned to the L_b band of the naphthalene chromophores; a positive band near 260 nm due to the naphthalene L_a band; and a negative band near 240 nm of uncertain origin. The two long-wavelength bands are about twice as intense in the CD spectrum of **9** as in those of **6** and **7**, as expected, but the 240 nm band is about 15 times as intense for the bischromophoric compound as for the monochromophoric molecules.

The CD spectra observed for **6** and **7** are similar to that reported^{8b} for a spiro analog to **6**, compound **11**, in which the azepine nitrogen is also part of a piperidine ring. In this latter case, the A value for the B_b exciton couplet near 220 nm is about +950 for the (S) configuration.

Calculations of the CD spectrum of **6** have been performed using the semi-empirical CNDO/S method⁹ to predict transition energies and rotational strengths. The molecular geometries used for the MO calculations were obtained by optimization using the AM1 method.¹² The minimum energy binaphthyl conformation had a dihedral angle of +52.6°, in excellent agreement with the dihedral angle of +52.9° determined by X-ray diffraction for a closely related molecule.^{10b} Figure 2 shows a comparison of the experimental CD spectrum for **6** with the spectrum calculated for the minimum energy conformation. The spectrum calculated by averaging over the low energy conformations using Boltzmann weighting factors was nearly identical to that for the minimum energy conformer.

The theoretical CD spectrum reproduces the major features of the experimental spectrum quite satisfactorily. A strong positive couplet associated with the B_b band near 225 nm is predicted, in agreement with the observed spectrum, although theory underestimates the amplitude somewhat (+675 calculated, +800 observed). A negative band is

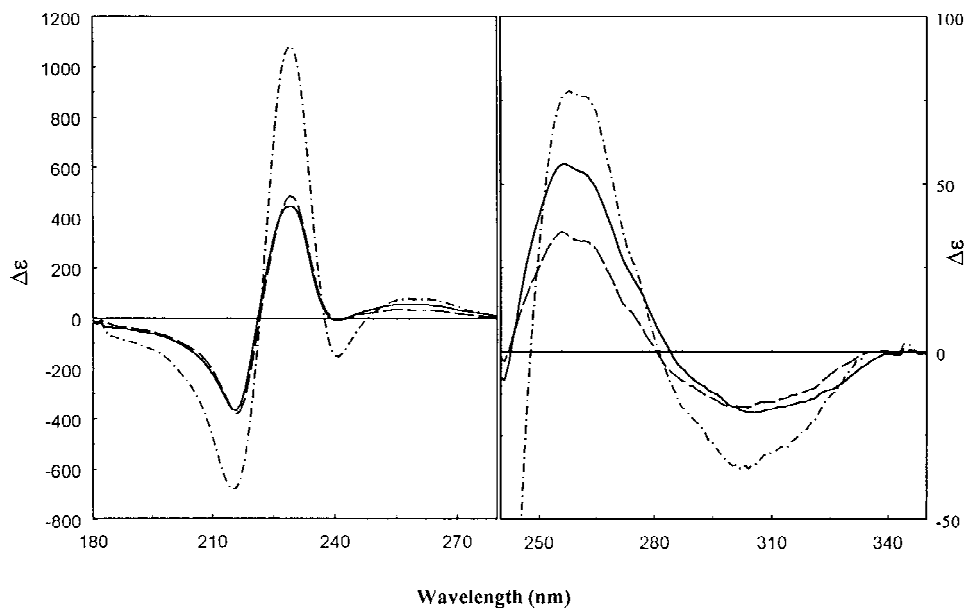


Fig. 1. Circular dichroism spectra of **6** (—), **7** (---), and **9** (- · - ·).

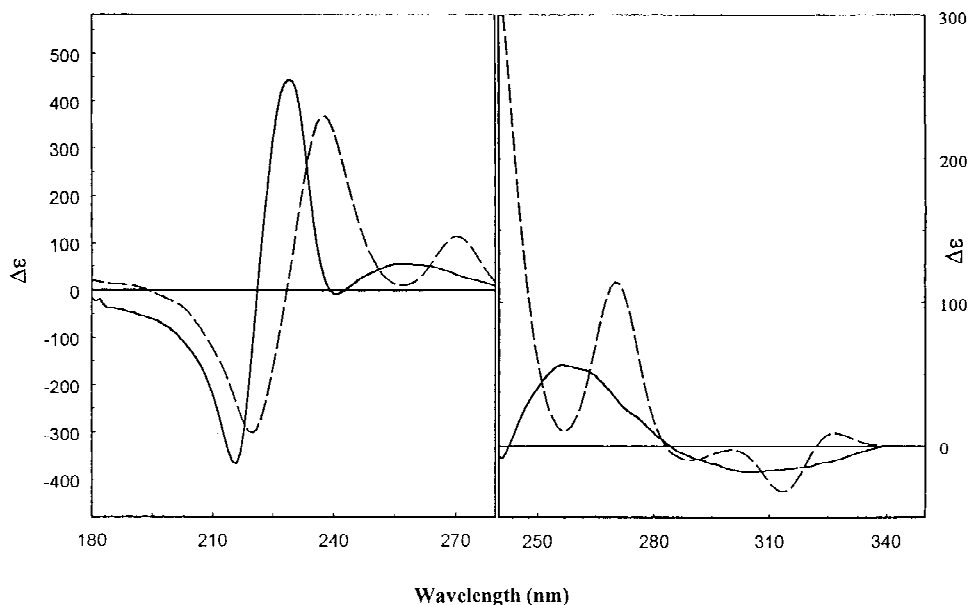


Fig. 2. Comparison of experimental (—) and theoretical (---) CD spectra of **6**. The calculated spectrum for the lowest energy conformer and the Boltzmann-weighted average over conformer are essentially indistinguishable.

predicted in the L_b region and a positive L_a band is predicted, again in good agreement with experiment. Weak positive and negative features are predicted on the long- and short-wavelength sides, respectively, of the L_b band, but these features are not observed. Conversely, the weak negative band observed near 240 nm does not appear in the calculated curve. Furthermore, the shape of the 260 nm L_a band is observed to be much less symmetrical than the predicted band. These minor discrepancies are largely attributable to the fact that the CNDO/S calculations only provide integrated CD intensities and do not give any information about band shapes. For the purposes of calculating a CD spectrum, Gaussian band shapes were assumed and these were assigned somewhat arbitrary bandwidths.

MATERIALS AND METHODS

Synthesis

Naphthyl Phosphoramidate, **7**. Benzazepine **6**⁷ (250 mg, 0.85 mmol) was taken up in 7 mL of THF, 160 mg, 0.94 mmol of *N,N,N',N'*-tetramethylphosphorodiamidic chloride (Fluka, Buchs, Switzerland) and 1 mL of triethyl amine were added and the mixture was brought to reflux overnight. After cooling, water (10 mL) was added and the solution was extracted with CH_2Cl_2 (2×20 mL), dried with K_2CO_3 , filtered, and the solvent was removed under reduced pressure to give a yellow foam. Purification by silica gel column chromatography (95% CH_2Cl_2 :5% MeOH) gave a white foam (330 mg, 91%). $[\alpha]_D^{25} = 130^\circ$ (c 0.4, CHCl_3); IR (film): 3,051, 2,877, 2,215, 1,684 cm^{-1} ; uv (MeOH) λ_{max} 301 nm ($\epsilon = 9.3 \times 10^3$); ^1H NMR (300 MHz, CDCl_3): δ 2.63 (d, $J = 9.6$ Hz, 3H), 2.75 (d, $J = 9.6$ Hz, 3H), 3.58 (dd, $J = 12.6$ Hz, $J = 4.8$ Hz, 2H), 4.34 (dd, $J = 12.9$ Hz, $J = 6.9$ Hz, 2H), 7.28–7.31 (m, 2H), 7.43–7.51 (m, 4H), 7.60–7.62 (m, 2H), 7.94–8.00 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ 37.0 (dd), 48.0 (d), 125.7, 125.9, 127.3, 127.4, 128.3, 129.2, 131.4, 133.2, 133.4, 133.4, 135.1. HRMS, m/z calcd for

$\text{C}_{26}\text{H}_{28}\text{N}_3\text{OP}$ (M⁺) 430.2048, found 430.2047. Anal. calcd for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{OP}$: C, 82.00; H, 6.37. Found: C, 82.12; H, 6.37.

Bis-Naphthyl Phosphoramidate, **9**. To a solution of $\text{P}(\text{O})\text{Cl}_3$ (0.15 mL, 1.61 mmol) and Et_3N (1.5 mL, 10.8 mmol) in dry toluene (4 mL) was added the azepine **6** (295 mg, 1.0 mmol) in toluene (2 mL). The mixture was stirred for 8 h at 25°C. The solvent was removed and the residue was purified by flash chromatography (1:1 hexanes/ether) to give the dichloride **10** (280 mg, 68.1%) as a white solid. To a solution of the dichloride **10** (245 mg, 0.6 mmol) in dry xylenes (6 mL) was added Et_3N (1.5 mL) and a solution of azepine **6** (178 mg, 0.6 mmol) in xylenes (3 mL) and the mixture was refluxed for 20 h. The solvent was removed and the residue was purified by flash chromatography (3:7 hexanes/ether) to give the chloride **8** (366 mg, 91.0%) as a white solid. To a solution of this product in xylenes was added piperidine (0.6 mL, 6 mmol) and the mixture refluxed for 20 h. The solvent was removed and the residue was purified by flash chromatography (1:1 EtOc/ CH_3CN) to give the product **9** (280 mg, 90.6%) as a white solid: $[\alpha]_D^{25} = +127$ (c 1.0, acetone); m.p. 192.8–194.0°C; uv (MeOH), λ_{max} 303 nm ($\epsilon = 2.0 \times 10^4$); ^1H -NMR (CDCl_3): 1.55 (6 H, br. m), 2.90–3.00 (2 H, m), 3.11–3.20 (2 H, m), 3.46–3.52 (2 H, m), 3.62–3.68 (2 H, m), 4.37–4.50 (2H, m), 7.21–7.30 (4 H, m), 7.37–7.51 (10 H, m), 7.58 (2 H, d, $J = 8.3$ Hz), 7.77 (2 H, d, $J = 8.1$ Hz), 7.87–7.94 (6 H, m); ^{13}C -NMR (CDCl_3) 24.7 (t), 26.4 (dt), 45.9 (t), 47.8 (dt), 48.2 (dt), 125.1 (d), 125.5 (d), 125.7 (d), 125.8 (d), 127.1 (d), 127.3 (d), 128.2 (d), 129.1 (d), 131.2 (s), 131.3 (s), 133.0 (s), 133.1 (s), 133.2 (s), 133.3 (s), 134.9 (s), 135.1 (s).

CD Measurements

CD spectra for **6**, **7**, and **9** were measured on a Jasco (Easton, MD) J720 CD Spectrophotometer from 180 to 350 nm. Acetonitrile was used as the solvent. The sample concentrations were about 10^{-4} M and the cell pathlength was 1 mm. Spectra were acquired at ambient temperature, about 25°C, averaging five scans.

Theoretical Methods

The molecular geometry for **6** was fully optimized using the AM1 method¹² as implemented in MOPAC.¹³ The optimal dihedral angle between the naphthyl rings was calculated to be 52.6°. Higher energy conformers were generated by varying the binaphthyl dihedral angle and optimizing all other bond lengths, and bond and dihedral angles.

CNDO/S⁹ calculations of the transition energies and rotational strengths for **6** in its optimized geometry were performed using a modified version of a program originally written by Downing et al.¹⁴ The original Del Bene and Jaffé parameters⁹ were used, except that in calculating the two-center core integrals, in addition to scaling the π - π overlaps by a factor of 0.585, the σ - σ overlaps were scaled by a factor of 1.267.¹⁵ Configuration interaction included the 169 singlet configurations constructed by excitation from one of the thirteen highest occupied MO's to one of the thirteen lowest virtual MO's. The dipole velocity formulation¹⁶ of the rotational strength was used to ensure origin independence. The calculated rotational strengths and transition energies were combined with Gaussian band shapes to calculate the CD spectrum. The band width parameter (half the band width at e^{-1} of the maximum) was taken as 7.68 nm for bands with maxima between 235 and 350 nm; 6.72 for bands in the 180–235 nm region; and 6.07 nm for bands below 180 nm. The CD spectrum averaged over low-energy conformations was calculated by first computing the spectrum for each conformation with an AM1¹² energy lying within 5 kcal/mol of the lowest energy conformer. The spectra were then weighted by the Boltzmann factor calculated from the relative AM1 energy at $T = 298^\circ\text{K}$.

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