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Enantioselective recognition of amines with an atropisomeric 1,8-bisphenolnaphthalene

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ABSTRACT

1,8-Bis[5′(2′-hydroxy-4′-methylbiphenyl)]naphthalene, **2**, was prepared from 1,8-dibromonaphthalene and 4-methoxy-2-methylphenylboronic acid in four steps with 51% overall yield. The axially chiral *anti*-isomer of **2** is stable to racemization at room temperature and the free energy of activation for the conversion of the *anti*-isomer to the *syn*-form was determined as 110.0 kJ/mol at 77.1 °C. At submillimolar concentration, enantiopure **2** can be used as circular dichroism sensor to detect a wide range of chiral amines.

1. Introduction

Although the synthesis of 1,1′-binaphthyl-2,2′-diol (BINOL) was first reported in 1873 it took another 100 years until this prime example of a C_2-symmetric bidentate atropisomer gained considerable attention.[1] Since the mid 1970s, BINOL and its derivatives have found extensive use in numerous asymmetric reactions, molecular recognition studies, and other applications.[2] The intriguing structure of BINOL and its success as a chiral ligand and reagent in asymmetric synthesis has propelled the development of countless analogues that vary in stereoelectronic properties and bite angle. For many years, the synthesis of axially chiral 1,8-bisphenolnaphthalenes has been pursued due to the apparent structural analogy to BINOL and the associated promise in asymmetric catalysis and other areas. However, the incorporation of sufficient steric bulk into the chiral 1,8-bisphenolnaphthalene framework to halt rotation about the aryl–aryl axes and concomitant racemization has proven difficult.[3] Accordingly, few stereodynamic 1,8-bisphenolnaphthalenes, such as **1**, have been reported to date and used in racemic form.[4] Based on our experience with the synthesis and atropisomerization of chiral biaryls and triaryls[5] and 1,8-diheteroarylnaphthalene-derived sensors,[6] we recently found that incorporation of steric bulk proximate to the aryl–aryl bonds in axially chiral 1,8-bisphenolnaphthalenes affords isolable enantiomers (Fig. 1).[7] We believe that this finding will have important implications to chiral ligand development for asymmetric catalysis, recognition, and other fields. We now wish to report the first example of an application of a conformationally stable, axially chiral *anti*-1,8-bisphenolnaphthalene.

2. Results and discussion

The synthesis of 1,8-bis[5′(2′-hydroxy-4′-methylbiphenyl)] naphthalene, **2**, began with the quantitative formation of 1,8-bis(2′-methyl-4′-methoxyphenyl)naphthalene, **4**, via palladium(0) catalyzed Suzuki coupling of 4-methoxy-2-methylphenylboronic acid, **3**, and 1,8-dibromonaphthalene (Scheme 1). The efficiency of this reaction is quite remarkable as it requires two consecutive Suzuki couplings and the construction of two sterically crowded aryl–aryl bonds. Based on ^{1}H NMR analysis, **4** was produced as a 3:1 mixture

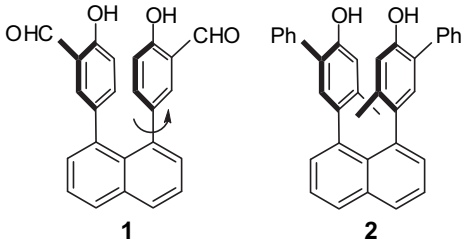

Fig. 1. Structures of axially chiral 1,8-bisphenolnaphthalenes.

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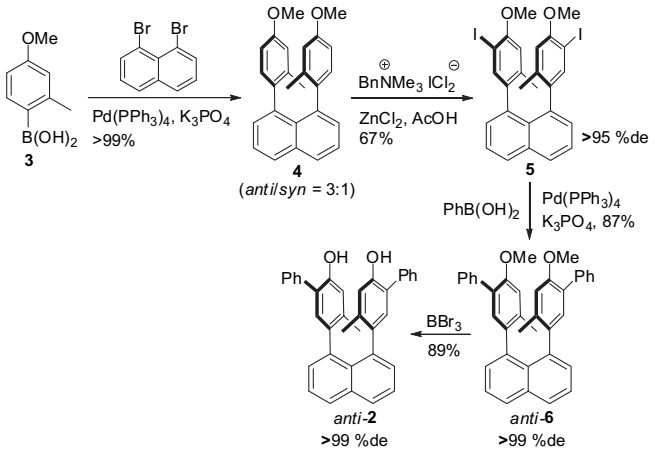
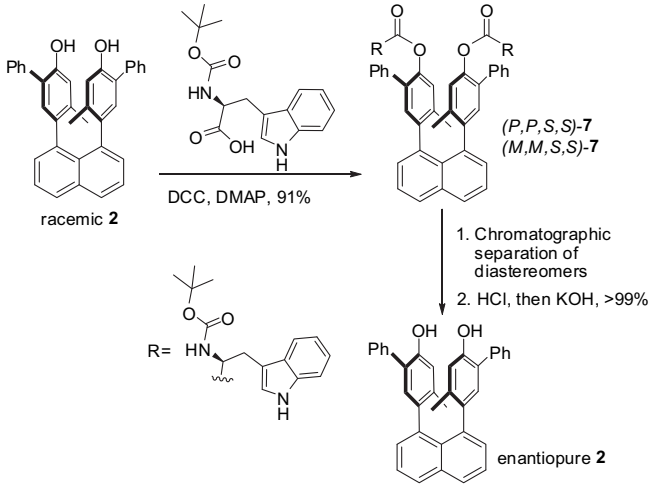


Scheme 1. Synthesis of 1,8-bisphenolnaphthalene *anti*-**2**.

of *anti*- and *syn*-isomers. Iodination of the diastereomeric mixture of **4** with benzyltrimethylammonium dichloroiodate and Suzuki coupling with phenylboronic acid proceeded with 67% and 87% yield. The *anti*-isomers of 1,8-bis(2′-methyl-4′-methoxy-5′-iodophenyl)naphthalene, **5**, and 1,8-bis(6′-methoxy-4′-methyl-3′-biphenyl)naphthalene, **6**, were isolated in >95% and >99% diastereomeric excess, respectively. Finally, deprotection of **6** with boron tribromide furnished the desired 1,8-bisphenolnaphthalene **2** in 89% yield. Overall, this approach furnishes racemic *anti*-**2** in four steps with 51% overall yield.

We found that the enantiomers and the *meso syn*-isomer of **2** can be resolved by chiral HPLC on Chiralpak AD (see SD). To avoid time-consuming preparative HPLC on a chiral column, the suitability of several chiral auxiliaries for large scale separation of the enantiomers of **2** was examined. We were pleased to find that esterification of racemic **2** with *N*-Boc-L-tryptophan generates dia-stereomeric diester derivatives **7** that can be separated by flash chromatography on silica gel (Scheme 2). Hydrolysis of the isolated diastereomers gave quantitative amounts of bisphenol **2** in enantiomerically pure form.



Scheme 2. Resolution of **2** via formation of diastereomeric tryptophan derivatives.

Preparative isolation of the levorotatory enantiomer of **2** enabled us to monitor the racemization kinetics at 77.1 °C by chiral HPLC separation of cooled aliquots (Fig. 2). Interconversion of the enantiomers of triaryls, such as **2**, proceeds via a diastereomeric *meso* intermediate and involves two rotations about the pivotal aryl–aryl bonds obeying reversible first-order kinetics. This is an

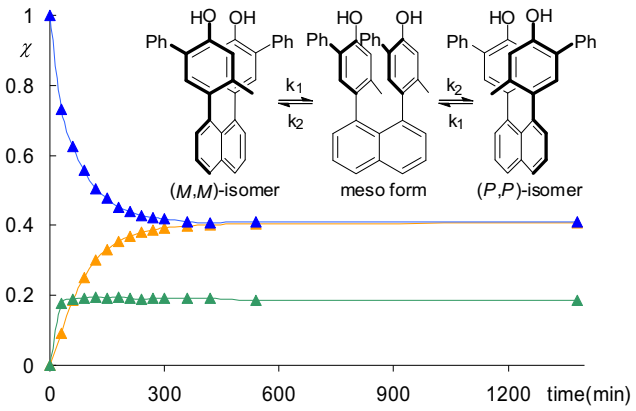


Fig. 2. Change in the mole fractions of (−)-**2** (blue), (+)-**2** (orange) and *syn*-**2** (green) during heating at 77.1 °C.

intramolecular process and the rotational energy barrier is mostly controlled by steric effects although electronic contributions are known to play a minor role.[8] The *syn*/*anti*-ratio of **2** at equilibrium was determined as 0.46 and the reversible first-order reaction kinetics were simulated and analyzed according to Vriens.[9] The free energy of activation for the conversion of the *anti*-isomer to the *syn*-intermediate, $\Delta G^{\neq}_{anti\rightarrow syn}$, was determined as 110.0 kJ/mol at 77.1 °C. As expected, the Gibbs activation energy for the reversed process, $\Delta G^{\neq}_{syn\rightarrow anti}$, is slightly lower and was calculated as 107.7 kJ/mol (see SD). Accordingly, the incorporation of two methyl groups into the *ortho*-positions of the triaryl framework of **1**, which rapidly racemizes at room temperature, generates a conformationally stable scaffold that does not show a sign of racemization after stirring in solution at 20 °C after 24 h.[10]

Having determined the stability of **2** to rotation about the chiral axes at room temperature, we decided to investigate the three-dimensional structure of this atropisomer. A single crystal of *anti*-**2** was obtained by slow evaporation of a dichloromethane solution.[11] Crystallographic analysis revealed that the two cofacial phenol rings are almost perfectly aligned. The separation between the centroids of the two phenol rings, which are splayed by 19.5°, was determined as 3.5 Å, indicating substantial π-overlap (Fig. 3).

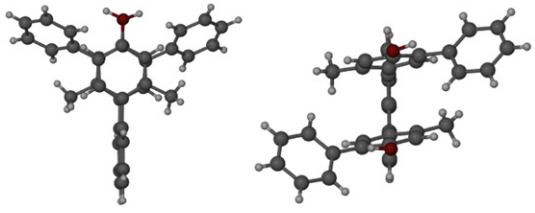


Fig. 3. Single crystal structure of *anti*-**2**.

The CD spectrum of enantiopure bisphenol **2** undergoes a remarkable change in the presence of base (Fig. 4). For example, deprotonation of (+)-**2** results in a dramatic red shift of the negative Cotton effect at higher wavelength and the corresponding bisphenolate has a large reversed amplitude at 290 nm. We found that addition of chiral amines to the bisphenolate regenerates the original CD spectrum. This proceeds with high stereoselectivity and therefore allows enantioselective CD sensing of the amine used. The reciprocity of the chiral recognition process was observed with different analytes, including 1-phenylethylamine (Fig. 5).

Using the bisphenoxide of (−)-**2** as sensor, we observed that the negative CD amplitude at 290 nm is more readily regenerated upon titration with (*R*)-1-phenylethylamine, (*R*)-**8**, than with (*S*)-**8**. The opposite trend was obtained when the bisphenoxide of (+)-**2** was

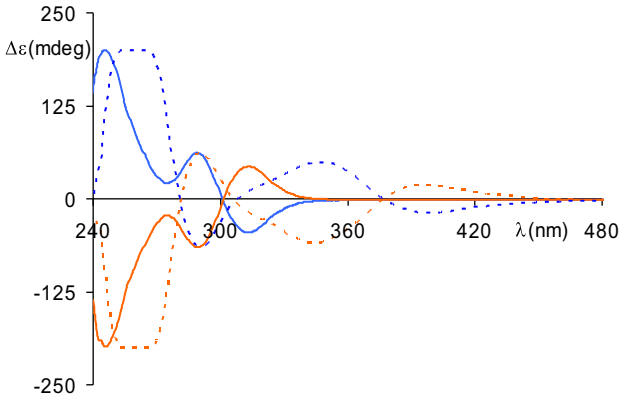


Fig. 4. CD spectra of dextrorotatory (blue) and levorotatory (orange) enantiomers of **2** (9.45×10^{-5} M, ACN). The dashed lines show the CD spectra upon treatment with sodium *tert*-butoxide.

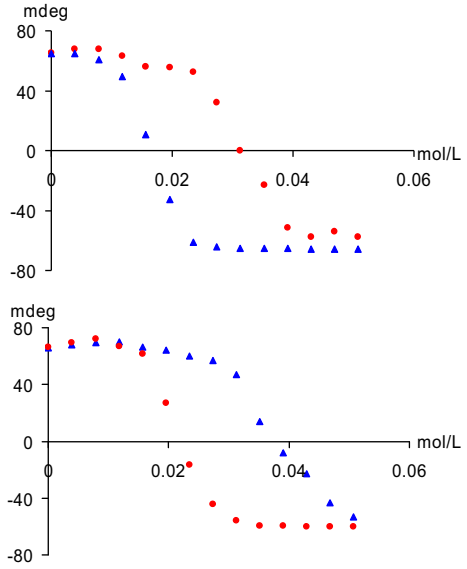


Fig. 5. Change in the CD amplitude at 290 nm of the bisphenoxides of (−)-**2** (top) and (+)-**2** (bottom) upon addition of (*R*)-**8** (blue) and (*S*)-**8** (red). The concentration of **2** was 9.45×10^{-5} M in acetonitrile.

employed in the same titration experiment. Screening of several other aromatic and aliphatic amines gave similar results, which highlights the general usefulness of this enantioselective recognition approach (Figs. 6 and 7).[12]

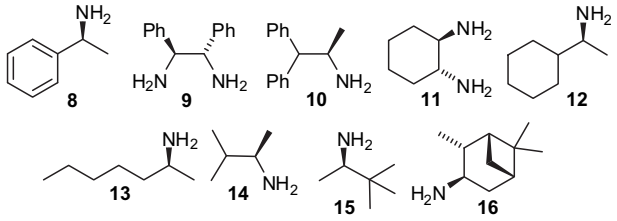


Fig. 6. Structures of amines tested. Only one enantiomer is shown.

3. Conclusion

In summary, we have described the synthesis of axially chiral 1,8-bisphenolnaphthalene **2**, which is stable to racemization at room temperature and readily available in enantiopure form. Crystallographic analysis revealed that **2** has a C_2-symmetric structure suitable for enantioselective interactions with chiral substrates. The intense CD spectra of the enantiomers of **2** undergo significant changes upon deprotonation that are reversible when hydrogen bond donors are added in excess. Titration of the enantiopure bisphenoxide of **2** with a wide range of amines showed that this process is stereoselective and can be utilized for enantiodifferentiation of aliphatic and aromatic chiral substrates. We believe that the structural analogy of the C_2-symmetric 1,8-bisphenolnaphthalene framework introduced herein to BINOL and its derivatives is likely to lead to future applications in chiral recognition and asymmetric catalysis. These studies are currently underway in our laboratories.

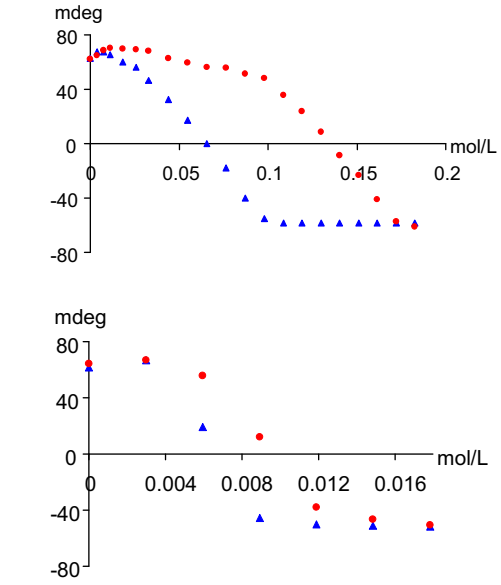


Fig. 7. Change in the CD amplitude at 290 nm of the bisphenoxide of (−)-**2** upon addition of aliphatic amines. Top: (*R*)-**15** (blue) and (*S*)-**15** (red). Bottom: (*R*,*R*,*R*,*S*)-**16** (blue) and (*S*,*S*,*S*,*R*)-**16** (red). The concentration of **2** was 9.45×10^{-5} M in acetonitrile.

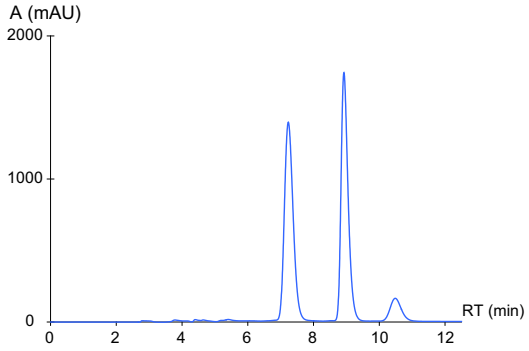


Fig. 8. HPLC chromatogram showing the separation of the stereoisomers of **2**.

4. Experimental section

4.1. Synthetic procedures

All reagents and solvents were used as purchased without further purification. All reactions were carried out under nitrogen atmosphere and anhydrous conditions. Products were purified by flash chromatography on SiO_2 (particle size 0.032–0.063 mm). NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz

(^{13}C NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to TMS.

*4.1.1. 1,8-Bis(2′-methyl-4′-methoxyphenyl)naphthalene (**4**).* A solution of 1,8-dibromonaphthalene, (1.29 g, 4.5 mmol), 2-methyl-4-methoxyphenylboronic acid, **3**, (2.24 g, 13.5 mmol), $Pd(PPh_3)_4$ (0.78 g, 0.68 mmol), and K_3PO_4, (4.30 g, 20.0 mmol) in 50 mL toluene was stirred at 110 °C for 18 h. The resulting mixture was allowed to come to room temperature, quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/hexanes 2:3) afforded 1.66 g (4.5 mmol, >99%) of off-white crystals containing *syn*- and *anti*-isomers of **4** in a ratio of approximately 1:3.

^{1}H NMR: δ=1.76 (s, 4.6H), 1.83 (s, 1.4H), 3.69 (s, 4.4H), 3.71 (s, 1.4H), 6.28–6.39 (m, 4H), 6.66 (d, J=8.2 Hz, 0.5H), 6.87 (d, J=8.2 Hz, 1.5H), 7.16 (d, J=6.8 Hz, 2H), 7.46 (dd, J=6.8, 8.0 Hz, 2H), 7.89 (d, J=8.0 Hz, 2H). ^{13}C NMR: δ=20.9, 21.0, 55.1, 55.2, 109.9, 110.3, 114.3, 114.4, 124.8, 125.0, 128.5, 129.0, 130.2, 130.4, 131.0, 131.6, 132.3, 134.8, 134.9, 135.2, 135.4, 136.5, 136.9, 139.5, 157.6, 158.1. Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

*4.1.2. 1,8-Bis(2′-methyl-4′-methoxy-5′-iodophenyl)naphthalene (**5**).* To a solution of **4** (0.18 g, 0.49 mmol) in 8 mL of acetic acid, benzyltrimethylammonium dichloroiodate (0.38 g, 1.08 mmol), and zinc dichloride (0.15 g, 1.08 mmol) dissolved in 8 mL of acetic acid were added dropwise over 30 min, and the mixture was stirred at 55 °C for 20 h. It was then cooled to 0 °C, carefully quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with 1 M sodium thiosulfate, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes/CH_2Cl_2 3:1) afforded 0.20 g (0.33 mmol, 67%) of **5** as a white solid.

^{1}H NMR: δ=1.86 (s, 6H), 3.83 (s, 6H), 6.41 (s, 2H), 7.15 (d, J=6.9 Hz, 2H), 7.27 (s, 2H), 7.48 (dd, J=6.9, 8.1 Hz, 2H), 7.92 (d, J=8.1 Hz, 2H). ^{13}C NMR: δ=20.7, 56.2, 82.0, 111.2, 125.0, 129.0, 130.2, 134.9, 136.8, 137.5, 137.6, 138.3, 156.2. Anal. Calcd for $C_{26}H_{22}I_2O_2$: C, 50.35; H, 3.58. Found: C, 50.15; H, 3.52.

*4.1.3. 1,8-Bis(6′-methoxy-4′-methyl-3′-biphenyl)naphthalene (**6**).* A solution of **5** (0.20 g, 0.32 mmol), phenylboronic acid (0.12 g, 0.96 mmol), $Pd(PPh_3)_4$ (0.055 g, 0.048 mmol), and K_3PO_4 (0.31 g, 1.44 mmol) in 5 mL of toluene was stirred at 110 °C for 18 h. The resulting mixture was allowed to come to room temperature, quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/hexanes 1:2) afforded 0.14 g (0.28 mmol, 87%) of **6** as a white solid.

^{1}H NMR: δ=1.70 (s, 6H), 3.67 (s, 6H), 6.36 (s, 2H), 7.00 (s, 2H), 7.21–7.31 (m, 6H), 7.38 (dd, J=7.5, 7.7 Hz, 4H), 7.45–7.52 (m, 6H), 7.92 (d, J=8.2 Hz, 2H). ^{13}C NMR: δ=20.7, 55.5, 125.1, 126.3, 126.5, 127.9, 128.6, 129.2, 130.2, 130.6, 130.9, 134.8, 135.3, 136.4, 138.6, 139.1, 154.7. Anal. Calcd for $C_{38}H_{32}O_2$: C, 87.66; H, 6.19. Found: C, 87.42; H, 6.47.

*4.1.4. 1,8-Bis(6′-hydroxy-4′-methyl-3′-biphenyl)naphthalene (**2**).* To a solution of 1,8-bis(2′-methyl-4′-methoxy-5′-phenylphenyl) naphthalene, **6** (0.14 g, 0.28 mmol) in 10 mL of anhydrous CH_2Cl_2 at 0 °C, BBr_3 (1.67 mL, 1.67 mmol) was added dropwise and the mixture was stirred for 16 h at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2) afforded 0.12 g of **2** (0.25 mmol, 89%) as a white solid.

^{1}H NMR: δ=1.66 (s, 6H), 5.01 (s, 2H), 6.45 (s, 2H), 6.89 (s, 2H), 7.25 (d, J=7.0 Hz, 2H), 7.36 (dd, J=6.8, 7.2 Hz, 2H), 7.42–7.51 (m, 10H), 7.91 (d, J=8.1 Hz, 2H). ^{13}C NMR: δ=20.3, 115.9, 124.2, 125.0, 127.5, 128.6, 128.8, 129.2, 129.9, 130.3, 130.9, 135.3, 135.8, 137.2, 137.8, 139.4, 150.7. Anal. Calcd for $C_{36}H_{28}O_2$: C, 87.78; H, 5.73. Found: C, 88.04; H, 5.79.

4.2. Resolution of the enantiomers of 2

The stereoisomers of **2** are separable on a CHIRALPAK AD column using hexanes/isopropyl alcohol (9:1) as mobile phase (Fig. 8>/>). The first eluted enantiomer appears at 7.2 min, while the second elutes at 8.9 min. The *syn*-intermediate elutes last at 10.5 min. For quantitative analysis, the ratio of the absorption coefficients of the diastereomers, $\alpha_{anti}/\alpha_{syn}$, was determined as 1.43.

To avoid time-consuming preparative chiral HPLC, several chiral auxiliaries were examined for large scale separation of the enantiomers of **2** through the formation of diastereomers. We were pleased to find that esterification of racemic **2** with *N*-Boc-(*S*)-tryptophan generates diastereomeric diester derivatives that can be separated by chromatographic separation. Finally, the diastereomers were hydrolyzed to regenerate free bisphenols **2** in enantiomerically pure form.

*4.2.1. 1,8-Bis(6′-N-Boc-(S)-tryptophan-4′-methyl-3′-biphenyl)naphthalene (**7**).* A solution of **6** (0.17 g, 0.35 mmol), *N*-Boc-(*S*)-tryptophan (0.24 g, 0.77 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.17 g, 0.81 mmol), and DMAP (0.05 g, 0.42 mmol) was stirred in 5 mL of dichloromethane for 16 h at room temperature. The resulting suspension was directly subjected to gradient flash chromatography on silica gel (dichloromethane/ethyl acetate 70:1 to 60:1) to afford 0.18 g (0.17 mmol, 49%) and 0.16 g (0.15 mmol, 42%) of the first and second eluted diastereomers of **7** as white solids.

^{1}H NMR (first eluted isomer): δ=1.43 (s, 6H), 1.50 (s, 18H), 3.22 (m, 4H), 4.26 (m, 1H), 5.01 (m, 1H), 5.63 (s, 2H), 6.79 (s, 2H), 6.97–7.28 (m, 26H), 7.94 (d, J=8.1 Hz, 2H), 9.33 (s, 2H). ^{13}C NMR: δ=20.1, 28.3, 54.5, 80.0, 109.8, 111.3, 118.7, 119.5, 121.9, 122.0, 123.3, 124.9, 127.0, 127.7, 128.4, 128.7, 121.9, 123.3, 124.9, 127.0, 127.7, 128.7, 129.8, 131.2, 136.2, 137.3, 138.1, 140.5, 145.5, 155.2, 170.9. Anal. Calcd for $C_{68}H_{64}N_4O_8$: C, 76.67; H, 6.06; N, 5.26. Found: C, 76.44; H, 6.16; N, 5.62.

^{1}H NMR (second eluted isomer): δ=1.40 (s, 18H), 1.70 (s, 6H), 3.12 (m, 4H), 4.82 (m, 1H), 5.02 (m, 1H), 6.65 (s, 2H), 6.88 (s, 2H), 7.11–7.31 (m, 18H), 7.51 (m, 2H), 7.92 (d, J=8.2 Hz, 2H), 8.41 (s, 2H). ^{13}C NMR: δ=20.1, 28.3, 54.5, 80.0, 109.8, 111.1, 118.7, 119.5, 122.0, 122.9, 123.1, 124.9, 127.3, 127.9, 128.2, 128.8, 130.3, 131.5, 135.2, 136.0, 136.1, 137.2, 138.1, 140.51, 145.7, 155.46, 170.4. Anal. Calcd for $C_{68}H_{64}N_4O_8$: C, 76.67; H, 6.06; N, 5.26. Found: C, 76.43; H, 6.27; N, 5.42.

A suspension of the first eluted diastereomer of **7** (0.040 g, 0.038 mmol) in 3.8 M KOH (10 mL, 4:1 ethanol/water) was stirred for 3 h at room temperature. The resulting mixture was quenched with 0.5 mL of concentrated HCl at 0 °C. It was then extracted with dichloromethane, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was then subjected to flash chromatography on silica gel using dichloromethane as mobile phase to afford 0.019 g (0.038 mmol, 99%) of enantiopure (−)-**2** as a white solid. The same procedure was used to obtain (+)-**2** from the second eluted diastereomer of **7**.

4.3. UV, CD, and Polarimetry

The CD instrument was purged with nitrogen for 20 min. Spectra were collected at room temperature between 270 and 390 nm with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width of 1 nm, a scanning speed of 500 nm s^{-1} and a response of 0.5 s using a quartz cuvette (1 cm path length).

Polarimetric measurements at 21.5 °C allowed for the determination of the specific rotation $[\alpha]_D$ as 354° for the enantiomer eluted first from Chiralpak AD, and −355° for the more strongly retained enantiomer (Fig. 9).

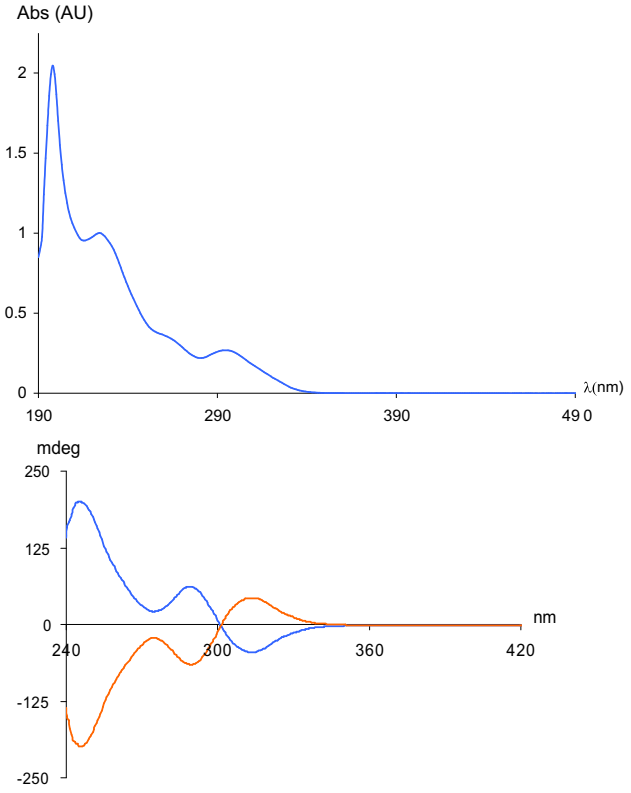


Fig. 9. Top: UV spectrum of **2** (1.02×10^{-3} M, hexanes/IPA 1:1). Bottom: CD spectra of dextrorotatory (blue) and levorotatory (orange) enantiomers of **2** (9.45×10^{-5} M, ACN).

4.4. Crystallization and X-ray diffraction

Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo Kα radiation (λ=0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters.

A crystal of **2** was obtained by slow evaporation of a solution of 10.0 mg of **2** in 5 mL of CH_2Cl_2. Crystal structure data for **2**: formula $C_{36}H_{28}O_2$, M=492.61, crystal dimensions 0.15×0.15×0.15 mm, monoclinic, space group $P21/c$, a=11.3010 (23) Å, b=11.8081 (24) Å, c=19.1846 (40) Å, β=96.897 (3), V=2541.53 Å^3, Z=4, ρ_{calcd}=1.2872 g cm^{-3}.

4.5. Enantioselective sensing studies

Prior to each use, the CD instrument was purged with nitrogen for 20 min. Spectra were collected between 240 and 600 nm with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width of 0.5 nm, a scanning speed of 1000 nm s^{-1}, and a response of 0.5 s using a quartz cuvette (1 cm path length). The concentration of (−)-**2** was 9.45×10^{-5} M in ACN. To 2000 μL of (−)-**2**, 4 equiv of Na^{t}BuO (0.521 M in DMSO) were added to generate the bisphenoxide of (−)-**2**, which was titrated with several amine substrates until the original bisphenol CD spectrum was recovered. Ellipticites at 290 nm were then plotted against the concentration of added amine enantiomers.

Acknowledgements

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Supplementary data

Details of kinetic studies, NMR spectra of the products, and CD analyses. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.001.

References and notes

1. von Richter, V. *Chem. Ber.* **1873**, *6*, 1249–1260.
2. Selected examples: (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211; (c) Brunel, J. M. *Chem. Rev.* **2007**, *107*, PR1–PR45; (d) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117–1127; (e) Najera, C.; Sansano, J. M.; Saa, J. M. *Eur. J. Org. Chem.* **2009**, 2385–2400; (f) Bunzen, J.; Kiehne, U.; Benkhauser-Schunk, C.; Luetzen, A. *Org. Lett.* **2009**, *11*, 4786–4789; (g) He, X.; Cui, X.; Li, M.; Lin, L.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2009**, *50*, 5853–5856; (h) Redondo, J.; Capdevila, A.; Latorre, I. *Chirality* **2010**, *22*, 472–478; (i) Xu, K. X.; Yang, L.-R.; Wang, Y.-X.; Zhao, J.; Wang, C.-J. *Supramol. Chem.* **2010**, *22*, 563–570; (j) Bao, H.; Wu, J.; Li, H.; Wang, Z.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2010**, 6722–6726; (k) Blay, G.; Fernandez, I.; Munoz, M. C.; Pedro, J. R.; Vila, C. *Chem.—Eur. J.* **2010**, *16*, 9117–9122; (l) Yukawa, T.; Seelig, B.; Xu, Y.; Morimoto, H.; Matsunaga, S.; Berkessel, A.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11988–11992; (m) Yu, S.-S.; Pu, L. *J. Am. Chem. Soc.* **2010**, *132*, 17698–17700; (n) Yang, W.; Du, D.-M. *Eur. J. Org. Chem.* **2011**, 1552–1556; (o) Liu, H.-L.; Zhao, Q.-L.; Hou, X.-L.; Pu, L. *Chem. Commun.* **2011**, 3646–3648; (p) Schenker, A.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, 2209–2222.
3. (a) Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *Tetrahedron Lett.* **2000**, *41*, 6915–6918; (b) Cross, W.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 459–467; (c) Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588–598; (d) Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510–1519.
4. (a) Watkinson, M.; Whiting, A.; McAuliffe, C. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2141–2142; (b) Ghosn, M. W.; Wolf, C. *J. Am. Chem. Soc.* **2009**, *131*, 16360–16361; (c) Ghosn, M. W.; Wolf, C. *Tetrahedron* **2010**, *66*, 3989–3994.
5. (a) Wolf, C.; Ghebramariam, B. T. *Tetrahedron: Asymmetry* **2002**, *13*, 1153–1156; (b) Wolf, C.; Tumambac, G. E. *J. Phys. Chem. A* **2003**, *107*, 815–817; (c) Tumambac, G. E.; Wolf, C. *J. Org. Chem.* **2004**, *69*, 2048–2055; (d) Tumambac, G. E.; Mei, X.; Wolf, C. *Eur. J. Org. Chem.* **2004**, 3850–3856; (e) Wolf, C. *Chem. Soc. Rev.* **2005**, *34*, 595–608; (f) Tumambac, G. E.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 2930–2938; (g) Wolf, C.; Xu, H. *Tetrahedron Lett.* **2007**, *48*, 6886–6889.
6. (a) Mei, X.; Wolf, C. *Chem. Commun.* **2004**, 2078–2079; (b) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737; (c) Tumambac, G. E.; Wolf, C. *Org. Lett.* **2005**, *7*, 4045–4048; (d) Mei, X.; Martin, R. M.; Wolf, C. *J. Org. Chem.* **2006**, *71*, 2854–2861; (e) Liu, S.; Pestano, J. P. C.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 4267–4270; (f) Mei, X.; Wolf, C. *Tetrahedron Lett.* **2006**, *47*, 7901–7904; (g) Wolf, C.; Liu, S.; Reinhardt, B. C. *Chem. Commun.* **2006**, 4242–4244; (h) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326–13327.
7. Ghosn, M.; Wolf, C. *J. Org. Chem.* **2011**, *76*, 3888–3897.
8. *Dynamic Stereochemistry of Chiral Compounds*; Wolf, C., Ed.; RSC: Cambridge, 2008; p 89.
9. Vriens, G. N. *Ind. Eng. Chem.* **1954**, 669–671.
10. We note that it is possible that the HPLC method used to monitor the stereochemical integrity of enantiopure **2** could not have detected formation of 1–2% of the minor enantiomer and the *meso* intermediate. The isolated enantiomers of **2** can be stored at room temperature for several months without showing measurable racemization.
11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC 821187. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
12. For CD analysis of amines with chiral metal complexes, see: (a) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *Org. Lett.* **2008**, *10*, 5167–5170; (b) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 9232–9233; (c) Nieto, S.; Dragna, J. M.; Anslyn, E. V. *Chem.—Eur. J.* **2010**, *16*, 227–232.