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Efficient chromatographic resolution of a configurationally fragile atropisomeric diphenol via its *N*-(α)-Boc-tryptophan diesters

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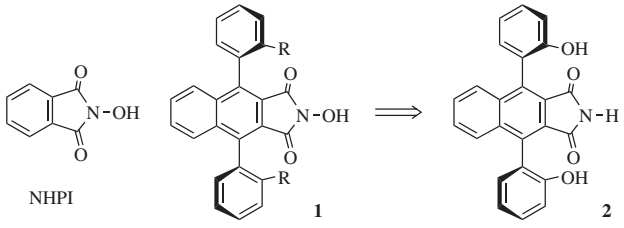
Abstract—Racemic 4,5-bis-(2-hydroxy-phenyl)-benzo[*f*]isoindole-1,3-dione **2**, an atropisomeric diphenol prone to thermal isomerisation, has been efficiently resolved by conversion into its *N*-(α)-Boc-tryptophan diesters. Easy chromatographic separation of the diastereomeric pair of diesters, followed by ester cleavage under mild conditions gave each enantiomer in good yield and high enantiomeric purity. X-ray diffraction on a single crystal of one of the diastereomeric diesters allowed attribution of the absolute configuration of the stereogenic axes.

1. Introduction

N-Hydroxyphthalimide (NHPI) and several of its structural analogues are valuable catalysts for the aerobic oxidation of organic compounds under mild conditions.[1] Room temperature oxidations have even been performed, using NHPI or NHPI-analogues in association with acetaldehyde or CuCl.[1b,c] We have previously reported the first synthesis of axially chiral *N*-hydroxyimides and their use as catalysts for some representative asymmetric oxidations. They displayed modest but nevertheless encouraging enantioselectivities.[2] The discovery of more efficient chiral analogues of NHPI is a goal of current interest, due to various potential applications in asymmetric catalysis. Promising candidates are C_2-symmetrical compounds of type **1**, R being a variable substituent. Several catalysts of type **1** have already been prepared in their racemic form starting from racemic **2**,[3] which has been obtained previously with a high diastereomeric purity via thermal isomerisation in the solid state.[4]



The availability of the pure enantiomers of **2** is therefore crucial for our project. Direct resolution of (±)-**2** on a chiral HPLC column, although effective on an analytical scale, is impractical on a preparative scale, owing to its low solubility in most of the usual solvents. On the other hand, diphenol **2** is configurationally fragile: though a solution of pure (±)-**2** in toluene shows only negligible isomerisation after 24 h at room temperature, its heating at reflux for a few hours resulted in an atropisomerisation of the stereogenic axes and equilibration to a ca. 1:1 mixture of cis:(±)-**2**.[4] This thermal lability renders the resolution of (±)-**2** particularly challenging. Indeed, many classical methods developed for the resolution of BINOL or other atropisomeric diphenols via covalent linking to a chiral auxiliary, separation of the diastereomeric pair and final cleavage of the auxiliary were ineffective when applied to (±)-**2**. Herein we report an efficient resolution of (±)-**2** via its *N*-(α)-Boc-L-tryptophan diesters, and the determination of the absolute stereochemistry of the stereogenic axes by X-ray diffraction on a single crystal of one of the diastereomeric diesters.

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2. Results and discussion

We have previously reported a convenient and efficient chromatographic resolution of BINOL and 6,6′-dibromo-BINOL.[5] A preliminary screening revealed that esterification of (±)-BINOL with various amino acid derivatives gave diastereomeric esters, whose chromatographic separation factors were highly dependent on the amino acid pattern. Unusually high separation factors were observed using *N*-(α)-Boc-L-tryptophan. Both selective mono- and diesterifications have been performed while the diastereomeric pairs of mono- or diesters were efficiently separated by simple column chromatography techniques. We have attempted similar mono- and diesterifications of (±)-**2** with several amino acid derivatives, using the standard DCC/DMAP esterification method. In contrast with the case of BINOL and that of 6,6′-dibromo-BINOL, clean conversions of (±)-**2** into monoesters were not achieved and intractable mixtures of starting **2**, mono- and diesters were always obtained. Fortunately, clean diesterifications were more easily performed, without any disturbance caused by the free imide functionality. Again, the largest TLC separation factors were observed in the tryptophan series:[6] TLC of the crude mixture of diesters **3a** and **3b** (Scheme 1) gave two spots with $R_{f1} = 0.56$ and $R_{f2} = 0.46$ ($\alpha = R_{f1}/R_{f2} = 1.2$) with a 1:1 mixture of hexane and ethyl acetate as the eluent. Elution with a 4:1 mixture of dichloromethane and ethyl acetate gave $R_{f1} = 0.41$ and $R_{f2} = 0.21$ ($\alpha = 2$), while a 4:1 mixture of dichloromethane and ether gave $R_{f1} = 0.30$ and $R_{f2} = 0.13$ ($\alpha = 2.3$).

We then undertook the synthesis and separation of **3a** and **3b** on a preparative scale. Diesterification of 5 mmol of (±)-**2**, using 2.2 equiv of *N*-(α)-Boc-L-tryptophan, 2.2 equiv of DCC and 10 mol % of DMAP in anhydrous dichloromethane was complete after 2 h at room temperature (TLC monitoring). Column chromatography of the crude reaction mixture was performed on 200 g of silica gel, using mixtures of dichloromethane/ether (9:1 to 1:1) as eluents. The first eluted diester was obtained diastereomerically pure in 94% yield, as a white microcrystalline solid. Numerous attempts to obtain a monocrystal suitable for X-ray diffraction failed. The second eluted diester was isolated diastereomerically pure in 91% yield as a yellowish foam, which crystallised after 24 h stirring at room temperature in a 4:1 mixture of hexane/ethyl acetate. A monocrystal suitable for X-ray diffraction was obtained by slow diffusion of hexane into an ethyl acetate solution of this compound. Figure 1 shows an ORTEP plot obtained from the X-ray data.[7]

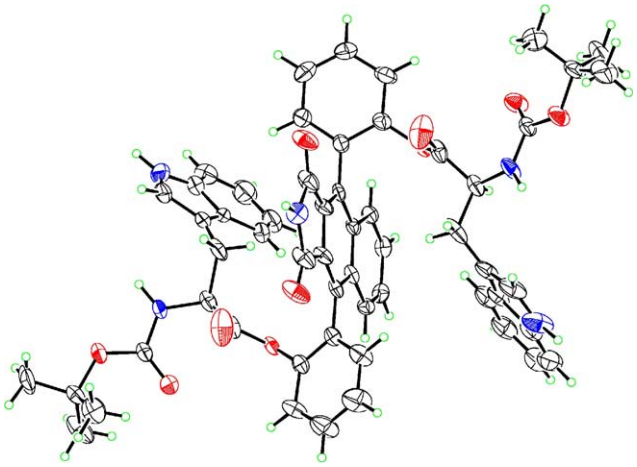
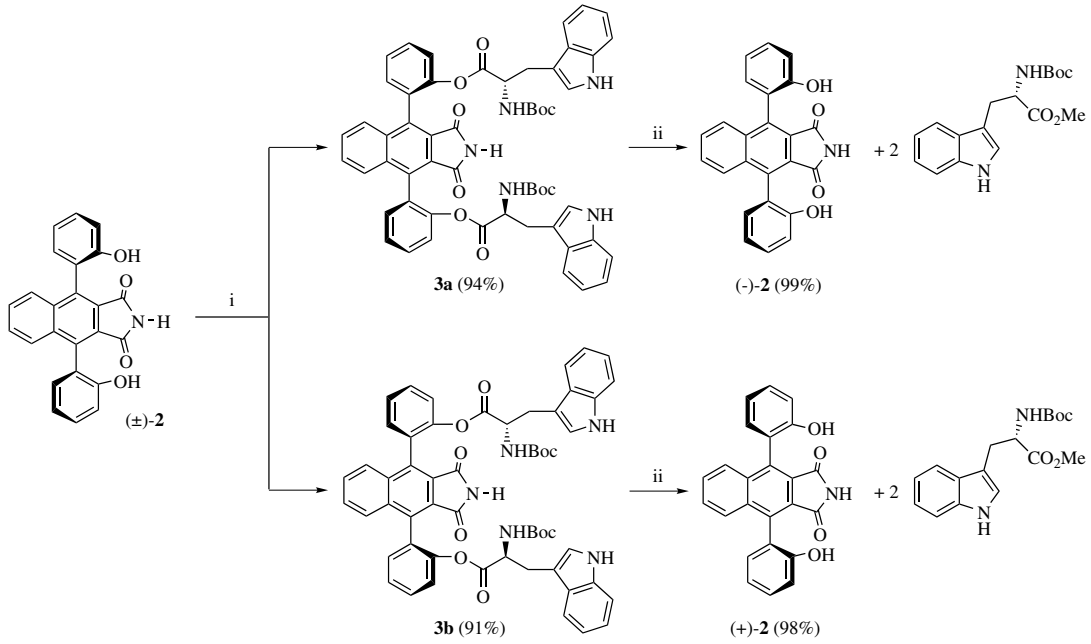


Figure 1. ORTEP plot of the second eluted diastereomer **3b**.



Scheme 1. Resolution of (±)-**2** via its *N*-(α)-Boc-L-tryptophan diesters. Reagents and conditions: (i) (a) DCC, DMAP, *N*-(α)-Boc-L-tryptophan, CH_2Cl_2, rt; (b) column chromatography. (ii) (a) $LiOH{\cdot}H_2O$, MeOH, rt; (b) TFA.

An (a*S*,a*S*) absolute stereochemistry of the stereogenic axes can be deduced from the (*S*) absolute stereochemistry of the stereogenic centres of the amino acid moieties. Consequently, the stereochemistry of the second eluted diester corresponds to formula **3b** (Scheme 1). The stereochemistry of the first eluted diester therefore corresponds to formula **3a**. It is worth mentioning that similar behaviours have been observed for mono- and diesters of BINOL and of 6,6′-dibromo-BINOL with *N*-(α)-Boc-L-tryptophan: in each case, the stereogenic axis of the faster running diastereomer had an (a*R*)-configuration.[8]

As diphenol **2** is prone to thermal atropisomerisation, the ultimate success of the resolution rested on the clean removal of the chiral auxiliary under mild conditions. Classical saponification using aqueous NaOH or KOH gave somewhat erratic results. Gratifyingly, almost instantaneous cleavage occurred at room temperature, by using stoichiometric amounts of LiOH in methanol. Acidification with trifluoroacetic acid, followed by column chromatography, gave resolved **2**,[9] along with recovered enantiomerically pure *N*-(α)-Boc-L-tryptophan as its methyl ester (Scheme 1).[5] Thus, **3a** gave 99% yield of pure (a*R*,a*R*)-(−)-**2** (ee >99%).[10] Similarly, **3b** gave 98% yield of pure (a*S*,a*S*)-(+)-**2** (ee >99%).[10]

3. Conclusion

Racemic, configurationally fragile diphenol **2** has been converted into its diastereomeric *N*-(α)-Boc-L-tryptophan diesters **3a** and **3b**, which have been easily separated by column chromatography. X-ray diffraction on a monocrystal of the second eluted diester allowed the attribution of the absolute configuration of the stereogenic axes. Finally, mild cleavage of the chiral auxiliaries gave each enantiomer of **2** with an ee >99%. The overall yield of the resolution was 93% for (a*R*,a*R*)-(−)-**2**, and 89% for (a*S*,a*S*)-(+)-**2**, when carried out on a 5 mmol scale. The transformation of enantiomerically pure **2** into various enantiomerically pure catalysts of type **1** is now under investigation.[11]

4. Experimental

4.1. General

Dichloromethane was distilled over calcium hydride before use. Methanol and other chemicals were of commercial grade and used as received. Analytical TLC was performed on Merck silica gel plates (60 F_{254}). Column chromatography was carried out on silica gel 60 (70–230 mesh). Chiral HPLC was performed on a Chiralpak AS column. Melting points were measured on a Buchi Melting Point B-545 apparatus and are uncorrected. NMR spectra were recorded on a Brucker AC300 spectrometer. ^{1}H NMR were recorded at 300 MHz in DMSO-d_6 with chemical shifts being reported as δ (ppm), calibrated to the residual solvent signal at $\delta = 2.50$. ^{13}C NMR spectra were recorded at 75 MHz in DMSO-d_6, calibrated to the solvent signal at $\delta = 39.52$. Mass spectra were recorded on a Thermo Quest Finnigan spectrometer. Elemental analyses were performed at the Service Central d'Analyses du CNRS. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. IR spectra were recorded as KBr pellets on a Magna-IR 550 spectrometer.

4.2. Synthesis and separation of diesters 3a and 3b

Racemic diphenol **2** (1.9 g, 5 mmol), DCC (2.28 g, 11 mmol), DMAP (0.062 g, 0.5 mmol), and *N*-(α)-Boc-L-tryptophan (3.348 g, 11 mmol) were dissolved in anhydrous dichloromethane (150 mL) and the mixture stirred at room temperature for 2 h. After filtration of dicyclohexylurea, the solvent was removed at a reduced pressure. The residue was chromatographed over silica gel (200 g) using a 9:1 mixture of dichloromethane/ether for the elution. The proportion of ether was progressively raised to 50%. Diester **3a** was eluted first (2.23 g, 94% yield), followed by diester **3b** (2.16 g, 91% yield).

4.2.1. (a*R*,a*R*)-4,9-Bis(phenyl-2-yl)-benzo[*f*]isoindole-1,3-dione [(2*S*)-2-*tert*-butoxycarbonylamino-3-(1*H*-indol-3-yl)]dipropionate 3a. White crystalline solid, mp 195 °C (from hexane/ethyl acetate). $[\alpha]_D^{20} = -4.1$ (*c* 1.01, THF). ^{1}H NMR (DMSO-d_6) δ (ppm) 1.13 and 1.23 (2br s in a 0.2:1 ratio, 18H), 1.76–2.14 (m, 4H), 3.79–3.87 (m, 2H), 6.65–7.09 (m, 12H), 7.16–7.36 (m, 6H), 7.53–7.60 (m, 4H), 7.65–7.70 (m, 2H), 10.65 (br s, 2H), 11.48 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm) 25.07, 28.03, 54.18, 78.28, 109.32, 111.50, 117.20, 118.48, 121.02, 122.50, 123.59,125.52, 125.62, 126.45, 127.56, 127.67, 129.05, 129.05, 129.74, 131.02, 133.54, 134.52, 136.00, 148.19, 155.32, 167.18, 170.65. IR (KBr pellet) ν (cm^{-1}) 3404, 3061, 2980, 2931, 1771, 1722, 1494, 1471, 1167, 743. MS (CI^-, NH_3+isobutane) *m*/*z* (%) 953(84), 853(100), 753(31), 667(10), 567(3). Anal. Calcd for $C_{56}H_{51}N_5O_{10}$: C, 70.50; H, 5.39; N, 7.34. Found: C, 69.85; H, 5.38; N, 7.47.

4.2.2. (a*S*,a*S*)-4,9-Bis(phenyl-2-yl)-benzo[*f*]isoindole-1,3-dione [(2*S*)-2-*tert*-butoxycarbonylamino-3-(1*H*-indol-3-yl)]dipropionate, 3b. Yellowish crystals, mp 217 °C (from hexane/ethyl acetate). $[\alpha]_D^{20} = -10.2$ (*c* 1.09, THF). ^{1}H NMR (DMSO-d_6) δ (ppm) 1.07 and 1.21 (2br s in a 0.2:1 ratio, 18H), 1.92–2.50 (m, 4H), 4.01–4.09 (m, 2H), 6.77–7.30 (m, 12H), 7.39–7.55 (m, 6H), 7.72–7.79 (m, 4H), 7.86–7.91 (m, 2H), 10.94 (br s, 2H), 11.55 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm) 25.18, 27.99, 54.43, 78.25, 109.28, 111.40, 117.34, 118.36, 120.92, 122.28, 123.59, 125.53, 125.63, 126.40, 127.65, 127.77, 129.02,129.76, 131.28, 133.60, 134.57, 135.94, 148.31, 155.29, 167.08, 170.38. IR (KBr pellet) ν (cm^{-1}) 3404, 3061, 2980, 2931, 1771, 1722, 1494, 1167, 743. MS (CI^-, NH_3+isobutane) *m*/*z* (%) 953(33), 853(100), 753(79), 667(17), 567(9). Anal. Calcd for $C_{56}H_{51}N_5O_{10}$: C, 70.50; H, 5.39; N, 7.34. Found: C, 70.65; H, 5.46; N, 7.50.

4.2.3. (a*R*,a*R*)-4,9-Bis(2-hydroxyphenyl)-benzo[*f*]isoindole-1,3-dione, (−)-2. To a solution of diester **3a** (2.22 g, 2.3 mmol) in methanol (40 mL) was added a 1 M solution of $LiOH{\cdot}H_2O$ in methanol (4.6 mL,

4.6 mmol). The yellow solution was stirred for 5 min at room temperature. After cooling to 0 °C, trifluoroacetic acid (0.36 mL, 4.6 mmol) was added, giving a nearly colourless solution. The solvent was next removed at reduced pressure.[9] The residue was chromatographed over silica gel (100 g) using mixtures of dichloromethane/ether (95:5 to 4:1) as eluent. *N*-(α)-Boc-L-tryptophan methyl ester was eluted first[5] (98% recovery), followed by (−)-**2**[8] (0.874 g, 99% yield): slightly yellow amorphous solid. $[\alpha]_D^{20} = -13.25$ (*c* 0.93, THF); ee >99% (Chiral HPLC on a Chiralpack AS column, elution hexane:*i*-PrOH, 6:4, 1 mL min^{-1}, t_R = 5.03 min). ^{1}H NMR (DMSO-d_6) δ (ppm) 6.93–7.03 (m, 4H), 7.16–7.20 (m, 2H), 7.30–7.37 (m, 2H), 7.60–7.69 (m, 4H), 9.35 (br s, 2H), 11.18 (br s, 1H). ^{13}C (DMSO-d_6) δ (ppm) 115.46, 118.71, 121.79, 125.39, 127.81, 128.36, 129.37, 131.02, 134.88, 135.61, 154.96, 167.69. IR (KBr pellet) ν (cm^{-1}) 3400, 3073, 2975, 2893, 1752, 1712, 1617, 1601, 1591, 1506, 1451, 1379, 1345, 1288, 1221, 1121, 1093, 1021, 837, 761 cm^{-1}. MS (CI$^+$, NH_3+isobutane) *m*/*z* (%) 382(54), 399(100). Anal. (determined on the ethyl acetate solvate)[10] Calcd for $C_{52}H_{38}N_2O_{10}$: C, 73.40; H, 4.50; N, 3.29. Found: C, 72.49; H, 4.56; N, 3.46.

4.2.4. (a*S*,a*S*)-4,9-Bis(2-hydroxyphenyl)-benzo[*f*]isoindole-1,3-dione, (+)-2. The same procedure as above was applied to diester **3b** (1.98 g, 2.07 mmol) and gave diphenol (+)-**2** (0.770 g, 98% yield): slightly yellow amorphous solid. $[\alpha]_D^{20} = +13.9$ (*c* 0.94, THF); ee >99% (Chiral HPLC on a Chiralpack AS column, elution hexane:*i*-PrOH, 6:4, 1 mL min^{-1}, t_R = 7.89 min). Anal. (determined on the ethyl acetate solvate)[10] Calcd for $C_{52}H_{38}N_2O_{10}$: C, 73.40; H, 4.50; N, 3.29. Found: C, 72.76; H, 4.56; N, 3.49.

Acknowledgements

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6. Diesterification has been performed on an analytical scale [10 μmol of (±)-**2**], with the following commercially available *N*-protected-L-amino acids: *N*-Boc-proline, *N*-Boc-valine, *N*-Boc-phenylglycine, *N*-Boc-phenylalanine, *N*-(α)-Boc-tryptophan, *N*-(α)-Cbz-tryptophan, and *N*-(α)-Fmoc-tryptophan. Clearly separated TLC spots were observed only in the phenylalanine, or much better, in the tryptophan series. *N*-(α)-Cbz and -Fmoc derivatives offer no advantages over -Boc derivatives.
7. X-ray data were collected with a Bruker Nonius kappa CCD diffractometer using graphite-monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR 92: Altomare A., Cascarano G., Giacovazzo C., Guagliardi A. *J. Appl. Cryst.* **1993**, *26*, 343–350) and refined by full-matrix least-squares techniques against F. Ortep [Johnson CK. (1976). ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA] was used for structure representations. Crystal data: $C_{56}H_{51}N_5O_{10}$, M = 954.03, trigonal, space group $P322_1$, a = 14.476(1), c = 21.310(2) Å, γ = 120.0°, V = 3867.5(4) Å^3, T = 293(2) K, μ (Mo-Kα) = 0.085 mm^{-1}, D_c = 1.229 g cm^{-3}, 6614 reflections measured, 3549 were independent of symmetry and 2706 were observed [$I > 1.20\sigma(I)$], R_1 = 0.0734, wR_2 = 0.1083, 318 parameters. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 260846. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB21EZ. UK [fax: +44(0) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk].
8. For similar observations about the resolution of BINOL derivatives via diastereomeric bis(camphorsulfonates), see: Chow, H.-F.; Wan, C.-W.; Ng, M.-K. *J. Org. Chem.* **1996**, *61*, 8712–8714.
9. As diphenol **2** is prone to thermal isomerisation, special care should be taken to avoid excessive heating during its handling, especially during solvent removal.
10. Crystalline solvates formed when amorphous (−)- or (+)-**2** was stirred at room temperature for 24 h in a 4:1 mixture of hexane/ethyl acetate. These crystals contained half a molecule of ethyl acetate per molecule of (−)- or (+)-**2**.
11. The thermal sensitivity of **2** does not preclude application to chiral catalysis: various NHPI type oxidations can be conducted near room temperature,[1b,c,2] at which no racemisation of **2** occurs. Moreover, several catalysts of type **1** bearing bulky R substituents have already been prepared. Preliminary results indicate that they are much more thermally stable than **2**. This preliminary study has been conducted with racemic catalysts of type **1**, as the absence of *cis*/*trans* isomerisation in the racemic series will preclude racemisation (via the *cis* form) under the same conditions in the optically active series.