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Simple chiral derivatisation protocols for NMR analysis of the enantiopurity of 1,2-diphenylethane-1,2-diamine and *N*-Boc-cyclohexane-1,2-diamine

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Abstract—Practically simple three-component chiral derivatisation protocols for determining the enantiopurity of vicinal C_2-symmetric diamines by ^{1}H NMR spectroscopic analysis are described. This involves the treatment of 1,2-diphenylethane-1,2-diamine or *N*-Boc-cyclohexane-1,2-diamine with 2-formylphenylboronic acid and enantiopure BINOL, which afford mixtures of diastereoisomeric boronate esters whose ratio is an accurate reflection of the enantiopurity of the parent diamine.

1. Introduction

The C_2-symmetric diamines 1,2-diphenylethane-1,2-diamine **1** and cyclohexane-1,2-diamine **2** have proven to be popular chiral building blocks for the synthesis of chiral auxiliaries and chiral reagents,[1] chiral sensors[2] and chiral derivatising or solvating agents (Fig. 1).[3] They have also been widely used as chiral ligands for preparing transition metal complexes for asymmetric catalysis,[4] and have recently been used for the preparation of highly enantioselective organocatalysts.[5] Whilst a range of different strategies have been developed for their asymmetric synthesis, they are most commonly prepared in enantiopure form via resolution protocols.[6] This most often involves treatment of their respective racemic amines with either tartaric or mandelic acid.[7] This affords mixtures of diastereoisomeric salts that are then separated and individually decomplexed to afford both enantiomers of the parent diamine. Since these C_2-symmetric amines are normally used in chiral environments it is essential that their enantiopurity is determined accurately.[8] Consequently, we herein report simple ^{1}H NMR spectroscopic based methods which enable us to determine their enantiopurity in less than 10 min.

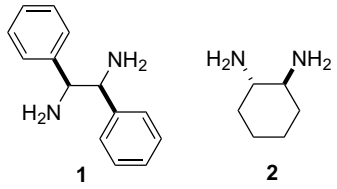

Figure 1. Chiral C_2-symmetric diamines **1** and **2**.

We have recently reported the development of a versatile three-component derivatisation protocol for determining the enantiomeric excess of chiral primary amines[9] and chiral diols.[10] For the case of amines, this approach involves derivatisation of the parent chiral amine **3** with 2-formylphenylboronic acid **4** and enantiopure BINOL (*S*)-**5** in $CDCl_3$ to quantitatively afford a mixture of diastereoisomeric imino-boronate esters (*S*,*S*)-**6** and (*S*,*R*)-**7**. The diasteroisomeric ratio of (*S*,*S*)-**6**: (*S*,*R*)-**7** is then determined by ^{1}H NMR spectroscopic analysis, and since no kinetic resolution occurs in the derivatisation process this value is an accurate reflection of the enantiomeric excess of the parent amine (Scheme 1).

2. Results and discussion

We reasoned that this type of three-component NMR derivatisation protocol might also be useful for analyzing the enantiopurity of chiral vicinal diamines, such as 1,2-diphenylethane-1,2-diamine **1** or cyclohexane-1,2-diamine

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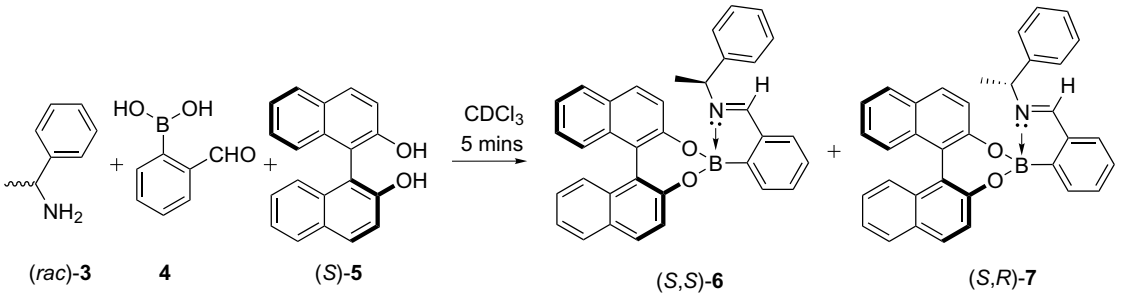
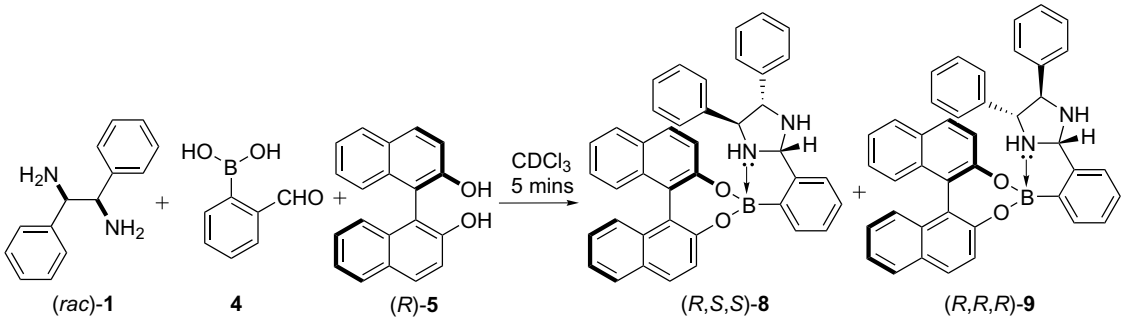


Scheme 1. Three-component protocol for determining the enantiomeric purity of chiral amines by ^{1}H NMR spectroscopic analysis.



Scheme 2. Three-component coupling protocol for determining the enantiomeric purity of chiral diamine **1** by ^{1}H NMR spectroscopic analysis.

2. Therefore, *rac*-diamine **1** was treated with 1 equiv of 2-formylphenylboronic acid **4** and one equivalent of enantiopure (*R*)-BINOL **5** in $CDCl_3$ and its ^{1}H NMR spectrum acquired after 5 min (Scheme 2). This ^{1}H NMR spectrum revealed that an efficient complexation reaction had occurred to afford a 50:50 mixture of two diastereoisomeric imidazolidine complexes (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** in quantitative yield.[11] Therefore, it was clear that a highly selective three component reaction had occurred in which the boronic acid fragment of 2-formyl-phenylboronic acid **4** had reacted exclusively with the diol functionality of (*R*)-BINOL **5** to afford a cyclic boronate ester, whilst its aldehyde fragment had reacted exclusively with diamine **1** to afford an imidazolidine functionality.

The individual resonances of each diastereoisomer were assigned by comparison with the ^{1}H NMR spectra of authentic samples of (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** prepared independently via reaction of the individual (*S*,*S*)- and (*R*,*R*)-enantiomers of 1,2-diphenyl-1,2-ethanediamine **1** with 2-formyl-phenylboronic acid **4** and (*R*)-BINOL **5**.

Analysis of the ^{1}H NMR spectra of the (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** revealed structures consistent with the formation of complexes containing an imidazolidine ring system. For example, resonances corresponding to the two N*H* protons of (*R*,*S*,*S*)-**8** were easily assigned using a standard D_2O exchange experiment,[12] which revealed that one of its nitrogen atoms NH_A was coordinated to the central boron atom.[13,14] This was evident from the non-equivalence of the NH resonances of the imidazolidine ring system of (*R*,*S*,*S*)-**8**, with the deshielded NH_A proton coordinated to the boron atom appearing at δ 5.02, with the uncoordinated NH_B proton appearing at δ 2.80. The imidazolidine proton H_C of complex (*R*,*S*,*S*)-**8** appeared as a doublet of doublets at δ 6.17, with a large coupling constant $J_{(AC)} = 12.3$ Hz, and a small axial–equatorial coupling constant $J_{(BC)} = 5.8$ Hz. Finally, NOESY experiments revealed cross-peaks between the imidazolidine H_C proton and the benzylic proton H_E that was vicinal to H_B, consistent with the imidazolidine ring structure of (*R*,*S*,*S*)-**8** (Fig. 2a).[15]

The diastereoisomeric complexes (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** were sufficiently stable enough to allow for deuterium exchange of both their N*H* protons with D_2O. This resulted in both diastereoisomers exhibiting much simplified ^{1}H NMR spectra, with their imidazolidine H_C protons collapsing from a quartet to a singlet, and both pairs of benzylic H_D/H_E protons simplifying to doublets. Close examination of the ^{1}H NMR spectrum of the 50:50 mixture of complexes (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** revealed baseline resolution of a number of complementary pairs of diastereoisomeric resonances. Most notably, two sets of resonances corresponding to their H_A protons ($\Delta\delta$, 0.45 ppm) and H_D protons ($\Delta\delta$, 0.25 ppm) were baseline resolved, which allowed them to be integrated to accurately determine the diastereoisomeric ratio of the sample. The detection limits of this method were determined by the derivatisation of three samples of scalemic (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine **1** of 80%, 90% and 98% ee, respectively. Comparison of the relative intensities of the integrals for the diastereoisomeric pairs of H_A and H_D protons in the 500 MHz ^{1}H NMR spectrum of these mixtures revealed 81%, 90% and 99% diastereoisomeric excesses calculated for the resultant mixtures of (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** (Fig. 2b and c). These values were in excellent agreement with the known enantio-

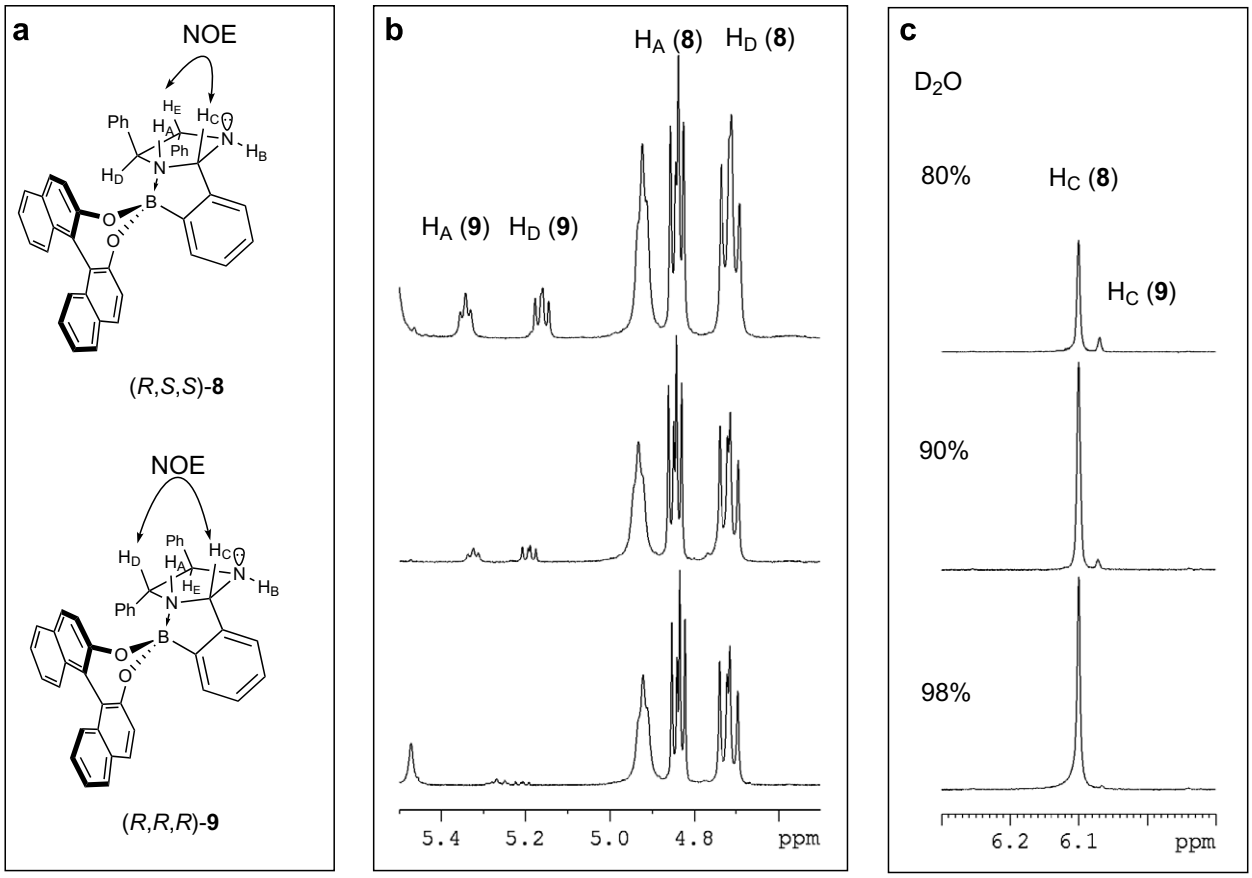


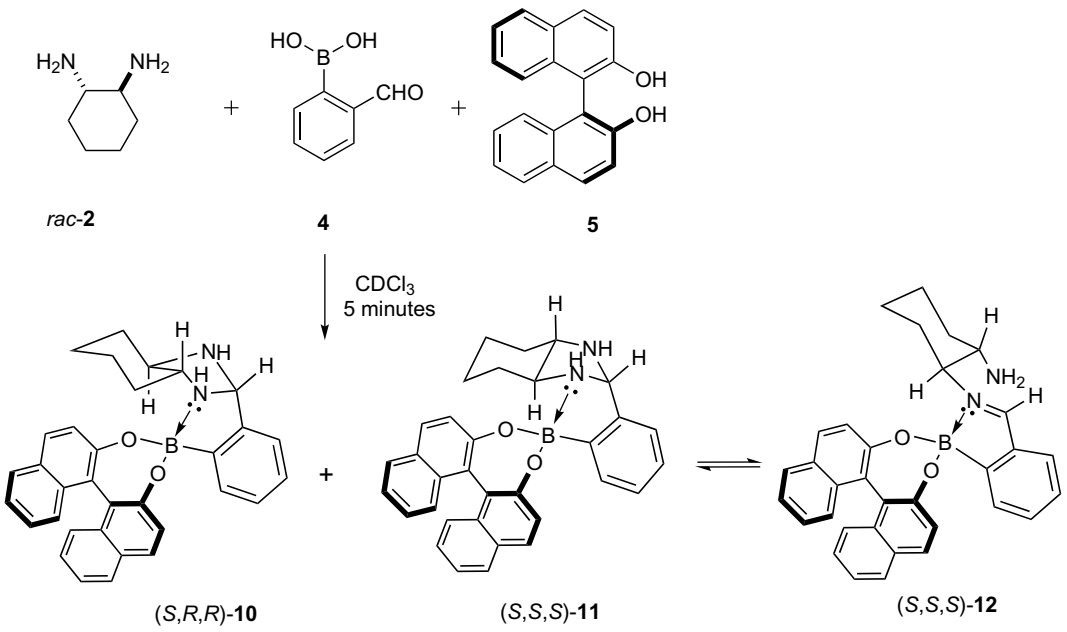
Figure 2. (a) Selected NOE's observed for diastereoisomeric boronate ester complexes (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9**. (b) Expansion of the ^{1}H NMR spectrum of a mixture of (*R*,*S*,*S*)-**8** and (*R*,*R*,*R*)-**9** prepared from (*S*,*S*)-**1** of 80%, 90%, and 98% ee. (c) D_2O exchange to resolve Hc.

meric purity of their corresponding starting diamine **1**, thus indicating that little or no kinetic resolution had occurred in the derivatisation process.

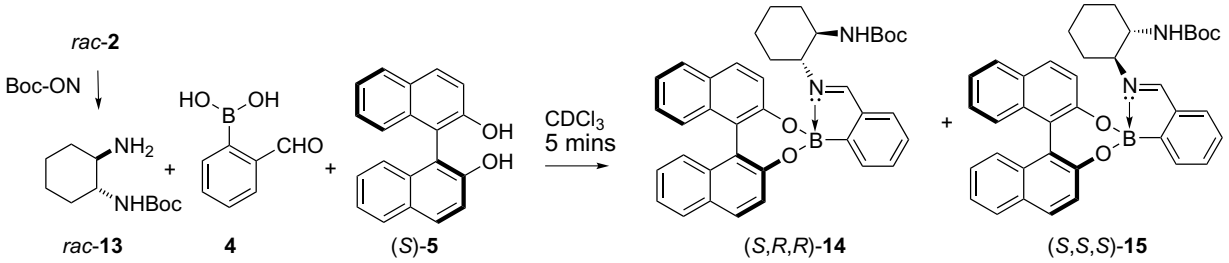
Our attention then turned to using this chiral derivatisation protocol to determine the enantiomeric excess of cyclohexane diamine **2**. Unfortunately, whilst derivatisation of the (*R,R*)-enantiomer of diamine **2** with 2-formyl-phenylboronic acid and (*S*)-BINOL proceeded in quantitative yield to afford its corresponding imidazolidine (*S*,*R*,*R*)-**10**, derivatisation of the (*S*,*S*)-enantiomer of diamine **2** afforded a 50:50 mixture of its imidazolidine (*S*,*S*,*S*)-**11** and its corresponding imine (*S*,*S*,*S*)-**12**. The failure of the (*S,S*)-enantiomer of **2** to undergo clean ring-closure reaction under these conditions is presumably due to the added strain involved in forming a tricyclic imidazolidine ring system caused by unfavorable interactions between the methylene backbone of the cyclohexane ring system and the proximal aryl ring of the binaphthyl fragment (Scheme 3).

This clearly meant that the imidazolidine derivatisation protocol employed for diamine **1** was unsuited for determining the enantiomeric excess of diamine **2**. Consequently, an alternative approach was conceived involving mono-*N*-Boc protection of one of the amino functionalities of *rac*-diamine **2** to afford *rac*-mono-*N*-Boc-diamine **13**[16] that was then derivatized using our previously reported procedure. Therefore, 1.0 equiv of *rac*-mono-*N*-Boc-diamine **13** was treated with 1.0 equiv of 2-formylphenylboronic acid and 1.0 equiv of (*S*)-BINOL in $CDCl_3$ and the ^{1}H NMR spectrum of an aliquot acquired after 5 min (Scheme 4). The resulting ^{1}H NMR spectrum revealed that a mixture of two diastereoisomeric imino-boronate ester complexes (*S*,*R*,*R*)-**14** and (*S*,*S*,*S*)-**15** had been formed in a 50:50 ratio in quantitative yield with baseline resolution of several pairs of diastereoisomeric signals. Comparison of the relative intensities of a number of these resonances could therefore be used to accurately confirm the enantiopurity of a scalemic sample of the parent cyclohexane-1,2-diamine **2** by ^{1}H NMR spectroscopy.

The detection limits of this method were determined by derivatisation of three samples of (*S*,*S*)-*tert*-butyl 2-aminocyclohexylcarbamate **13** of 60% ee, 80% ee and 96% ee. Analysis of the ^{1}H NMR spectrum of each sample revealed that the calculated diastereoisomeric excess of the resulting mixtures of (*S*,*R*,*R*)-**14** and (*S*,*S*,*S*)-**15** were in excellent agreement with the known enantiomeric purity of the parent diamine. Therefore, the integrals measured for their respective imine resonances revealed that (*S*,*S*,*S*)-**15** was present in 60%, 84% and 98% de, respectively, which correlated well with the known enantiopurities of their starting (*S*,*S*)-diamine, thus indicating that no kinetic resolution had occurred.



Scheme 3. Derivatisation of *rac*-diamine **2** affords a mixture of imidazolidines (*S*,*R*,*R*)-**10** and (*S*,*S*,*S*)-**11** and imine (*S*,*S*,*S*)-**12**.



Scheme 4. Three-component protocol for determining the enantiomeric purity of chiral *N*-BOC-diamine **13** by ^{1}H NMR spectroscopic analysis.

3. Conclusions

In conclusion, we have developed practically simple, three-component chiral derivatisation protocols for determining the enantiopurity of vicinal C_2-symmetric diamines such as 1,2-diphenyl-1,2-ethanediamine **1** or cyclohexane-1,2-diamine **2** by ^{1}H NMR spectroscopic analysis.

4. Experimental

4.1. General methods

^{1}H, ^{13}C and ^{11}B NMR spectra were recorded on a Brüker AC-300 or Avance 500 spectrometer; chemical shifts (δ) are expressed in parts per million (ppm), referenced to an internal $SiMe_4$ standard for ^{1}H NMR, and relative to solvent for ^{13}C and ^{11}B NMR. Coupling constants (J) are given in Hertz. Two dimensional NMR techniques were utilised to aid assignment of signals in ^{1}H and ^{13}C NMR spectra. IR spectra (4000–400 cm^{-1}) were recorded on a Perkin–Elmer (1600) FT IR spectrophotometer, using KBr discs or as a thin film between NaCl plates, with an internal calibration. Mass spectra were carried out with the EPSRC national mass spectrometry service at the University of Wales, Swansea. Melting points were obtained on a Gallenkamp apparatus. Optical rotations were recorded at +20 °C on an AA-10 Automatic Polarimeter and specific rotations are in 10^{-1} deg cm^2 g^{-1}. Commercially available reagents were obtained and used without further purification. All reactions were performed under a dry nitrogen atmosphere.

4.2. (4*S*,5*S*)-2-(2-((*R*)-Naphtho[2,1,9,14-*def*][1,3,2]dioxaborepin-4-yl)phenyl)-4,5-diphenylimidazolidine 8

(*S*,*S*)-1,2-Diphenyl-1,2-ethanediamine (85 mg, 0.4 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol) and (*R*)-BINOL (114 mg, 0.4 mmol) were stirred at room temperature in chloroform for 1 h (5 ml). Evaporation of the solvent in vacuo gave the title compound **8** as a yellow solid (233 mg, 98 %), mp 220–230 °C (dec); $[\alpha]_D^{20} = -302$ (*c* 1.2, CH_2Cl_2); δ_H (400 MHz; $CDCl_3$) 8.01–7.93 (2H, m, Ar*H*), 7.78 (1H, d, *J* 7.8, Ar*H*), 7.55–7.22 (18H, m, Ar*H*), 7.17–7.13 (1H, m, Ar*H*), 6.87 (2H, t, *J* 6.0, Ar*H*), 6.75 (1H, d, *J* 6.0, Ar*H*), 6.69 (1H, d, *J* 8.6, Ar*H*), 6.17 (1H, dd, *J* 12.3 and

5.8, C*H*(NH)$_2$), 5.02 (1H, app t, *J* 5.8, N*H*(→B)), 4.87 (1H, dd, *J* 10.6 and 5.8, C*H*(Ph)N→B), 4.75 (1H, dd, *J* 12.3 and 10.6, C*H*(Ph)NH), 2.80 (1H, app t, *J* 12.3, N*H*); δ_C (75 MHz; $CDCl_3$); 154.6, 153.5, 153.1, 139.9, 136.3, 136.3, 133.9, 133.7, 133.5, 131.7, 130.9, 130.6, 130.5, 129.9, 129.8, 129.4, 129.2, 128.8, 128.8, 128.5, 128.5, 128.0, 127.8, 127.6, 127.4, 127.3, 125.7, 124.7, 124.4, 124.0, 123.8, 123.7, 123.7, 123.3, 123.0, 121.6, 118.2, 111.6, 85.5, 73.4, 67.3; δ_B (100 MHz) 13.3; *m*/*z* LRMS (ES+) [$(M+Na)^+$ 617, 39%], 395 (44), 363 (52), 309 (70), 292 (100); HRMS (ES+) found 595.2559 ([M+H]$^{\cdot+}$ $C_{41}H_{32}BN_2O_2$ requires 595.2551).

4.3. (4*R*,5*R*)-2-(2-((*R*)-Naphtho[2,1,9,14-*def*][1,3,2]dioxaborepin-4-yl)phenyl)-4,5-diphenylimidazolidine 9

(*R*,*R*)-1,2-Diphenyl-1,2-ethanediamine (85 mg, 0.4 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol) and (*R*)-BINOL (114 mg, 0.4 mmol) were stirred in chloroform (5 ml) for 1 h followed by removal of the solvent in vacuo to afford the title compound **9** as a yellow solid (222 mg, 95%), mp 220–235 °C (dec); $[\alpha]_D^{20} = +314$ (*c* 1.7, CH_2Cl_2); δ_H (400 MHz; $CDCl_3$) 8.00–7.93 (2H, m, Ar*H*), 7.87 (1H, d, *J* 9.0, Ar*H*), 7.82 (1H, d, *J* 8.1, Ar*H*), 7.65 (1H, d, *J* 9.1, Ar*H*), 7.50–6.98 (20H, m, Ar*H*), 6.58 (1H, d, *J* 7.1, Ar*H*), 6.1 (1H, dd, *J* 12.6 and 5.8 C*H*(NH)$_2$), 5.47 (1H, app t, *J* 5.8, N*H*(→B)), 5.12 (1H, dd, *J* 9.3 and 5.8, C*H*(Ph)N→B), 4.70 (1H, dd, *J* 12.6 and 9.3, C*H*(Ph)NH), 2.82 (1H, app t, *J* 12.6, N*H*); δ_C (75 MHz; $CDCl_3$) 154.3, 153.8, 153.0, 140.6, 137.1, 136.4, 133.9, 133.8, 133.7, 131.6, 131.4, 130.8, 129.8, 129.6, 129.4, 129.3, 129.0, 129.0, 128.9, 128.7, 128.5, 128.1, 127.8, 127.6, 127.5, 127.4, 127.3, 125.6, 124.7, 124.4, 124.0, 123.8, 123.6, 123.5, 123.3, 121.4, 118.2, 111.7, 84.7, 72.7 and 66.9; δ_B (100 MHz) 12.2; *m*/*z* LRMS (EI+) [$(M+H)^+$ 595, 8%] 489.4 (50), 268.3 (84), 239.2 (100); HRMS (EI+) found 594.2469 ([M+H]$^{\cdot+}$ $C_{41}H_{32}BN_2O_2$ (11B) requires 594.2473).

4.4. *tert*-Butyl (*E*,1*R*,2*R*)-2-((2-((*S*)-naphtho[15,10,1,2-*def*][1,3,2]dioxaborepin-4-yl)phenyl)methylideneamino)-cyclohexylcarbamate 14

tert-Butyl (1*R*,2*R*)-2-aminocyclohexylcarbamate (86 mg, 0.4 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol) and (*S*)-BINOL (114 mg, 0.4 mmol) were stirred in chloroform (5 ml) for 1 h before the solvent was removed under reduced pressure to afford the title compound **14** as a yellow solid (236 mg, 99 %), mp 170–175 °C (dec); $[\alpha]_D^{20} = -429$ (*c* 1.1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 1620 (C=N); δ_H (400 MHz; $CDCl_3$) 8.56 (1H, s, C*H*N), 7.82–7.75 (4H, m, Ar*H*), 7.48–7.45 (1H, m, Ar*H*), 7.34–7.05 (10H, m, Ar*H*), 6.78–6.74 (1H, m, Ar*H*), 4.66 (1H, d, *J* 10.0, N*H*COO*t*Bu), 3.89–3.76 (1H, m, C*H*NHBoc), 3.20 (1H, dt, *J* 11.3 and 3.8, C*H*N=C), 2.36–2.30 (1H, m, CH_{eq}CNHBoc), 1.99–1.93 (1H, m, CH_{eq}CN=C), 1.58–0.99 (14H, m, C_4H_5 and CO_2t-*Bu*), 0.83–0.67 (1H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 169.6, 154.9, 154.5, 153.1, 137.6, 134.0, 133.6, 131.5, 130.7, 130.5, 130.2, 130.0, 129.5, 128.9, 128.8, 128.3, 128.1, 127.7, 127.4, 126.9, 125.5, 124.8, 123.9, 123.7, 123.6, 123.2, 123.1, 122.6, 118.3, 80.8, 63.9, 52.2, 35.3, 34.0, 25.3 and 25.1; δ_B (100 MHz) 12.0; *m*/*z* LRMS (CI+) [$(M+H)^+$ 596, 23%], 268.2 (100), 239.1 (97), 211.2 (76); HRMS (EI+) found 595.2351 ([M+H]$^{\cdot+}$ $C_{38}H_{37}BN_2O_4$ (10B) requires 595.2353).

4.5. *tert*-Butyl (*E*,1*S*,2*S*)-2-((2-((*S*)-naphtho[15,10,1,2-*def*][1,3,2]dioxaborepin-4-yl)phenyl)methylidene-amino) cyclohexylcarbamate 15

tert-Butyl (1*S*,2*S*)-2-aminocyclohexylcarbamate (85 mg, 0.4 mmol), 2-formylphenylboronic acid (60 mg, 0.4 mmol) and (*S*)-BINOL (114 mg, 0.4 mmol) were stirred in chloroform (5 ml) for 1 h before removal of the solvent under reduced pressure gave the title compound **15** as a yellow solid (222 mg, 95%), mp 170–175 °C (dec);. $[\alpha]_D^{20} = +414$ (*c* 2.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 1617 (C=N); δ_H (400 MHz; $CDCl_3$) 8.47 (1H, s, C*H*N), 7.85–7.73 (4H, m, Ar*H*), 7.45 (1H, app d, *J* 7.5, Ar*H*), 7.36–7.06 (10H, m, Ar*H*), 6.82 (1H, app d, *J* 6.8, Ar*H*), 5.43 (1H, d, *J* 8.1, N*H*COO*t*Bu), 3.60–3.48 (1H, m, C*H*NHBoc), 3.09 (1H, dt, *J* 11.9 and 3.4, C*H*N=C), 2.34–2.29 (1H, m, CH_{eq}CNHBoc), 1.95–1.91 (1H, m, CH_{eq}CN=C), 1.76–0.71 (15H, m, C_4H_6 and CO_2tBu) δ_C (75 MHz; $CDCl_3$) 169.4, 156.7, 154.5, 137.6, 134.2, 133.6, 133.6, 131.4, 130.8, 130.5, 130.3, 129.8, 129.4, 129.2, 128.8, 128.5, 128.2, 127.5, 127.2, 125.8, 125.7, 124.9, 124.2, 123.9, 123.7, 123.6, 122.6, 122.3, 79.6, 61.0, 55.5, 34.1, 33.3, 28.6, 25.1 and 25.0; δ_B (100 MHz) 12.1; *m*/*z* LRMS (ES+) [$(M+Na)^+$ 619, 10%], 561.4 (26), 347.2 (100), 329.2 (85), 273.1 (24); HRMS (ES+) found 619.1855 ([M+Na]$^{\cdot+}$ $C_{38}H_{37}BN_2O_4Na$ requires 619.1849).

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